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Research article

Impact of A Waning Vaccine and Altered Behavior on the Spread of Influenza

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Abstract: Influenza remains one of the major infectious diseases that targets humankind. Understanding within-host dynamics of the virus and how it translates into the spread of the disease at a population level can help us obtain more accurate disease outbreak predictions. We created an ordinary differential equation model with parameter estimates based on the disease symptoms score data to determine various disease stages and parameters associated with infectiousness and disease progression. Having various stages with different intensities of symptoms enables us to incorporate spontaneous behavior change due to the onset/offset of disease symptoms. Additionally, we incorporate the effect of a waning vaccine on delaying the time and decreasing the size of an epidemic peak. Our results showed that the epidemic peak in the model was significantly lowered when public vaccination was performed up to two months past the onset of an epidemic. Also,

behavior change in the earliest stages of the epidemic lowers and delays the epidemic peak. This study further provides information on the potential impact of pharmaceutical and non-pharmaceutical interventions during an influenza epidemic.

Keywords: influenza; mathematical modeling; vaccination; waning vaccine; behavior change

1. Introduction

Influenza is one of the most well-known infectious diseases with three to five million cases reported and between 250,000 to 500,000 deaths annually worldwide [1]. In the United States alone, there are an estimated 3,000 to 49,000 deaths related to influenza annually with ninety percent of deaths occurring in the population aged 65 and older [2]. Despite its relatively mild symptomatology of fever, cough, headache, and generalized fatigue, influenza remains a deadly disease in selected populations of patients [2]. In an age of constant travel, influenza remains a worldwide threat for the development of pandemics, such as the 2009 H1N1 epidemic. Therefore, the Center for Disease Control and Prevention (CDC) and the World Health Organization (WHO) consider influenza a major public health issue requiring vigilant surveillance [3,4].

Currently, the most effective way to prevent an influenza epidemic is seasonal vaccination [5]. Several reports from Europe and Australia have highlighted the impact of inter-seasonal influenza vaccine waning (*from reference 5–10 of Ferdiand's article)*. Ferdinands et al. [6] collected data in the U.S. from 2011/12 to 2014/15 influenza seasons and controlled for the number of received seasonal vaccinations (1/season/person) and time (at least 14 days before illness onset to monitor for the appropriate mounting of the immune response). The study by Ferdinands et al. [6] supports intra-seasonal waning of influenza vaccination effectiveness across all influenza strains, including Influenza A and Influenza B. Influenza vaccines are categorized into inactivated vaccines (recombinant) or live attenuated vaccines. Depending on the numbers of strains of influenza viruses covered flu vaccines are also divided into trivalent and quadrivalent. Today, influenza vaccinations are most commonly derived from injecting the influenza virus into the fluid of a fertilized chicken egg. The influenza-infected egg is left to incubate so that the virus is able to replicate for several days. Fluid from the egg is collected, and then the influenza virus is killed or weakened for vaccine use. The virus antigen is then made pure for vaccine production. This is the most common way that vaccines are produced [7]. Inactivated vaccines activate the host's immune response against the inactivated viral antigen contained within the vaccine. The host's immune system activates B lymphocytes to produce antibodies against the viral antigen, thereby producing humoral immunity. In contrast, live attenuated vaccines induce viral replication within the host, consequently producing humoral and cellular immunity [8].

Vaccine efficacy is influenced by other factors in addition to vaccine waning. The constantly mutating influenza virus itself influences vaccine efficacy as well as how vaccines are produced for

public consumption. Each year during the influenza season, viral specimens from around the world are analyzed, tested, and submitted to one of the research sites associated with the World Health Organization Collaborating Centers for Reference and Research on Influenza. An expert panel meets each February to make recommendations for next year's vaccine composition [7]. Even without full protection against certain viral subtypes and strains, vaccines create herd immunity by decreasing the incidence of active infection within the unvaccinated population and by reducing the severity of disease and subsequent influenza-related complications and deaths [7–10]. Considering these benefits, the Advisory Committee on Immunization Practices (ACIP) recommended for the 2015–2016 influenza season that each person aged 6 months and older receive influenza vaccination if there are no contraindications [11].

