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Critical immune and vaccination thresholds in heterogeneous populations

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Abstract

Previous inuenza pandemics (1918, 1957, and 1968) have all had multiple waves. The current pandemic inuenza A(H1N1) (pandemic H1N1) started in April 2009 and was followed, in the US and temperate Northern Hemisphere, by a second wave during the fall of 2009. The ratio of susceptibles and immunes in a population, at the end of a given wave, greatly determines the possibility and magnitude of a following wave. We developed a two-group epidemic model with vaccination that allows us to determine critical thresholds for vaccine-induced immunity and natural immunity for preventing further spread of inuenza. We used this method to predict the possibility of a third wave of inuenza in the US: If the basic reproduction number R0 were 1.6 or below, a third wave is very unlikely, plausible if the original R0 were 1.8, and likely if the original R0 were higher than 1.8.

Introduction

In the past century, there were three major influenza pandemics (1918, 1957, and 1968) and they all have had multiple waves. There is evidence of an early wave in the spring of 1918 in the United States and Europe, followed by a large wave in the fall of 1918 and a

third, more mild, wave in the winter of 1919 [16],[3]. In the US and temperate Northern Hemisphere, the current pandemic influenza A(H1N1) (pandemic H1N1) started in April 2009, and it was followed by a second wave during the fall of 2009. The ratio of susceptibles and immunes in a population, at the end of a given wave, plays a crucial role in determining the possibility and magnitude of a following wave. While vaccination was not available in the previous pandemics, we have now the capability to produce vaccines that are not completely protective, but can be made fast and in large quantities [21]. In fact, more than 20 vaccines were developed during the late spring to early summer 2009. In several countries, vaccination started as early as mid-September [17], so that, at the end of the second wave, a fraction of the population can be expected to have vaccine-induced immunity, while some fraction of the population would have natural-induced immunity. Since influenza vaccines are not completely protective, and estimating the number of people infected and the number of people vaccinated is not always possible, it becomes important to determine if this "mixture" of natural and vaccine induced immunity in the population would be enough to prevent a third wave of influenza.

Using techniques for computing the basic reproduction number R_0 and the effective reproduction number R_f (defined to be the reproduction number when the fraction of the population is immune or vaccinated), we developed a mathematical model to determine critical thresholds of vaccine-induced immunity and of natural-induced immunity for preventing further spread of influenza virus.

The model

Our model for influenza is based on the standard SIR model. We considered a closed population of size N. Since influenza has a very short time scale compared to immigration or demographics, none of these features are included. We divided the population into two sub-populations of children and adults of size N_1 and N_2, so that $N = N_1 + N_2$. Members in each group are either susceptibles, infected asymptomatic, infected symptomatic or recovered, and each person can be either unvaccinated or vaccinated. The susceptibles are denoted by S_{ij}, infectious asymptomatic by A_{ij}, infectious symptomatic by I_{ij}, and recovered by R_i, where $i = 1, 2$ denotes the group ($1-$ children and $2-$ adults) and j describes the vaccination status ($j = 0$ for the unvaccinated and $j = 1$ for the vaccinated). The following assumptions were made.

- A fraction ρ of the infected people will never develop symptoms, but will still transmit the infection to others. Asymptomatic people have their infectiousness reduced by a factor m compared to infected symptomatic people, where $m \in [0, 1]$.

- c_{ij} is the number of contacts per day between people in group i and people in group j, where $i, j = 1, 2$.
- p is the probability of infection given contact; it will be used here as a parameter to vary the transmissibility of the infection.
- Children and adults have different length infectious periods and recover at rates γ_1 and γ_2.
- Following the ideas in [10], we consider that vaccination has three major effects in the vaccinee:

  (i) $\mathsf{VE_S}$, the vaccine efficacy for susceptibility, is the ability of the vaccine to prevent infection.

  (ii) $\mathsf{VE_I}$, the vaccine efficacy for infectiousness (conditioned upon being infected), is the effect of the vaccine in reducing infectiousness.

  (iii) $\mathsf{VE_P}$, the vaccine efficacy for pathogenicity (conditioned upon being infected), accounts for the effect of the vaccine in reducing the symptoms given infection.

