RESEARCH ARTICLE

Interplay between COVID-19 vaccines and social measures for ending the SARS-CoV-2 pandemic [version 1; peer review: 1 approved with reservations, 1 not approved]

Glenn Young ¹, Pengcheng Xiao¹, Ken Newcomb², Edwin Michael²

¹Department of Mathematics, Kennesaw State University, Marietta, Georgia, 30060, USA

²Center for Global Health Infectious Disease Research, University of South Florida, Tampa, Florida, 33612, USA

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Abstract

Background: The development and authorization of COVID-19 vaccines has provided the clearest path forward to eliminate community spread and thus end the ongoing SARS-CoV-2 pandemic. However, the limited pace at which the vaccine can be administered motivates the question, to what extent must we continue to adhere to social intervention measures such as mask wearing and social distancing?

Methods: We develop a mathematical model of COVID-19 spread incorporating both vaccine dynamics and socio-epidemiological parameters. We use this model to study two important measures of disease control and eradication, the effective reproductive number R_t and the peak intensive care unit (ICU) caseload, over three key parameters: social measure adherence, vaccination rate, and vaccination coverage.

Results: Our results suggest that, due to the slow pace of vaccine administration, social measures must be maintained by a large proportion of the population until a sufficient proportion of the population becomes vaccinated for the pandemic to be eradicated. By contrast, with reduced adherence to social measures, hospital ICU cases will greatly exceed capacity, resulting in increased avoidable loss of life. We then investigate the threat of localized outbreaks in low-vaccinated populations that have removed all social intervention mandates, and show that such populations could remain highly susceptible to major outbreaks particularly in the face of more easily transmissible variants.

Conclusions: These findings highlight the complex interplay involved between vaccination and social protective measures, and indicate the practical importance of continuing with extant social measures while vaccines are scaled up to allow the development of the herd immunity needed to end or control SARS-CoV-2 sustainably.

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COVID-19, SARS-CoV-2, mathematical modeling, vaccination, non-pharmaceutical intervention, epidemiology, differential equations, boundary value problems

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Corresponding author: Glenn Young (gyoung19@kennesaw.edu)

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Introduction

The advent of COVID-19 vaccines and mass vaccinations of populations have led to widespread public expectation that we may be able to end the ongoing SARS-CoV-2 pandemic in some economically advanced countries by as early as the of beginning 2022¹. While the pace at which these vaccines have been developed and authorized by governments for population-wide usage has been unprecedented² reflecting the desire to fast track the ending or control of the pandemic given the socio-economic costs of protracted non-pharmaceutical interventions (NPIs), such as cyclical lockdowns and social distancing measures³, it is also clear that several features of the current vaccines and vaccination strategies for achieving this goal remain unresolved^{4,5}.

First, it is important to consider that vaccines serve two major purposes: to protect the individual from contracting the disease and to stop the transmission of community infection. While the initial vaccine trial data for the three major vaccines approved for use thus far in developed world settings, viz. Pfizer-BioNTech, Moderna, and Oxford-AstraZeneca, indicate that these could induce very high levels of protection (70–90%) against symptomatic disease⁶, more recent data with regard to the AstraZeneca vaccine suggests that vaccination may also reduce community transmission of the virus significantly⁷. These data suggest that both disease outcomes and transmission could be significantly reduced in communities as a result of mass deployments of these vaccines. A key factor, however, is that in both cases current vaccines are not 100% protective. Second, it is apparent that the number of vaccines initially available and the logistical challenges connected with their delivery will hamper the rapid vaccination of populations, which will prolong the time to eradicate the disease through vaccination in populations⁸. An added challenge is the reduced effectiveness of these vaccines as currently formulated against newly emerging virus variants⁹.

A third important factor is to consider the epidemiological and social contexts in which vaccinations will take place. This is important because many populations undergoing vaccinations will have already experienced one or more waves of COVID-19, as a result of which some level of natural immunity to SARS-CoV-2 will likely to be in operation in these communities. Such pre-existing immunity could indicate that the vaccine coverage to end the pandemic (reduce the prevailing effective reproduction number, R_t to below 1 sustainably) need not be too high even if vaccine effectiveness is not perfect¹⁰, increasing the prognosis of using the current vaccines to end the pandemic. On the other hand, these populations are also currently experiencing various levels of NPIs³. Such social mitigation or containment measures, while protecting the susceptible fraction from infection will act also to depress the development of natural immunity in the population. These outcomes suggest that there may be complex interactions between the two interventions, a better understanding of which will be crucial in determining how best to optimally deploy these tools for controlling or ending the pandemic. Further, investigating such interactions will also be important in fully understanding the implications of relaxing these NPIs as vaccinations roll out^{10,11}.

Here, we extend our existing data-driven socio-epidemiological SEIR-based COVID-19 mathematical model¹² by incorporating imperfect vaccination dynamics in order to undertake a theoretical investigation of this topic. To enhance realism we use the basic model calibrated to infection data on the course of the pandemic in the Tampa Bay region, and use the resulting model to investigate the interplay between vaccination and social protective measures for effective control or elimination of the pandemic. In particular, we explore the dynamical implications of imperfect vaccine effectiveness, vaccine rollout rates, and coverage of vaccination and social measures on the eradication of the disease in the community, and the effects these will have for virus transmission and critical care requirements. We also inspect the effect that the current vaccination roll out will have on the extent to which a population may relax social measures to return to normalcy, and the threat of future outbreaks in communities with low vaccination rates.

Methods

Model formulation

Here we develop an extended SEIR model to assess population-level disease dynamics of COVID transmission. We consider a population of fixed size that we divide into eleven interacting sub-populations: susceptible without access to a vaccine (S), vaccinated susceptible (V), unvaccinated susceptible (with access to a vaccine) (X), exposed but not infectious (E), asymptomatic infected (I_a), pre-symptomatic infected (I_p), mildly symptomatic infected (I_m), hospitalized infected (I_h), critical care infected (I_c), recovered (R), and died (D). Since the population size is fixed, we can impose the condition that $S + X + V + E + I_a + I_p + I_m + I_h + I_c + R + D = 1$, and each population can therefore be interpreted as a proportion of the total population.

