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A. Introduction

In early 2020, just as the Coronavirus disease 2019 (COVID-19) pandemic began, the Institute for Defense Analyses (IDA) published research that provided an analytical foundation for implementing measures to control outbreaks of contagious disease in an operational environment (*Burr et al 2020*). The analysis began from the premise that the primary objective of outbreak control measures is to reduce R—the average number of infections caused by a contagious individual at any point in a given outbreak—below one. Further, the analysis postulated that the requirements for outbreak control measures to meet this objective—alone and in combination—are driven by a set of defined characteristics of the disease involved.

As the pandemic evolved, our IDA research team extended the analysis to outbreaks of COVID-19 (*Burr et al 2021*). Our purpose was twofold: to provide insights into the requirements for COVID-19 outbreak control measures, and to use the pandemic as a case study for assessing the application and utility of the methodology we had previously developed. We expanded the underlying methodology to account for unique aspects of this disease, such as extensive asymptomatic and pre-symptomatic transmission, that force us to consider execution of response measures in ways not considered in our earlier research.

This paper discusses key insights from the COVID-19 analysis, specifically focusing on the influence of vaccine compliance and vaccine effectiveness on requirements for implementing outbreak control measures. Collectively, outbreak control measures are designed to limit the opportunities for contagious individuals to spread disease and/or to limit the vulnerability of healthy individuals if they are exposed. Our analysis focuses on three types of control measures: medical countermeasures, isolation of contagious individuals, and quarantine of individuals who may have been exposed to a disease and are at risk of becoming contagious.

National, state, and local governments have implemented several additional outbreak mitigation measures to reduce community spread of COVID-19, such as, social distancing, masking requirements, limits on the size of gatherings, closure of businesses of specific types, and stay-at-home orders.

When we completed our analysis in October 2021, the public health community was just beginning to quantify the population-level impact of these measures. Because of the nascent state of the data in this arena, our analysis did not formally address the requirements for or the effectiveness of measures such as these.

The results discussed in this paper are closely tied to our understanding of COVID-19 around which there is significant ongoing uncertainty. Because we have endeavored to account for this uncertainty, we can readily update our results as the collective understanding of COVID-19 increases.

B. Characterization of COVID-19 Disease Progression

Our analysis begins with a characterization of the disease progression of COVID-19. Table 1 summarizes the COVID-19-specific values used in the analysis. These values were obtained from a review of the scientific and medical literature available during the conduct of our analysis. Given uncertainty in the scientific community's understanding of COVID-19, we also consider a set of excursion values. These excursion values allow us to explore the sensitivity of our methodology to the uncertainty in the scientific understanding of the disease. See *Burr et al 2021*

for a detailed discussion of the literature review and rationale for the selection of values for both base case and excursions.

Table 1. COVID-19 Parameter Values Used in Assessment of Outbreak Control Measures

Parameter	Base-Case Value(s)	Excursion Value(s)
R_0	5.9[A]	2.5[B]
Vaccine effectiveness	95%[C]	75%[C]
Mean incubation period	6 days[D]	
Mean latent period	3 days[E]	
Mean period of pre-symptomatic contagiousness	3 days[F]	
Mean period of symptomatic contagiousness	9 days[G]	
Mean total duration of contagious period	12 days[H]	
Mean time of peak contagiousness	One day prior to symptom onset[I]	At symptom onset[I]
% of transmission that occurs during pre-symptomatic period	32.5%[J]	25%[J]
% of cases that are asymptomatic	30%[K]	70%[L]
Relative contagiousness of asymptomatic cases	.25[M]	

[A] *Ke et al 2021*.

[B] *US CDC June 2021*.

[C] Assumed.

[D] *McAloon et al 2020*.

[E] Calculated as the difference between the mean incubation period and the mean period of pre-symptomatic contagiousness.

[F] *Wei et al 2020*.

[G] *Cevik et al 2020*.

[H] Calculated as the sum of the pre-symptomatic and symptomatic contagious periods.

[I] Assumed based on evidence of peak contagiousness occurring around the time of symptom onset. *He et al 2020*.

[J] Calculated from our characterization of disease progression.

[K] *Byambasuren et al 2020* and *Poletti et al 2020*.

[L] *Letizia et al 2020*.

[M] Our literature review suggested an emerging scientific consensus on the existence of asymptomatic transmission, however, we did not observe consensus on the level of such contagiousness. We assume a value of 0.25.

In combination, the parameters in Table 1 allow us to represent a mean individual profile of COVID-19 transmission over time. Figure 1 illustrates this profile and further differentiates between overall mean transmission, and mean transmission from symptomatic and asymptomatic cases. The choice of representing the transmission profile as a triangle function was made by assumption. Similarly, we assumed that the profile of transmission over time from asymptomatic cases will mirror that of symptomatic cases. That is, transmission will begin, peak, and end at the same points in time relative to the point of exposure, although the overall magnitude of that

transmission will be significantly less. For all profiles, the area of the triangles is equal to the expected number of new infections caused per infected individuals. In the case of the population mean, this value is equal to R_0.

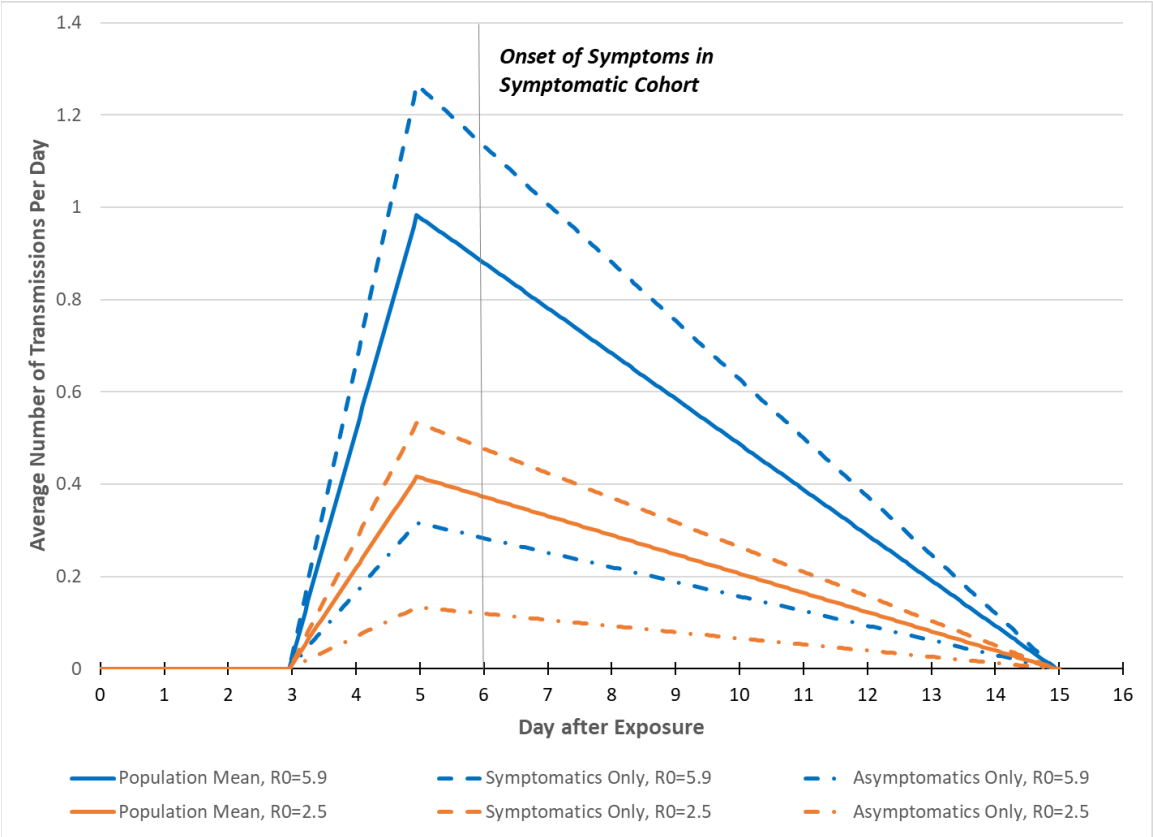

Figure 1. Representation of COVID-19 Transmission over Time from Various Cohorts, with Peak Transmission on Day 5 after Exposure

Recall that R_0 represents the average number of infections a contagious individual would be expected to cause in a completely susceptible population. However, in a COVID-19 outbreak, we have assumed that those contagious individuals who eventually become symptomatic will, on average, cause four times as many infections as those individuals who remain asymptomatic for the duration of their infection; the R_0 value for symptomatic individuals is four times as high as that for asymptomatic individuals. We have also assumed that symptomatic individuals comprise 70% of the contagious population, while asymptomatic individuals comprise 30%. Therefore, when the overall R_0 is 5.9, each symptomatic individual will, on average, cause 7.6 additional infections, while an asymptomatic individual will cause 1.9 additional infections. When the overall R_0 is 2.5, each symptomatic individual will, on average, cause 3.2 additional infections, while an asymptomatic individual will cause 0.8 additional infections.

The percentage of transmission that would occur before and after symptom onset can be calculated as the area under the transmission profile corresponding to pre-symptomatic and symptomatic periods respectively. When peak transmission occurs one day before symptom onset, 32.5% of transmission would take place before symptom onset. While hypothetical, and based on

the transmissibility of COVID-19 over time as observed in laboratory analysis and epidemiological studies, this value is consistent with those calculated in published population-level modeling studies (*Liu, Funk, and Flasche 2020*, *He et al 2020*) and cited by the US Centers for Disease Control (CDC) and Prevention in its COVID-19 Planning Scenarios document (*US CDC March 2021*).

The transmission profile (Figure 1) illustrates some of the disease-specific challenges to containing outbreaks of COVID-19: pre-symptomatic transmission, asymptomatic transmission, and a high R_0 value. Some 10% of disease transmission is caused by asymptomatic cases, and just under 30% of transmission is caused by symptomatic cases during their pre-symptomatic period. That means that 40% of transmission overall cannot be prevented by outbreak control measures that target sick individuals, such as isolation. In the sections that follow, we assess the impact of these challenges on the potential effectiveness and limitations of various outbreak control measures.

C. Analytical Approach

Our analytical approach of assessing requirements for response measures is based on the relationship between two variables: 1) the basic reproductive number of a disease, R_0, defined as the mean number of infections that would be caused by an infected individual in an entirely susceptible population (*Lloyd-Smith et al 2005*) and 2) R, the mean number of infections caused by an infected individual in a population where susceptibility is constrained for various reasons. Values for R_0 are disease specific and are influenced by factors such as mode of transmission and infectivity.