Although the best protection from influenza is routine yearly vaccination, behavioral changes play a critical role in disease prevention and spread [7]. Protective behaviors include hand washing, covering one's mouth and nose, avoiding sick contacts, imposing personal isolation when sick, and disinfecting frequently touched surfaces in common areas that may have been exposed to infectious individuals [7]. Numerous studies validate these behaviors as effective measures in reducing risk to the public [12,13].

Therapeutic pharmacological interventions also reduce the severity of symptoms and shorten recovery time. A previous study by Chowell et al. [14] considered multiple vaccination strategies (no vaccination, seasonal vaccination, and adaptive vaccination) using an age-structured transmission model. When they considered vaccine coverage being 20%, the adaptive vaccination strategy lowered the number of hospitalizations by 37% and the number of deaths by 42% (with $\Re_0 = 1.6$) when the vaccination was given to 20% of the population on the 25^{th} day of the epidemic. Another model by Feng et al. [15] used a Susceptible-Infectious-Recovered-type epidemiological model to show that the effectiveness of control strategies, such as vaccines, are sensitive to the time that they are introduced into the population. It also showed that if the control design is not adequate, the results of vaccine and antiviral use might be compromised. A study by Larson et al. [16] also demonstrated the importance of administering vaccines before the peak of an influenza epidemic. That study used vaccination data from several states to quantify the impact on the overall incidence. In our study, we expand upon the vaccination profile and the effect of non-adherence of protective behaviors, which dually influence the dynamics of influenza spread and progression within the population.

A number of within-host mathematical models have given insight into the dynamics of influenza virus infection and immune responses. There are currently models that consider the impact of changes in human behavior [17] and models linking information obtained from within-host modeling to epidemiological model parameters [18]. In this study, we use a novel model to investigate behavior change and infectiousness based on within-host data and waning vaccines.

2. Materials and Methods

2.1 Mathematical model with waning vaccine protection and behavior changes

We developed a model that expands upon our previous work. In particular, we added an effect of vaccination and an exposed class to the four stage model presented in [18]. Our new model consists of susceptible (S), exposed (E), vaccinated (V), infected (I), and recovered (R) individuals. As in one of the models in [18], we assume that the infected population is divided into four groups denoted by $I_j^{N,B}$ where the subscript j = 1, ..., 4 and superscripts B and N represent the infected individuals that alter their behavior and individuals that do not follow CDC recommendations, respectively. The division of infected individuals is based on the age of the infection, which is assumed to be directly related to viral load. Based on our previous study [18], the infection rate for each stage is denoted by β_i, where i = 1, …, 4. The incubation period is denoted by $1/p_0$. The infection progression rate is denoted by p_i, where i = 1, 2, 3. Individuals recover at the rate p_4 and are assumed to gain a permanent immunity to influenza during a particular epidemic [18].

In our model, a fraction of infected individuals can alter their behavior due to their disease symptoms (μ and ω) and a fraction of them may resume their daily routines after the symptoms begin to vanish (ψ and κ). A fraction of exposed individuals may change their behavior due to the infection risk perception typically caused by the sharing of information about the rapid spread of an influenza infection (ρ). Infected individuals that are following CDC recommendations during an outbreak have a reduced force of infection by a factor of η [18]. A fraction of susceptible individuals (α) can become vaccinated (V) and the vaccine 'takes' (i.e., fully activates) at rate p_α. Duration of antibody development due to vaccination is taken to be14 days [7]. In our model, the vaccine is assumed to be waning at the rate τ and vaccinated individuals can become susceptible to the infection again. A schematic representation of the model is shown in Figure 1.

The mathematical model for the four-stage infection with behavior changes and a waning vaccine is given by the following equations:

$$dS/dt = -S\Lambda - \alpha p_\alpha S + \tau V$$
$$dE/dt = S\Lambda - p_0 E$$
$$dI_1^B/dt = \rho p_0 E - p_1 I_1^B$$
$$dI_2^B/dt = p_1 I_1^B + \mu p_1 I_1^N - p_2 I_2^B$$
$$dI_3^B/dt = (1-\psi) p_2 I_2^B + \omega p_2 I_2^N - p_3 I_3^B$$
$$dI_4^B/dt = (1-\kappa) p_3 I_3^B - p_4 I_4^B$$
$$dI_1^N/dt = (1-\rho) p_0 E - p_1 I_1^N$$
$$dI_2^N/dt = (1-\mu) p_1 I_1^N - p_2 I_2^N$$
$$dI_3^N/dt = (1-\omega) p_2 I_2^N - p_3 I_3^N + \psi p_2 I_2^B$$
$$dI_4^N/dt = p_3 I_3^N - p_4 I_4^N + \kappa p_3 I_3^B$$
$$dR/dt = p_4 I_4^B + p_4 I_4^N$$
$$dV/dt = \alpha p_\alpha S - \tau V$$

