

1 Considering indirect benefits is critical when evaluating
2 SARS-CoV-2 vaccine candidates

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15 **Abstract**

16 Significant progress has already been made in development and testing of SARS-CoV-2 vaccines, and
17 Phase III clinical trials have begun for 6 novel vaccine candidates to date. These Phase III trials seek to
18 demonstrate direct benefits of a vaccine on vaccine recipients. However, vaccination is also known to bring
19 about indirect benefits to a population through the reduction of virus circulation. The indirect effects of
20 SARS-CoV-2 vaccination can play a key role in reducing case counts and COVID-19 deaths. To illustrate
21 this point, we show through simulation that a vaccine with strong indirect effects has the potential to reduce
22 SARS-CoV-2 circulation and COVID-19 deaths to a greater extent than an alternative vaccine with stronger
23 direct effects but weaker indirect effects. Protection via indirect effects may be of particular importance
24 in the context of this virus, because elderly individuals are at an elevated risk of death but are also less
25 likely to be directly protected by vaccination due to immune senescence. We therefore encourage ongoing
26 data collection and model development aimed at evaluating the indirect effects of forthcoming SARS-CoV-2
27 vaccines.

28 SARS-CoV-2 has spread globally since its emergence in December 2019 [1], resulting in more
29 than 17 million confirmed infections and 650,000 COVID-19 deaths to date [2]. Current pub-
30 lic health interventions aimed at curbing the spread of SARS-CoV-2 have been limited to non-
31 pharmaceutical interventions (NPIs), including travel-associated quarantines, contact tracing, and
32 implementation of social distancing regulations. These measures have had various degrees of suc-
33 cess worldwide [3, 4, 5]. While critical to slowing viral spread, some of these NPIs have resulted
34 in widespread job loss and economic hardship [6, 7, 8], and profoundly changed the way we inter-
35 act with one another locally, regionally, and internationally. Given the substantial political and
36 economic costs associated with NPIs, long-term solutions are needed. A vaccine remains the most
37 promising solution. Thanks to tremendous research efforts worldwide, vaccine development is well
38 underway, with more than 30 vaccine candidates in clinical trials, including 6 novel candidates in
39 Phase III trials as of July 31st, 2020 [9].

40 Clinical trials for SARS-CoV-2 vaccines evaluate both the safety and efficacy of vaccine candi-
41 dates. Ethically, a vaccine cannot be licensed if it does not provide a direct protective benefit to
42 the vaccinee [10]. Direct protective benefits of vaccines include protection from infection, reduced
43 symptom development, and lower mortality rates. While significant attention should be given to a
44 SARS-CoV-2 vaccine’s direct benefits, vaccination can also bring about indirect effects [11]. These
45 indirect effects decrease the infection risk of both vaccinated and unvaccinated susceptible individ-
46 uals by reducing the extent of virus circulation in a community. Virus circulation can decrease
47 because vaccinated individuals are less susceptible to infection, or because vaccinated individuals
48 have shorter durations of infection or lower viral loads that reduce their infectiousness.

49 Vaccination campaigns can significantly reduce the number of infections and deaths in subpop-
50 ulations that remain unvaccinated, even when vaccination coverage is quite low [12] - a crucial
51 consideration, given that extensive vaccine coverage will be a formidable challenge. Vaccine doses,
52 and the public health infrastructure needed to administer them, will almost certainly be limited
53 in supply relative to demand, and given the current politically and emotionally charged climate,
54 vaccine refusal could pose an additional barrier [13, 14]. The vast majority of the global population
55 remains susceptible to the virus and we are likely well below the herd immunity threshold, despite
56 the staggering rates of infection that some regions have already experienced. Therefore the indi-
57 rect effects of vaccine candidates are critically important to consider when evaluating SARS-CoV-2
58 vaccine candidates and formulating strategies for their roll-out.