The approach builds from foundational concepts of mathematical epidemiology (*Vynnycky and White 2010*) and is informed by an existing body of literature that uses mathematical models to assess response measure effectiveness—see *Peak et al. 2017* and *Fraser et al. 2004* for examples. At a basic level, outbreaks grow when each contagious individual, on average, infects more than one other individual and wane when each contagious individual, on average, infects less than one other individual. To illustrate this concept, consider an outbreak of a disease with a given R_0 within a well-mixed population of N individuals, of which some subset S is susceptible to infection. The assumption of a well-mixed population implies that every contagious individual is equally likely to infect any susceptible individual. This foundational assumption is a common starting point for many contagious disease models. On average, in the absence of any response, each contagious individual is expected to cause $R_{no\ response}$ new infections during their infectious period:

$$R_{no\ response} = R_0 \frac{S}{N}. \quad (1)$$

If the population is entirely susceptible, then $\frac{S}{N} = 1$, and on average, each contagious individual will cause R_0 infections. This is consistent with the definition of R_0 as the average number of new infections caused by an individual in an entirely susceptible population. However, as the number of susceptible individuals in the population decreases, so does the number of new infections that are expected to be caused by each contagious individual. Equation 1 can be used to illustrate the point at which the outbreak will begin to wane by considering the case when each contagious individual infects fewer than one other individual on average (i.e., $R_{no\ response} < 1$):

$$R_0 \frac{S}{N} < 1 \quad (2)$$

$$\frac{S}{N} < \frac{1}{R_0}. \quad (3)$$

In other words, an outbreak will wane when the fraction of the population that is susceptible to disease drops below $\frac{1}{R_0}$. The higher the value of R_0, the more the susceptible population needs to be reduced, which is one reason why outbreaks of some diseases may be more difficult and take longer to control than others.

Eventually, outbreaks of a contagious disease within a closed population will end naturally as susceptible individuals fall ill and the residual susceptible population falls. This certainty suggests two possible, related approaches for outbreak response: limiting the opportunities for contagious individuals to infect others and limiting the inherent susceptibility of the population.

The first approach focuses response efforts on contagious individuals, and the second approach focuses on the population with whom they interact. In evaluating either approach, the basic question is as follows: *Will a given response measure decrease the number of infections caused, on average, by each contagious individual to less than one?* More formally, suppose that some function $f_{response}$ exists that characterizes the reduction in an individual's transmission due to a given response measure. The functional form of $f_{response}$ and the parameters $(x_1, x_2, \dots x_n)$ that describe it will depend on the specifics of what response(s) are being considered for a particular disease. By incorporating $f_{response}$ into Equation 1, Equation 4 expresses the expected number of infections an individual will cause given some response, $R_{response}$:

$$R_{response} = f_{response}(x_1, x_2, \dots x_n) R_0 \frac{S}{N}. \quad (4)$$

When $f_{response}(x_1, x_2, \dots x_n) = 1$, the response measure is **completely ineffective**. Each contagious individual will generate on average $R_0 \frac{S}{N}$ cases (i.e., $R_{response} = R_{no\ response}$). On the other hand, when $f_{response}(x_1, x_2, \dots x_n) = 0$, the response measure is **completely effective** (i.e., $R_{response} = 0$). No individual who is infectious will cause any new cases, and therefore no further disease transmission will occur. That being said, a given response does not need to be completely effective to cause an outbreak to wane and eventually stop. For this analysis, a given response will be considered effective if it is capable of causing an outbreak to wane:

$$R_{response} = f_{response}(x_1, x_2, \dots x_n) R_0 \frac{S}{N} < 1. \quad (5)$$

The inequality in Equation 5 can then be used to identify values for the set of response parameters $x_1, x_2, \dots x_n$ that are needed for a given response to be effective.

At the beginning of an outbreak in a disease-naive population, the entirety of the population is likely to be susceptible to infection, $S = N$, or equivalently, $\frac{S}{N} = 1$. Therefore, at the beginning of such an outbreak the inequality in Equation 5 can be rewritten as

$$R_{response} = f_{response}(x_1, x_2, \dots x_n) R_0 < 1. \quad (6)$$

Because $\frac{S}{N} \leq 1$ for the entirety of any outbreak, the left-hand side of inequality in Equation 5 is always less than that of the inequality in Equation 6. Given that, the values of the response parameters $x_1, x_2, \ldots x_n$ that satisfy the inequality in Equation 6 will also satisfy the inequality in Equation 5. In other words, satisfying the requirements for a response to be effective at the beginning of an outbreak will also ensure that the response is effective at later stages of the outbreak. Therefore, the IDA team used the inequality in Equation 6 as the point of departure for analyzing each of the responses under consideration in the present analysis.

As can be seen in the above inequality, as the value of R_0 changes, the parameter values associated with an effective outbreak response may also change. Since R_0 will vary with disease, a response that would be effective in controlling one disease may not be effective against another. This concept reinforces the need to provide commanders with guidelines that consider the challenges posed by diseases of various types.

When evaluating candidate outbreak responses, reducing R to less than 1 is necessary but may not be sufficient to minimize operational impact. After all, as shown in the beginning of this section, R can eventually be reduced to less than 1 in the absence of any outbreak response measure as a larger percentage of the population falls ill. To be fully effective, response measures should reduce the number of infected individuals and the duration of the outbreak, both of which can be accomplished by reducing R as much and quickly as possible. The sooner $R < 1$, and the closer R gets to zero, the shorter the outbreak and the fewer total cases.

D. Evaluation of Outbreak Response Measures

Given the theoretical foundation set forth in our analytical approach, the IDA team reviewed various outbreak response measures and established key parameters that could be used to describe and evaluate each response measure. With the objective of reducing the mean number of infections caused by a contagious individual to less than one ($R < 1$), the IDA team then established the range of parameter values over which a given response measure would be effective. Our analysis considered the following COVID-19 outbreak responses: vaccination, isolation triggered either by symptom onset or positive diagnosis, and quarantine. Figure 2 shows the four combinations of response measures and illustrates the concept of driving R down from R_0 to some value less than one. The following sections detail how we assessed the response measures using our analytical approach.

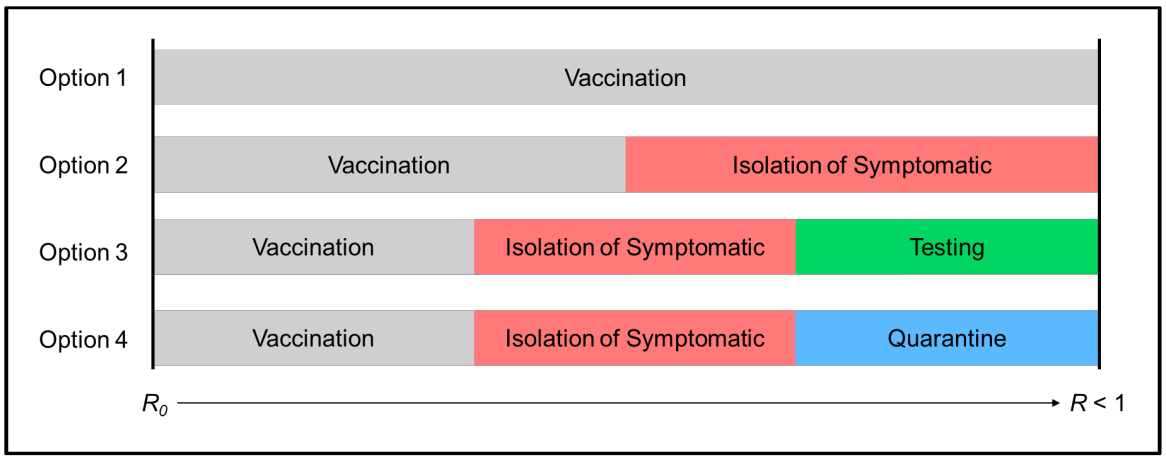

Figure 2. Analytical Construct for Assessing Combinations of COVID-19 Response Measures

1. Vaccination

Medical countermeasures are medical interventions—generally, pharmaceuticals that diminish the susceptibility of personnel exposed to pathogens, or that treat illnesses resulting from such exposure. As a means of responding to outbreaks of contagious disease, medical countermeasures can limit the vulnerability of individuals to a given disease, and thus reduce the size of the susceptible population below that needed to sustain the outbreak. Vaccines are the archetype medical countermeasure of this type, and are perhaps the most important means of preventing the spread of disease. Accordingly, our analysis focuses solely on COVID-19 vaccines.

We considered two factors in our assessment of vaccines: effectiveness and compliance.

- *Effectiveness* is the probability that a medical countermeasure will have its desired effect within the real-world population of interest. The effectiveness of vaccines in preventing infection is the endpoint of interest when assessing the ability of medical countermeasures to reduce *R*. While COVID-19 vaccine clinical trials broadly focused on reducing severe disease and preventing death, these vaccines demonstrated significant effectiveness in preventing COVID-19 infections, both in clinical trials and in the first groups of people vaccinated (*Pilishvili et al 2021*).
- *Compliance* is the percentage of the susceptible population that is vaccinated.

When we completed our analysis, US military populations were not yet fully vaccinated against COVID-19, and vaccination rates within the general population remained relatively low. Consequently, we investigated how the requirements for vaccine effectiveness are influenced by compliance rates, as well as the extent to which low levels of compliance will limit the contribution of vaccines to the reduction of *R* and lead to the continued need for additional outbreak control measures.

We start by determining the minimum required effectiveness for vaccines, under an assumption of universal compliance; in this case, the only portion of the population that can continue to acquire and transmit disease are those for whom vaccination is ineffective. We then examine the impact of lower compliance rates, where disease transmission occurs among both those for whom vaccination is ineffective and those who remain unvaccinated.

Recall that the methodology for assessing requirements for a given control measure focuses on the formulation of a function $f_{response}$ that characterizes the reduction in an individual's transmission due to a given response measure. The IDA team defined the function $f_V(\epsilon_V)$, which describes the reduction in an infectious individual's transmission due to the entire population being administered a vaccine with effectiveness ϵ_V.

