A Vaccination Model for Transmission Dynamics of Influenza*

M. E. Alexander†, C. Bowman‡, S. M. Moghadas†, R. Summers†, A. B. Gumel§, and B. M. Sahai¶

Abstract. Despite the availability of preventive vaccines and public health vaccination programs, influenza inflicts substantial morbidity, mortality, and socio-economic costs and remains a major public health problem. This is largely because the protection conferred by current vaccines is dependent on the immune status of the individual, ranging between 70%-90% in healthy young adults and 30%-40% among the elderly and others with weakened immune systems. Whether a strategic use of such partially effective vaccines can control the spread of influenza within a certain population is unknown but of great public health interest. To address this question, we construct a deterministic mathematical model to study the transmission dynamics of influenza. The model is analyzed qualitatively to determine criteria for control of an influenza epidemic and is used to compute the threshold vaccination rate necessary for community-wide control of influenza. Using two specific populations of similar size, an office and a personal care home, our model shows that the spread of influenza can be controlled if the combined effect of the vaccine efficacy and vaccination rate reaches a threshold determined by the duration of infectiousness and the rate of contact between infected and susceptible individuals.

Key words. epidemic models, bistability, influenza, outbreaks, vaccination

AMS subject classifications. Primary, 34C23, 92B05; Secondary, 37N25

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1. Introduction. Influenza (also known as flu) is a respiratory disease caused by certain RNA viruses of the Orthomyxoviridae family [13, 22, 30]. These viruses have a segmented RNA genome that is replicated by an error-prone RNA polymerase leading to seasonal mutations (drifts) in parts of the viral genome. Human influenza viruses appear as three distinct serotypes: A, B, and C. Only influenza A viruses infect and multiply in avian species and non-primates, and their genomic segments are subject to occasional reassortment (shift) giving rise to new viral strains consisting of novel hemagglutinin (HA) and/or neuraminidase (NA) genes [23, 30, 39] (see Figure 1). The influenza A viruses have been responsible for the vast majority of epidemics and all recorded pandemics (see Table 1), which usually result from...
Figure 1. Types and known strains of human influenza viruses. Influenza A viruses are primarily associated with epidemics in humans, and sometimes their replication in a host coinfectected with more than one viral strain leads to new viral strains due to the reassortment of HA and NA subtype genes. The individual strains further diverge into independent lineages by genetic drift. The H1N1 and H3N2 are the most common strains circulating in the human population [39].

Table 1

<table>
<thead>
<tr>
<th>Year</th>
<th>Outbreak/epidemic region</th>
<th>Viral strain (lineage)</th>
<th>Refs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1918</td>
<td>Pandemic (Spanish flu)</td>
<td>H1N1 (A/Brevig Mission/1/18; A/South Carolina/1/18; and A/New York/1/18)</td>
<td>[31, 39]</td>
</tr>
<tr>
<td>1957</td>
<td>Pandemic (Asian flu)</td>
<td>H2N2 (A/Singapore/1/57)</td>
<td>[31, 39]</td>
</tr>
<tr>
<td>1968</td>
<td>Pandemic (Hong Kong flu)</td>
<td>H3N2 (A/NT/60/68; and A/Hong Kong/1/68)</td>
<td>[31, 39]</td>
</tr>
<tr>
<td>1977</td>
<td>Pandemic in children and young adults (Russian flu)</td>
<td>H1N1 (A/USSR/90/77)</td>
<td>[31, 39]</td>
</tr>
<tr>
<td>2001-02</td>
<td>USA, Canada, Singapore, Malaysia, Egypt, Europe</td>
<td>H1N2 (A/New Caledonia/20/99; H1 and A/Moscow/10/99 N2)</td>
<td>[41]</td>
</tr>
<tr>
<td>2001-02</td>
<td>Northern Italy</td>
<td>Influenza B (B/Victoria/2/87)</td>
<td>[2]</td>
</tr>
<tr>
<td>2001-02</td>
<td>St. Elisabeth Hospital, Tilburg</td>
<td>H3N2 (A/Sydney/5/97)</td>
<td>[6]</td>
</tr>
<tr>
<td>2003</td>
<td>Poultry farms in Netherlands</td>
<td>H7N7 (Avian influenza A)</td>
<td>[21]</td>
</tr>
<tr>
<td>2003-04</td>
<td>USA, Canada, Europe, Japan</td>
<td>H5N2 (A/Fujian/411/2002)</td>
<td>[37, 38]</td>
</tr>
</tbody>
</table>

Influenza viruses have coexisted with humans for centuries and have historically been a cause of excessive morbidity and mortality [9, 10, 34]. Annually, the virus affects 25 to 50 million people, with an estimated 20 to 40 thousand influenza-related deaths, in the United States [34]. Because of the illness and high number of deaths associated with influenza, particularly among the elderly [10, 11], much attention has been focused on preventive strategies.
Although vaccination has been an effective strategy against influenza infection [5, 12, 17, 26, 28, 34, 40], current preventive vaccines consisting of inactivated virions do not protect all vaccine recipients equally. The vaccine-based protection is dependent on the immune status of the recipient (see [18, 35] for general references). Typically, influenza vaccines protect 70%–90% of the recipients among healthy young adults and as low as 30%–40% of the elderly and others with weakened immune systems (such as HIV-infected or immunosuppressed transplant patients) [5, 12, 15, 26]. Furthermore, due to the seasonal drift in the viral genome, annual vaccination against the influenza virus strains anticipated to be in circulation during the upcoming season is necessary to prevent new infections and subsequent outbreaks.

The failure of current influenza vaccines to protect all vaccine recipients warrants the determination of conditions necessary for a substantial reduction, approaching eradication, of influenza infection in a population. Consequently, the aim of this study is to explore, via mathematical modeling, the impact of immunization with a partially effective vaccine on the transmission dynamics of influenza infection. The study addresses the question of whether such a vaccine could ever completely stop the spread of infection and determines the minimal vaccine efficacy and vaccination rate required to control or eradicate infection in a population.

Mathematical models have been used to determine the ability of an imperfect vaccine to control other infectious diseases, and some of the findings have been corroborated by clinical studies (see [14, 16, 19, 20, 27] for general references). There have been several published mathematical models suggested for the transmission dynamics of influenza [4, 13, 18, 23, 36], but to our knowledge none has fully analyzed the impact of an imperfect vaccine (see also [24] and the references therein). Furthermore, these studies tend to classify all recruited individuals into the population as susceptibles. In the context of influenza epidemiology, it is more realistic to consider models that also allow for the continuous recruitment of infected individuals into the population, as previously considered for other diseases such as HIV infection [7]. In the model presented here, the use of an imperfect vaccine and recruitment of infected individuals prove to be crucial factors determining the transmission dynamics of influenza.

The paper is organized as follows. A mathematical model for the transmission dynamics of influenza infection is formulated and normalized in section 2. The existence of the equilibria of the normalized-reduced (NR) model is discussed in section 3. Stability analysis of the NR model is carried out in section 4, where it is also shown that the model has a stable endemic equilibrium even when the threshold condition for disease eradication holds. In section 5, some quantitative results are derived from the model to illustrate the effect of vaccination in two typical environments consisting of equal-size populations: a personal care home and an office setting. We conclude with a brief discussion of our findings.