where

$$\Lambda = \beta_1 I_1^N + \beta_2 I_2^N + \beta_3 I_3^N + \beta_4 I_4^N + (1-\eta)(\beta_1 I_1^B + \beta_2 I_2^B + \beta_3 I_3^B + \beta_4 I_4^B)$$

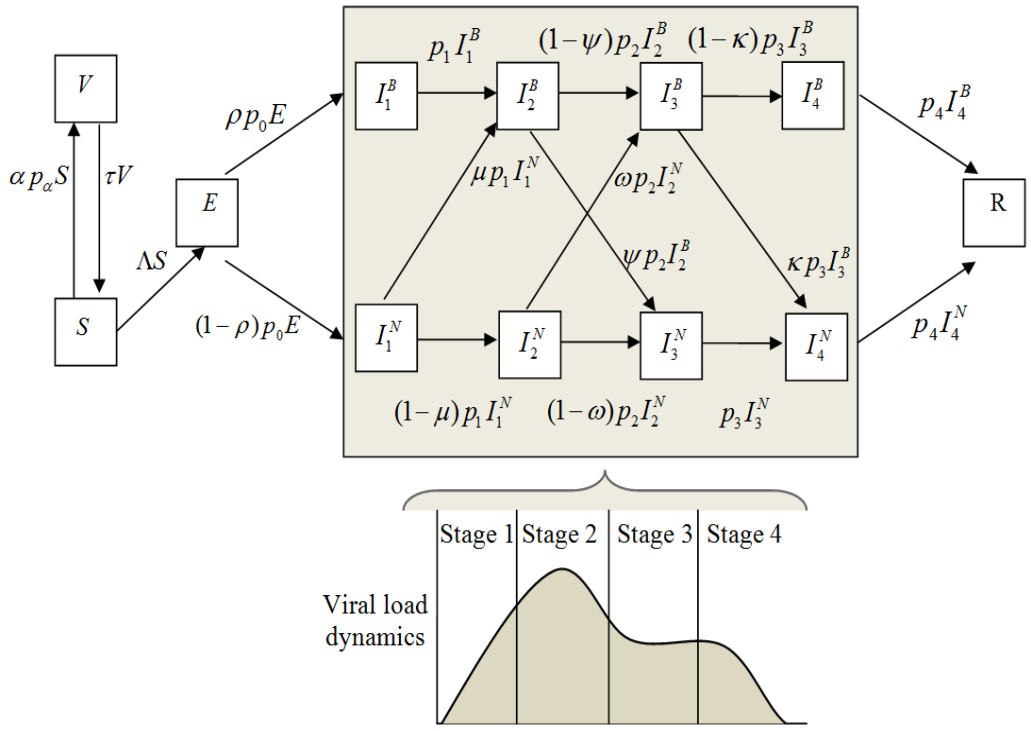

Figure 1. Schematic representation of the model (top) and viral load profile (bottom). Model variables and parameters are given in Tables 1 and 2, respectively. The viral load profile was taken from [18].

2.2 Basic reproductive number

We utilized the Next Generation Method [19] to find $\Re_0$, which is the average number of secondary infections caused by an infectious individual during its infectious period in a fully susceptible population. This definition is related to a disease's ability to invade or remain in a population [20]. $\Re_0$ has been used to measure the severity of past influenza epidemics. For example, Sertsou et al., calculates for the New Zealand population from the 1918 influenza epidemic to estimate its severity [21]. When calculating $\Re_0$, it can be presumed that the susceptible population is in a numerically stably state and is not exposed to the infection [22]. $\Re_0$ can be used in order to evaluate the extent of an outbreak in addition the extent in which medical and behavioral interventions need to be applied [23].