Vaccines alter disease transmission by reducing individual susceptibility to infection. Assuming universal administration of a vaccine within a population, the portion of individuals whom an infectious individual can potentially infect is $(1 - \epsilon_V)$. As a result, $f_V(\epsilon_V) = 1 - \epsilon_V$, and, therefore, the values of ϵ_V that will cause an outbreak to wane are those that satisfy

$$R_V = (1 - \epsilon_V)R_0 < 1. \quad (7)$$

Given the R_0 value for the disease of interest, determining the value of ϵ_V needed to ensure $R < 1$ is straightforward:

$$\epsilon_V > 1 - \frac{1}{R_0}. \quad (8)$$

Given our baseline R_0 value of 5.9, and assuming universal compliance, the vaccine effectiveness required is 83%. For the excursion R_0 value of 2.5, the vaccine effectiveness required is 60%. In our base case, we model COVID-19 vaccines as 95% effective; this means that vaccines have the potential, in and of themselves, to cause an outbreak to wane. The same is true for the excursion R_0 and vaccine effectiveness values of 2.5 and 75%, respectively. However, at the base-case R_0 value of 5.9, a 75% vaccine effectiveness is insufficient.

As compliance falls below 100%, an increasing fraction of the population will continue to be vulnerable to infection beyond those in whom the vaccine was ineffective. As this fraction grows, it must be offset by increases in vaccine effectiveness; at a certain point, even 100% effective vaccines would fail to control outbreaks. Of course, this assumes that the unvaccinated population remains completely susceptible to disease. As outbreaks progress, more and more individuals become infected, and survivors would typically retain a degree of immunity for some period of time. The overall immunity within a given population would then be a combination of vaccine-induced immunity and post-infection immunity.

To account for vaccine compliance, we adapt our function f_V to depend on both the effectiveness of the vaccine, ϵ_V, and the portion of the population that has been vaccinated, ρ_V. Now the portion of the population that is protected against infection is $\epsilon_V \times \rho_V$. Accordingly, the portion of the population still susceptible to infection is $1 - (\epsilon_V \times \rho_V)$. Therefore, Equation 7 becomes:

$$R_V = \big(1 - (\epsilon_V \times \rho_V)\big)R_0 < 1. \quad (9)$$

The relationship between vaccine effectiveness and compliance is illustrated in Figure 3. In the figure, the areas above and to the right of the curves represent combinations of vaccine effectiveness and compliance that will control an outbreak (i.e., cause R to fall below 1); in areas below and to the left of the lines, disease transmission will be sustained. This relationship is heavily influenced by the R_0 of the disease. For the baseline COVID-19 vaccine effectiveness of 95% and the baseline R_0 value of 5.9, at least 87% of the population must be vaccinated for vaccines alone

to be sufficient to truncate an outbreak. This compliance value falls to 63% for the excursion R_0 value of 2.5. For the excursion vaccine effectiveness of 75%, even 100% compliance will be insufficient for an R_0 of 5.9, while 80% compliance will be needed for an R_0 of 2.5. The level of compliance needed for various combinations of R_0 and vaccine effectiveness is shown in Table 2.

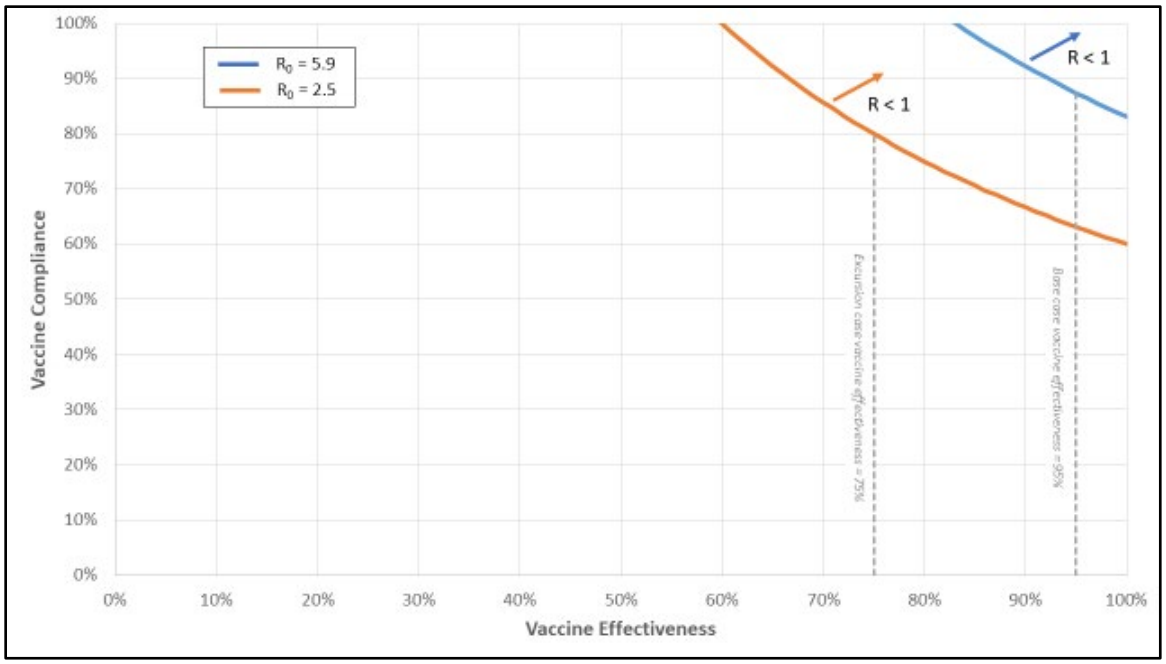

Figure 3. Relationship between COVID-19 Vaccine Compliance and Vaccine Effectiveness

Table 2. Vaccine Compliance Required Given Vaccine Effectiveness and R_0

R_0	Vaccine Effectiveness = 95% (Baseline)	Vaccine Effectiveness = 75% (Excursion)
5.9	87%	N/A*
2.5	63%	80%

*Even with 100% compliance, a vaccine with 75% effectiveness is insufficient to prevent sustained transmission when R_0 = 5.9.

In sum, given the transmissibility of COVID-19, required vaccine compliance is high enough that it could be challenging to truncate an outbreak with vaccines alone unless vaccination is mandatory among the population of interest. At the same time, there are few contraindications to COVID-19 vaccines that would limit the population that could be encompassed by a mandatory vaccine policy: the only contraindication listed in current CDC guidelines are a history of allergic reaction to a previous dose of vaccine or a known allergy to a component of the vaccine (*US CDC July 2021*). One study of nearly 65,000 individuals vaccinated against COVID-19 found the rate of acute allergic reactions to the vaccine to be 2.1%, with a maximum estimated rate of anaphylaxis of 0.0011% (*Blumenthal, Robinson, and Camargo 2021*). Yet, while vaccines that are 95% effective in preventing infection can cause an outbreak to wane, should vaccine-resistant COVID-19 variants emerge, even mandatory vaccination could be insufficient to control an outbreak on its own.

2. Isolation

Isolation is the separation of contagious individuals from a healthy population. Depending on the ease of transmission and the severity of disease, procedures for isolation in a military setting can range from confinement to quarters, retention in a hospital isolation ward, or treatment within a high-level containment care facility, such as those used in 2014 to treat Ebola patients.

Isolation of contagious patients is a routine medical practice in combination with infection control practices—collectively referred to as Standard Precautions—that include: "hand hygiene; use of gloves, gown, mask, eye protection, or face shield depending on the anticipated exposure; and safe injection practices" (*Siegel et al 2007*). For most contagious diseases, these practices are sufficient to limit the spread of disease and avoid outbreaks. However, there are circumstances in which standard infection control practices, including routine isolation, would be insufficient.

COVID-19 creates numerous challenges to rapid isolation of contagious individuals: 1) early symptoms tend to be very mild and non-specific, delaying recognition of illness and allowing individuals to continue activities that bring them into contact with others; 2) the disease is contagious prior to symptom onset, so a significant portion of transmission cannot be avoided in a regime where isolation is triggered by symptom onset; and 3) a significant fraction of COVID-19 infections are asymptomatic yet still contagious to some extent. Moreover, as the pandemic progressed, the capacity for isolation within medical facilities and under medical supervision became extremely limited. The basic guidance to individuals has in essence been "if you are sick, stay home." Yet this approach to isolation creates other problems as household members can be placed at risk.

The IDA team analyzed the effectiveness of isolation by considering who must be isolated (contagious individuals) and when they must be isolated (before they have the opportunity to infect others). To parameterize these factors, the IDA team defined the reduction in a contagious individual's transmission due to some isolation response capability, $f_{Iso}(\epsilon_{Iso}, D_{Iso})$, as a function of two parameters:

- ϵ_{Iso}: the fraction of the contagious population that will be isolated and
- D_{Iso}: the delay from exposure to the isolation of that individual.

Under the assumption that an isolated individual is unable to transmit the disease, the expected number of new infections per contagious individuals is determined from the profile of disease transmission (Figure 1). Let $g(t)$ be the average number of transmissions per day (i.e., the profile of disease transmission), where t is the time since exposure. Then the average number of new infections per contagious individual who is isolated at D_{Iso} is $\int_0^{D_{Iso}} g(t)dt$. If only a fraction of the contagious population, ϵ_{Iso}, is isolated, then the average number of new infections per contagious individual becomes:

$$R_{Iso} = (1 - \epsilon_{Iso})R_0 + \epsilon_{\text{Iso}} \int_0^{D_{Iso}} g(t)dt. \qquad (10)$$

The first term in the equation above represents those who are never isolated and in turn have unmitigated transmission (i.e., are expected to infect R_0 individuals). The second term represents those who are isolated and therefore transmit the disease up until the point of their isolation, D_{Iso}.

To cause an outbreak to wane, isolation must prevent contagious individuals from infecting one or more susceptible individuals on average. Therefore, the range of values for ϵ_{Iso} and D_{Iso} that constitute an effective response are those that satisfy the following inequality (based on the inequality in Equation 6).

$$R_{Iso} = (1 - \epsilon_{Iso})R_0 + \epsilon_{\text{Iso}} \int_0^{D_{Iso}} g(t)dt < 1. \quad (11)$$

If we assume for the moment that all contagious individuals will be isolated (i.e., $\epsilon_{Iso} = 1$), the effectiveness of isolation is solely dependent on how quickly those individuals are isolated and cease transmitting infection. The maximum time that isolation can be delayed and still be an effective response provides an upper bound on the window of opportunity for isolation.

Figure 4 shows how long isolation can be delayed relative to symptom onset and still ensure that a contagious individual, on average, infects less than one other person when calculated using the base-case values for parameters of interest. The orange curve shown in the figure below is $\int_0^{D_{Iso}} g(t)dt$, that is, the cumulative area under the triangular transmission profile (solid blue line in Figure 1).