This gives rise to the following system of differential equations:

Unvaccinated	Vaccinated	
$\frac{dS_{10}}{dt} = -\lambda_1 S_{10}$	$\frac{dS_{11}}{dt} = -\lambda_1 \theta S_{11}$	(1)
$\frac{dS_{20}}{dt} = -\lambda_2 S_{20}$	$\frac{dS_{21}}{dt} = -\lambda_2 \theta S_{21}$	(2)
$\frac{dA_{10}}{dt} = \lambda_1(1-\rho)S_{10} - \gamma_1 A_{10}$	$\frac{dA_{11}}{dt} = -\lambda_1(1-\rho\psi)\theta S_{11} - \gamma_1 A_{11}$	(3)
$\frac{dA_{20}}{dt} = \lambda_2(1-\rho)S_{20} - \gamma_2 A_{20}$	$\frac{dA_{21}}{dt} = -\lambda_2(1-\rho\psi)\theta S_{21} - \gamma_2 A_{21}$	(4)
$\frac{dI_{10}}{dt} = \lambda_1 \rho S_{10} - \gamma_1 I_{10}$	$\frac{dI_{11}}{dt} = -\lambda_1 \rho\psi\theta S_{11} - \gamma_1 I_{11}$	(5)
$\frac{dI_{20}}{dt} = \lambda_2 \rho S_{20} - \gamma_2 I_{20}$	$\frac{dI_{21}}{dt} = -\lambda_2 \rho\psi\theta S_{21} - \gamma_2 I_{21}$	(6)
$\frac{dR_{01}}{dt} = \gamma_1(A_{10} + I_{10})$	$\frac{dRA_{11}}{dt} = \gamma_1(A_{11} + I_{21})$	(7)
$\frac{dR_{02}}{dt} = \gamma_1(A_{20} + I_{20})$	$\frac{dRA_{21}}{dt} = \gamma_1(A_{21} + I_{21})$	(8)

where $\mathsf{VE_S} = 1-\theta$, $\mathsf{VE_I} = 1-\phi$ and $\mathsf{VE_P} = 1-\psi$. The forces of infection for children and adults, repetitively, are given by:

$$\lambda_1 = \frac{pc_{11}}{N_1}\Big(mA_{10} + m\phi A_{11} + I_{10} + \phi I_{11}\Big) + \frac{pc_{12}}{N_2}\Big(mA_{20} + m\phi A_{21} + I_{20} + \phi I_{21}\Big)$$

and

$$\lambda_2 = \frac{pc_{21}}{N_1}\Big(mA_{10} + m\phi A_{11} + I_{10} + \phi I_{11}\Big) + \frac{pc_{22}}{N_2}\Big(mA_{20} + m\phi A_{21} + I_{20} + \phi I_{21}\Big).$$

Computation of the basic reproductive number

In this section, we follow the ideas from [13] and [11]. We recall that the basic reproduction number R_0 for a given disease is defined as the expected number of secondary infections resulting from a single infected person in a completely susceptible population, and R_f is defined to be the effective reproduction number, which is the reproduction number in presence of vaccination. We use the approach given in [8] and [19, 6] to compute the effective reproduction number as follows. Let

$$\begin{array}{llll}
S_{10}(0) = \mathbf{S}_{10}, & S_{11}(0) = \mathbf{S}_{11}, & S_{20}(0) = \mathbf{S}_{20}, & S_{21}(0) = \mathbf{S}_{21} \\
A_{10}(0) = \mathbf{A}_{10}, & A_{11}(0) = \mathbf{A}_{11}, & A_{20}(0) = \mathbf{A}_{20}, & A_{21}(0) = \mathbf{A}_{21} \\
I_{10}(0) = \mathbf{I}_{10}, & I_{11}(0) = \mathbf{I}_{11}, & I_{20}(0) = \mathbf{I}_{20}, & I_{21}(0) = \mathbf{I}_{21} \\
R_{10}(0) = 0, & R_{11}(0) = 0, & R_{20}(0) = 0, & R_{21}(0) = 0
\end{array}$$

be the initial conditions for the system ((1))-((8)) where

$$\begin{aligned}
\mathbf{S}_{10} + \mathbf{S}_{11} + \mathbf{A}_{10} + \mathbf{A}_{11} + \mathbf{I}_{01} + \mathbf{I}_{11} = N_1, \\
\mathbf{S}_{20} + \mathbf{S}_{21} + \mathbf{A}_{20} + \mathbf{A}_{21} + \mathbf{I}_{21} + \mathbf{I}_{21} = N_2
\end{aligned}$$

and $\mathbf{A}_{10}, \mathbf{A}_{11}, \mathbf{I}_{01}, \mathbf{I}_{11}, \mathbf{A}_{20}, \mathbf{A}_{21}, \mathbf{I}_{21}, \mathbf{I}_{21}$ are very small numbers, i.e., 0^+. Define

$$p_0 = (\mathbf{S}_{10}, \mathbf{S}_{11}, \mathbf{S}_{20}, \mathbf{S}_{21}, \mathbf{A}_{10}, \mathbf{A}_{11}, \mathbf{I}_{01}, \mathbf{I}_{11}, \mathbf{A}_{20}, \mathbf{A}_{21}, \mathbf{I}_{21}, \mathbf{I}_{21}, 0, 0).$$