2. Model formulation. In order to derive the equations of the mathematical model, we divide the population (\( \hat{N} \)) into four subpopulations: susceptible (\( \hat{S} \)), vaccinated (\( \hat{V} \)), infected (\( \hat{I} \)), and recovered (\( \hat{R} \)). Since a typical outbreak of influenza is caused by the replication and spread of a single viral strain [1], irrespective of the existing immunity to previous strains, our model monitors the dynamics of influenza based on a single strain without effective cross-immunity against the strain. It should be noted, however, that the model does not exclude the possibility of two concurrent outbreaks, each caused by a different strain. In this case, the
The model does not consider the effects of partial cross-immunity between the viral strains.

The susceptible population is increased by recruitment of individuals (either by birth or immigration), and by the loss of immunity, acquired through previous vaccination or natural infection. This population is reduced through vaccination (moving to class $\tilde{V}$) and infection (moving to class $\tilde{I}$), and by natural death or emigration.

The population of vaccinated individuals is increased by vaccination of susceptibles. Since the vaccine does not confer immunity to all vaccine recipients, vaccinated individuals may become infected but at a lower rate than unvaccinated (those in class $\tilde{S}$). The vaccinated class is thus diminished by this infection (moving to class $\tilde{I}$) and further decreased by waning of vaccine-based immunity (moving to class $\tilde{S}$) and by natural death.

The population of infected individuals is increased by recruitment of infected individuals from outside the population, as well as by infection of susceptibles including those who remain susceptible despite being vaccinated. It is diminished by natural death and by recovery from the disease (moving to class $\tilde{R}$).

Since the immunity acquired by infection wanes with time, the recovered individuals become susceptible to the disease again. Thus the recovered class is increased by individuals recovering from their infection and is decreased as the natural immunity wanes (moving back to class $\tilde{S}$).

The transfer diagram for these processes is shown in Figure 2. The details of the transitions between the subpopulations can be mathematically expressed by the following differential equations:

$$\frac{d\tilde{S}}{dt} = (1 - \epsilon)\Pi + \tilde{\omega}\tilde{V} + \delta\tilde{R} - \beta\tilde{S}\tilde{I} - \xi\tilde{S} - \mu\tilde{S}, \quad (2.1)$$

$$\frac{d\tilde{V}}{dt} = \tilde{\xi}\tilde{S} - (1 - \sigma)\beta\tilde{V}\tilde{I} - (\tilde{\omega} + \mu)\tilde{V}, \quad (2.2)$$

$$\frac{d\tilde{I}}{dt} = \epsilon\Pi + \tilde{\beta}\tilde{S}\tilde{I} + (1 - \sigma)\beta\tilde{V}\tilde{I} - (\tilde{\alpha} + \mu)\tilde{I}, \quad (2.3)$$

$$\frac{d\tilde{R}}{dt} = \tilde{\alpha}\tilde{I} - (\mu + \delta)\tilde{R}, \quad (2.4)$$

where $\Pi$ is the rate of recruitment of individuals into the population; $\epsilon$ is the fraction of recruited individuals who are already infected; $\xi$ is the rate at which susceptible individuals
Table 2

Model parameters and their interpretations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Pi$</td>
<td>recruitment rate of individuals</td>
</tr>
<tr>
<td>$\epsilon$</td>
<td>fraction of recruited individuals who are infected</td>
</tr>
<tr>
<td>$\hat{\beta}$</td>
<td>contacts $\times$ probability of infection per contact with an infected</td>
</tr>
<tr>
<td>$\hat{\xi}$</td>
<td>rate at which susceptible individuals are vaccinated</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>vaccine efficacy</td>
</tr>
<tr>
<td>$1/\hat{\omega}$</td>
<td>average time to lose vaccine-induced immunity</td>
</tr>
<tr>
<td>$1/\hat{\alpha}$</td>
<td>average length of infection (duration of infectiousness)</td>
</tr>
<tr>
<td>$1/\hat{\delta}$</td>
<td>average time to lose immunity acquired by infection</td>
</tr>
<tr>
<td>$1/\mu$</td>
<td>average life-span</td>
</tr>
</tbody>
</table>

receive the vaccine; $\mu$ is the rate at which people leave the population, whether by death or emigration (this rate is assumed to be the same for all subpopulations); $\hat{\beta}$ represents the probability of infection for susceptible individuals; $\hat{\omega}$ is the rate at which vaccine-based immunity wanes; $\sigma$ is the vaccine efficacy; $\hat{\alpha}$ is the recovery rate from infection; and $\hat{\delta}$ is the rate of loss of immunity acquired by infection.

It is worth noting that recruitment of individuals into the vaccinated class ($\hat{V}$) does not significantly alter the dynamics of the model (see the appendix). Furthermore, since the model monitors the dynamics of the human populations, it is assumed that all the model parameters and state variables are nonnegative. A description of the model parameters is given in Table 2.

To simplify the mathematical analysis of this study, we normalize the model (2.1)–(2.4) by defining the new variables,

$$
S = \frac{\mu}{\Pi} \hat{S}, \quad V = \frac{\mu}{\Pi} \hat{V}, \quad I = \frac{\mu}{\Pi} \hat{I}, \quad R = \frac{\mu}{\Pi} \hat{R},
$$

and parameters,

$$
t = \mu \hat{t}, \quad \beta = \frac{\Pi \hat{\beta}}{\mu^2}, \quad \omega = \frac{\hat{\omega}}{\mu}, \quad \xi = \frac{\hat{\xi}}{\mu}, \quad \delta = \frac{\hat{\delta}}{\mu}, \quad \alpha = \frac{\hat{\alpha}}{\mu},
$$

giving

(2.5) \quad \frac{dS}{dt} = \left(1 - \epsilon \right) - \beta SI - \xi S - S + \omega V + \delta R,

(2.6) \quad \frac{dV}{dt} = \xi S - (1 - \sigma) \beta VI - (1 + \omega)V,

(2.7) \quad \frac{dI}{dt} = \epsilon + \beta SI + (1 - \sigma) \beta VI - (1 + \alpha)I,

(2.8) \quad \frac{dR}{dt} = \alpha I - (1 + \delta)R.

Let $N = S + V + I + R$ be the total population size of the model (2.5)–(2.8). Adding equations (2.5)–(2.8) gives the equation for the total population:

(2.9) \quad \frac{dN}{dt} = 1 - N.
Since \( N(t) \to 1 \) as \( t \to \infty \), it can be seen that the feasible region
\[
\Omega = \{(S, V, I, R) : S, V, I, R \geq 0; S + V + I + R = 1\}
\]
is positively invariant for the model (2.5)–(2.8). Therefore, we restrict our attention to the dynamics of the model in \( \Omega \). Using \( R = 1 - S - V - I \) in \( \Omega \), (2.8) can be removed from the model. This substitution gives the following NR model:

\[
\frac{dS}{dt} = (1 - \epsilon) - \beta SI - \xi S - S + \omega V + \delta(1 - S - V - I),
\]
(2.10)

\[
\frac{dV}{dt} = \xi S - (1 - \sigma)\beta VI - (1 + \omega)V,
\]
(2.11)

\[
\frac{dI}{dt} = \epsilon + \beta SI + (1 - \sigma)\beta VI - (1 + \alpha)I.
\]
(2.12)

3. Equilibria of the NR model. In this section, the conditions for the existence of the equilibria of the NR model, given by (2.10)–(2.12), are established. In order to do this, we first consider the case \( \epsilon = 0 \); that is, the population does not admit new infected individuals. The results obtained in this case will subsequently be adapted and used in section 3.3 to discuss the existence of the equilibria of the NR model with \( \epsilon > 0 \).