We denote *F* as the matrix of new infections and *G* represents the matrix of transfers between groups evaluated at the disease-free equilibrium ($S_0 = N$ and $E = V = I_{1,2,3,4}^{B,N} = R = 0$) as follows:

$$F = \begin{bmatrix} 0 & (1-\eta)\beta_1 N & (1-\eta)\beta_2 N & (1-\eta)\beta_3 N & (1-\eta)\beta_3 N & \beta_1 N & \beta_2 N & \beta_3 N & \beta_4 N \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

and

$$G = \begin{bmatrix} p_0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ -\rho p_0 & p_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & -p_1 & p_2 & 0 & 0 & -\mu p_1 & 0 & 0 & 0 \\ 0 & 0 & (\psi-1)p_2 & p_3 & 0 & 0 & -\omega p_2 & 0 & 0 \\ 0 & 0 & 0 & (\kappa-1)p_3 & p_4 & 0 & 0 & 0 & 0 \\ (\rho-1)p_0 & 0 & 0 & 0 & 0 & p_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & (\mu-1)p_1 & p_2 & 0 & 0 \\ 0 & 0 & -\psi p_2 & 0 & 0 & 0 & (\omega-1)p_2 & p_3 & 0 \\ 0 & 0 & 0 & -\kappa p_3 & 0 & 0 & 0 & -p_3 & p_4 \end{bmatrix}$$

$\Re_0$ is given by the dominant eigenvalue of the FG^{-1} disease-free equilibrium and without vaccination:

$$\Re_0 = N\left[\frac{\beta_1}{p_1}(1-\eta\rho)+\frac{\beta_2}{p_2}\left(1+\eta\left(\mu(\rho-1)-\rho\right)\right)+\frac{\beta_3}{p_3}\left(1+\eta\left(\mu(1-\omega-\psi)(\rho-1)-\rho(1-\omega-\psi)-\omega\right)\right)\right]$$
$$+N\frac{\beta_4}{p_4}\left[\left(1+\eta\left(\kappa\left(\mu(1-\omega-\psi)(\rho-1)+\rho(1-\omega-\psi)+\omega\right)+\mu(1-\omega-\psi)(\rho-1)-\rho(1-\omega-\psi)-\omega\right)\right)\right]$$

The formula for $\Re_0$ contains portions of individuals that change behavior and the reduction of infectivity due to the behavior change, which can lower $\Re_0$. Each of the terms in $\Re_0$ corresponds to the contribution from each of the four stages (i.e., β_i, for $I = 1, \ldots, 4$).

2.3 Estimation of model parameters based on within-host disease dynamics and the basic reproductive number

Parameter estimates based on within-host data were taken from our previous study [18]. We assume that infectivity and symptoms vary with the age of infection, as they are taken to be proportional to the amount of viral shedding. Considering the viral load profile during the course of an infection, Stage 1 is the initial increase of the viral load, and Stage 2 contains the viral load peak. The viral load decreases into Stage 3, where there is a plateau effect. The viral load resolves in Stage 4 (see Figure 1).

In addition, we estimated the basic reproductive number ($\Re_0$) for the model. In modeling studies, if $\Re_0 > 1$, then an epidemic will occur, and if $\Re_0 < 1$, then an epidemic will die out.

Table 1. Definitions of variables used in the model and their initial values.

Variable	Definition	Initial condition
S	Number of susceptible individuals	N = 1,400,000
V	Number of vaccinated individuals	$V(0) = 0$
E	Number of exposed individuals	$E(0) = 0$
I_j^N	Number of infected individuals not changing their behavior at the infection-stage *i,* for i = 1, 2, 3, and 4 for a four-stage model	$I_1^N(0) = 14$ $I_{2,3,4}^N(0) = 0$
I_j^B	Number of infected individuals changing their behavior at the infection-stage *i,* for i = 1, 2, 3, and 4 for a four-stage model	$I_{1,2,3,4}^B(0) = 0$
R	Number of recovered individuals	$R(0) = 0$

3. RESULTS

3.1 Impact of vaccination

First, we estimated the impact of vaccinating the population at various points during the epidemic. Our model shows that vaccinating the public 0–2 months from the epidemic onset substantially lowers the epidemic peak. However, vaccinating after 3–4 months is ineffective in controlling an influenza epidemic (Figure 2A). Moreover, our model suggests that if the vaccine administration program is limited and can only be given for a month, it is more effective to give it to the public just after 3 months than after 1, 2 or 4 months; if it is given after 3 months, the epidemic peak is reduced 33% (Figure 2B). Our results also show that the higher the proportion of the public being vaccinated, the lower and slightly delayed the epidemic peak will be (Figure 2C). The waning rate of the vaccine can lead to higher and later epidemic peaks (Figure 2D).