If we set $\mathbf{A}_{10} = \mathbf{A}_{11} = \mathbf{I}_{01} = \mathbf{I}_{11} = \mathbf{A}_{20} = \mathbf{A}_{21} = \mathbf{I}_{21} = \mathbf{I}_{21} = 0$, and $\mathbf{S}_{10} + \mathbf{S}_{11} = N_1$, $\mathbf{S}_{20} + \mathbf{S}_{21} = N_2$ the model (1)-(8) has an infinite number of disease free equilibria, namely, one per each initial condition given. We linearize the system for the infectious equations (3) - (6) around the disease free equilibrium p_0 . This gives us the matrices (following the notation from [6]) F and V defined as follows.

$$F = pA \cdot \begin{pmatrix} \frac{c_{11}}{N_1}m & \frac{c_{12}}{N_2}m & \frac{c_{11}}{N_1}m\varphi & \frac{c_{12}}{N_2}m\varphi & \frac{c_{11}}{N_1} & \frac{c_{12}}{N_2} & \frac{c_{11}}{N_1}\varphi & \frac{c_{12}}{N_2}\varphi \\ \frac{c_{21}}{N_1}m & \frac{c_{22}}{N_2}m & \frac{c_{21}}{N_1}m\varphi & \frac{c_{22}}{N_2}m\varphi & \frac{c_{21}}{N_1} & \frac{c_{22}}{N_2} & \frac{c_{21}}{N_1}\varphi & \frac{c_{22}}{N_2}\varphi \\ \frac{c_{11}}{N_1}m & \frac{c_{12}}{N_2}m & \frac{c_{11}}{N_1}m\varphi & \frac{c_{12}}{N_2}m\varphi & \frac{c_{11}}{N_1} & \frac{c_{12}}{N_2} & \frac{c_{11}}{N_1}\varphi & \frac{c_{12}}{N_2}\varphi \\ \frac{c_{21}}{N_1}m & \frac{c_{22}}{N_2}m & \frac{c_{21}}{N_1}m\varphi & \frac{c_{22}}{N_2}m\varphi & \frac{c_{21}}{N_1} & \frac{c_{22}}{N_2} & \frac{c_{21}}{N_1}\varphi & \frac{c_{22}}{N_2}\varphi \\ \frac{c_{11}}{N_1}m & \frac{c_{12}}{N_2}m & \frac{c_{11}}{N_1}m\varphi & \frac{c_{12}}{N_2}m\varphi & \frac{c_{11}}{N_1} & \frac{c_{12}}{N_2} & \frac{c_{11}}{N_1}\varphi & \frac{c_{12}}{N_2}\varphi \\ \frac{c_{21}}{N_1}m & \frac{c_{22}}{N_2}m & \frac{c_{21}}{N_1}m\varphi & \frac{c_{22}}{N_2}m\varphi & \frac{c_{21}}{N_1} & \frac{c_{22}}{N_2} & \frac{c_{21}}{N_1}\varphi & \frac{c_{22}}{N_2}\varphi \\ \frac{c_{11}}{N_1}m & \frac{c_{12}}{N_2}m & \frac{c_{11}}{N_1}m\varphi & \frac{c_{12}}{N_2}m\varphi & \frac{c_{11}}{N_1} & \frac{c_{12}}{N_2} & \frac{c_{11}}{N_1}\varphi & \frac{c_{12}}{N_2}\varphi \\ \frac{c_{21}}{N_1}m & \frac{c_{22}}{N_2}m & \frac{c_{21}}{N_1}m\varphi & \frac{c_{22}}{N_2}m\varphi & \frac{c_{21}}{N_1} & \frac{c_{22}}{N_2} & \frac{c_{21}}{N_1}\varphi & \frac{c_{22}}{N_2}\varphi \end{pmatrix}$$

with A is given by

$$A = diag(S_{10}(1-\rho),\ S_{20}(1-\rho),\ S_{11}(1-\rho\psi)\theta, S_{21}(1-\rho\psi)\theta, S_{10}\rho,\ S_{20}\rho,\ S_{10}\rho\psi\theta,\ S_{20}\rho\psi\theta),$$

and V is given by

$$V = diag(\gamma_1, \gamma_2, \gamma_1, \gamma_2, \gamma_1, \gamma_2, \gamma_1, \gamma_2)$$

where $diag(a, b)$ denotes a diagonal matrix with elements a and b in the diagonal.