3.1. Disease-free equilibrium (DFE). When \( \epsilon = 0 \), the model assumes that all individuals recruited into the population are susceptible. In this case, the NR model has a DFE given by
\[
E_0 = \left( \frac{1 + \omega}{1 + \omega + \xi}, \frac{\xi}{1 + \omega + \xi}, 0 \right).
\]

To establish the conditions for the existence of endemic equilibria when \( \epsilon = 0 \), it is useful to analyze the stability of \( E_0 \). This analysis provides a key threshold quantity which will be used for stability analysis of the NR model throughout the paper. To determine the local stability of \( E_0 \), the Jacobian of the NR model is evaluated at the DFE to yield
\[
J_0 = \begin{pmatrix}
-(1 + \delta + \xi) & \omega - \delta & -\frac{\beta (1 + \omega)}{1 + \omega + \xi} - \delta \\
\xi & -(1 + \omega) & -\frac{(1 - \sigma)\beta \xi}{1 + \omega + \xi} \\
0 & 0 & \frac{\beta (1 + \omega)}{1 + \omega + \xi} + \frac{(1 - \sigma)\beta \xi}{1 + \omega + \xi} - (1 + \alpha)
\end{pmatrix}.
\]

The eigenvalues of \( J_0 \) are
\[
\lambda_1 = \frac{\beta (1 + \omega)}{1 + \omega + \xi} + \frac{(1 - \sigma)\beta \xi}{1 + \omega + \xi} - (1 + \alpha),
\]
and the eigenvalues of the submatrix
\[
J_1 = \begin{pmatrix}
-(1 + \delta + \xi) & \omega - \delta \\
\xi & -(1 + \omega)
\end{pmatrix}.
\]
It is easy to see that the eigenvalues of $J_1$ are negative. Thus, the local stability of $E_0$ depends on the sign of $\lambda_1$. Let
\begin{equation}
R_0 = \frac{\beta[(1+\omega)+(1-\sigma)\xi]}{(1+\alpha)(1+\omega+\xi)}.
\end{equation}

**Lemma 3.1.** The DFE of the NR model is locally asymptotically stable if $R_0 < 1$ and unstable if $R_0 > 1$.

**Proof.** Since the eigenvalues of $J_1$ are negative, it follows that the DFE is locally asymptotically stable if $\lambda_1 < 0$ and unstable if $\lambda_1 > 0$. Noting that $\lambda_1 < 0$ if and only if $R_0 < 1$, the proof is complete.

The threshold quantity $R_0$ in (3.1) is the reproductive number of infection [3] which can be interpreted as the number of infected people produced by one infected individual introduced into the population in the presence of vaccination (see [35]). Biologically speaking, Lemma 3.1 implies that the disease can be eradicated from the population (when $R_0 < 1$) if the initial sizes of the subpopulations are in the basin of attraction of $E_0$. This is, however, an insufficient condition for disease control, since for arbitrary initial sizes of the subpopulations, the local stability of $E_0$ does not guarantee community-wide eradication of the disease. This scenario will be discussed in section 4.

The quantity $R_0$ can be rewritten as
\begin{equation}
R_0 = \left(1 - \frac{\sigma \xi}{1+\omega+\xi}\right) r_0,
\end{equation}
where $r_0 \equiv \frac{\beta}{1+\alpha}$ is the basic reproductive number of the disease in the absence of vaccination [3], in which case $R_0$ reduces to $r_0$. Clearly, if $r_0 < 1$, then $R_0 < 1$ irrespective of the value of $\xi$, and thus $E_0$ is locally asymptotically stable.

Using the expression for $R_0$ in (3.2) and the fact that $\xi \geq 0$, it can be seen that
\begin{equation}
(1-\sigma)r_0 = \frac{\beta}{\beta^*} < R_0 \leq r_0,
\end{equation}
where
\begin{equation}
\beta^* \equiv \frac{1+\alpha}{1-\sigma}.
\end{equation}
Thus, if $\beta > \beta^*$, then $R_0 > 1$, and consequently no amount of vaccination can bring $R_0$ below 1. The requirement $\beta < \beta^*$ can be rewritten so as to define a threshold vaccine efficacy, $\sigma_c$:
\begin{equation}
\sigma_c = 1 - \frac{1}{r_0}.
\end{equation}
If $\sigma < \sigma_c$, then $\beta > \beta^*$, and $R_0 > 1$ regardless of vaccination rate. Figure 3 shows the regions of vaccine efficacy and vaccination rate for which $R_0 < 1$ for some chosen parameter values.

From now on, it is assumed that $\beta$ satisfies
\begin{equation}
1 + \alpha < \beta < \frac{1+\alpha}{1-\sigma} \equiv \beta^*.
\end{equation}
Figure 3. Regions for reducing basic reproduction number to less than unity given an imperfect vaccine with efficacy $\sigma$ applied at rate $\xi$. The gray and white regions correspond to $R_0 > 1$ and $R_0 < 1$, respectively. Other model parameters are $\alpha = 4500$, $\delta = 1000$, $\omega = 100$, $\sigma = 0.9$, and $\beta = 10000$.

In this case, setting $R_0 = 1$ and solving for $\xi$ give the threshold vaccination rate

\begin{equation}
\xi_c = \frac{(1 + \omega)(r_0 - 1)}{1 - (1 - \sigma)r_0},
\end{equation}

which is positive.

3.2. Endemic equilibria ($\epsilon = 0$). The endemic equilibria of the NR model with $\epsilon = 0$ (if they exist) cannot be cleanly expressed in closed form. In order to find the conditions for the existence of these equilibria, we use (2.10)–(2.12) to express the variables $S$ and $V$ in terms of the variable $I$ when $I \neq 0$. This gives (at equilibrium)

\begin{align}
S &= \frac{(1 - \sigma)\beta I + 1 + \omega}{[(1 - \sigma)(\beta I + \xi) + 1 + \omega]r_0}, \\
V &= \frac{1 - r_0S}{(1 - \sigma)r_0}.
\end{align}

Substituting (3.6)–(3.7) into (2.12) gives (at equilibrium)

\begin{equation}
Q(I) \equiv a_1I^2 + a_2I + a_3 = 0,
\end{equation}

where

\begin{align}
a_1 &= \beta^2(1 - \sigma)(1 + \alpha + \delta), \\
a_2 &= \beta\{(1 + \alpha + \delta)[(1 - \sigma)\xi + 1 + \omega] - (1 + \delta)(1 - \sigma)[\beta - (1 + \alpha)]\}, \\
a_3 &= (1 + \delta)\{(1 + \alpha)(1 + \omega + \xi) - \beta[(1 - \sigma)\xi + 1 + \omega]\}.
\end{align}
Since all the model parameters are nonnegative, it follows from (3.9) that \( a_1 > 0 \). Furthermore, if \( R_0 > 1 \), then \( a_3 < 0 \). The existence of the equilibria is summarized in the following theorem and illustrated in Figure 5.

**Theorem 3.2.** Suppose \( \epsilon = 0 \) in (2.10)–(2.12).

(a) If \( a_2(\xi_c) \geq 0 \), then
   (i) the model has a unique endemic equilibrium if \( \xi < \xi_c \),
   (ii) the model has no endemic equilibria if \( \xi > \xi_c \).