Vaccine waning is important to include in modeling studies as the vaccine efficacy may decline over the time course of the flu season. This study shows how the peak of infection shifts with a waning vaccine: a vaccine that does not wane protects individuals and gives a much lower peak, whereas even modest amounts of waning (10% or 15%) allow an epidemiological peak of infection that is 4-fold to 8-fold higher (Figure 2D). Thus, vaccine waning should be taken into account in predictions of how well a vaccine will protect susceptible individuals.

Table 2. Parameter definitions, units, values, and references.

Parameter	Definition	Value, Reference
β_j	Infection rate	$\beta = 0.23\times10^{-6}$, $\beta_1 = \beta_4 = 0.4\times\beta$ $\beta_2 = 1.25\times\beta$, $\beta_3 = 0.75\times\beta$ [18]
$1/p_0$	Incubation period	2 days [7]
$1/p_j$	Duration of the stage j	$1/p_1$=1 day [18] $1/p_2$=$1/p_3$= $1/p_4$= 2 days [18]
$\rho, \mu, \omega, \gamma$	Fraction of the population that changed their behavior immediately after the infection, or during stages 1, 2, or 3, respectively	varied
η	Reduction in infection rate due to the behavior change	varied
ψ, κ	Fraction of the population that revert their behavior during stages 2 or 3, respectively	varied
A	Fraction of the susceptible population that received vaccine	varied
$1/p_\alpha$	Duration of antibody development due to vaccination	14 days [7]
$1/\tau$	Duration of immune system response to vaccine (i.e., 1/Waning rate of vaccine)	varied