Our model is visualized as a diagram in [Figure 1](#). Importantly, we assume that asymptomatic, pre-symptomatic, and mildly symptomatic individuals transmit the disease at the same rate β , and that these are the only sources of

transmission. The transmission rate is reduced due to social measures (face masks, social distancing, self quarantine, etc) by a factor of $1 - ac$ among all infectious individuals, where c is the efficacy of social measures and a is the proportion of the population adhering to social measures.

The vaccine becomes available to the population at rate μ , and individuals can choose whether or not to get the vaccine. Specifically, proportion ϕ of the susceptible population S enters the vaccinated population V at rate μ , while proportion $1 - \phi$ of the susceptible population enters the unvaccinated class X at the same rate. This parameter ϕ allows us to analyze the effects of vaccine coverage, specifically as a consequence of individuals who are unwilling to receive the vaccine¹³. Vaccinated individuals are infected at a rate reduced by $1 - \xi$, where ξ is the efficacy of the vaccine, while the unvaccinated class X has the same dynamics as the susceptible without access to a vaccination class S .

With these assumptions, our model is given by the following system of eleven ordinary differential equations:

$$\begin{aligned}
 S' &= -(1-d)\beta S(I_a + I_p + I_m) - \mu S \\
 X' &= \mu(1-\phi)S - (1-d)\beta X(I_a + I_p + I_m) \\
 V' &= \mu\phi - (1-\xi)(1-d)\beta V(I_a + I_p + I_m) \\
 E' &= (1-d)\beta(I_a + I_p + I_m)[S + X + (1-\xi)V] - \sigma E \\
 I_a' &= \sigma\rho E - \gamma_a I_a \\
 I_p' &= \sigma(1-\rho)E - \delta_1 I_p \\
 I_m' &= \delta_1 I_p - x_1\delta_2 I_m - (1-x_1)\gamma_m I_m \\
 I_h' &= x_1\delta_2 I_m - x_2\delta_3 I_h - (1-x_2)\gamma_h I_h \\
 I_c' &= x_2\delta_3 I_h - (1-x_3)\gamma_c I_c - x_3 m I_c \\
 R' &= \gamma_a I_a + (1-x_1)\gamma_m I_m + (1-x_2)\gamma_h I_h + (1-x_3)\gamma_c I_c \\
 D' &= x_3 m I_c
 \end{aligned} \tag{1}$$

The state variables and parameters are defined in Table 1 and Table 2, respectively. The parameters are estimated by the methods described below.

Parameter estimation

We used a Monte Carlo based Bayesian Melding approach to parameterize the base model using case notification, death, and mobility data reported for the Tampa Bay region for the period between March 10th and August 24th 2020. (details of methods provided in 12). Briefly, all social and epidemiological model parameters that could not be fixed at initiation were sequentially updated using 10-day blocks or segments of data between the above estimated period from their initial prior values using this procedure, and the final model thus estimated was used for the simulations carried out in this paper. Confirmed case data for the four

Figure 1. Model diagram.

Table 1. State variables. Each variable should be interpreted as a proportion of the total population.

State Variable	
S	Susceptible population without access to a vaccine
X	Susceptible, unvaccinated population with access to a vaccine
V	Susceptible, vaccinated population
E	Exposed population (pre-infectious)
I_a	Asymptomatic, infectious population
I_p	Pre-symptomatic, infectious population
I_m	Symptomatic, infectious population without need of hospitalization
I_h	Hospitalized infected population
I_c	Infected population in intensive care unit (ICU)
R	Recovered population
D	Deceased population

Table 2. Parameters. The value for each parameter is used throughout this work unless stated otherwise. All rate parameters are measured in units of $(\text{day})^{-1}$.

	Parameter	Value
β	Transmission rate	0.76
a	Proportion of population adhering to social measures	varies
c	Reduction in transmission due to social measures	0.85
ϕ	Vaccine coverage	varies
ξ	Vaccine efficacy	0.9
μ	Rate of vaccination	0.02
σ	Rate of symptom onset among exposed	0.32
ρ	Proportion of expose who never develop symptoms	0.37
γ_a	Rate of recovery among I_a	0.23
γ_m	Rate of recovery among I_m	0.23
γ_h	Rate of recovery among I_h	0.22
γ_c	Rate of recovery among I_c	0.23
δ_1	Rate of progressing from I_p to I_m	0.69
δ_2	Rate of progressing from I_m to I_h	0.15
δ_3	Rate of progressing from I_h to I_c	0.55
x_1	Proportion of mild cases that progress to hospital	0.18
x_2	Proportion of hospital cases that process to ICU	0.25
x_3	Proportion of ICU cases that die	0.51
m	Mortality rate among ICU patients	0.37

counties comprising Tampa Bay, viz. Hillsborough, Pasco, Pinellas and Polk, were obtained from the Johns Hopkins University Coronavirus Resource Center¹⁴. Mobility data serve as an estimate for population mixing and the fraction of the population under restricted movement in the counties concerned were obtained from the location data firm, [Unacast](#). Our consolidated parameter data can be accessed in [15](#).

Effective reproduction number

The effective reproductive number R_t quantifies the average number of secondary infections caused by each new infection. We can calculate R_t using the next generation matrix method developed in [16](#). The next-generation matrices for system (1) are:

$$F = \begin{pmatrix} 0 & \lambda & \lambda & \lambda \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 \end{pmatrix}$$

and

$$V = \begin{pmatrix} -\sigma & 0 & 0 & 0 \\ -\rho\sigma & \gamma_A & 0 & 0 \\ -(1-p)\sigma & 0 & \delta_1 & 0 \\ 0 & 0 & -\delta_1 & x_1\delta_1 + (1-x_1)\gamma_M \end{pmatrix},$$

where

$$\lambda = (1-ac)\beta(S+X+(1-\xi)V)$$

is the force of infection.