(b) If \( a_2(\xi_c) < 0 \), then there exists \( \xi^* > \xi_c \) such that
   (i) the model has a unique endemic equilibrium if \( \xi < \xi_c \),
   (ii) the model has no endemic equilibria if \( \xi > \xi^* \),
   (iii) the model has two endemic equilibria if \( \xi_c < \xi < \xi^* \).

**Proof.** Since \( R_0 \) is a continuous decreasing function of \( \xi \) for \( \xi > 0 \), if \( \xi < \xi_c \), then \( R_0 > 1 \) (\( a_3 < 0 \)). Since \( a_1 > 0 \), it follows that \( Q(I) \) has a unique positive root.

Suppose \( \xi \geq \xi_c \). In this case, \( R_0 \leq 1 \) (\( a_3 > 0 \)). It is easy to see that \( a_2(\xi) \) is an increasing function of \( \xi \). Thus, if \( a_2(\xi_c) \geq 0 \), then \( a_2(\xi) > 0 \) for \( \xi > \xi_c \), and \( Q(I) \) has no positive real root, which implies that the model has no endemic equilibrium in this case. If \( a_2(\xi_c) < 0 \), consider \( D(\xi) = a_2^2(\xi) - 4a_1a_3(\xi) \), the discriminant of \( Q(I) \). Since \( a_3(\xi_c) = 0 \), \( D(\xi_c) > 0 \), and \( D(\xi) \) is a quadratic function of \( \xi \) with positive coefficient for \( \xi^2 \). Furthermore, since \( a_2(\xi) \) is a linear increasing function of \( \xi \), there is a unique \( \xi^{**} > \xi_c \) so that \( a_2(\xi^{**}) = 0 \), and thus \( D(\xi^{**}) < 0 \) (since \( a_1 \) and \( a_3 \) are both nonnegative for \( \xi \geq \xi_c \)). Let \( \xi^* \) be the unique root of \( D(\xi) \) in \( [\xi_c, \xi^{**}] \). Then, \( a_2(\xi) < 0 \), \( a_1 > 0 \), \( a_3 > 0 \), and \( D(\xi) > 0 \) for \( \xi \in (\xi_c, \xi^*) \). Hence, \( Q(I) \) has two positive roots, so that the model has two endemic equilibria, if \( \xi_c < \xi < \xi^* \). Taking into account \( a_2(\xi) > 0 \) for \( \xi > \xi^{**} \) and \( D(\xi) < 0 \) for \( \xi \in (\xi^*, \xi^{**}) \), it follows that the model has no endemic equilibria if \( \xi > \xi^* \).

If \( R_0 = 1 \) (\( a_3 = 0 \)), then \( Q(I) \) reduces to \( (a_1I + a_2)I = 0 \). In this case, the NR model has a unique endemic equilibrium if \( a_2 < 0 \) and no endemic equilibrium if \( a_2 \geq 0 \). \( Q(I) \) is defined in (3.8).

3.3. Equilibria (\( \epsilon > 0 \)). Since influenza can also be introduced into the population by the recruitment of infected individuals, it is more realistic to consider the NR model with \( \epsilon > 0 \). Mathematically speaking, if recruitment of infected individuals is allowed, the DFE does not exist, and eradication of the disease may not be feasible. In this case the public health objective is to minimize the level of epidemicity.

Consider now the NR model (2.10)–(2.12) with \( \epsilon > 0 \). It can be shown that the equilibria of the model are now the roots of the following cubic:

\[
P(I, \epsilon) = a_1I^3 + a_2I^2 + [a_3 - \epsilon\beta(1 + \delta)(1 - \sigma)]I - \epsilon(1 + \delta)(\xi + \omega + 1)
\]

(3.12)

\[
= IQ(I) - \epsilon[\beta(1 + \delta)(1 - \sigma)I + (1 + \delta)(\xi + \omega + 1)],
\]

where \( Q(I) \) is defined in (3.8).

Notice that when \( \epsilon = 0 \), \( P(I) \) has roots which correspond to the roots of \( Q(I) \) (along with \( I = 0 \)). Furthermore, \( P(I, \epsilon) < IQ(I) \) for \( \epsilon > 0 \) and \( I > 0 \). We now consider three cases as follows.

Case 1: \( a_3 < 0 \). In this case, \( Q(I) \) has a unique positive root, denoted by \( I^* \). Since \( P(I, \epsilon) \) is a decreasing function of \( \epsilon \) for positive \( I \), it follows that \( P(I^*, \epsilon) < 0 \) for \( \epsilon > 0 \). Furthermore, \( P(I, \epsilon) \to \infty \) as \( I \to \infty \). Thus, \( P(I, \epsilon) \) has a unique positive root for all \( \epsilon \geq 0 \), and this
unique positive root must be at \( I > I^* \). That is, when the NR model has a unique endemic equilibrium with \( \epsilon = 0 \), recruitment of infected individuals introduces no new equilibria but serves to shift the existing (unique) equilibrium to a higher disease state.

Case 2: \( a_3 > 0 \) and \( a_2 > 0 \). Let \( \eta_1, \eta_2, \) and \( \eta_3 \) represent the roots of \( P(I, \epsilon) \). In this case, since \( a_1 > 0 \) and \( a_2 > 0 \), it follows that \( \eta_1 + \eta_2 + \eta_3 = -a_2/a_1 < 0 \) and \( \eta_1\eta_2\eta_3 > 0 \). This implies that \( P(I) \) has a unique positive root for any \( \epsilon > 0 \).

Case 3: \( a_3 > 0 \) and \( a_2 < 0 \). If \( a_2^2 - 4a_1a_3 > 0 \), then from Theorem 3.2 it follows that \( Q(I) \) has two positive roots. Thus, \( P(I, 0) \) has two positive roots if \( a_2^2 - 4a_1a_3 > 0 \). Since \( P(I, \epsilon) \) is a cubic function of \( I \) and is a decreasing function of \( \epsilon \) for \( I > 0 \), it can be seen that there is a positive \( \epsilon^* \) such that \( P(I, \epsilon) \) has three positive roots if \( 0 < \epsilon < \epsilon^* \); two positive roots (one with multiplicity 2) if \( \epsilon = \epsilon^* \); and a unique positive root if \( \epsilon > \epsilon^* \). It should be noted that \( \epsilon^* < \epsilon_0 \), where

\[
\epsilon_0 = \frac{a_3}{\beta(1 - \sigma)(1 + \delta)}.
\]

To see this, suppose \( \epsilon \geq \epsilon_0 \). If \( P(I, \epsilon) \) has exactly one real root, then it follows from

\[
\eta_1\eta_2\eta_3 = (1 + \delta)(\xi + \omega + 1)/a_1 > 0
\]

that this root must be positive. If the roots of \( P(I, \epsilon) \) are all real, since

\[
\eta_1\eta_2 + \eta_1\eta_3 + \eta_2\eta_3 = \frac{a_3 - \epsilon\beta(1 + \delta)(1 - \sigma)}{a_1} \leq 0,
\]

when \( \epsilon \geq \epsilon_0 \), it can be seen that \( P(I, \epsilon) \) also has a unique positive root in this case.

The above discussion shows that if the NR model has multiple endemic equilibria when \( \epsilon = 0 \), increasing \( \epsilon \) to \( \epsilon > \epsilon^* \) serves to remove this phenomenon and instead shifts the NR model to a higher epidemicity which is characterized by a unique endemic equilibrium with a higher number of infected individuals than for the case \( \epsilon = 0 \). These results are summarized below.

**Theorem 3.3.** (a) If \( \xi < \xi_c \) or \( \epsilon > \epsilon_0 \), then the model (2.10)–(2.12) has a unique positive endemic equilibrium.