59 Clinical trials to test vaccine effectiveness do not evaluate population level effects. Quantify-
60 ing both the direct and indirect effects of vaccines on population level outcomes, such as disease
61 incidence and mortality, requires evaluating data after a vaccine has been in use for some time.
62 Therefore, mathematical models are needed to assess the potential indirect effects in advance.
63 These models can also help us gauge which vaccines should be further considered, even if direct
64 effects may be lower than desired. To demonstrate the utility of these types of models, consider

65 two hypothetical vaccines. Vaccine 1 reduces the risk of clinical infection in vaccinated individuals
66 to 30% of the original risk (a direct effect), and reduces the infectiousness of vaccinated individuals
67 to 70% of the original value (an indirect effect). Vaccine 2 reduces the risk of clinical infection
68 to 70% of the original and the infectiousness to 30% of the original. To evaluate the direct and
69 total (direct + indirect) effects of these vaccines, we can use a compartmental susceptible-exposed-
70 infected-recovered (SEIR) model with infected individuals experiencing either clinical or subclinical
71 infection (Figure 1A and supplemental material). This model classifies individuals as susceptible
72 to infection (S), exposed (E), actively infected with either a clinical (I_c) or subclinical (I_{sc}) infec-
73 tion; or recovered from infection (R). Although not explicitly included, COVID-19 mortality can
74 be gauged by assuming that a certain fraction of clinically infected individuals succumb to infec-
75 tion. In our model, we assume that susceptible individuals, once vaccinated, remain susceptible to
76 infection but are both less likely to develop a clinical infection and less likely to transmit the virus.
77 Simulation of this model, in the absence of vaccination, results in a maximum of nearly 190
78 new clinical infections daily per 100,000 individuals, and a cumulative total of almost 9,000 clinical
79 infections per 100k (Figure 1B). If we model the effects of distributing 40,000 vaccine doses in a
80 population of 100k, for 40% vaccination coverage, we find that both vaccines 1 and 2 lower peak rates
81 of clinical infections and the cumulative number of clinical infections relative to the no-vaccination
82 scenario. However, vaccine 1 (with a greater direct effect) does not reduce the number of clinical
83 infections to the extent that vaccine 2 (with a smaller direct effect) does. Further, vaccine 1 does
84 not act to ‘flatten the curve’ to the extent that vaccine 2 does. The effectiveness of vaccine 2 at the
85 population level stems from the magnitude of the indirect effects it brings about. Repeating these
86 simulations while considering only the direct effects of the vaccines results in a less pronounced
87 reduction in clinical infections. This result is true in both cases, but particularly for vaccine 2
88 (Figure 1C).