Then the effective reproduction number R_t is exactly the spectral radius of FV^{-1} :

$$R_t = \lambda \left(\frac{1-\rho}{\delta_1} + \frac{1-\rho}{(1-x_1)\gamma_M + x_1\delta_2} + \frac{\rho}{\gamma_A} \right). \quad (2)$$

We use this formula to assess the viability of vaccination programs on disease eradication in the following sections.

Time $R_t = 1$ and peak ICU cases

Here we use our model 1 to establish two boundary value problems (BVPs). The first allows us to determine the time necessarily to drive $R_t < 1$, and thereby control the spread of the disease, under varied vaccination rates. Solution of the second determines the peak ICU case load over the same vaccination rate.

For both BVPs, we consider system (1) extended to include an auxiliary variable τ :

$$\begin{aligned} S' &= -(1-d)\beta S(I_a + I_p + I_m) - \mu S \\ X' &= \mu(1-\phi)S - (1-d)\beta X(I_a + I_p + I_m) \\ V' &= \mu\phi - (1-\xi)(1-d)\beta V(I_a + I_p + I_m) \\ E' &= (1-d)\beta(I_a + I_p + I_m)[S+X+(1-\xi)V] - \sigma E \\ I_a' &= \sigma\rho E - \gamma_a I_a \\ I_p' &= \sigma(1-\rho)E - \delta_1 I_p \\ I_m' &= \delta_1 I_p - x_1\delta_2 I_m - (1-x_1)\gamma_m I_m \\ I_h' &= x_1\delta_2 I_m - x_2\delta_3 I_h - (1-x_2)\gamma_h I_h \\ I_c' &= x_2\delta_3 I_h - (1-x_3)\gamma_c I_c - x_3 m I_c \\ R' &= \gamma_a I_a + (1-x_1)\gamma_m I_m + (1-x_2)\gamma_h I_h + (1-x_3)\gamma_c I_c \\ D' &= x_3 m I_c \\ \tau' &= 0. \end{aligned} \quad (3)$$

This new variable provides an additional degree of freedom allowing us to solve the system as a BVP with a terminal, parameter-dependent boundary condition (BC).

To determine the time until $R_t < 1$, we solve system (3) with BCs

$$\begin{aligned} S(0) &= S_0 \\ E(0) &= 1 - S_0 \\ R_t(\tau) &= 1 \\ X(0) = V(0) = I_a(0) = I_p(0) = I_m(0) = I_h(0) = I_c(0) = R(0) = D(0) &= 0, \end{aligned} \quad (4)$$

where $R_t(t)$ is defined in equation (7). The variable τ within solutions of this BVP represents the time at which $R_t(t) = 1$. Since $R_t(t)$ is strictly decreasing over time, $R_t(t) < 1$ for all $t > \tau$, and τ is therefore the time at which the disease is eradicated.

To determine peak ICU cases, we consider system (3) with BCs

$$\begin{aligned} S(0) &= S_0 \\ E(0) &= 1 - S_0 \\ 0 &= x_2 \delta_3 I_h(\tau) - (1 - x_3) \gamma_c I_c(\tau) - x_3 m I_c(\tau) \\ X(0) = V(0) = I_a(0) = I_p(0) = I_m(0) = I_h(0) = I_c(0) = R(0) = D(0) &= 0. \end{aligned} \quad (5)$$

The third boundary condition is equivalent to $I'_c(\tau) = 0$ and therefore requires I_c to be at a local maximum at time τ . The variable τ is therefore the time at which I_c reaches its maximum¹⁷. Evaluating I_c at $t = \tau$ for any solution of BVP (3)–(5) provides the peak ICU cases for the fixed parameter set.

Using XPPAUT (Version 8.0)¹⁸, we can numerically continue solutions to system (3) with BCs (4) or (5) over any system parameter; in particular, we use this method to evaluate the influence of ϕ and μ in the following section.

Software

All model simulation and numerical analysis was performed using XPPAUT (Version 8.0). Our code can be accessed at¹⁵. Data from XPPAUT was exported to MATLAB (Version R2019a) to create Figure 2–Figure 6. Julia (Version 1.6.2) is an open-source software that could alternatively be used to the same effect.

Results

Disease control dynamics

We begin by determining the extent to which a population can relax social measures once a vaccine becomes available and still control the virus. Here, we use simulations of the number of individuals requiring intensive care as a measure of control, and thus consequently, we consider the relationship between vaccine coverage ϕ and social measure compliance a on ICU hospitalization to address this question. Figure 2 shows ICU hospitalizations over time under various vaccine coverages and social measures. The red curve shows ICU cases without any vaccine or social measures, serving as a baseline for comparison. The black curve shows these cases with some vaccination and no social measures; the green curve shows ICU cases with strong social measures and no vaccine; the blue curve shows ICU cases with both vaccine coverage and social measures. Of course, greater vaccine coverage and stronger social measures result in fewer cases; however, social measures reduce the incidence of cases requiring intensive care much more than vaccine coverage. This is due to the slow vaccination rate μ , as we show in Time to eradication, below.

Conditions for eradication

We use the effective reproduction number R_t to study strategies by which the virus can be eradicated. Importantly, $R_t = R_t(t)$ is a function of time due to its dependence on S , X , and V : as the susceptible populations decrease, so does R_t . We consider the temporal dynamics of R_t in the following section. Here, we consider the idealized case in which proportion ϕ of the population is *instantaneously* vaccinated, $V = \phi S_r$ and $X = (1 - \phi)S_r$, where S_r is a new parameter representing the remaining susceptible proportion of the population at the time the vaccine is administered (that is, $1 - S_r$ is the proportion of the population who are currently infected, recovered, or deceased). In this case, λ can be written

$$\lambda = (1 - ac)\beta S_r(1 - \xi\phi),$$

Figure 2. ICU cases under various vaccination coverages and social measures. The vaccination rate and efficacy are $\mu = 0.02$ and $\xi = 0.94$, respectively. The right panel shows the same blue and green curves from the left panel, but zoomed in.