(b) If \( \xi > \xi_c \) and \( a_2 > 0 \), then the model (2.10)–(2.12) has a unique positive endemic equilibrium for \( \epsilon > 0 \).

(c) If \( \xi > \xi_c \), \( a_2 < 0 \), and \( a_2^2 - 4a_1a_3 > 0 \), then there is a positive \( \epsilon^* < \epsilon_0 \) such that \( P(I) \) has

(i) three positive roots if \( 0 < \epsilon < \epsilon^* \);

(ii) two positive roots if \( \epsilon = \epsilon^* \);

(iii) a unique positive root if \( \epsilon > \epsilon^* \).

When \( \xi > \xi_c \), \( a_2 < 0 \), and \( a_2^2 - 4a_1a_3 < 0 \), the existence of the equilibria of the model is more complicated. In this case, the model can have one, two, or even three endemic equilibria for \( \epsilon > 0 \). Bifurcation diagrams for a set of parameter values and various values of \( \epsilon \), depicted in Figure 6, support this claim. However, since \( P(I) \) is a decreasing function of \( \epsilon \), \( P(0, 0) = 0 \) and \( \lim_{I \to \infty} P(I, \epsilon) = +\infty \), it follows that \( P(I, \epsilon > 0) \) has at least one positive root and hence, at least one endemic equilibrium always exists.
4. Stability analysis of the NR model. In order to establish the stability of the equilibria of the NR model, we first investigate the nonexistence of certain types of solutions such as homoclinic orbits, periodic orbits, or polygons. From (2.10)–(2.12), it can be seen that the following region is positively invariant for the NR model:

\[ \Omega_1 = \{ (S, V, I) : S, V, I \geq 0, S + V + (1 + d)I = 1 \} \]

where \( d = \frac{\alpha}{1 + \delta} \). Therefore, the omega-limit set of each solution of the NR model is contained in \( \Omega_1 \). Thus, by applying Lemma 3.1 in [8] to the model equations (2.10)–(2.12), the following can be shown.

Lemma 4.1. The NR model (2.10)–(2.12) has no periodic orbits, homoclinic orbits, or polygons (heteroclinic cycles) in \( \Omega_1 \).

4.1. Global stability with \( \epsilon = 0 \). From Theorem 3.2, it is clear that if \( \xi < \xi_c \), then the NR model has a unique endemic equilibrium (which is located in \( \Omega_1 \)) and the DFE is unstable. Since \( \Omega_1 \) is positively invariant, it follows from Lemma 4.1 that the omega-limit set of each solution of the NR model in \( \Omega_1 \setminus \Omega_0 \) must be the endemic equilibrium of the model, where

\[ \Omega_0 = \{ (S, V, 0) \in \Omega_1 : S + V = 1 \} \]

It is easy to see that the DFE attracts the solutions in \( \Omega_0 \). Thus, the unique endemic equilibrium of the NR model is globally asymptotically stable in \( \Omega_1 \setminus \Omega_0 \).

Suppose \( \xi > \xi_c \). In this case, the DFE is the only equilibrium of the NR model if \( a_2 > 0 \) or \( a_2^2 - 4a_1a_3 < 0 \) (Theorem 3.2). Since \( \Omega_1 \) is positively invariant, it follows from Lemma 4.1 that the DFE is globally asymptotically stable. Therefore, we have established the following theorem.

Theorem 4.2. (a) If \( \xi < \xi_c \), then the unique endemic equilibrium of the NR model is globally asymptotically stable in \( \Omega_1 \setminus \Omega_0 \).

(b) Suppose \( \xi > \xi_c \). The DFE \( (E_0) \) is globally asymptotically stable if one of the following statements holds:

(i) \( a_2(\xi_c) \geq 0 \);

(ii) \( a_2(\xi_c) < 0 \) and \( \xi > \xi^* \).

Now consider the case where the NR model has two endemic equilibria \( (\xi_c < \xi < \xi^*) \). Using the expressions for \( \xi_c \) and \( r_0 \), the coefficient \( a_3 \) can be rewritten as

\[ a_3 = (1 + \delta)(1 + \alpha)(1 - (1 - \sigma)r_0)(\xi - \xi_c) \]

Noting that \( 1 < r_0 < 1/(1 - \sigma) \) (from (3.4)), it follows that \( a_3 > 0 \) as long as \( \xi > \xi_c \). Otherwise, the model has a unique endemic equilibrium which is globally asymptotically stable (by Theorem 4.2).

Here, we shall show that the two endemic equilibria of the NR model cannot be repellers (in \( \Omega_1 \)) simultaneously. Thus, one of these equilibria must have a stable manifold in \( \Omega_1 \). This stable manifold is located on a curve which is in the interior of \( \Omega_1 \).

Lemma 4.3. Suppose \( \xi_c < \xi < \xi^* \) and \( a_2(\xi_c) < 0 \). Then the two endemic equilibria of the NR model cannot both be repellers in \( \Omega_1 \) simultaneously. Furthermore, the DFE is not globally asymptotically stable.
Proof. Let $\Gamma$ be the basin of attraction of $E_0$ and $\Sigma = \Gamma \cap \Omega_1$. Furthermore, since $E_0$ attracts $\Omega_0$, it follows that $\Omega_0 \subset \Sigma$. Since $\Gamma$ is an open set, it can be seen that $\partial \Sigma \cap \text{int}(\Omega_1) \neq \emptyset$, where $\partial \Sigma$ is the boundary of $\Sigma$ and $\text{int}(\Omega_1)$ is defined to be $\Omega_1 \setminus \partial \Omega_1$. Suppose $X^0 = (S^0, V^0, I^0)$ is an arbitrary point in $\partial \Sigma \cap \text{int}(\Omega_1)$, and let $\Phi(t, X^0)$ be a solution of the NR model (2.10)–(2.12) with $\Phi(0, X^0) = X^0$ (see Figure 4). Since the endemic equilibria are located in the interior of $\Omega_1$, we can pick $X^0$ such that $X^0$ is different from the two endemic equilibria, denoted by $E_1$ and $E_2$. Since $X^0$ is not in the basin of attraction of $E_0$, it follows that $\Phi(t, X^0)$ cannot converge to $E_0$. Since $X^0 \in \Omega_1$ and $\Omega_1$ is positively invariant, it follows that the omega-limit set of the solution $\Phi(t, X^0)$ must be in $\Omega_1 \setminus \Sigma$. Furthermore, since the model has no periodic orbits in $\Omega_1$ (Lemma 4.1), the solution $\Phi(t, X^0)$ must converge to one of the two endemic equilibria. This implies that both endemic equilibria cannot be repellers in $\Omega_1$ simultaneously. Thus, although $E_0$ is locally asymptotically stable (since $R_0 < 1$), this equilibrium is not globally asymptotically stable.

The above result shows that one of the two endemic equilibria (namely, $E_1$) has at least a one-dimensional stable manifold. If $E_1$ is in the interior of $\Omega_1 \setminus \partial \Sigma \cap \text{int}(\Omega_1)$, then since the basin of attraction of $E_0$ is an open set, a discontinuity appears in the direction field of the model in $\partial \Sigma \cap \text{int}(\Omega_1)$. Note that solutions with initiating points very close to $X^0$, but in the basin of attraction of $E_0$, approach $E_0$. Hence, $E_1$ is located in $\partial \Sigma \cap \text{int}(\Omega_1)$. Therefore, the stable manifold of $E_1$ separates $\Omega_1$ into two basins of attraction. Consequently, the other endemic equilibrium (namely, $E_2$) is stable. In summary, in this case, the model has two stable equilibria and a saddle endemic equilibrium ($E_1$) where the stable manifold of $E_1$ separates the basins of attraction of $E_0$ and $E_2$. This is summarized in the following theorem.