The matrix $K = FV^{-1}$ is called the next generation matrix. Then, the effective reproduction number R_f is given by

$$R_f = \rho(K)$$

where $\rho(K)$ is the spectral radius of K, that is the largest eigenvalue in absolute value. If $R_f > 1$, the epidemic will grow, whereas if $R_f \leq 1$, the epidemic will die out. We then set $R_f = 1$ as a threshold condition.

Let f_1 be the fraction of vaccinated children and f_2 be the fraction of vaccinated adults, where we assumed that vaccination occurred prior to the beginning of the epidemic. If the number of initial infections is small, we have

$$\mathbf{S_{10}} = (1 - f_1)N_1 \qquad \mathbf{S_{11}} = f_1 N_1$$
$$\mathbf{S_{20}} = (1 - f_2)N_2 \qquad \mathbf{S_{21}} = f_2 N_2.$$

We note that if $f_1 = 0 = f_2$, then no vaccination occurred, and the effective reproduction number is in fact the basic reproduction number, R_0.

On the other hand, if $\mathsf{VE_S} = 1$, then the vaccinated fraction f_i of group i ($i = 1, 2$) would be fully protected against the infection, *i.e.* would have a zero probability of acquiring the infection. This is equivalent to assuming that the fraction f_i of group i is immune to influenza. This allows us to model the people in group i who previously got the infection and are now immune. We denote by R_n the effective reproduction number with immunity, that is, the effective reproductive number with $\mathsf{VE_S} = 1$.

If all the parameters of the model are known except for the values of f_1 and f_2, then R_f becomes a function of f_1 and f_2 and the threshold condition is equivalent to finding the contour lines in the $f_1 f_2$-plane where $R_f(f_1, f_2) = 1$. We define $R_f(f_1, f_2)$ as the effective reproductive number with f_1 of the children and f_2 of the adults vaccinated or immune. For all the points above, the curve $\Gamma = \{f = (f_1, f_2) | R_f(f_1, f_2) = 1\}$, $R_f < 1$ and the epidemic not occur, while for points below the curve Γ, $R_f > 1$ and the epidemic will occur. We note that while these curves may not be unique, they do separate the $f_1 f_2$-plane in simply connected regions where either $R_f < 1$ or $R_f > 1$.

We define a critical vaccination vector to be a pair (f_1, f_2) such that $R_f(f_1, f_2) = 1$. Analogously, we define a critical immune vector to be a pair (f_1, f_2) such that $R_n(f_1, f_2) = 1$. The critical vaccination vector gives us a pair of fractions of each subpopulation that should be vaccinated such that no significant transmission can occur. In addition, the critical immune vector gives us a pair of those fractions of each subgroup that must be completely immune in order for little transmission to occur in the entire population.

In general, finding a closed solution for the contour lines of $R_f(f_1, f_2) = 1$ might be very difficult, since we need to find the roots of a polynomial of degree eight. However, symbolic software such as *Sage*, *Mathematica* or *Maple* can be used to compute exact forms of the effective reproduction number, and, even if we cannot have a closed formula for it, we can still determine the set of critical vaccination and immune vectors.

Prediction of second waves based on the critical vaccination and critical immune vectors

Example: one group model applied to the 1918 pandemic influenza.

As an example, consider the case where there is only one subgroup. This is analogous to the model analyzed in [1]. Here the matrix F collapses to

$$F = \frac{cp}{N}\begin{pmatrix} (1-\rho)m\mathbf{S}_0 & (1-\rho)\mathbf{S}_0 & (1-\rho)m\phi\mathbf{S}_0 & (1-\rho)\phi\mathbf{S}_0 \\ \rho m\mathbf{S}_0 & \rho\mathbf{S}_0 & \rho m\phi\mathbf{S}_0 & \rho\phi\mathbf{S}_0 \\ \theta(1-\psi\rho)m\mathbf{S}_1 & \theta(1-\psi\rho)\mathbf{S}_1 & \theta\phi(1-\psi\rho)m\mathbf{S}_1 & \theta\phi(1-\psi\rho)\mathbf{S}_1 \\ \theta\psi\rho m\mathbf{S}_1 & \theta\psi\rho\mathbf{S}_1 & \theta\phi\psi\rho m\mathbf{S}_1 & \theta\phi\psi\rho\mathbf{S}_1 \end{pmatrix}$$

and $V = diag(\gamma, \gamma, \gamma, \gamma)$. In this case, the matrix K is simply given by $K = FV^{-1} = (1/\gamma)F$. Three of the eigenvalues of this matrix are zero; the fourth one is R_f, given by

$$\begin{aligned} R_f &= \frac{cp}{N\gamma}\Big(\mathbf{S}_0\big((1-\rho)m+\rho\big) + \mathbf{S}_1\theta\phi\big((1-\psi\rho)m+\psi\rho\big)\Big) \\ &= \frac{cp}{\gamma}\Big(\frac{\mathbf{S}_0}{N}\big((1-\rho)m+\rho\big) + \frac{\mathbf{S}_1}{N}\theta\phi\big((1-\psi\rho)m+\psi\rho\big)\Big). \end{aligned}$$