Figure 3. Vaccination and social measure thresholds to achieve $R_t < 1$. Each curve defines $R_t = 1$ over varied parameters with $\xi = 0.94$. (Left) $R_t = 1$ plotted over vaccine coverage ϕ and social measure compliance a . The region above each curve represents parameter pairs for which $R_t < 1$. (Right) $R_t = 1$ plotted over vaccine coverage ϕ and remaining susceptible population S_r with no, medium, and high proportions of social measure compliance. The region below each curve represents parameter pairs for which $R_t < 1$.

and so

$$R_t = (1 - ac)\beta S_r (1 - \xi\phi) \left(\frac{1 - \rho}{\delta_1} + \frac{1 - \rho}{(1 - x_1)\gamma_M + x_1\delta_2} + \frac{\rho}{\gamma_A} \right). \quad (6)$$

The ideal goal in eradicating the disease is to permanently reduce the effective reproductive number below the threshold $R_t = 1$. **Figure 3** shows curves in parameter space satisfying $R_t = 1$ with $\xi = 0.94$. On the left, curves are plotted over vaccine coverage ϕ and social measure compliance a and remaining susceptible population $S_r = 1$ (red curve) and $S_r = 0.8$ (blue curve). In order to achieve $R_t < 1$, (ϕ, a) pairs must lie above the curve. Note that disease eradication without social measures ($a = 0$) would require more than 80% of the population to receive a vaccine that is 94% effective in a naive population ($S_r = 1$); a population in which 20% have already been exposed would require approximately 75% to receive a vaccine in order to eradicate the disease without social measures. On the right, we show curves defined by $R_t = 1$ over vaccine coverage ϕ and remaining susceptible population S_r for varied social measures. For each fixed value of a , (ϕ, S_r) pairs must be below the

Figure 4. Controlling the pandemic with a vaccine depends on broad coverage and sustained social measure compliance. (Left) Time until $R_t < 1$ over ϕ . (Right) Peak ICU cases over ϕ (log scale). In both panels, $\mu = 0.02$, and the red curve corresponds to no social measures ($a = 0$), the blue curve corresponds to moderate social measure compliance ($a = 0.5$), and the black curve corresponds to high compliance ($a = 0.8$). The curves in this figure were created by solving boundary value problem (3) with boundary conditions (4) and (5) in the left and right panels, respectively.

Figure 5. Controlling the pandemic with a vaccine depends on fast dispersal and sustained social measure compliance. (Left) Time until $R_t < 1$ over μ . (Right) Peak ICU cases over μ (log scale). In both panels, $\phi = 0.6$, and the red curve corresponds to no social measures ($a = 0$), the blue curve corresponds to moderate social measure compliance ($a = 0.5$), and the black curve corresponds to high compliance ($a = 0.8$). The curves in this figure were created by solving boundary value problem (3) with boundary conditions (4) and (5) in the left and right panels, respectively.

curve to drive $R_t < 1$. Without social measures in place (red curve), approximately 75% of the population would have to be exposed to the virus before the disease is eradicated without a vaccine. In general, the larger the remaining susceptible population, the higher the vaccination coverage required to eradicate the disease. Importantly, the vaccine coverage threshold necessary to drive $R_t < 1$ decreases with increased social measures.

Time to eradication: interactions between vaccination coverage and rate and social measures

Vaccine rollout will not be instantaneous; it will likely take months to vaccinate a majority of the population. We therefore must consider the simultaneous effects of infection dynamics and slow vaccination rates on disease eradication, which requires considering the effective reproduction number as a function of time:

$$R_t(t) = (1 - ac)\beta(S(t) + X(t) + (1 - \xi)V(t)) \left(\frac{1 - \rho}{\delta_1} + \frac{1 - \rho}{(1 - x_1)\gamma_M + x_1\delta_2} + \frac{\rho}{\gamma_A} \right). \quad (7)$$

Figure 6. Magnitude of subsequent outbreaks over proportion vaccinated for various susceptible population sizes. The top row (A and B) visualizes outbreak scenarios with baseline transmission rate $\beta = 0.76$. The bottom row (C and D) visualizes outbreak scenarios with $1.5\times$ baseline transmission rate $\beta = 1.14$. The left column (A and C) shows peak ICU cases; the right column (B and D) shows total active cases when I_c is at its peak. In each panel, the colored curves correspond to varied remaining susceptible population sizes: fully susceptible (red curves), 80% susceptible (blue curves), and 60% susceptible (black curves). In each curve, $\phi = 0.6$, $\mu = 0.02$, $a = 0$, and the simulations were all initialized with $E(0) = 0.001$.

As the three susceptible populations S , X , and V change over time via infection and vaccination dynamics, $R_t(t)$ strictly decreases. We denote the time at which $R_t(t)$ decreases below 1 by t_h ; that is, $R_t(t_h) = 1$. Time t_h marks the beginning of the end of community spread, and we therefore refer to t_h as the time to eradication. The left panel of Figure 4 shows t_h as a function of vaccination coverage ϕ for varied social measure compliance a with vaccination rate $\mu = 0.02$. The time to eradication remains nearly constant over all ϕ for low social measure compliance ($a = 0, 0.5$; red and blue curves): this is due to the slow vaccination rate μ , and the comparably fast infection rate due to low social measure compliance. That is, for sufficiently small a , the virus spreads quickly through the population, infecting the susceptible population S much more quickly than the susceptibles become vaccinated. Thus, eradication is achieved primarily through infection, rather than through vaccination. For high social measure compliance ($a = 0.8$; black curve), t_h is large for small ϕ . This is because, for large a , the infection dynamics are slowed down, but because ϕ is small, the vaccination rate is also slow. The two mechanisms by which eradication is achieved (infection and vaccination) are therefore both slow, and so t_h is large. As ϕ increases, however, t_h decreases dramatically. The effective reproduction number R_t decreases as a increases, and thus achieving $R_t = 1$ requires less vaccination and infection for large a . Thus, despite the slow vaccination rate μ , there is a critical ϕ value past which the susceptible population becomes vaccination quickly enough so that R_t decreases below 1 due primarily to vaccine administration. In other words, the vaccination timescale overtakes the infection rate timescale for sufficiently large ϕ .