Theorem 4.4. Suppose $\xi_c < \xi < \xi^*$ and $a_2(\xi_c) < 0$. Then the NR model has bistable equilibria.

The epidemiological implication of this theorem is that a vaccination program with $\xi > \xi_c$ ($R_0 < 1$) would not guarantee disease eradication. In this case, the initial sizes of the
subpopulations determine whether the disease can be eradicated from the population. If these subpopulations are initially in the basin of attraction of the locally stable endemic equilibrium \(E_2\), the disease will persist, and similarly, the disease can be eradicated if they are in the basin of attraction of the DFE \(E_0\).

4.2. Region of bistability with \(\epsilon = 0\). Here, we shall show that under certain conditions, there is a positive interval such that the NR model with \(\epsilon = 0\) undergoes the phenomenon of bistability (possessing a stable endemic equilibrium along with the stable DFE) for any \(\beta\) in this interval.

By Theorem 3.2, bistability is determined by the sign of \(a_2(\xi_c)\), which is given by

\[
a_2(\xi_c) = \frac{\beta(b_2\beta^2 + b_1\beta + b_0)}{(1 + \alpha)(1 - (1 - \sigma)r_0)},\]

where

\[
b_0 = (1 + \alpha)\left((1 + \alpha + \delta)(1 + \sigma\omega) + (1 - \sigma)\alpha\delta\right),
\]
\[
b_1 = -(1 - \sigma)(2 - \sigma)(1 + \alpha)(1 + \delta),
\]
\[
b_2 = (1 - \sigma)^2(1 + \delta).
\]

Since \((1 + \alpha) < \beta < \beta^*\), it follows that \(1 - (1 - \sigma)r_0 > 0\). Thus, the sign of \(a_2(\xi_c)\) is determined by the sign of the quadratic \(f(\beta) = b_2\beta^2 + b_1\beta + b_0\). Consider the discriminant \(b_1^2 - 4b_0b_2\) of this quadratic, and let

\[
\Delta = \frac{\sigma(1 + \delta)(1 + \alpha)}{4(1 + \omega)(1 + \alpha + \delta)}.
\]

Noting that \(b_1^2 - 4b_0b_2 > 0\) if and only if \(\Delta > 1\) and that \(b_0, b_2 > 0\) and \(b_1 < 0\), it can be seen that \(f(\beta)\) has two positive roots, \(\beta_1\) and \(\beta_2\) (with \(\beta_1 < \beta_2\)), if \(\Delta > 1\). Then, bistability occurs when \(\beta_1 < \beta < \beta_2\) and \(\beta < \beta^*\). It remains to show that this intersection is nonempty. It is clear that \(\beta_1 < \beta_m\), where \(\beta_m = \frac{-b_1}{2b_2}\) is the value of \(\beta\) which minimizes \(f(\beta)\). Thus,

\[
\beta_1 < \beta_m = \frac{(2 - \sigma)(1 + \alpha)}{2(1 - \sigma)} < \frac{1 + \alpha}{1 - \sigma} = \beta^*,
\]

and hence, for \(\beta_1 < \beta < \min(\beta_2, \beta^*)\), the NR model with \(\epsilon = 0\) has two endemic equilibria for some value of \(\xi\) (see Figure 5). Therefore, we have established the following theorem.

**Theorem 4.5.** If \(\Delta > 1\), then there exists a positive interval (with nonzero measure) such that \(a_2(\xi_c) < 0\) for any \(\beta\) in this interval. Furthermore, there is a range of \(\xi > \xi_c\) such that the NR model (with \(\epsilon = 0\)) exhibits bistability.

**Proof.** The proof trivially follows from Theorems 3.2 and 4.4.

It should be noted that

\[
\Delta < \frac{1 + \delta}{4(1 + \omega)},
\]

irrespective of the value of the parameter \(\alpha\), and thus if \(\delta < 4\omega\), then \(\Delta < 1\). Therefore, bistability is only possible in our model if the immunity acquired by infection (\(\delta\)) wanes at least
Figure 5. Graph of the roots of quadratic $Q(I)$ as a function of the parameters $\xi$ and $\beta$ using $\alpha = 4500$, $\delta = 1000$, $\omega = 100$, and $\sigma = 0.9$. For $\mu = 0.02 \text{ (year)}^{-1}$ (representing an average life-expectancy of 50 years), the values of $\alpha$, $\delta$, $\omega$ represent an infectious period of 4 days, an average period of 10 days for the loss of immunity acquired by infection, and a period of 6 months for the loss of immunity induced by vaccine, respectively. The solid lines show the bifurcation behavior at $\beta = 7000$ (transcritical bifurcation) and $\beta = 17000$ (backward bifurcation), respectively.

four times faster than the vaccine-induced immunity ($\omega$); this is, however, unlikely because the immunity acquired by natural infection is usually more robust and lasts longer than that induced by a vaccine consisting of inactivated virus particles such as current influenza vaccines [29]. Thus, this study has shown that the coexistence of multiple stable solutions is not feasible in influenza epidemics, which implies that the threshold condition $R_0 < 1$ guarantees eradication of the disease within the population.

4.3. Stability analysis with $\epsilon > 0$. Since $\Omega_1$ is a positively invariant region for the NR model, it follows that the equilibria of the model are contained in $\Omega_1$. Thus, if the NR model has a unique endemic equilibrium, then it follows from Lemma 4.1 that this equilibrium is globally asymptotically stable. The epidemiological implication of this result is that the disease will persist within the population.

It is important to note that disease eradication is not biologically feasible as long as $\epsilon > 0$ (that is, the model allows for recruitment of infected individuals into the population). This fact can mathematically be shown by the following discussion. When $\epsilon > 0$, the model can have one, two, or even three endemic equilibria which all are contained in the positively invariant region $\Omega_1$ (see Figure 4). Since the two-dimensional simplex $\Omega_1$ is bounded and the model has no periodic orbits, homoclinic orbits, or polygons, it follows from the Poincaré–Bendixson theorem [33] that the omega-limit set of every solution in $\Omega_1$ is an equilibrium. Note that the model has no DFE, so that the disease will persist within the population.