This formula matches that obtained in [1]. Now, let f be the fraction of the population vaccinated, so that $\mathbf{S}_0 = (1-f)N$ and $\mathbf{S}_1 = fN$. The effective reproduction number becomes

$$R_f = \frac{cp}{\gamma}\Big((1-f)\big((1-\rho)m+\rho\big) + f\theta\phi\big((1-\psi\rho)m+\psi\rho\big)\Big).$$

If $f = 0$, then we recover the basic reproduction number, namely,

$$R_0 = \frac{cp}{\gamma}((1-\rho)m+\rho).$$

We then set $R_f = 1$ as a threshold condition, then we find the critical fraction f^* of the population that needs to be vaccinated,

$$f^* = \frac{1 - \frac{cp}{\gamma}\big((1-\rho)m+\rho\big)}{\frac{cp}{\gamma}\Big[\theta\phi\big((1-\psi\rho)m+\psi\rho\big) - \big((1-\rho)m+\rho\big)\Big]}.$$

Similarly, we obtain the critical immune fraction f_n,

$$f_n = 1 - \frac{1}{\frac{cp}{\gamma}\big((1-\rho)m+\rho\big)}.$$

Let $\gamma = 0.25, \rho = 2/3$ and $m = 0.5$ (taken from [14]). Figure 1 shows the critical vaccination fraction and the critical immune fraction for different values of R_0 . Based on the estimates found in [15],[20], we consider the basic reproduction number R_0 for the 1918 influenza A pandemic to range between 1.7 and 2.5. For these values of R_0, only very high levels (50% for $R_0 = 2$) of pre-existing immunity (immunity built from the "herald" wave, in early spring 1918) would have prevented a second wave.

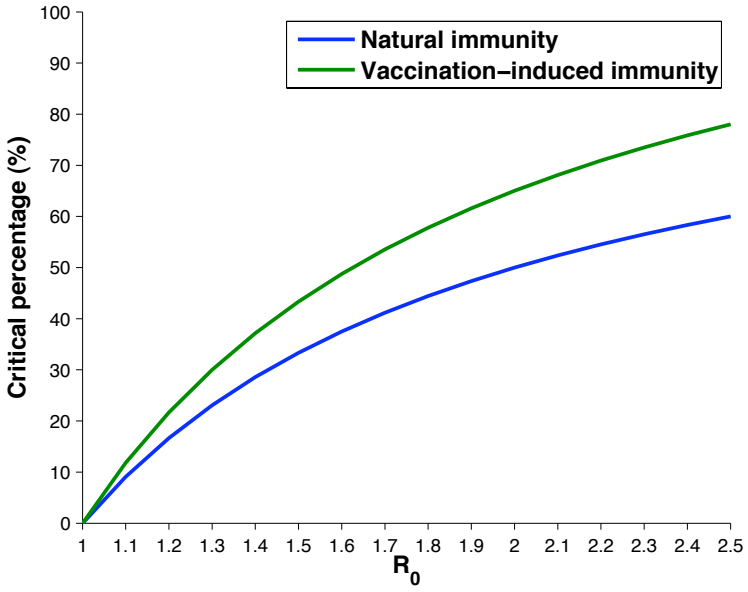

Figure 1: Critical vaccination fraction and immune fraction for different values of R_0 using a simple homogeneous mixing model.

Application: current H1N1 influenza epidemic

During the first (Spring 2009) and second (Fall 2009) waves of the new strain of influenza A/H1N1, a significant fraction of the population got infected and became immune afterward. Meanwhile, several vaccines were developed so that during the second wave, a fraction of children and adults could get vaccinated. Using the model developed above, we can make some predictions about the possibility of a third wave. Based on current estimates [9], [2], [22], we considered R_0 to lie in the interval $[1.2, 1.8]$. We used the parameter p to vary the intensity of the infection by selecting values of p for which the

original basic reproduction number would be in the range $[1.2, 1.8]$. We calibrated the model (1)-(8) for the current H1N1 epidemic according to the table 1 so that we obtained the final illness attack rates (defined as the percentage of the population that became ill) shown in table 2.

Parameter	Value	Reference
γ_1, γ_2	0.329, 0.449	[12][a]
ρ	2/3	[14]
m	0.5	[14]
percentage of children under 18	24.16	[18]
percentage of adults	75.84	[18]
$c_{11}, c_{12}, c_{21}, c_{22}$	1,0.2, 0.2, 0.4	calculated[b]
$\mathsf{VE_S}, \mathsf{VE_I}, \mathsf{VE_P}$	0.4, 0.45, 0.75	[4]

Table 1: Parameter values.