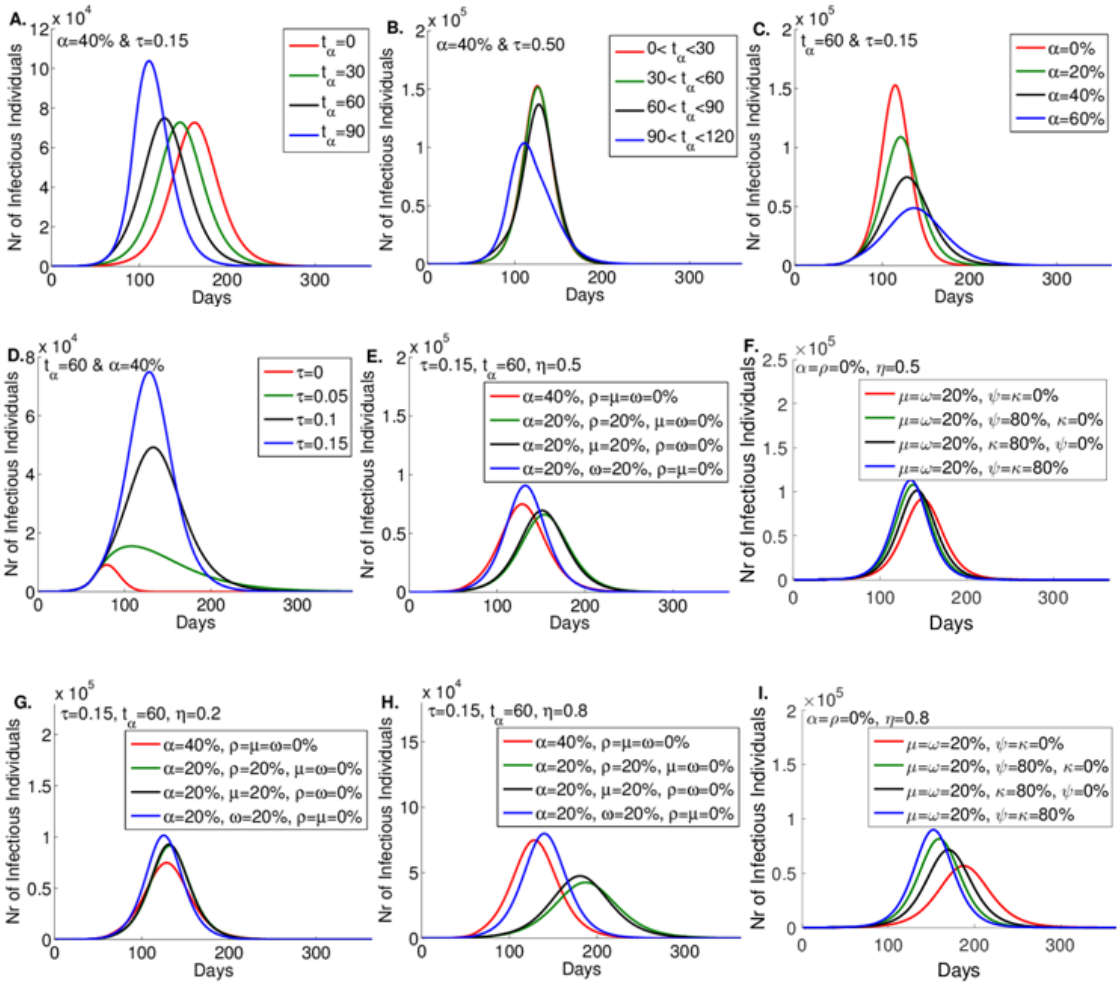

Figure 2. The model-predicted effect on the number (Nr) of infectious individuals given variation in the different conditions. A: Initiation of vaccination (t_α); B: Duration of the vaccine program; C: Percentage of public given vaccine coverage (α); D: Waning rate of the vaccine (τ); E: Behavior change with vaccination (ρ, μ, and ω) and half of reduction in infectivity ($\eta = 0.5$); F: Reversal of behavior change (ψ and κ) and reduction in infectivity $\eta = 0.5$; G: Behavior change with vaccination (ρ, μ, and ω) and reduction in infectivity $\eta=0.2$; H: Behavior change with vaccination (ρ, μ, and ω) and reduction in infectivity $\eta = 0.8$; I: Reversal of behavior change (ψ and κ) and reduction in infectivity $\eta = 0.8$.

3.2 Impact of behavioral changes

Changing behavior during the earliest stages of an infection, which corresponds to the most symptomatic period [18], as indicated in the viral load dynamics in Figure 1, is effective in delaying and lowering an epidemic peak (Figure 2E). Reversing behavior change during last stages (κ and ψ) has little effect on the overall impact of an outbreak (Figure 2F). We also tested the parameter

representing reduction in infectivity (η). There is little difference in the epidemic peak and timing when we consider $\eta = 0.2$ and 0.5. However, a considerably delayed and lowered peak can be observed when $\eta = 0.8$ (Figures 2F-I). This shows that when the reduction in infectivity is greater or the reversal of behavior change is decreased, we see a lowered and delayed epidemiological peak. It also shows that increased behavior change with vaccination causes a lower and delayed epidemiological peak.

Furthermore, behavior change is an important consideration in any epidemic control strategy. While most would agree about the importance of behavior change on the effectiveness of a control strategy, it is unclear how much behavior change affects the outcome of the strategy. This study gives guidelines on the expected effects of influenza vaccination strategies given various behavioral outcomes. Not surprisingly, the earlier behavioral changes are implemented, the smaller the epidemic peak (Figure 2G). This identifies the high-risk groups for transmission, and our modeling shows their impact on reducing new infections.

Lastly, we examined the impact of the fraction of the population that changed their behavior immediately after the infection (ρ), or during stage the most symptomatic stage (ω) on the basic reproductive number ($\Re_0$) (Figure 3A and B). Our modeling predictions suggest that it is possible to lower the basic reproductive number to below 1 through the public behavior change when the reduction in infection rate due to the behavior change (η) is sufficiently large. Note that in Figure 3A the basic reproductive number is not below 1 despite the behavior changes because $\eta = 0.1$, the reduction in infection rate is not sufficient (Figure 3A). However, when $\eta = 0.5$ the basic reproductive number can reach values below the threshold due to the spontaneous behavioral changes. Also, note that the higher the percentage of individuals following CDC recommendations and the earlier this preventive behavior is employed the lower the basic reproductive number (Figure 3).