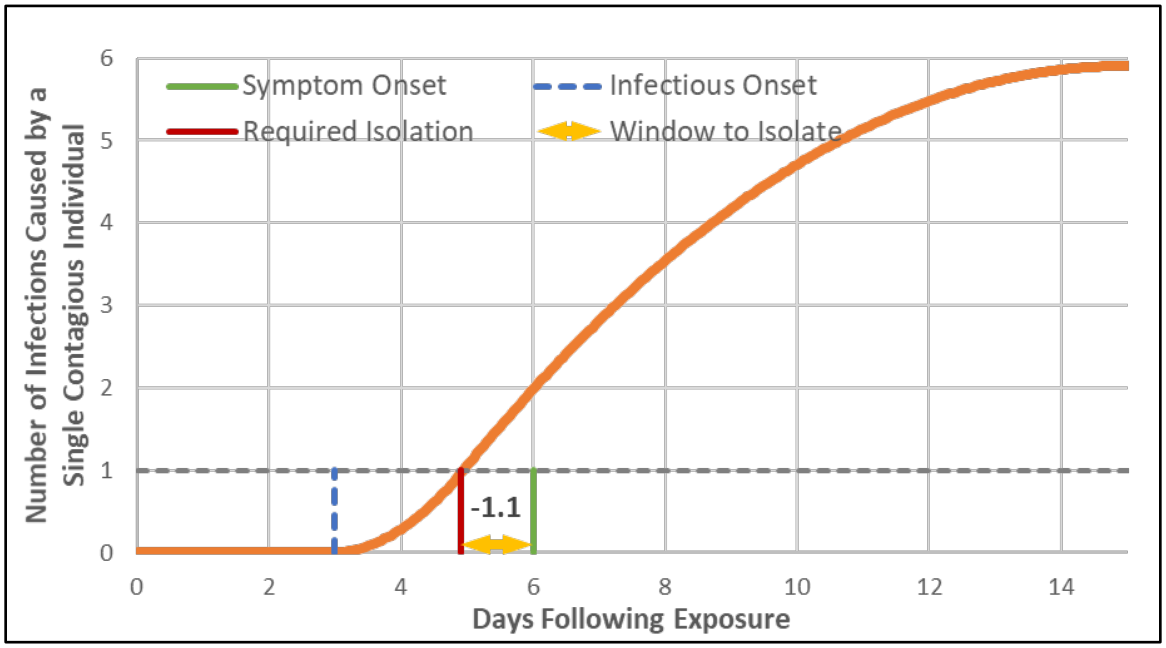

Figure 4. Mean Time Window for Isolation of an Individual with COVID-19 (Base-Case Parameter Values)

For the base-case parameter values and an R_0 of 5.9, cases of COVID-19 must be isolated within 4.9 days of exposure to ensure that on average, they infect less than one other individual. For those infections that do become symptomatic, this is 1.1 days prior to the mean onset of symptoms.

This negative time window for isolation of COVID-19 cases relative to mean symptom onset is driven by the combination of a high R_0 value, pre-symptomatic transmission, and a peak transmission time prior to onset of symptoms. Moreover, the requirement for isolation as shown

in Figure 4 applies to the totality of COVID-19 cases, both symptomatic and asymptomatic. Any outbreak response actions, such as isolation, that are typically triggered by symptom onset will by definition fail to capture those infections that are asymptomatic.

The inability to isolate the entirety of the contagious population will increase the urgency of isolation for that portion that can be captured, i.e. those who will become symptomatic. This is similar to the issue with vaccines: reduced rates of compliance increase the degree of vaccine effectiveness required among those who have been vaccinated. Figure 5 shows, for our base-case parameter set, the window of isolation when we assume that isolation is only applied to those who will become symptomatic, and that asymptomatic cases remain free to transmit disease unabated.

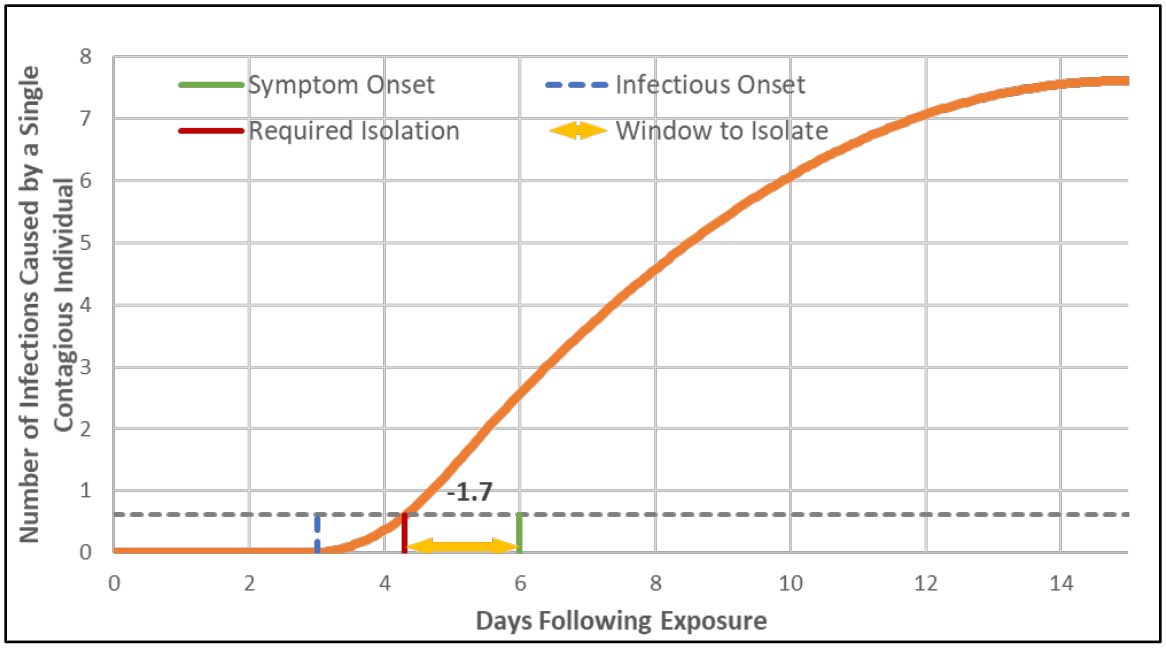

Figure 5. Mean Time Window for Isolation of Symptomatic Cases of COVID-19, Assuming Asymptomatic Transmission is Uncontrolled (Base-Case Parameter Values)

As seen in Figure 5, when we consider an isolation regime that only applies to symptomatic cases of COVID-19, the situation becomes even more dire: the time window for isolation changes from 1.1 days prior to symptom onset to 1.7 days prior to symptom onset. Note, too, that the dotted line on the y-axis has changed as well: instead of reducing average transmission from each symptomatic case to less than one other individual, average transmission must be reduced to less than 0.6 others. Recall that we have assumed that 30% of COVID-19 cases are asymptomatic, and each of these transmits disease at a rate of 25% of that of symptomatic cases. This means that each symptomatic case will, on average, generate more than 5.9 secondary cases, while asymptomatic cases will, on average, generate fewer than 5.9 cases. In fact, given our base case characterization of asymptomatic cases, the R_0 for the 70% of cases that are symptomatic is 7.6 and the R_0 for the 30% of cases that are asymptomatic is 1.9. Now, isolation of symptomatic cases becomes more challenging both because the cumulative number of secondary cases progresses faster with the higher R_0 for symptomatic cases, and because isolation of these cases needs to make up for the inability to isolate asymptomatic cases.

Table 3 provides the maximum time window for isolation, for our base-case and all excursions, when isolation is triggered by symptom onset and only applies to symptomatic cases.

Table 3. Maximum Time Window for Isolation of COVID-19 Cases (Triggered by Symptoms and Restricted to Symptomatic Cases)

R_0 Value	Time of Peak Transmission	Isolation Window (Days)
5.9	1 Day before Symptoms	-1.7*
5.9	At Symptom Onset	-1.4*
2.5	1 Day before Symptoms	0.0
2.5	At Symptom Onset	0.4

*A negative isolation window indicates that individuals would need to be isolated *prior* to symptom onset.

Finally, we also postulated an excursion where 70% of cases are asymptomatic (as compared to 30%), to reflect some evidence that the rates of asymptomatic infection are substantially higher in healthy young adults, the population of greatest interest in a military context. For the excursion R_0 value of 2.5, the window of isolation for the 30% of cases that would be symptomatic is at three days after exposure, and two days prior to symptom onset. At the base-case R_0 of 5.9, asymptomatic transmission alone can perpetuate an outbreak and there is no time at which isolation of symptomatic infections can be effective.

Given that the early symptoms of COVID-19 are generally very mild and non-specific, individuals may not promptly notice the onset of symptoms, and it is unlikely that all such cases will isolate immediately. In combination with the negative or—in the best possible circumstances, very short—window for isolation, we believe that isolation triggered by symptom onset ("if you are sick, stay home") cannot, in itself, effectively control outbreaks of COVID-19. Since this is true even if 100% of symptomatic cases are isolated, we did not at this point consider the impact of only isolation a portion of symptomatic individuals. This led us to consider whether isolation triggered by some other means, such as testing, could be a more effective approach. We also considered the potential value of quarantine as a means of complementing isolation. Before pursuing these avenues of investigation, however, we wanted to consider the potential for vaccines and isolation to be used in combination to control outbreaks of COVID-19.

3. Vaccines and Isolation in Combination

Given both the challenges that COVID-19 poses for isolation, and the need for high levels of vaccine compliance, we considered the extent to which these tools could be used together to effectively control outbreaks. Specifically, we wanted to determine what vaccine compliance would need to be, for base-case and excursion values of vaccine effectiveness and R_0, if we assumed that all symptomatic cases would be isolated at symptom onset, or at one or two days thereafter.

Our analytical approach can readily be adapted to account for combinations of response measures. Given two response measures A and B, the average number of new infections per contagious individual, R_{AB}, is calculated as

$$R_{AB} = f_B(x_1, x_2, \ldots x_n)R_A, \quad (12)$$

where f_B is the reduction in transmission due to response measure B and R_A is the average number of new infections per contagious individual given the presence of response A. The equation above is of the same form as Equation 6, however, instead of scaling transmission from the unmitigated rate, R_0, transmission is scaled from the rate if only response A is implemented, R_A.