[a]Computed as a weighted average from the rates given in [12].

[b]The contact rates were calculated so that the final illness attack rates to obtain the values shown in 2.

R_0	Overall illness attack rate	Illness attack rate in children	Illness attack rate in adults
1	0	0	0
1.2	12.2	21.4	9.3
1.3	18.8	30.8	15
1.4	23.6	36.9	19.4
1.5	28	41.9	23.5
1.6	31.8	45.9	27.3
1.7	35.2	49.1	30.7
1.8	38.2	51.8	33.9

Table 2: Final illness attack rates for the range of basic reproduction numbers considered.

In addition, we assumed that current H1N1 influenza vaccines have similar efficacies to the ones for seasonal vaccines, and hence we took the vaccine efficacies for susceptibility, infectiousness and pathogenicity as an average between well-matched live attenuated vaccine and a well-matched inactivated vaccine using the estimates given in [4]. Further, for each R_0 in the range given above, we used a symbolic software to analyze the eigenvalues of the next generation matrix K described in the previous section (see figure 2).

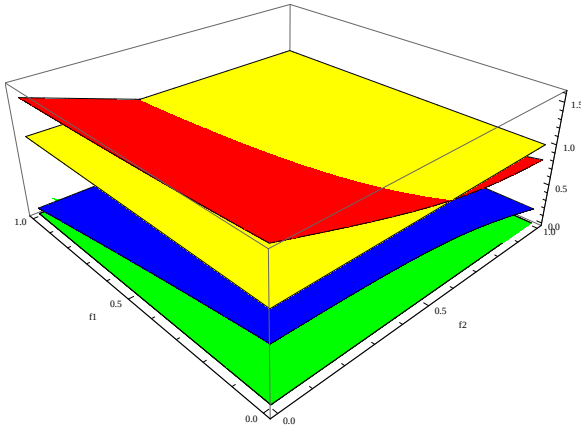

Figure 2: For $R_0 = 1.6$, all the eigenvalues of the matrix but two are zero (plotted in green). The ones that are non-zero are plotted above in red and blue. The yellow plot corresponds to the plane $z = 1$.

This allowed us to uniquely determine the spectral radius of this matrix, $R_f(f_1, f_2)$ and compute the contour lines for which $R_f(f_1, f_2) = 1$, which we will refer as the critical vaccination curves. The points above this curve correspond to coverages of a vaccinated fraction f_1 of children and a vaccinated fraction f_2 of adults that will make the effective reproduction number be below one, so that no further transmission of the infection would be possible. An example of such a curve, for a basic reproduction number of $R_0 = 1.6$, is given in figure 3. For example, the critical vaccination fraction for children is 53% when combined with 9% of coverage in adults, or 41% coverage in children when combined with 55% coverage in adults. The yellow region of the corresponds to the set of pairs of coverages that would yield to no further transmission, while the red region of the plot would yield to the possibility of a new wave.

We repeated this analysis for the effective reproduction number with immunity, that is, assuming that $\mathsf{VE_S} = 1$. An example of the critical immune curves, defined to be the contour lines for which $R_n(f_1, f_2) = 1$, for an original R_0 of 1.6, is given in figure 4 . For instance, once 45% or more of children coupled with 9% or more of adults have already been infected, there would be little chance of transmission; or 35% or more of children immune coupled with 55% or more of adults previously infected would have the same effect.

Since influenza vaccines are not completely protective, the critical vaccination curves will always lie above the critical immune curves. The threshold curve for a mixture of vaccination-induced immunity and natural immunity should then lie somewhere between

the critical vaccination curve and the critical immune curve. An example of this region, which we call **intermediate region**, for an original value of R_0 of 1.6, is shaded in figure 5.

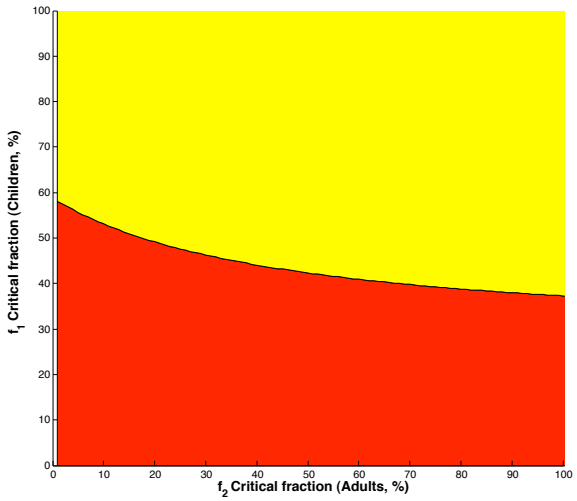

Figure 3: Contour curve for $R_f(f_1, f_2) = 1$. The points (f_1, f_2) in the are the critical vaccination vectors.