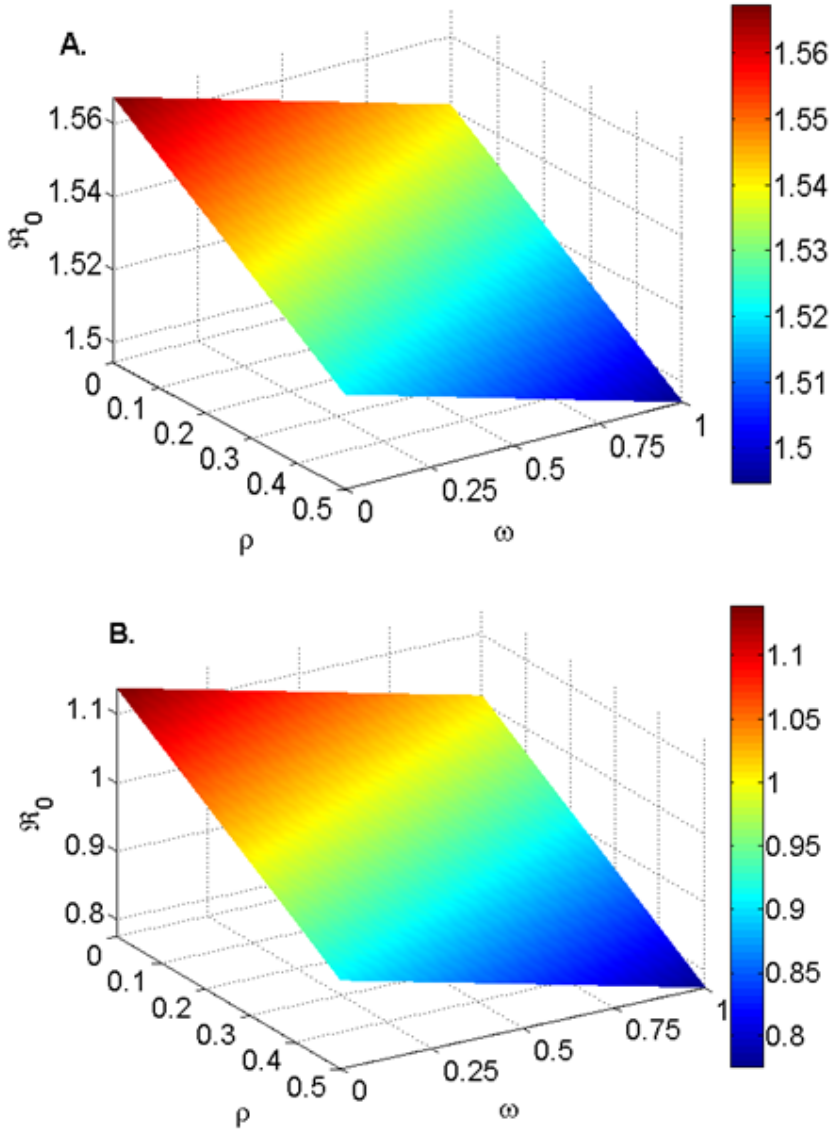

Figure 3. Impact of the fraction of the population that changed their behavior immediately after the infection (ρ), or during stage the most symptomatic stage (ω) on the basic reproductive number ($\Re_0$). A and B correspond to η = 0.1 and η = 0.5, respectively, where η represents the reduction in infection rate due to the behavior change. The remaining parameters are given in Tables 1 and 2.

4. Limitations

One of the limitations of our study is the use of homogeneous mixing to represent how disease is transmitted from person-to-person. Although several studies have shown the importance of incorporating heterogeneous mixing patterns when modeling disease dynamics [28–30], other studies [31] have also shown that simple models with homogeneous assumptions can still provide insights into the overall dynamics of disease transmission. Thus, we chose to analyze a simpler model in order to take full advantage of some of the mathematical tools readily available for these types of problems and still provide insights into the potential impact of vaccine waning and behavior on influenza dynamics. Based on the literature about the impact of heterogeneous mixing on disease dynamics, it is possible that the overall impact of the interventions may be lower in a heterogeneously mixing population.

Another potential limitation is the use of one vaccine compartment that allows people to move to/from the susceptible class if the vaccine wanes or before it "takes." However, it may be more accurate to model these dynamics as two separate compartments to capture people who are "effectively" vaccinated and people who are "ineffectively" vaccinated.

Finally, another limitation is the assumption of a completely susceptible population. Although in reality, the level of susceptibility from year to year and by age, the true level of susceptibility is unknown. Thus, we encourage public health officials to collect information about susceptibility within the population to better inform mathematical models and subsequently mitigation strategies.