For the consideration of vaccines and isolation in combination, the equation above becomes

$$R_{Iso+V} = f_V(\epsilon_V, \rho_V) R_{Iso} \tag{13}$$

$$R_{Iso+V} = \left(1 - (\epsilon_V \times \rho_V)\right)\left[(1 - \epsilon_{Iso})R_0 + \epsilon_{\text{Iso}} \int_0^{D_{Iso}} g(t)dt\right]. \tag{14}$$

The range of values of ϵ_V, ρ_V, ϵ_{Iso}, and D_{Iso} that result in $R_{Iso+V} < 1$ represent a combined response of vaccination and isolation that will cause an outbreak of COVID-19 to wane.

Figure 6 illustrates the relationship between COVID-19 vaccine effectiveness and vaccine compliance given no isolation (solid lines) and isolation of symptomatic cases immediately upon symptom onset (dashed lines) for both the base (blue) and excursion values (orange) of R_0. Again, the regions above and to the right of the curves represent the combinations of vaccine effectiveness and compliance that are required to control an outbreak.

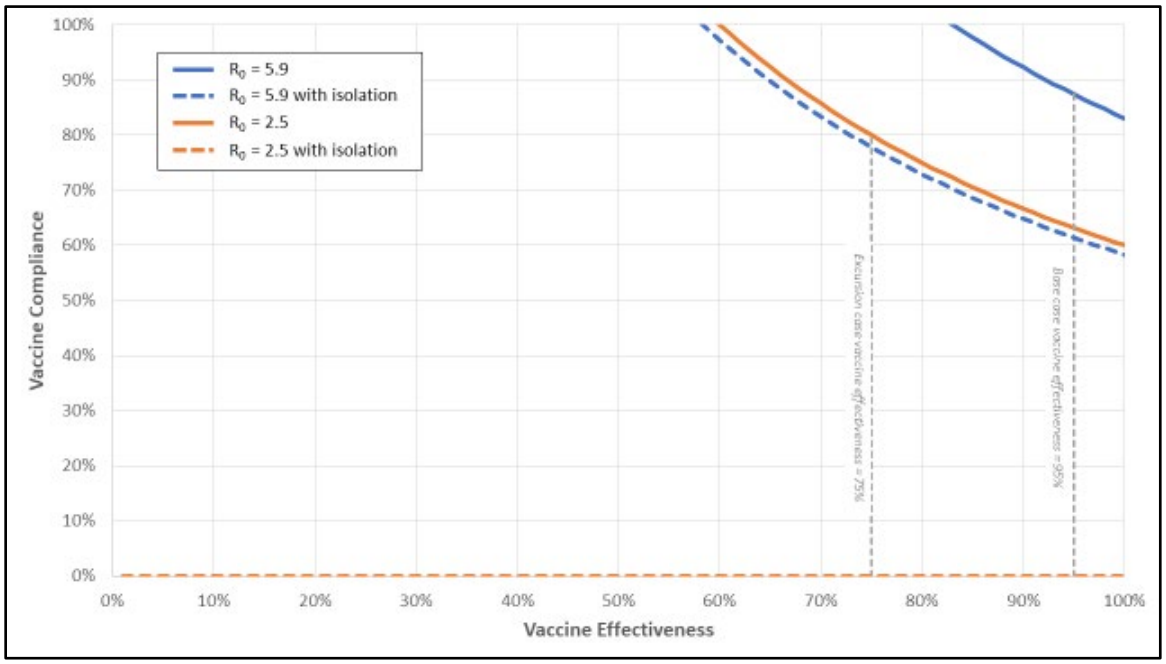

Figure 6. Impact of Isolation of Symptomatic Cases at Symptom Onset on the Relationship between Vaccine Effectiveness and Compliance

As discussed previously, at our base-case vaccine effectiveness of 95%, for vaccination alone to effectively control an outbreak compliance needed to be 87% for an R_0 value of 5.9; with the addition of immediate isolation of symptomatic cases, the required compliance rate falls to 61%. For an R_0 of 2.5, isolation at the time of symptom onset is itself sufficient and vaccines are unnecessary to control the outbreak. Therefore, all combinations of vaccine effectiveness and compliance are adequate.

However, as we have noted, isolation at symptom onset is very unlikely given the mild, non-specific symptoms experienced early in the course of COVID-19. Consequently, we tested the impact of isolation on the relationship between vaccine effectiveness and compliance, when isolation is implemented with delays of one and two days after the onset of symptoms. The resulting curves depicting this relationship are shown in Figure 7.

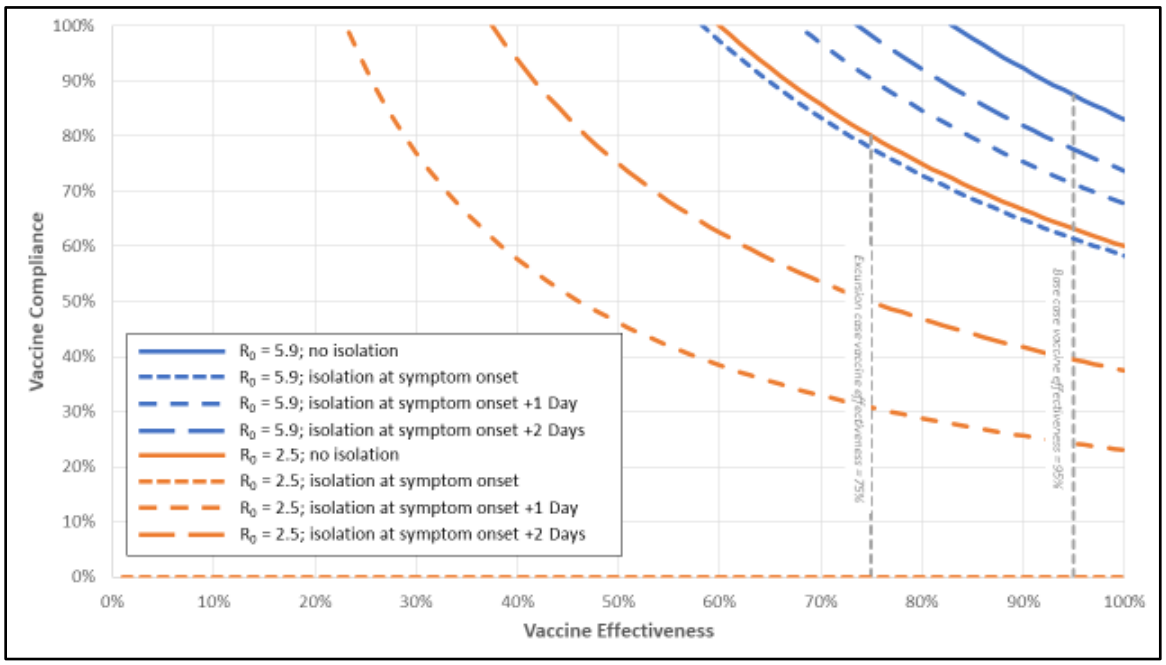

Figure 7. Impact of Delayed Isolation on the Relationship between Vaccine Effectiveness and Compliance

As seen in Figure 7, isolation can indeed have a significant impact on the extent of vaccine compliance required to control an outbreak: when $R_0 = 5.9$, we found that isolation of individuals at symptom onset can substitute for roughly 35 percentage points of vaccine compliance, regardless of vaccine effectiveness. Nonetheless, even given a very high 95% vaccine effectiveness and with the addition of isolation, vaccine compliance rates would still need to be quite high for the outbreak to wane. Should the effectiveness of COVID-19 vaccines fall to 75%, the compliance rates required to end the outbreak could well prove difficult to achieve in a population lacking compulsory vaccination.

Yet, there is room for optimism: together, vaccines and isolation triggered by symptoms can cause an outbreak of COVID-19 to wane in all combinations of parameter values considered in this analysis; this was not the case for either vaccination or isolation alone. Over time, infections among the unvaccinated population can reduce the size of the susceptible population to some extent, which in turn will suppress transmission and lead to a reduction in R. Perhaps most importantly, while vaccination and isolation are durable, continuing mechanisms for controlling the spread of disease, they are not the only available tools. In the remainder of this analysis, we investigate the potential value of COVID-19 testing as an alternative trigger for isolation, as well as the use of quarantine to compensate when isolation is not immediate or all-encompassing.

4. Diagnostic Testing as a Trigger for Isolation

As discussed earlier in this analysis, transmission from individuals after the onset of symptoms accounts for only about 60% of total COVID-19 transmissions. Isolation triggered by onset of symptoms will not truncate transmission from asymptomatic individuals, nor from symptomatic individuals during their pre-symptomatic contagious period. Consequently, isolation triggered by symptom onset will not, on its own, be sufficient to cause an outbreak of COVID-19 to wane; our calculated window of opportunity for isolation ranges from 1.7 days prior to symptom onset to 0.4 days after symptom onset, assuming everyone who becomes symptomatic is isolated (Table 3). We have also found that, in combination with vaccination, isolation triggered by symptom onset can be effective. Yet, for our base-case R_0 value of 5.9, the effectiveness of isolation relies on both high rates of vaccine compliance and isolation of all symptomatic cases within one day of symptom onset.

These observations led us to assess the benefit of diagnostic testing as a means of identifying individuals with asymptomatic and pre-symptomatic COVID-19 infections, and thus serving as a second trigger for isolation. We began by looking at the change in vaccine compliance needed when isolation can occur prior to symptom onset, shown in Figure 8. In this case, we considered isolation of both asymptomatic and symptomatic cases relative to the time of exposure. We also assumed that 100% of the contagious population would be isolated.