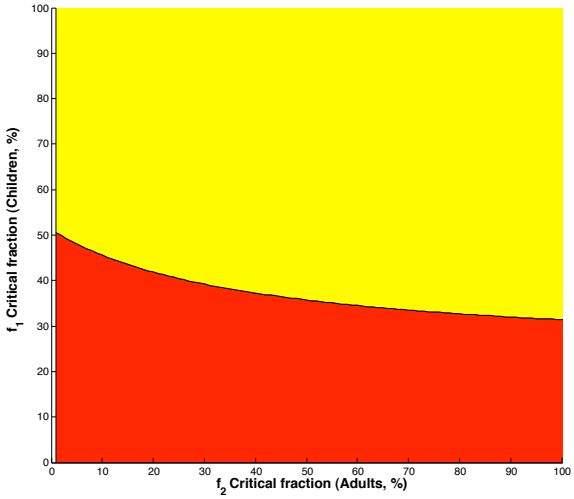

Figure 4: Contour curve for $R_n(f_1, f_2) = 1$. The points (f_1, f_2) on the curve are the critical immune vectors.

Suppose that we know that $x\%$ of the children got vaccinated and $y\%$ of the children got infected during the previous wave, then, ideally, $(x + y)\%$ of the children would be protected for the next wave. However, we currently don't know precisely the number of people who were infected nor the number of people who were vaccinated. Moreover, we cannot guarantee that people who got vaccinated were not immune already, especially given the fact that a fraction of the infected never develop symptoms. Therefore, we know that the level of protection of children should be somewhere between $y\%$ and $(y + x)\%$. A similar analysis can be done for the adult age group. Using the information given in [7], we obtained estimates for the current number of children and adults vaccinated and the ones who got infected. We estimated the combined immune and vaccinated percentage of children to be about 54% and for adults to be about 37%. Taking into account the variability in the estimates, the square of the $f_1 f_2$-plane in figure 6 gives us our most likely level of protection. We then computed the intermediate regions for each of the basic reproduction numbers in the interval $[1.2, 1.8]$. Provided that this square lies on or above the intermediate regions, there will be very little further transmission and this suggests that a third wave is unlikely to occur (see figure 6). Thus, if the original R_0 for H1N1 was 1.6

or less, no further substantial transmission is likely to occur in the US population. If the original R_0 were 1.8, further spread is possible only for the lower estimates of infection and vaccination levels. If R_0 was higher than 1.8, then further substantial spread is likely. We note that these results hold as long as the H1N1 virus doesn't drift into a new strain.

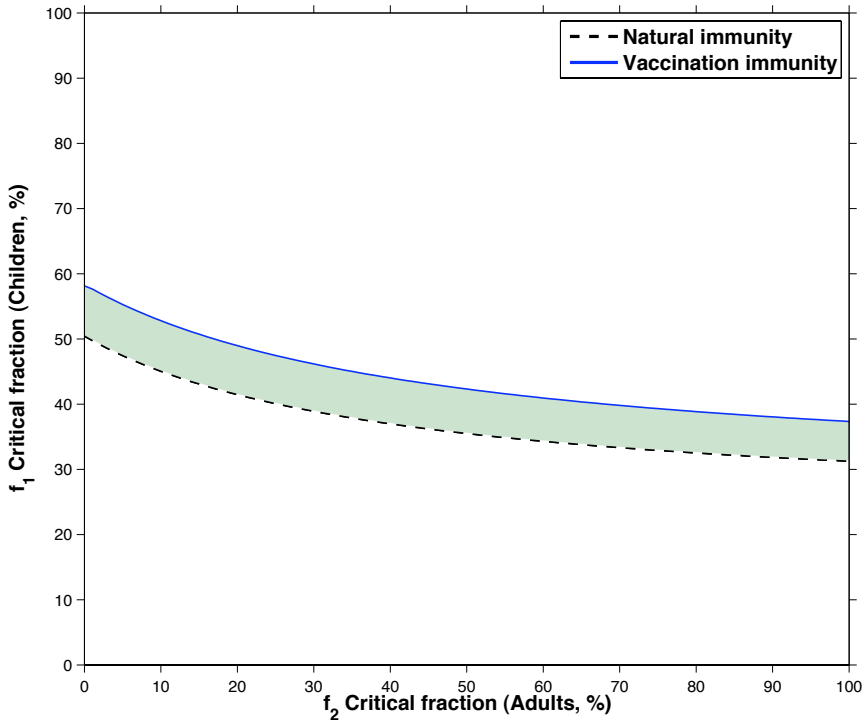

Figure 5: The shaded region corresponds to the region where the threshold for mixtures of vaccination-induced immunity and natural immunity would lie. Here, the basic reproduction number is set to 1.6