Although we have identified several limitations within our model, we still believe our model provides insights into the potential impacts of pharmaceutical and non-pharmaceutical interventions, which can inform the implementation of future mitigation strategies. In addition, we hope to continue building more mathematical models that may capture some of the complexities listed above to better inform public health policies.

5. Conclusion and Discussion

This study uses mathematical modeling to investigate the ideal time of vaccination, optimal time to vaccinate given a limited time vaccine program administration, vaccine coverage rate, vaccine waning rate, adoption of prophylactic behaviors to avoid the spread of infection, and the lack of adherence to these behavior changes, on the magnitude of the epidemic.

Our results indicate that the dynamics of viral shedding and symptoms, during the infection, are key features when considering epidemic prevention strategies. The literature has shown that the degree of infectiousness is related to viral load and viral shedding [18]. The most symptomatic stages are proportional to viral load and shedding as can be observed in the schematic representation for viral load dynamics in Figure 1. It is important to exercise prevention strategies, especially behavior changes such as social distancing, before the viral load peak is reached. Initiating behavior change in the earliest stage of an influenza infection is more effective than waiting until the second or third stages when the viral load and infectiousness have peaked [18].

We also showed that in the best possible scenario (i.e., to reduce the most infections), individuals should change their behavior in order to prevent infection, be fully compliant to behaviors that prevent them from getting infected, and change the behavior in the early stages of infection when they have the highest viral shedding (i.e., when they are the most infectious). However, in some cases it may be more realistic to expect other scenarios, such as behavior change that occurs later in infection, or early reversion of behaviors due to the difficulty in maintaining new hygienic habits; this behavior would result in a more modest effect of the vaccine. Note that this study demonstrates that it is of less concern if individuals who have changed their behavior revert back to less protective behavior as time goes on. Presumably this is because they are less likely to transmit the infection, so the increase in the risk that they will transmit to susceptible individuals is counterbalanced by their own decrease in infectiousness. In other words, not much vaccine effectiveness is lost if individuals abandon their behavior changes late in the epidemic. These guidelines suggest that the behavior change should ideally occur as soon as the individual becomes infectious, however, this recommendation is unrealistic for asymptomatic individuals who can be infectious. Our results also give us an estimate of how long the behavior change must be sustained, specifically, the behavior change should be in place for the duration of the infection.

Likewise, these results indicate ideal vaccination time by showing how many months after the start of infection is the vaccine effective at lowering the peak of infection. Vaccinating at the beginning of influenza season is more effective than later on when the epidemic has already begun to subside (Figure 2A). Unexpectedly, if the vaccine time administration is limited, the results show that it is actually less efficacious to vaccinate at the start of the epidemic compared to 3 months into the epidemic, when it is reaching its peak (Figure 2B). Moreover, as may be expected, greater vaccine coverage is correlated with the number of infections prevented (Figure 2C), emphasizing the need to increase the fraction of the population that is vaccinated.

Vaccine effectiveness is defined as a measurement of risk reduction for the development of a particular illness. In the past ten years, influenza vaccine effectiveness has fluctuated between 10 and 60 percent [7]. Vaccine effectiveness is unpredictable due to its reliance on intrinsic and extrinsic factors. Intrinsic effectiveness is related to the best-predicted viral antigen subtype match for the season. Viral antigen subtype match varies due to limited predictability of the antigenic drift and demographic variation [7]. Antigenic drift underlies the importance of annual vaccination and updates in the vaccine compositions.. It has been demonstrated that an individual's age, comorbid conditions, or degree of immunosuppression may affect a person's response to the influenza vaccine and may potentially decrease its effectiveness [24–27]. These mutations in addition to vaccine waning are important factors for why yearly vaccination is necessary [7]. Although our model does not include viral resistance to vaccines due to mutation, it opens a new opportunity for future studies.

In conclusion, our results provide insights into strategies for the control of the spread of influenza by behavior change and in consideration of vaccine waning. This study accentuates that vaccine programs ideally should take into account the fact that that behavior change, and adherence

to it, can increase the effectiveness of the vaccine program. Future work in this area should focus on the effect of vaccines that do not completely protect individuals from infection simultaneously considering the distribution to various age groups as well as their behavior change.

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