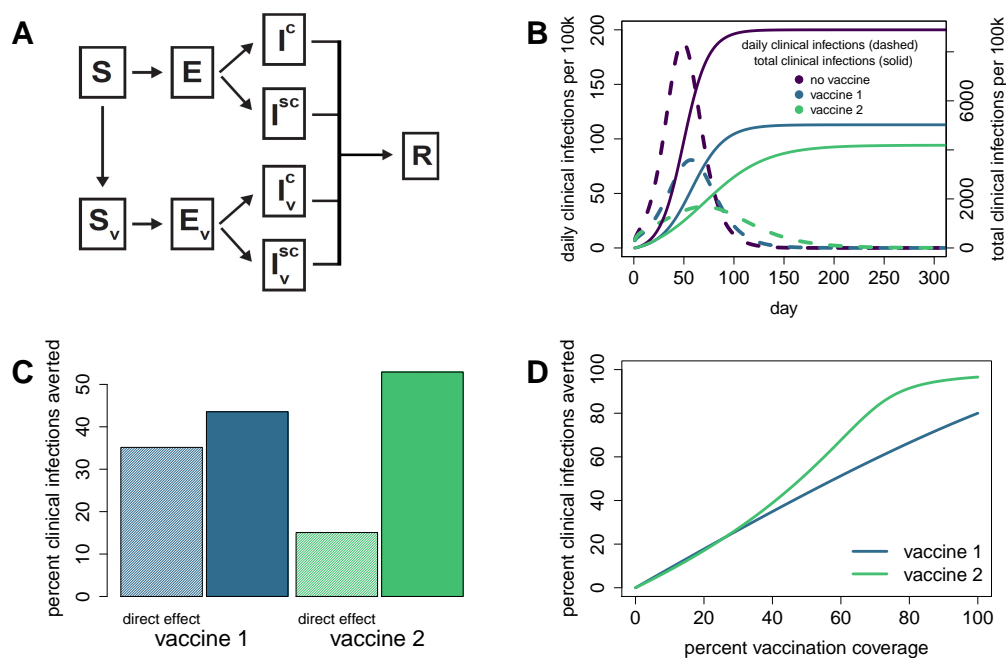


Figure 1: Direct and indirect effects of vaccines act together to lower population level clinical infection rates. A. Schematic of an SEIR mathematical model for SARS-CoV-2. Susceptible individuals are denoted by S , exposed individuals by E , infected individuals by I , and recovered individuals by R . Superscripts c and sc refer to clinical and subclinical infections. Subscript v denotes those that are vaccinated. Model is adapted from [15]. In simulations with vaccination, vaccination of susceptible individuals occurred on day 0 [16]. B. Daily clinical infection rates and the cumulative number of clinical infections over time under a no-vaccine scenario and under separate scenarios of vaccines 1 and 2 rolled out at 40% coverage. C. Percent of clinical infections averted by vaccine 1 (blue) and vaccine 2 (green) at 40% vaccination coverage. Shaded bars indicate the percent of infections averted by the direct effect only of each vaccine. These predictions were obtained by simulating models in which vaccination does not act to reduce the infectiousness of vaccinated individuals who become infected. Solid bars indicate the total percent of clinical infections averted by each vaccine’s reduction of both clinical infection risk and infectiousness. Note that the direct effect of vaccine 1 is much greater than vaccine 2, but the total effect of vaccine 2 averts the most infections. D. Percent clinical infections averted by each vaccine for a range of vaccination coverage levels. More infections are averted by vaccine 2 than by vaccine 1 for the majority of simulated vaccination rates.

89 Clinical trial evaluations would heavily favor vaccine 1 over vaccine 2 because it provides a much
 90 stronger individual (direct) benefit. However, we find that significantly reducing infectiousness via
 91 vaccine 2 is as or more effective at reducing clinical infections, and therefore mortality, at the
 92 population level. The model tells us that when evaluating vaccine candidates, we should be wary

93 of discounting a candidate that has a moderate direct effect if it also has the potential to have a
94 pronounced indirect effect. A vaccine with relatively weak direct effects could still potentially reduce
95 disease incidence and mortality at the population level more effectively than another vaccine that
96 offers stronger direct protection. In the example presented here, the result that vaccine 2 averts more
97 clinical infections than vaccine 1 is fairly robust across a range of values for vaccination coverage
98 (Figure 1D), although the total number of infections averted by each vaccine changes significantly
99 across coverage levels.

100 Our model simulations show that the reduction in clinical SARS-CoV-2 infections due to vac-
101 cination can be substantial and that indirect effects of vaccination are critically important at the
102 population level. These indirect benefits may be particularly crucial given the severity profile of
103 SARS-CoV-2. Indirect protection of older individuals (>65 years) may be especially important,
104 because vaccinating older individuals is often less effective in providing direct protection due to
105 immune senescence [17]. But quantifying the indirect effects of a vaccine is more difficult than
106 quantifying the direct effects, and requires information not yet available. The duration of immu-
107 nity, the risk of antibody-dependent enhancement, and the potential for viral evolution and vaccine
108 escape are all unknown. While some of these effects will require years of assessment, there are some
109 important factors that can be evaluated more quickly. For example, measurements of the level
110 and duration of viral shedding and symptoms, from both vaccinated and unvaccinated individuals
111 who become infected, would greatly inform our understanding of relative infectiousness. In parallel
112 to assessing the efficacy and safety of vaccine candidates for individual recipients, we argue that
113 research aimed at gauging indirect effects is a similarly critical area of investigation. Continued
114 data collection and assessment of the long-term impacts of vaccines through the use of mathemat-
115 ical models can provide decisive information about population level protective effects. Through
116 these efforts we can ultimately inform public health officials and politicians how to most effectively
117 incorporate vaccination into the global public health response to SARS-CoV-2.