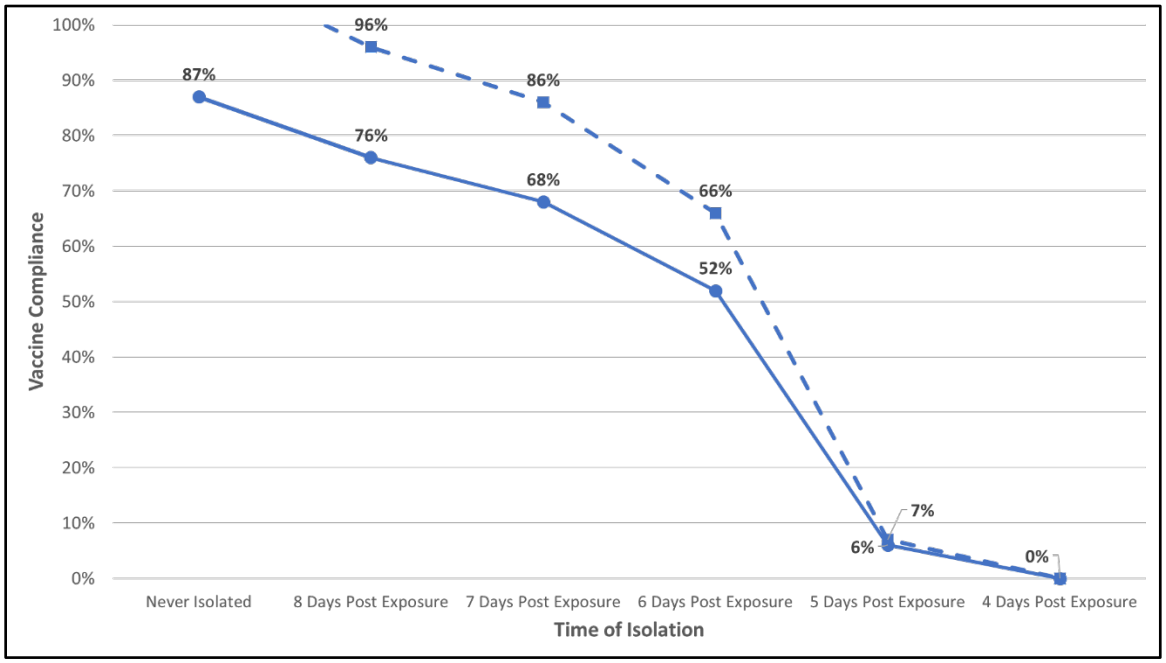

Figure 8. Vaccine Compliance Needed When Isolation Can Occur Before Symptom Onset (6 Days Post Exposure), R_0 = 5.9 for vaccine effectiveness of 95% (solid) and 75% (dashed)

For our base-case vaccine effectiveness of 95%, at the mean time of symptom onset—six days post-exposure—the vaccine compliance needed to achieve $R < 1$ falls to 52% when both symptomatic and asymptomatic cases are isolated by this time, compared to a 61% compliance rate needed (Figure 7) when only symptomatic cases are isolated. Similarly, for a vaccine effectiveness of 75%, needed compliance falls from 78% to 66%. If isolation can occur even

earlier, the magnitude of the benefit, measured in terms of reduction in required vaccine compliance, would be even greater.

Having observed and characterized the benefit of isolating asymptomatic and pre-symptomatic individuals, we then sought to determine the potential role of diagnostic testing as a means of realizing this benefit. More specifically, we characterized the relationship between vaccine compliance and frequency of testing to determine the circumstances in which a testing regime provides benefit in the reduction of R, and the frequency with which testing must occur to achieve $R < 1$. To do so, we developed a simple stochastic model.

The stochastic model simulates the disease progression of single individuals—it does not simulate the transmission of disease from one person to another. All individuals are subject to testing at randomly determined times relative to their exposure and the timing of positive test results dictate when that individual is isolated. The total number of new infections caused per individual is determined based on how long they were contagious prior to isolation. A large number of (10,000) individuals are simulated and the average number of new infections is calculated. Additional technical details and assumptions are discussed as follows.

All individuals are randomly characterized as belonging to one of two cohorts: asymptomatic or symptomatic. The classification of an individual as being either asymptomatic or symptomatic is randomly determined, however once classified, their disease progression is deterministic and follows the transmission profiles shown in Figure 1. In other words, all asymptomatic individuals have an identical disease progression and similarly, all symptomatic individuals have an identical disease progression. We did not consider variability of the duration of the various disease stages. The expected number of new infections caused by an individual is equal to the area under the corresponding transmission profile (Figure 1) up to the point they are isolated. The actual number of new infections is determined by a Poisson distribution parameterized by the individual's expected number of new infections. Testing occurs with a user-specified frequency that is randomly offset from the time of exposure for each individual.

As shown in Figure 9, isolation of asymptomatic individuals could only be triggered by a positive test, while isolation of symptomatic individuals could be triggered by either a positive test or onset of symptoms, whichever happened first. To assess the potential contribution of testing in the best possible light, we used optimistic assumptions about test performance and isolation:

- All individuals are subject to diagnostic testing,
- 100% of tests were positive when administered during the contagious period, and 100% negative when administered outside the contagious period, and
- Test results were available without delay; and individuals were isolated immediately upon either a positive test result or onset of symptoms.

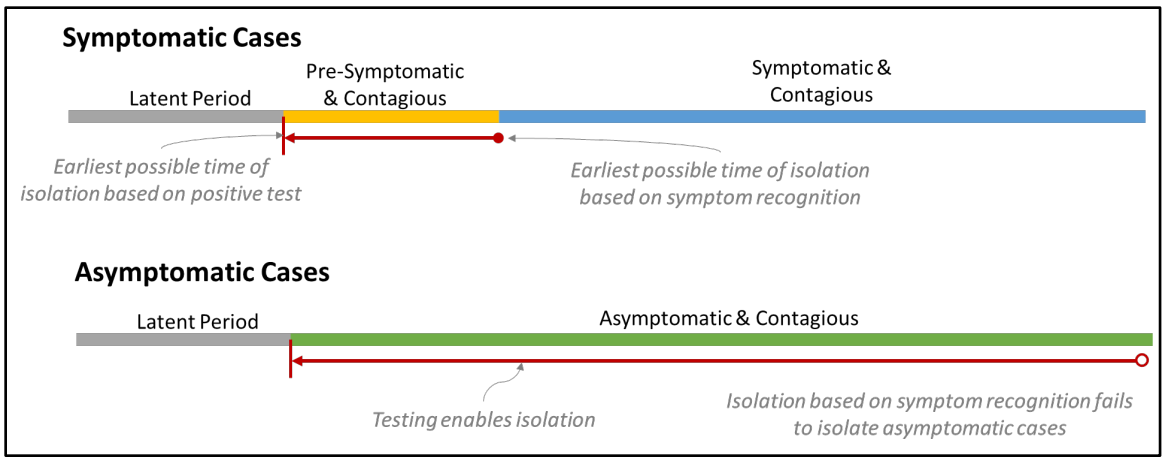

Figure 9. Diagnostic Testing Simulation Approach to Isolation of Symptomatic and Asymptomatic Cases of COVID-19

Figure 10 shows the results of our simulation as the relationship between testing frequency and required vaccine compliance, for vaccine efficacies of 95% and 75% and R_0 = 5.9. As the figure shows, testing provides a benefit when vaccine compliance rates drop below 61% or 75% for vaccines with an effectiveness of 95% and 75% respectively. At compliance rates above these values, the combination of vaccination and isolation at symptom onset is adequate to control outbreaks. At compliance rates below these values, once test frequency exceeds approximately 20 days, the marginal benefit quickly declines; at test frequencies of less than three days isolation alone will be an effective response. Between these two boundaries, at intervals ranging from three days to 20 days, diagnostic testing as a trigger for isolation can successfully push R below 1, even at relatively low rates of vaccine compliance.

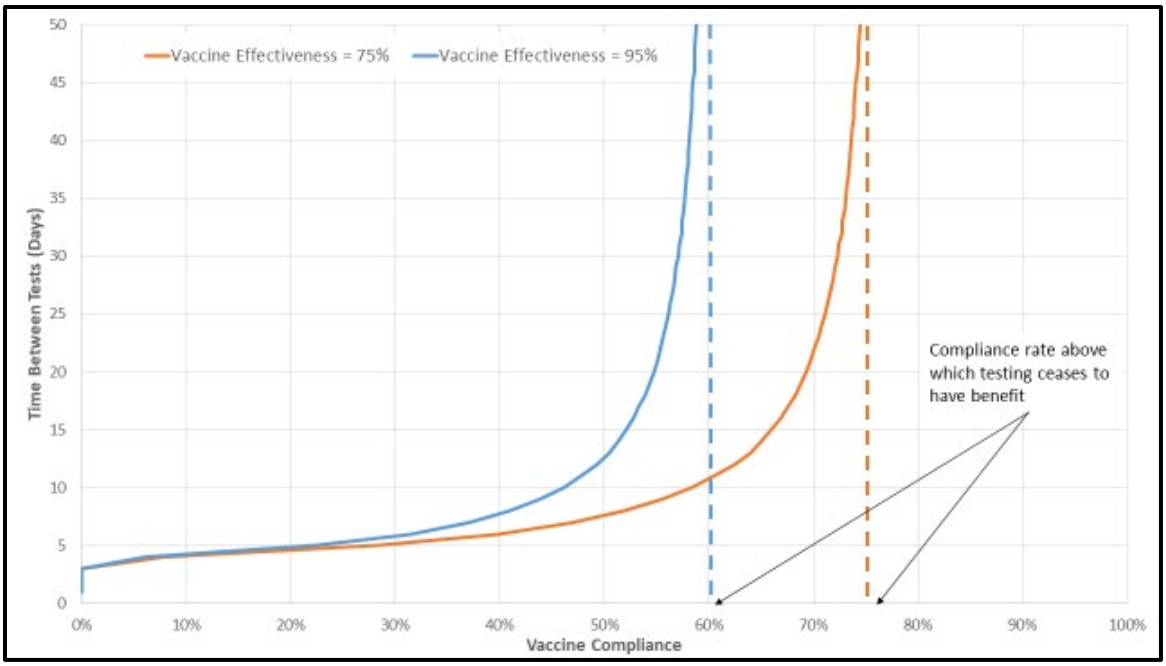

Figure 10. Frequency of Testing Needed to Trigger Isolation and Cause $R < 1$, Given Vaccine Compliance Rates, $R_0 = 5.9$

Point estimates of the vaccine compliance needed, given selected testing frequencies, are provided in Table 4 for our base-case R_0 of 5.9. In our simulation, testing every 14 days resulted in an average time to isolation of 6.9 days post-exposure for the population of contagious individuals—symptomatic and asymptomatic. Testing every seven days or every three days resulted in an average time to isolation of 5.7 days or 4.5 days post-exposure, respectively. Consequently, the addition of diagnostic testing to vaccination and isolation can reduce vaccine compliance rates significantly: by approximately 10% if conducted every two weeks, and by 20-25% if conducted weekly. Testing every three days could nearly eliminate the requirement for vaccination and make isolation alone an effective means of outbreak control.

Table 4. Impact of Diagnostic Testing on Vaccine Compliance Needed to Achieve $R < 0$

Testing Frequency	Compliance Needed if Vaccine Effectiveness = 95%	Compliance Needed if Vaccine Effectiveness = 75%
None	61%	75%
14 days	52%	66%
7 days	41%	52%
3 days	6%	8%

Assessing the feasibility of such a diagnostic testing regime is beyond the scope of our current work. Early in the pandemic, however, COVID-19 diagnostic testing was not widely available and used collection and analytical methods that would have been expensive and onerous to implement on the scale assumed here, and with the speed required. However, as rapid, inexpensive, self-administered antigen test kits continue to become more readily available, diagnostic testing could become a more practical solution. It could, for example, be used within specific populations, such

as military recruits, to help identify and isolate asymptomatic and pre-symptomatic cases of disease should local surges in COVID-19 cases occur.