What is perhaps more important is that, although increasing the vaccination rate does not
lead to disease eradication, it can prevent the high level of epidemicity which could occur for a large proportion of infected individuals. To verify this fact, we use the equation $P(I) = 0$ (at equilibrium) to obtain $\xi = G(I)/H(I)$ as a function of $I$, where

$$G(I) = \beta^2(1 - \sigma)(1 + \alpha + \delta)I^3 + \beta[(1 - \sigma)(1 + \delta)(1 + \alpha - \beta) + (1 + \omega)(1 + \alpha + \delta)]I^2$$

$$+ [(1 + \delta)(1 + \omega)(1 + \alpha - \beta) - \epsilon\beta(1 - \sigma)(1 + \delta)]I - \epsilon(1 + \omega)(1 + \delta),$$

and

$$H(I) = -\beta(1 - \sigma)(1 + \alpha + \delta)I^2 - (1 + \delta)[1 + \alpha - \beta(1 - \sigma)]I + \epsilon(1 + \delta).$$

Let $I_0$ be the unique positive root of $H(I)$. It is easy to show that $G(I)$ (and, consequently, $\xi(I)$) has a unique positive root. Let $I_1$ denote this root. We shall show that $I_1 > I_0$. It is clear that $I_1$ corresponds to an endemic equilibrium of the NR model when $\xi = 0$. Thus, it can be seen that $I_1$ is a root of the following quadratic:

$$E(I) = -\beta(1 + \alpha + \delta)I^2 - (1 + \delta)(1 + \alpha - \beta)I + \epsilon(1 + \delta).$$

A simple calculation yields

$$L(I) = E(I) - H(I) = \beta\sigma I[1 + \delta - (1 + \alpha + \delta)I].$$

The quadratic $L(I)$ has two roots, namely, $I = 0$ and $I_* = \frac{1 + \delta}{1 + \alpha + \delta}$. It is easy to see that $E(I_*) < 0$. Since $L(I_*) = 0$, it follows that $H(I_*) < 0$ and thus, $I_0 > I_0$. Noting that $L(I) > 0$ for $I \in (0, I_*)$, it can be seen that $I_1 > I_0$. This implies that $\xi(I) \geq 0$ for $I \in (I_0, I_1]$ and $\xi(I) < 0$ for $I \in [0, I_0] \cup \{I : I > I_1\}$. Since $\xi \rightarrow +\infty$ when $I \rightarrow I_1^+$, it follows that increasing vaccination coverage reduces the number of infected individuals at equilibrium, with $I_0$ representing the smallest possible level of endemicity.

The results of this section are summarized in the following theorem.

**Theorem 4.6.** Suppose $\epsilon > 0$.

(a) If the NR model has a unique endemic equilibrium, then it is globally asymptotically stable. Furthermore, the NR model has no DFE and the disease will persist within the population.

(b) Increasing vaccination coverage reduces the number of infected individuals (at equilibrium) and prevents the high level of epidemicity.

5. **Outbreaks in two typical populations.** We now provide a discussion of two specific examples that illustrate the quantitative aspects of the model. We consider the spread of influenza in two representative populations: one consisting of a geriatric population in a personal care home, and the other healthy office workers. These populations were chosen in view of the fact that outbreaks of influenza frequently occur among the elderly in personal care homes who inadequately respond to the vaccine [11, 15, 28]. The dynamics of influenza in this population was compared to that seen amongst office workers who in general adequately respond to the vaccine.

We assumed the same steady state population $\Pi/\mu = 100$ in each case and set the natural death rate (including the rate of emigration) for the personal care home and office to $\mu =$
Figure 6. Bifurcation diagram showing $I$ at equilibrium versus vaccination rate for three values of $\epsilon$, the fraction of recruited individuals who are infected. Other parameters are $\alpha = 4500$, $\delta = 1800$, $\omega = 100$, and $\sigma = 0.9$.

Table 3
Parameter values for the study populations.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Office</th>
<th>Personal care home</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steady state population, $\Pi/\mu$</td>
<td>100</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>Death and emigration rate, $\mu$</td>
<td>0.05</td>
<td>0.35</td>
<td>yr$^{-1}$</td>
</tr>
<tr>
<td>Effective waning rate of immunity, $\tilde{\delta}$</td>
<td>1</td>
<td>1</td>
<td>yr$^{-1}$</td>
</tr>
<tr>
<td>Waning rate of vaccine-induced immunity, $\tilde{\omega}$</td>
<td>1</td>
<td>1</td>
<td>yr$^{-1}$</td>
</tr>
<tr>
<td>Vaccine efficacy, $\sigma$</td>
<td>0.8</td>
<td>0.3</td>
<td>-</td>
</tr>
<tr>
<td>Transmission rate, $\tilde{\beta}$</td>
<td>4.5</td>
<td>4.5</td>
<td>yr$^{-1}$</td>
</tr>
<tr>
<td>Recovery period, $1/\tilde{\alpha}$</td>
<td>4</td>
<td>20</td>
<td>days</td>
</tr>
<tr>
<td>Vaccination rate, $\xi$</td>
<td>variable</td>
<td>variable</td>
<td>yr$^{-1}$</td>
</tr>
</tbody>
</table>

0.35 yr$^{-1}$ and $\mu = 0.05$ yr$^{-1}$, respectively. The higher rate of $\mu$ for the personal care home accounts for excessive deaths common to such a population. As shown in Table 3, the two populations differ in their ability to elicit protective immunity in response to the vaccine (the vaccine efficacy, $\sigma$) \cite{5, 12, 15, 26, 28} and their rate of recovery from influenza infection ($\tilde{\alpha}$) \cite{32}. The effective waning rate of immunity refers to the failure of any prior infection-induced immunity against the circulating influenza virus strain(s). The values of rates of waning of effective immunity and vaccine-induced immunity both reflect the annual drift in the virus genome. The value for the rate of transmission ($\tilde{\beta}$) is taken within the range estimated by Nuño et al. \cite{32}. The parameter values are summarized in Table 3, and bifurcation diagrams illustrating the relative fraction of infected cases as a function of vaccination rate in each population are shown in Figure 7.

The model clearly shows that, due to notably lower efficacies of influenza vaccines in
Figure 7. Fraction of the infected population versus vaccination rate for the two study populations. The solid and dashed-dot curves represent the profiles of infected individuals in the office setting, where the vaccine efficacy is 90%, without ($\epsilon = 0$) and with ($\epsilon = 0.2$) the recruitment of infected individuals into the office population, respectively. The color dashed and dotted curves show the same profiles in a personal care home with a vaccine efficacy of 30%. Evidently, infection ratios in the personal care home are considerably higher, and vaccination has little effect on controlling the outbreak.

personal care homes ($\sigma = 0.3$) [15, 28] than in the office setting ($\sigma = 0.8$), the former is more susceptible to a large-scale influenza outbreak. Vaccination would therefore have little effect in controlling outbreaks in personal care homes. In fact, the parameters in Table 3 for the personal care home yield $\sigma < \sigma_c$, and thus no amount of vaccination (with a partially effective vaccine) can control the outbreak. Likewise, reducing the rate at which infected individuals are recruited would have little effect in the personal care home scenario as well as in the sparsely vaccinated workers in the office setting. On the other hand, adding a continuous inflow of infected people to the office situation with high vaccination rate will drive the system away from its disease-free state into an endemic state with low infection. Simulation of the model using a larger population ($\Pi/\mu = 1000$) in both scenarios yields results that are qualitatively consistent with those reported in Figure 7, albeit in this case the epidemicity levels are higher.

We have chosen not to consider a large heterogeneous population (such as a city) for the present study, mainly on account of the lack of reliable data on demography which significantly affects the level of vaccine-based protection. Factors affecting the results of such a study include the proportion and distribution of immune-suppressed (such as HIV-infected and geriatric) individuals and the nature of interaction between susceptible and infected individuals. With specified demography and parameter values, our model will be able to illustrate the dynamics of influenza irrespective of the size of the population.

6. Conclusion. This paper evaluates the impact of a partially effective preventive vaccine on the control of influenza infection, using a new deterministic mathematical model. The
model allows for continuous recruitment of individuals into the susceptible and infected populations. It should be noted that this model can be applied to other infectious diseases that also exhibit transitions between subpopulations as shown in Figure 2. In fact, this model extends the classical model for infectious diseases, such as measles and whooping cough, with $\delta = 0$; that is, the immunity acquired by infection is permanent (see [3] for a general reference).