The right panel of [Figure 4](#) shows the maximum ICU case load (that is, the peaks of the curves in [Figure 2](#)) as a function of vaccination coverage for varied a . Unsurprisingly, as ϕ increases, the maximum ICU load decreases for each a . However, the peak ICU load remains comparatively high for $a = 0$ and $a = 0.5$ (red and blue curves, respectively) compared with $a = 0.8$ (black curve). For this latter case, the peak ICU load decreases dramatically from $\phi = 0$ until around $\phi = 0.4$, then remains low for all larger ϕ . ICU capacity in most states is between 10^{-4} and 3×10^{-4} ; peak ICU cases only remain below this threshold for high social measure compliance and vaccination coverage.

[Figure 4](#) suggests that sustained social measures help to eradicate the disease more efficiently than vaccination programs. This at least in part due to a relatively slow vaccination rate: $\mu = 0.02$. We now investigate the influence of vaccination rate μ on the time to eradication and on peak ICU cases. The left panel of [Figure 5](#) shows the time until the disease is eradicated, t_h , as a function of vaccination rate, μ , with $\phi = 0.6$. Without or with sufficiently low social measure compliance ($a = 0$ and $a = 0.5$; red and blue curves), the time until eradication increases with μ . For both cases, vaccination coverage ϕ is too low to eradicate the disease in a completely susceptible population ([Figure 3](#)), and consequently a non-negligible percentage of the population must become infected before $R_t < 1$. As μ increases, the infection dynamics slow down, causing the time it takes for R_t to drop below 1 to increase. For high social measure compliance ($a = 0.8$; black curve), the time to eradication decreases with μ . When a is sufficiently large, $\phi = 0.6$ is large enough to eradicate the disease through vaccination alone ([Figure 3](#)), and increasing the vaccination rate therefore reduces the time to eradication. Thus, rapid eradication of the virus is only achievable with sustained, widely obeyed social measures.

The right panel of [Figure 5](#) shows the peak ICU load over μ . Naturally, the faster the vaccine is administered to the population, the lower the peak ICU case load will be. However, peak ICU load only remains below typical ICU capacity ($1\text{--}3 \times 10^{-4}$) for small μ when social measure compliance is high (black curve). This again suggests that social measures must remain in place throughout the vaccination program in order to avoid hospital strain and associated loss of life.

Looking ahead: assessing ongoing risk within low-vaccinated communities

Here we consider the potential for localized outbreaks within low-vaccinated populations in which social measures are no longer observed ($a = 0$). We focus on two important quantities: the proportion of the population that have already received the vaccination at the onset of the outbreak, $V(0)$, and the proportion of the population that are still susceptible at the onset, S_r . The quantity S_r is interpreted as the proportion of the population that has not contracted and recovered from COVID-19, and consequently $1 - S_r$ is the proportion that has contracted the virus and is no longer susceptible. [Figure 6](#) visualizes peak ICU cases (I_c ; [Figures 6A and C](#)) and total active cases ($I_a + I_p + I_m + I_h + I_c$) at the time when ICU cases are at their peak ([Figures 6B and D](#)) as a function of $V(0)$. In the upper two figures (A and B), the transmission rate is the baseline value we have used throughout this work ($\beta = 0.76$). We assess the risk that a fast-spreading variant poses in the lower two figures (C and D) by increasing the transmission rate by 50% relative to baseline ($\beta = 1.14$). In each curve, the model is initialized with $E(0) = 0.001$. The colored curves correspond to varied values of S_r : $S_r = 1$ is shown in red, $S_r = 0.8$ in blue, and $S_r = 0.6$ in black. Naturally, outbreaks are reduced in magnitude for smaller S_r . Similarly, each curve decreases as $V(0)$ increases. Both of these observations provide an obvious but important conclusion: the smaller the proportion of fully-susceptible individuals, the smaller the outbreak will be. Moreover, for each curve, there is a critical $V(0)$ value after which the total number of cases is constant. This is the $V(0)$ value for which $R_t = 1$ given the corresponding value of S_r . For all $V(0)$ larger than this critical value, $R_t < 1$, and the only active cases are those that develop among the initially exposed individuals.

Discussion and conclusion

We introduce an extended SEIR socio-epidemiological model incorporating vaccination dynamics to evaluate the interactions between vaccination and social measures for controlling or ending the spread of COVID-19. Following standard analytical techniques¹⁶, we derived an explicit form for the effective reproduction number R_t . This value is of central concern to controlling the pandemic: through a combination of natural infection, social measures, and vaccination administration, we must drive $R_t < 1$ in order to eradicate the disease. Our analysis therefore focused on the influence of social measures and vaccination rates on the time until the disease is eradicated, but also considered hospital demand as a function of these interventions. Importantly, we show that while eliminating social measures entirely might help eradicate the disease faster, the hospital demand, and therefore death toll, are reduced dramatically with even partial adherence to social intervention strategies.

Our analysis focused on three parameters: the proportion of the population willing to receive a vaccine ϕ , the proportion of the population willing to adhere to social measures a , and the rate at which vaccines are

administered to the population μ . Figure 3–Figure 5 summarize the major results arising from these interactions, and suggest that, with low vaccination rate μ , sustained social measures become increasingly important to keep the hospitalization rates low, even if a large proportion of the population are willing to receive the vaccine (that is; even if ϕ is large). This finding is consistent with previous studies under varied assumptions^{10,19,20}.