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123

124 **Supplementary Material**

125 **Model Equations**

126 We model the dynamics of SARS-CoV-2 using a set of deterministic ordinary differential equations,
 127 with susceptible individuals S , exposed individuals E , infected individuals I , and recovered indi-
 128 viduals R . Subscripts c and sc refer to clinical and subclinical infections. Subscript v denotes those
 129 that are vaccinated. Population size N is constant.

130 β represents the transmission rate (infectiousness), $\frac{1}{\sigma}$ represents the average latent period, ν repre-
 131 sents the proportion of exposed individuals who develop clinical symptoms, $\frac{1}{\gamma}$ represents the average
 132 infectious period, and ρ_c represents the probability of death due to clinical infections.

133 Vaccine 1: reduces risk of clinical infection to 30% of the original value and transmission rate to
 134 70% of the original value:

135 $\nu_v = 0.3\nu, \beta_v = 0.7\beta$

136 Vaccine 2: reduces risk of clinical infection to 70% of the original value and transmission rate to
 137 30% of the original value:

138 $\nu_v = 0.7\nu, \beta_v = 0.3\beta$

139

$$\begin{aligned}
 \frac{dS}{dt} &= -\beta \frac{S}{N} (I_c + I_{sc}) - \beta_v \frac{S}{N} (I_{c,v} + I_{sc,v}) & (1) \\
 \frac{dS_v}{dt} &= -\beta \frac{S_v}{N} (I_c + I_{sc}) - \beta_v \frac{S_v}{N} (I_{c,v} + I_{sc,v}) \\
 \frac{dE}{dt} &= \beta \frac{S}{N} (I_c + I_{sc}) + \beta_v \frac{S}{N} (I_{c,v} + I_{sc,v}) - \sigma E \\
 \frac{dE_v}{dt} &= \beta \frac{S_v}{N} (I_c + I_{sc}) + \beta_v \frac{S_v}{N} (I_{c,v} + I_{sc,v}) - \sigma E_v \\
 \frac{dI_c}{dt} &= \nu \sigma E - \gamma I_c \\
 \frac{dI_{c,v}}{dt} &= \nu_v \sigma E_v - \gamma I_{c,v} \\
 \frac{dI_{sc}}{dt} &= (1 - \nu) \sigma E - \gamma I_{sc} \\
 \frac{dI_{sc,v}}{dt} &= (1 - \nu_v) \sigma E_v - \gamma I_{sc,v} \\
 \frac{dR}{dt} &= \gamma (I_c + I_{c,v} + I_{sc} + I_{sc,v})
 \end{aligned}$$

140 Conditions and Parameter Values

141 Total population size for the simulations was fixed at $N = 100\text{k}$ and we assume 20% of the population
142 is already in the ‘recovered’ class R . The initial size of the exposed class E was set to 200 individuals,
143 and values for the I_c and I_{sc} classes were calculated under a fast dynamics assumption:

$$I_c = \frac{\nu\sigma E}{\gamma} = 140$$
$$I_{sc} = \frac{(1-\nu)\sigma E}{\gamma} = 260$$

144 The initial size of the susceptible class $S = 0.8(1-f)N$ and the initial susceptible vaccinated
145 class $S_v = 0.8fN$, where f is the vaccination coverage level. All other vaccinated classes (E_v , $I_{sc,v}$,
146 $I_{c,v}$) are initially set to 0, and simulations were run for one year.

147 We set the average latent period ($1/\sigma$) to 4.6 days and the average infectious period ($1/\gamma$) to 5
148 days [18]. We set the transmission rate β to 0.5 per day, resulting in a basic reproduction number
149 of $R_0 = 2.5$ [19]. We set the risk of an unvaccinated individual developing a clinical infection at
150 $\nu = 0.14$ [20], and the risk of dying from a clinical infection at $\rho_c = 0.02$ [21, 22].

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