5. Quarantine in Combination with Isolation and Vaccination

As an alternative to diagnostic testing, we assessed the potential for quarantine to limit asymptomatic and pre-symptomatic transmission of disease when used in concert with vaccination and symptom-triggered isolation. Quarantine is the segregation of healthy but potentially exposed individuals from the remainder of the healthy population until it can be determined that the segregated individuals are free of infection. The purpose of quarantine is to promote rapid identification and isolation of contagious individuals, from the onset of their contagious period to the time at which they are isolated. The necessary duration of quarantine is determined by the incubation period of the disease, and individuals in quarantine would typically be subject to active, continued health monitoring by medical personnel (*ATP 4-02.84 2019*).

Quarantine augments isolation in a number of ways. Individuals in quarantine will already be separated from the susceptible population when they become symptomatic, so there is no transmission caused by delays in isolation. For COVID-19, if quarantine is implemented promptly, and individuals are quarantined before the end of the latent period, pre-symptomatic transmission will also be constrained. At the same time, quarantine is likely to capture some fraction of asymptomatic cases, and prevent them from contributing to onward transmission. If individuals in quarantine are regularly tested, asymptomatic and pre-symptomatic cases can be detected early and promptly isolated, not just from the general population but from those with whom they may be quarantined, further constraining transmission of disease.

The IDA team analyzed the effectiveness of quarantine in combination with isolation using a method similar to how we analyzed isolation in combination with vaccinations. First, we defined the function $f_Q(\epsilon_Q)$ that describes the reduction in disease transmission due to some fraction of the infected individuals, ϵ_Q, being quarantined and subsequently isolated, thus eliminating their opportunity to spread disease. We assumed that quarantine is capable of completely preventing transmission from those quarantined. Therefore, while individuals who are not quarantined will generate R_0 new infections, only those who are not subsequently quarantined will further propagate the outbreak. That is, $f_Q(\epsilon_Q) = 1 - \epsilon_Q$, and $R_Q = (1 - \epsilon_Q)R_0$.

Given the function form of f_Q, the next step was to consider quarantine and isolation in combination. We assume that only the contacts of isolated individuals will be quarantined. Individuals who are never isolated are assumed to have unmitigated transmission. Therefore, to account for the combined effect of quarantine and isolation, we simply scale the average number of new infections caused per isolated individual by f_Q. The average number of new infections per contagious person given some quarantine and isolation regime is

$$R_{Iso+Q} = (1 - \epsilon_{Iso})R_0 + (1 - \epsilon_Q)\epsilon_{\text{Iso}} \int_0^{D_{Iso}} g(t)dt. \qquad (15)$$

We then extended the above equation to account for vaccination to allow us to assess the effectiveness of all three response measures in combination. To do this, we simply scale R_{Iso+Q} by f_V. The resulting expression for the average number of new infections per contagious individual given vaccination, isolation, and quarantine is

$$R_{Iso+Q+V} = (1-\epsilon_V)\left[(1-\epsilon_{Iso})R_0 + (1-\epsilon_Q)\epsilon_{\text{Iso}}\int_0^{D_{Iso}} g(t)dt\right]. \qquad (16)$$

One major question is how to achieve a given level of quarantine effectiveness in time to realize its potential benefit. Contact tracing is labor-intensive and can be time-consuming; although we have assumed that contacts would be quarantined immediately upon identification of an index case, in practical terms this process would take several days if done on an individual basis (*Keeling, Hollingsworth, and Read 2020*), and can quickly be overwhelmed in a large outbreak.

However, given that the mean latent period of COVID-19 is three days there is considerable urgency in identifying and quarantining incubating infections if we are to avoid further transmission. This led us to explore whether contacts could be broadly grouped based on the risk of acquiring disease from an index case; if so, quarantine strategies could be adopted that relied on some simple rules for identifying individuals likely to have been exposed.

Our exploration of characterizing infection risk by contact type centered on a study published by the Ministry of Health of Singapore in March 2021. Officials there conducted a large-scale retrospective cohort study of all close contacts of confirmed COVID-19 cases in Singapore, identified between January 23 and April 3, 2020 (*Ng et al 2021*). During the study period, cases of COVID-19 were confirmed via PCR in 105 household contacts, in 30 work close contacts, and in 45 social close contacts. Based on the serology data collected, however, the authors estimated that the symptom-based testing strategy in place in Singapore missed 62% of COVID-19 infections, and that the overall prevalence of asymptomatic infections was 36%. Using a Bayesian inference model to account for test sensitivities and participation in serological testing, the authors further estimated the rate of secondary infection to be 11%, 4%, and 5% among household, work, and social contacts respectively.

Using the Singapore data set, we calculated the percentage of transmission that occurred within each of the three identified contact groups: household, work, and social. Given that Singapore officials observed few infections outside these groups, we postulate here that they collectively account for all expected secondary infections. The results are shown in Table 5.

Table 5. Estimated Fraction of Secondary Transmission by Contact Group Based on Singapore Dataset (*Ng et al 2021*)

Contact Type	Number in Cohort	Estimated Number of Cases	Estimated Attack Rate	Fraction of Total Cases
Household	1,779	196	11%	43%
Work	2,231	89	4%	19%
Social	3,508	175	5%	38%
Total	7,518	460	6%	100%

Using the information provided in Table 5, we considered an approach to increase the efficiency of quarantine by limiting it, where possible, to contact groups that would truncate the required fraction of transmission by quarantining the fewest possible number of contacts. This approach is illustrated in Figure 12. In that figure, each point in the plot represents either a single category of contacts (e.g., household) or a combination of the categories (e.g., household and

work). The horizontal axis represents the portion of all contacts contained within a given group or combined groups. The vertical axis represents the proportion of all transmission that occurred in the group. The dashed line represents a 1:1 relationship between contacts and transmission. The points above the dashed line have proportionately more transmission per contact and the points below the line have proportionately less transmission per contact. To truncate a defined portion of transmission, one would begin by quarantining household contacts, then add on work, social, and finally, all contacts until the requirement had been met. Contact groups would be added to quarantine based on the slope of the line associated with each point in decreasing order.

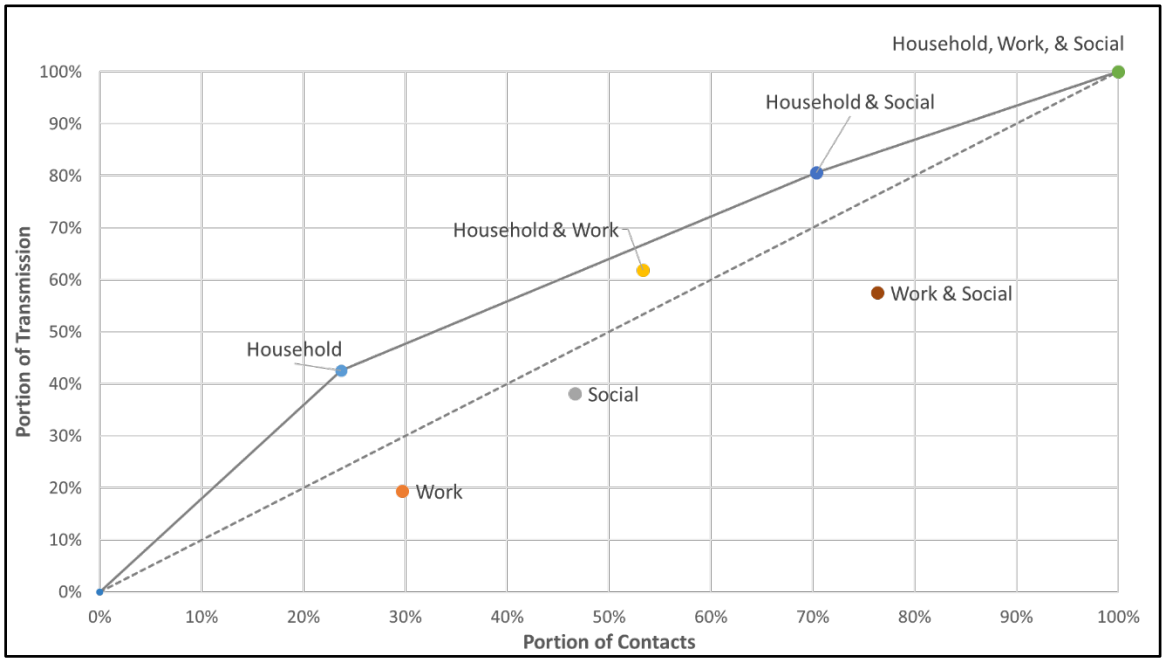

Figure 11. Percentage of Contacts that Must Be Quarantined to Avoid a Given Portion of Transmission

The approach to quarantine demonstrated here could be readily extended to other nations and populations, such as military units. The attack rates by contact group type are based on a variety of COVID-19 risk factors associated with membership in those groups (e.g. talking, shared meals, shared sleeping space). The proportion of contacts in each group are likely to vary to some extent by place, due to both cultural and economic factors, and by time, due to the existence of other mitigation measures such as business closures or limits on social gatherings.

In sum, to achieve required values for the parameter ϵ_Q (the fraction of the infected individuals in quarantine):

- For values up to 43%, quarantine can be limited to household contacts only;
- For values between 43% and 62%, quarantine should encompass household and work contacts;
- For values between 62% and 81%, quarantine should encompass household and social contacts; and

- For values greater than 81%, quarantine should encompass all close contact groups.

It is worth reiterating that the values presented above are directly tied to the epidemiological circumstances in Singapore during the time of the study and may not represent COVID-19 outbreaks in populations with different behaviors. We use these values as examples to illustrate the use of our methodology.

We assessed the potential value of quarantine when used in conjunction with vaccination and isolation of symptomatic cases. Here, we considered quarantine as a means of overcoming some of the limitation of isolation due to pre-symptomatic and asymptomatic transmission, akin to our consideration of diagnostic testing in earlier sections of this analysis. As in that earlier discussion, we defined the benefit of quarantine in terms of vaccine compliance. Again, we assume that all symptomatic individuals are isolated at the defined time, that contacts of symptomatic individuals are quarantined before they can transmit disease, and that contacts of asymptomatic cases are never quarantined. The relationship between quarantine effectiveness and vaccine compliance is shown in Figure 12 for $R_0 = 5.9$.