The interplay between social measures and vaccine administration is perhaps most complicated when considering the time until eradication. When the proportion of the population who adhere to social measures is small, the time to eradication is relatively fast (Figure 4 and Figure 5, left panels). This is because, without social measures, the virus spreads quickly, thereby increasing the number of individuals with infection-conferred immunity (or who die due to the disease). On the other hand, when social measure adherence is high, the time to eradication is large for low vaccination coverage and rate, but decreases with both parameters. For low vaccination coverage or rate, population-level immunity is primarily being conferred via infection, and infection rates are low due to high levels of social measures. As vaccination coverage or rate increases, however, the rate at which individuals become vaccinated begins to outpace the rate at which individuals become infected, and the time until eradication becomes small. Importantly, only in the case of high social measure compliance and high vaccination rate or coverage do the number of ICU cases remain manageable (Figure 4 and Figure 5, right panels).

We further use our model to predict the magnitude of future outbreaks in partially-vaccinated communities. Naturally, if a sufficiently high proportion of the population is vaccinated or has infection-derived immunity, then the R_t value within that community is less than unity, and any new infections are not expected to cause an outbreak (Figure 6). However, if too few individuals are vaccinated, outbreaks remain a significant threat, particularly in light of new, highly contagious variants²¹.

We developed our model under a set of assumptions that captured important features of COVID-19 transmission. However, we omitted one or more realities of COVID-19 dynamics that could quantitatively influence our results. First, we did not include any age structure to our model. It is well known that mortality rates due to COVID-19 are disproportionately high among elderly populations. By including age structure, one can study targeted vaccination programs in which the elderly are given earlier access to the vaccine. Second, we include only a single vaccine in our model, while many with varying efficacies are likely to enter the market before the pandemic is over^{22–24}. While incorporating these features into our model would surely result in quantitative differences, the qualitative predictions of our current model would likely remain unchanged; that is, social measures must remain in place throughout the vaccination campaign in order to mitigate hospital and mortality rates. An important consideration for future work is the degree to which variants of the SARS-CoV-2 will increase community spread²¹, which can be incorporated into our model as a second set of infected classes.

Notwithstanding these limitations, this work highlights several major implications for the use of vaccination for either controlling or eradicating the current pandemic. The first is that slow vaccination roll out rates mean that continuing with currently applied social measures is imperative to containing the clinical outcomes (demand for ICU care and deaths) of the pandemic for a population. Only a ramped-up vaccination rate will allow easing of these social measures. The second important finding arising from the present results is that while social measures under the current slow rate of vaccinations will be crucial to prevent hospitalizations and the death toll from the virus, this intervention will also delay the development of herd immunity in the population. However, two critical results here are that at high levels of social measures, the numbers of individuals that are required to be vaccinated to achieve $R_t < 1$ can be significantly small, and that there might be a vaccination coverage level past which this can be achieved. We term this as “herd immunity due to social measures”, which will be much lower than the corresponding herd immunity in the absence of social measures. Note, however, that the imposition of social measures will keep a large fraction of the population continuing to be susceptible, and while achieving the lower level of herd immunity through vaccination under these measures will allow interruption of transmission, any relaxation of the latter in the presence of infected individuals, or if infected individuals were to arrive into an area lifting such restrictions, would seed resurgences of infection. This conclusion suggests that only by ramping up vaccinations to achieve natural herd immunity (i.e. the higher level of herd immunity that will be required to prevent transmission in the absence of any social containment measures) will the pandemic be fully suppressed over the longer-term.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Software availability

Github: COVID-Vaccination-Paper. <https://github.com/EdwinMichaelLab/COVID-Vaccination-Paper>.

This project contains the following parameter data and code:

- ParameterSets (Parameter values found using the methods described in Parameter estimation)
- IC_BVP_ac.ode (XPPAUT code used to find the peak ICU cases over varied parameters, shown in the right panels of Figures 4 and 5 in the paper)
- Rt_BVP_ac.ode (XPPAUT code used to track the time to $R_t = 1$ across parameters, shown in the left panels of Figures 4 and 5)
- model_Vax_ac.ode (XPPAUT code used to run model simulations)

All code and parameter data available at <http://doi.org/10.5281/zenodo.5138332>¹⁵

MIT License.

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Matthew Adewole

Department of Computer Science and Mathematics, Mountain Top University, Prayer City, Nigeria

This work is relevant in this present world as it discusses an ongoing issue. Authors of this work have put in good efforts to get this work done. The presentation is quite good however, it is not without flaws:

1. Authors assumed a closed population where there is no demographic data. This kind of scenario can only be true when the time-duration is small enough. However, Figure 2 shows a time series plot over a period of about 400 days. Saying there is no demographic process within this period is far from reality. I suggest that the authors include demographic data.
2. It was said that S represents "susceptible without access to vaccine". How come individuals in S compartments are vaccinated at a rate μ ? I think something is wrong with the nomenclature.
3. The first term on the right side of Equation 1c should be $\mu\phi S$.
4. A significant part of this work is the parameter estimation. Authors should make this more explanatory. Authors should display graphs showing data and fitted curves. Authors should differentiate between estimated parameter values and the parameter values taken from literature.
5. The data used for parameter estimation are quite outdated. Therefore the estimated parameter values and, consequently, the results of this work may not represent the present-day reality.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Mathematical Biology, Numerics of PDEs

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Oct 2022

Glenn Young, Kennesaw State University, Marietta, USA

We thank the reviewer for his useful suggestions for improving our paper. We have addressed all comments below.

1. Authors assumed a closed population where there is no demographic data. This kind of scenario can only be true when the time-duration is small enough. However, Figure 2 shows a time series plot over a period of about 400 days. Saying there is no demographic process within this period is far from reality. I suggest that the authors include demographic data.