In the absence of recruitment of infected individuals, linear stability analysis shows that the model has a DFE which is locally asymptotically stable when the basic reproductive number ($R_0$) [3] is less than unity and unstable otherwise. However, in general, the local stability of the DFE does not necessarily imply its global stability, and the stable DFE and an endemic equilibrium may coexist. Several epidemic models have been proposed in which bistability has been observed, particularly in models in which the population is divided into classes with different degrees of susceptibility to the disease (see [20] for a general reference). In this case, the persistence or control of the disease depends on the initial size of the subpopulations. However, for reasonable estimates of the model parameters for influenza, and indeed for any infection where immunity acquired by natural infection does not wane significantly faster than that acquired by vaccination, we have shown that bistability does not occur, and therefore the disease can be controlled if and only if the basic reproductive number ($R_0$) is reduced to values less than unity. This can be achieved only if infected individuals are not continuously introduced into the population and if the vaccination rate ($\xi$) and vaccine efficacy ($\sigma$) simultaneously exceed the thresholds $\xi_c$ and $\sigma_c$, respectively (see (3.5) and (3.3)). However, if infected individuals are continuously recruited, no amount of vaccination would be enough to eradicate the disease. Increasing the level of vaccination nonetheless will always reduce the level of epidemicity of the disease, and vaccination can still be used to prevent a severe epidemic.

Due to the fact that typical outbreaks of influenza in a localized population are mostly caused by replication and spread of a single virus strain [1] (see also Table 1), the model presented here considers the dynamics of influenza transmission involving a single strain. If an outbreak occurs due to simultaneous person-to-person transmission of two or more viral strains (both of which are unaffected by partial cross-immunities), the model predicts a similar dynamics of influenza infection in the population. Further, in the event of two concurrent outbreaks, their dynamics would be similar, provided the viral strains involved are not subject to partial cross-immunity, which would affect the transmissibility of the strains [25, 32]. Although this fact is not considered in our study, the model presented here can be extended to monitor the effect of partial cross-immunity on the influenza dynamics involving two or more strains. It can also be extended to explore the long-term multiseason dynamics of influenza infection by employing time dependent parameters to deduce vaccination timing strategies (also known as pulse vaccination; see [23]).

Our model provides the vaccination rate, with a vaccine of known efficacy, necessary to control the spread of influenza in a population. This rate is determined based on the duration of infectiousness and the rate of contact between infected and susceptible individuals leading to the infection. This information is crucial for public health implementation of influenza control measures with the aid of a partially effective vaccine.
Appendix. Here, we shall show that recruitment of individuals into the vaccinated class \( \tilde{V} \) does not affect the dynamics of the model, as long as \( \xi > 0 \). To do so, we consider the model with sources in all subpopulations as follows:

\[
\begin{align*}
\frac{dS}{dt} &= (1 - \epsilon_V - \epsilon_R - \epsilon_I) - \beta SI - \xi S - S + \omega V + \delta R, \\
\frac{dV}{dt} &= \epsilon_V + \xi S - (1 - \sigma)\beta VI - (1 + \omega)V, \\
\frac{dI}{dt} &= \epsilon_I + \beta SI + (1 - \sigma)\beta VI - (1 + \alpha)I, \\
\frac{dR}{dt} &= \epsilon_R + \alpha I - (1 + \delta)R.
\end{align*}
\]

(A.1) \hspace{2cm} (A.2) \hspace{2cm} (A.3) \hspace{2cm} (A.4)

Making the assumption that the total population has reached its limiting value, so that \( R = 1 - S - V - I \), gives the reduced model

\[
\begin{align*}
\frac{dS}{dt} &= (1 - \epsilon_V - \epsilon_R - \epsilon_I) - \beta SI - \xi S - S + \omega V + \delta R, \\
\frac{dV}{dt} &= \epsilon_V + \xi S - (1 - \sigma)\beta VI - (1 + \omega)V, \\
\frac{dI}{dt} &= \epsilon_I + \beta SI + (1 - \sigma)\beta VI - (1 + \alpha)I.
\end{align*}
\]

(A.5) \hspace{2cm} (A.6) \hspace{2cm} (A.7)

Using the change of variables

\[
S = \kappa S_1 - \frac{\epsilon_V}{\xi}, \\
V = \kappa V_1, \\
I = \kappa I_1, \\
R = \kappa R_1, \\
t = \mu t_1
\]

\[
\begin{align*}
\frac{dS_1}{dt_1} &= (1 - \epsilon_I - \epsilon_R + \delta)\frac{\mu}{\kappa} + (1 + \delta)\frac{\epsilon_V \mu}{\kappa \xi} + (1 - \xi)\mu S_1 \\
&\quad + (\omega - \delta)\mu V_1 + \left(\frac{\beta \epsilon_V \mu}{\xi} - \delta\right)I_1, \\
\frac{dV_1}{dt_1} &= \mu \xi S_1 - (1 - \sigma)\mu \kappa \beta V_1 I_1 - \mu (1 - \omega)V_1, \\
\frac{dI_1}{dt_1} &= \frac{\epsilon_I \mu}{\kappa} + \beta \mu \kappa S_1 I_1 + (1 - \sigma)\beta \mu \kappa V_1 I_1 - \frac{\beta \epsilon_V \mu}{\xi} I_1 - (1 + \alpha)\mu I_1.
\end{align*}
\]

\[
(A.8) \hspace{2cm} (A.9) \hspace{2cm} (A.10)
\]

Setting the sum of the constant coefficients in (A.8)–(A.10) to \( \mu(1 + \delta) \) allows one to solve for \( \kappa \), giving

\[
\kappa = 1 + \frac{\epsilon_V}{\xi} - \frac{\epsilon_R}{1 + \delta}.
\]

(A.11)
Similarly, setting the coefficient of $I_1$ in (A.8) equal to $1 - \mu(1 + \delta)$ gives the following equation for $\mu$:

$$\mu = \frac{\xi}{\xi + \beta \epsilon V}.$$  

(A.12)

Now redefining the constants

$$1 + \delta_1 = \mu(1 + \delta),$$
$$1 + \omega_1 = \mu(1 + \omega),$$
$$\xi_1 = \mu \xi,$$
$$\beta_1 = \mu \beta \kappa,$$
$$1 + \alpha_1 = \mu \left( 1 + \alpha + \beta \frac{\epsilon V}{\xi} \right),$$
$$\epsilon'_1 = \frac{\epsilon_1 \mu}{\kappa}$$

yields

$$\frac{dS_1}{dt} = (1 + \delta_1 - \epsilon'_1) - S_1(1 + \delta_1 + \xi_1) - \beta_1 S_1 I_1 + (\omega_1 - \delta_1) V_1 - \delta_1 I_1,$$

(A.13)

$$\frac{dV_1}{dt} = \xi_1 S - (1 - \sigma) \beta_1 V_1 I_1 - (1 + \omega_1) V_1,$$

(A.14)

$$\frac{dI_1}{dt} = \epsilon'_1 + \beta_1 S_1 I_1 + (1 - \sigma) \beta_1 V_1 I_1 - (1 + \alpha_1) I_1.$$  

(A.15)

Therefore, these transformations change the system into the form of (2.10)–(2.12). Thus the model (A.5)–(A.7) with sources in all subpopulations can be reduced to a model with sources only in $I$ and $S$, albeit with different parameters.

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**REFERENCES**