Discussion

The method proposed here provides simple thresholds for the vaccine-induced protection and natural immunity needed to prevent further spread of influenza once a wave has passed. This can be particularly useful in a situation where most of the parameters are difficult

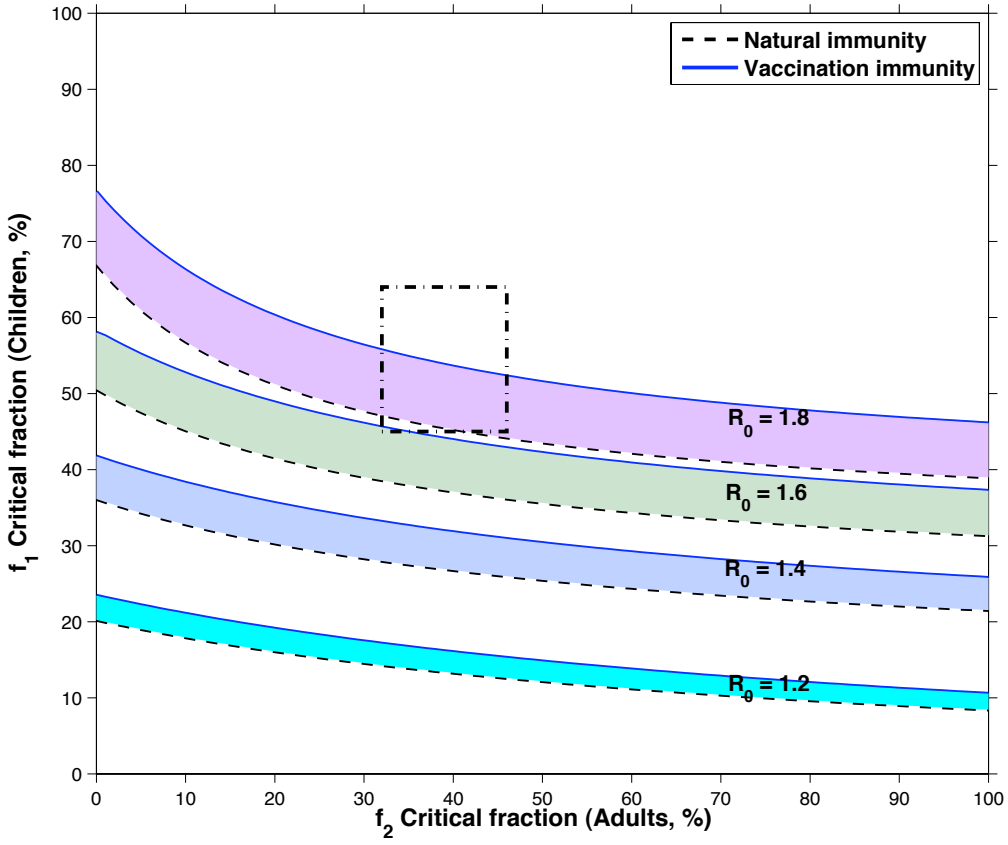

Figure 6: The shaded regions indicate the intermediate regions for a specific R_0, (where $R_0 \in [1.2, 1.8]$) that is, the region where the threshold for a mixture of vaccine-induced immunity and natural immunity should lie. The dotted square represents the region where our current level of immunity is, based on [7]

to determine accurately. Most of the time we only have ranges of possible values. For example, determining the number of people infected from reported influenza illness data is difficult, given that a fraction of infections are asymptomatic. In addition, serosurveys are problematic because of cross reacting antibodies. Our computations suggest that for the current epidemic, a third wave is unlikely if the original R_0 was 1.6 or lower, plausible for the low estimates of mixed immunity if the original R_0 was 1.8, and likely if the original R_0 was higher than 1.8.

In the model proposed by Hill and Longini in [11], the authors established thresholds for a model that not include asymptomatics or vaccine efficacy for pathogenicity. In this sense, the current work is a natural extension of their model. The SIR model proposed here is similar to the one proposed by Brauer in [5], but we omitted the latent period and considered vaccination instead of treatment. They established useful final size relations and we established threshold conditions, so we consider that these results complement each other. While our model was tailored for influenza, the methods used here can be easily adapted for similar acute infectious diseases. Moreover, the methods we develop here can easily be extended to other applications. For instance, one could account for more subgroups, more complex dynamics or different contact patterns.

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