- While Figure 3 displays data out through 365 days, the most important dynamics (namely time to peak ICU caseload) occur within 100 days of outbreak. Similarly, the caseload reduces to 20% of its maximum within about half a year. These are a short enough timespans relative to the dynamics of the model that the demographics within the population should not change enough to influence the course of the outbreak. For this reason we do not suspect that the addition of demographic processes will influence our results in any qualitative way.

2. It was said that S represents “susceptible without access to vaccine”. How come individuals in S compartments are vaccinated at a rate μ ? I think something is wrong with the nomenclature.

- The S population is the proportion of individuals who have not yet had the opportunity to receive a vaccination. We agree that our description within the manuscript is unclear and confusing. We have changed the description of S from “susceptible without access to vaccine” to “susceptible population prior to vaccine access.”

3. The first term on the right side of Equation 1c should be $\mu\phi S$.

- You are correct. Thanks for catching this mistake.

4. A significant part of this work is the parameter estimation. Authors should make this more explanatory. Authors should display graphs showing data and fitted curves. Authors should differentiate between estimated parameter values and the parameter values taken from literature.

- The primary goal of this work is to investigate the tradeoffs between pharmaceutical and non-pharmaceutical interventions for controlling the spread of COVID, not on parameter estimation. The parameter estimation work was done in another paper by co-authors Newcomb and Michael [1], and we consequently leave the details of the method out of the present manuscript. However, we agree that additional detail regarding the method could benefit readers, and so we have added a new figure (now Figure 2) showing a fitted curve of COVID case data and include a slightly longer, though still brief, description of the method used to fit parameters.

5. The data used for parameter estimation are quite outdated. Therefore the estimated parameter values and, consequently, the results of this work may not represent the present-day reality.

- This is true and is of course a limitation of any covid modeling work that is not continuously updated with new data. However, the goal of this work is not to inform real-time decisions, but to understand the qualitative effects of coupled pharmaceutical and non-pharmaceutical interventions on the spread of the virus. In an effort to understand how robust our results are to changes in parameters, we have included a sensitivity analysis in our revised manuscript. Please see our response to Reviewer #1 comment 4.

[1] Newcomb, Ken, et al. "Iterative data-driven forecasting of the transmission and management of SARS-CoV-2/COVID- 19 using social interventions at the county-level." Scientific Reports 12, no. 1 (2022): 1-19.

Competing Interests: No competing interests were disclosed.

Reviewer Report 11 March 2022

<https://doi.org/10.5256/f1000research.58239.r124239>

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Sam Moore

Zeeman Institute for Systems Biology and Infectious, University of Warwick, Coventry, UK

The authors present a compartmental model fitted to COVID-19 metrics observed in the Tampa Bay region of the US during part of 2020. The model is extended to include simple vaccination and NPI (non-pharmaceutical intervention) dynamics which are explored to provide an assessment of the levels of each necessary to reduce the effective reproductive number below the critical threshold. The paper is clearly written and the presented results mathematically consistent. However, the scope of the model lacks many of the features required for the results to be

meaningful in the context of the current pandemic.

The model firstly assumes a homogeneous population. While all modelling necessitates a certain degree of approximation, a detailed spatial structure may be intractable and of limited benefit, some stratification by age and/or vulnerability is arguably essential in the study of COVID-19 dynamics given the highly uneven level of risk, especially given results in the paper are principally presented in terms of severe disease outcomes. Due to the highly contagious nature of the disease and damaging socio-economic consequences of prolonged NPIs, most countries around the world have aimed to use vaccination principally to reduce the worst disease effects by targeting the vulnerable rather than aiming for epidemic turnover as concentrated on in this study.

The vaccine dynamics included in the model are also overly simplistic. While in the introduction the authors do make some discussion about the multiple benefits of vaccination, in terms of reducing severe disease outcomes and symptom prevalence as well as infection and transmission, their model makes no attempt to incorporate this. Many of the vaccines used have proved highly effective in reducing severe disease outcomes (as much as ~98% effective in preventing mortality) which would have significant consequences for the projected hospital/ICU numbers presented.

Results throughout the study are framed with a view to disease eradication, assumingly achieved by reducing the effective reproduction below 1. There are several issues with this measure in the context however; firstly, waning immunity and rapidly emerging viral variants both mean that the herd immunity threshold is by no means fixed, and secondly the study frames presents the threshold as a function of a fixed NPI level, while in reality no country is likely to leave control measures in place in perpetuity and these should rather be explored as a temporary dynamic and not to effect a final threshold.

Finally, the model is fitted to provide a single a static set of parameters. However, a broad parameter set can clearly match the same data. Due to the sensitivity of the results to the fitting, it would be greatly beneficial to see this explored to some extent, to provide some sort of prediction intervals. Due to significant changes in both viral characteristics and available treatment over time, many of these parameters are also not constant as presented—for instance one assumes the parameters are chosen to match the characteristics of variants in circulation at one particular time, but this is a rapidly changing situation. The control parameter presented is also entirely abstract, and one feels it would be greatly more informative if it had some grounding in reality—what range has actually been observed in practice?

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiological modelling

I confirm that I have read this submission and believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Author Response 04 Oct 2022

Glenn Young, Kennesaw State University, Marietta, USA

We thank the reviewer for his useful suggestions for improving our paper. We have addressed all comments below.

1. The model firstly assumes a homogeneous population. While all modelling necessitates a certain degree of approximation, a detailed spatial structure may be intractable and of limited benefit, some stratification by age and/or vulnerability is arguably essential in the study of COVID-19 dynamics given the highly uneven level of risk, especially given results in the paper are principally presented in terms of severe disease outcomes. Due to the highly contagious nature of the disease and damaging socio-economic consequences of prolonged NPIs, most countries around the world have aimed to use vaccination principally to reduce the worst disease effects by targeting the vulnerable rather than aiming for epidemic turnover as concentrated on in this study.

- Thank you for your feedback. We understand that considering a homogeneous population limits our model's predictive scope, as we mention in our manuscript's discussion. However, the stated goal of the work in this manuscript is to qualitatively understand how pharmaceutical and non-pharmaceutical interventions influence the spread of COVID-19, particularly by focusing on the incidence of severe cases requiring intensive care. These theoretical results are most effectively found through the rigorous analytical methods we employ here, methods that would not be available to us with an age-structured model. Our assumption of a homogeneous population is therefore appropriate because homogeneity simplifies the required analysis and parameterization, and our results are robust to parameter perturbations. We have added text to the discussion elaborating on the necessity of our model's simplicity.

2. The vaccine dynamics included in the model are also overly simplistic. While in the introduction the authors do make some discussion about the multiple benefits of vaccination, in terms of reducing severe disease outcomes and symptom prevalence as well as infection and transmission, their model makes no attempt to incorporate this. Many of

the vaccines used have proved highly effective in reducing severe disease outcomes (as much as 98% effective in preventing mortality) which would have significant consequences for the projected hospital/ICU numbers presented.

- We agree that many of the vaccines have proven highly effective in reducing severe disease outcomes. In fact, when we submitted this manuscript, initial data on the widely administered mRNA vaccines (Pfizer, Moderna) reduced all COVID-19 cases by $\approx 95\%$, not just severe [1]. This is reflected in our assumption that vaccinated individuals' risk of infection is reduced by a factor of $\xi = 0.94$. We further emphasize that this assumption, that vaccination reduces only the risk of infection and does not subsequently reduce the risk of severe outcomes, was based on data available at the time, and that limitations on available data would have made any assumption on the vaccine's downstream effects impossible to parameterize in any meaningful way.
- Further: in our model, hospitalization is being driven primarily by the unvaccinated, and consequently differentiating the rates at which vaccinated versus unvaccinated individuals develop severe symptoms has no qualitative effect on our results. We include here a visualization of ICU cases with total ICU cases (solid curves) and ICU cases among unvaccinated individuals (dotted curves) visualized separately. For both zero (green curves) and high (blue curves) NPI adherence, the unvaccinated population comprises over 97% of ICU cases at their peak. These results suggest that even if we assume that vaccinated individuals cannot develop severe symptoms, our results remain qualitatively unchanged. We have added text and Figure 5 in the manuscript clarifying this important point.

3. Results throughout the study are framed with a view to disease eradication, assumingly achieved by reducing the effective reproduction below 1. There are several issues with this measure in the context however; firstly, waning immunity and rapidly emerging viral variants both mean that the herd immunity threshold is by no means fixed, and secondly the study frames presents the threshold as a function of a fixed NPI level, while in reality no country is likely to leave control measures in place in perpetuity and these should rather be explored as a temporary dynamic and not to effect a final threshold.

- We again ask the reviewer to understand that this work was submitted in August 2021, shortly before evidence of waning immunity began to emerge [2] (note that the cited article was first published on medRxiv on August 31, 2021). Before this evidence was released, many considered herd immunity through a combination of vaccination and infection to be an achievable goal [3]. Moreover, while we do present conditions such that the effective reproductive number is reduced below unity, we also consider the impact of subsequent outbreaks in on communities with low vaccination rates and relaxed social measures in Figure 6. This consideration was aimed to address the reality that the virus might never be eradicated. We have added text regarding waning immunity to the discussion.
- However, we do agree that terms like “eradication” overstate what was ever considered feasible. We have modified the language throughout the manuscript to focus on control, rather than eradication.

4. Finally, the model is fitted to provide a single a static set of parameters. However, a broad parameter set can clearly match the same data. Due to the sensitivity of the results to the fitting, it would be greatly beneficial to see this explored to some extent, to provide some

sort of prediction intervals. Due to significant changes in both viral characteristics and available treatment over time, many of these parameters are also not constant as presented for instance one assumes the parameters are chosen to match the characteristics of variants in circulation at one particular time, but this is a rapidly changing situation. The control parameter presented is also entirely abstract, and one feels it would be greatly more informative if it had some grounding in reality what range has actually been observed in practice?

- Thank you for the comment; we agree that many of the parameters in our model can and will change over time. As stated above, the goal of our work is to assess the influence of intervention strategies on the incidence of severe covid cases, and while changing parameters affects the quantitative results of our model, the qualitative results remain unchanged. We illustrate this by the addition of two new figures, both in Fig 3 in the manuscript. Since we do not know for certain how parameters will change over time, we allow every parameter in our model except φ (vaccine coverage), ξ (vaccine efficacy), μ (vaccination rate), and a (proportion of population adhering to NPIs) to randomly vary by up to 20% above or below its baseline value. We then simulate our model and collect data to make the figures, as described below.
- The left figure shows the region in which 80% of simulations fall as we vary parameters as described above over 5000 iterations. The solid curve shows the ICU caseload over time with $\varphi = 0.6$ and $a = 0$ (the same curve shown in black in Figure 4 in our manuscript) and 80% of simulations fall within the two dashed curves.
- The right figure shows peak ICU caseloads over φ . The solid middle curve shows the peak ICU caseload for our baseline parameters with $\varphi = 0.6$ and $a = 0$ (same curve shown in red in Figure 7 in our manuscript). We then vary φ from 0 and 1 in 0.2-unit steps and simulate our model 5000 times for each value of φ with parameters randomly selected as described above. 80% of peak ICU caseloads fall within the dash-dotted curves above and below the central curve.
- These results suggest that our model's results are qualitatively robust; that is, we expect disease eradication or control to require a combination of vaccination and NPI strategies even as these characteristic parameters change over time.

[1] Polack, Fernando P., et al. "Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine." New England Journal of Medicine (2020).

[2] Goldberg, Yair, et al. "Waning immunity after the BNT162b2 vaccine in Israel." New England Journal of Medicine 385.24 (2021): e85.

[3] Randolph, Haley E., and Luis B. Barreiro. "Herd immunity: understanding COVID-19." Immunity 52.5 (2020): 737- 741.

Competing Interests: No competing interests were disclosed.

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