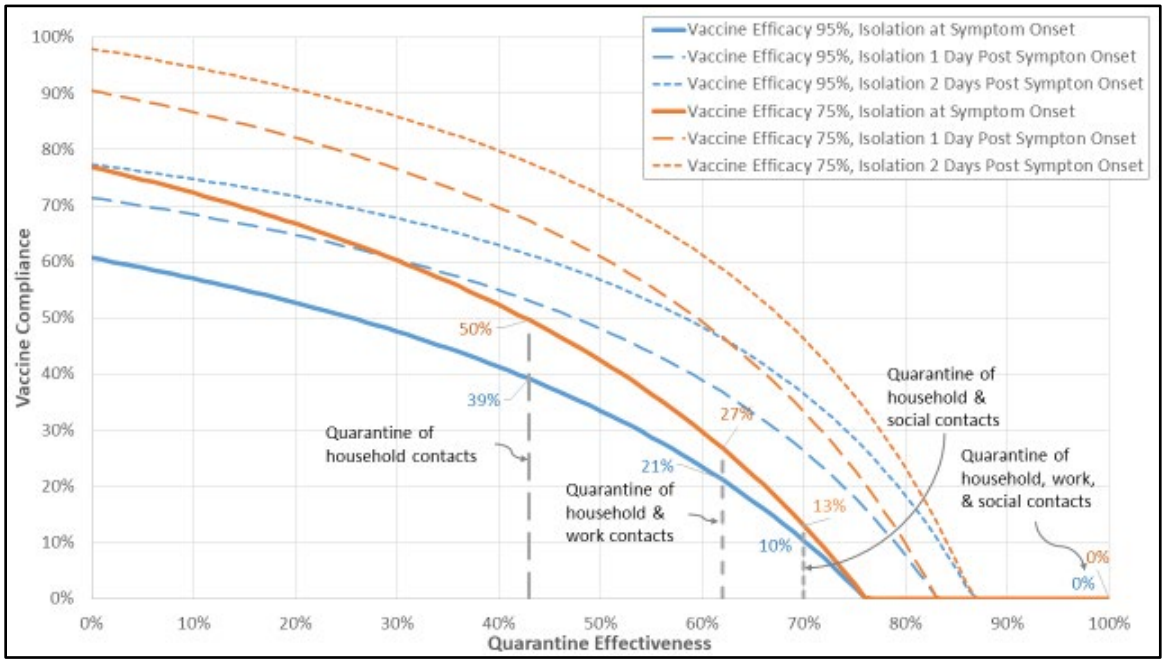

Figure 12. Relationship between Required Vaccine Compliance and Quarantine Effectiveness, Given Isolation of Symptomatic Individuals Only

We found that for both our base-case and excursion values for vaccine effectiveness, at compliance rates of 50% or higher, quarantine of household contacts is sufficient to achieve $R < 1$ when symptomatic cases are isolated at onset of symptoms. If isolation is delayed, however, quarantine must be extended to additional groups to compensate: for isolation at one day post-symptom onset, household and work contacts must be quarantined, and for isolation at two days post-symptom onset, household and social contacts must be quarantined. Alternatively, if quarantine is limited to household contacts and isolation occurs two days post-symptom onset, vaccine compliance rates must increase to 60% or 75%, depending on vaccine effectiveness.

E. Results: Outbreak Control Measure Combinations that Achieve $R < 1$ for COVID-19 Given Prevailing Rates and Effectiveness of Vaccination

This paper discusses the influence of vaccine compliance and vaccine effectiveness on the feasibility of successfully implementing three types of COVID-19 outbreak control measures: medical countermeasures, isolation, and quarantine. The results of our analysis are depicted in Figure 13, which shows the combinations of outbreak control measures that can result in $R < 1$ for a given combination of vaccine effectiveness and compliance. The curves in the figure bound the regions of the plot areas in which the specified combination of control measures will be successful: the combinations of vaccine effectiveness and compliance above and to the right of the curve will result in R < 1, those below and to the left of the curve will not.

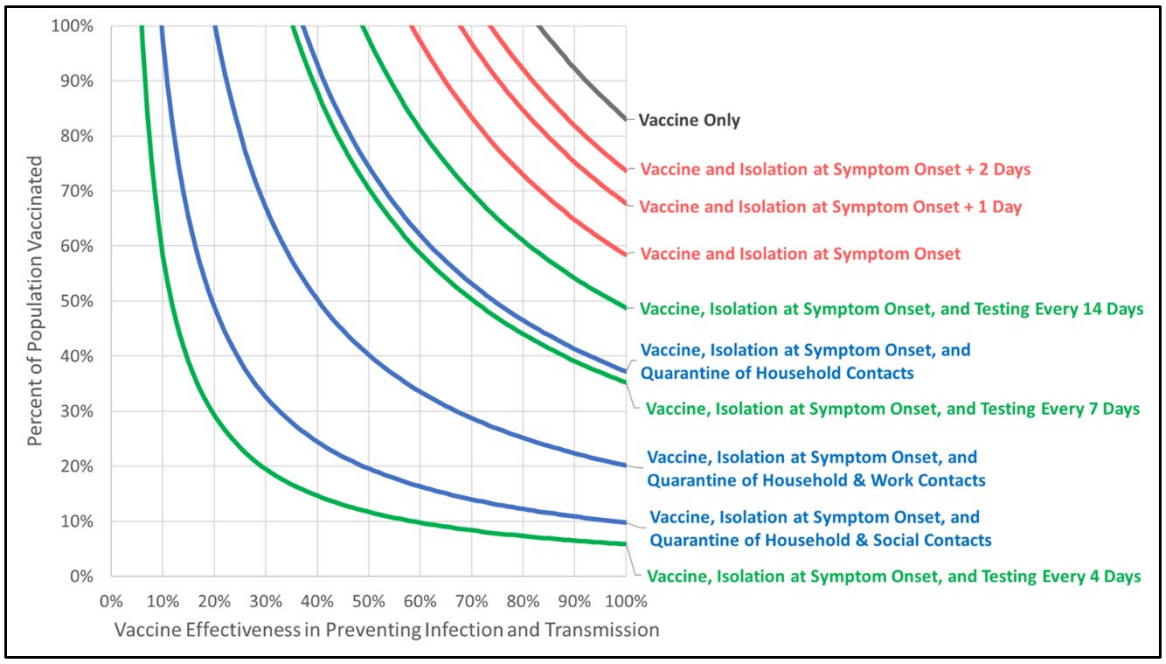

Figure 13. Outbreak Control Measures Needed to Achieve $R < 1$ for All Combinations of Vaccine Effectiveness and Vaccine Compliance

For COVID-19, the region of the plot area in which vaccination alone can achieve $R < 1$ is very small. Our COVID-19 base-case R_0 of 5.9 is quite high relative to other diseases, and therefore so too is the combination of vaccine effectiveness and vaccine compliance required to control an outbreak. As the black curve in Figure 13 shows, the vaccine effectiveness required is 83% when compliance is universal. As compliance falls below 100%, effectiveness needs to increase, and at a certain point, even completely effective vaccines would fail to control outbreaks.

As we incorporate additional and more effective control measures into outbreak response, however, the region of benefit in the plot area grows larger and larger. Outbreaks can be controlled despite less effective vaccinations, or with a smaller fraction of the population vaccinated.

The first set of such control measures shown in Figure 13 involve the isolation of symptomatic individuals within a defined period of time from symptom onset. We found that isolation of symptomatic individuals can indeed have a significant impact on the extent of vaccine

compliance required to control an outbreak: for example, isolation of individuals at the time of symptom onset can substitute for approximately 25 percentage points of vaccine compliance. Even so, the region of benefit for vaccination plus isolation remains small. Moreover, immediate isolation is very unlikely given the mild, non-specific symptoms experienced early in the course of COVID-19. As isolation is delayed one or two days from onset of symptoms, the benefit over vaccination alone is significantly reduced.

For COVID-19, the limitations on isolation as a response measure are driven by the degree of pre-symptomatic and asymptomatic transmission. We have estimated that transmission from individuals after onset of symptoms accounts for only about 60% of total COVID-19 transmission. This led us to consider whether diagnostic testing might be useful as a means of identifying individuals with asymptomatic and pre-symptomatic COVID-19 infections, and serve as an additional trigger for isolation. We explored testing regimes in which everyone in the population is tested every four days, every week, or every two weeks, under the optimistic assumptions that every test is 100% accurate and immediate. Our assessment showed that the addition of diagnostic testing to vaccination and isolation can reduce the required vaccine compliance rates by approximately 10% if conducted every two weeks, and by 20-25% if conducted weekly. Testing every three days could nearly eliminate the requirement for vaccination, and would allow outbreaks to be controlled solely through isolation.

Finally, we assessed the potential for quarantine to limit asymptomatic and pre-symptomatic transmission of disease when used in concert with vaccination and symptom-triggered isolation. One major question we considered is how to achieve a given level of quarantine effectiveness in time to realize its potential benefit. Based on comprehensive contact-tracing studies, we propose that quarantine can be expedited if the population at risk of exposure is parsed into three main contact groups: household contacts, work contacts, and social contacts. Quarantine would be limited, where possible, to contact groups that would truncate the required fraction of transmission by quarantining the fewest possible number of contacts.

We found that for both our base-case and excursion values for vaccine effectiveness, 95% and 75% respectively, at compliance rates of 50% or higher, quarantine of household contacts is sufficient to achieve $R < 1$ when symptomatic cases are isolated at onset of symptoms. If isolation is delayed, however, quarantine must be extended to additional groups to compensate: for isolation at one day post-symptom onset, household and work contacts must be quarantined, and for isolation at two days post-symptom onset, household and social contacts must be quarantined. Alternatively, if quarantine is limited to household contacts and isolation occurs two days post-symptom onset, vaccine compliance rates must increase to 60% or 75%, depending on vaccine effectiveness.

The construct of layering outbreak control measures, described in this paper and illustrated in Figure 13, can be used to inform response decisions over the course of a disease outbreak as vaccines are developed and disseminated, and as disease variants continue to emerge and circulate to challenge the effectiveness of those vaccines. At the time we completed this work (*Burr et al 2021*), the Delta variant was just beginning to become the dominant strain of COVID-19 in the United States. Prior to that time, approximately 45% of the population was vaccinated and the vaccine appeared to be approximately 95% effective at preventing infection. This meant that control measure combinations would need to include testing or quarantine to effectively cause the outbreak to wane. While vaccine effectiveness against the Delta variant—measured as protection against infection—appeared to be less than that of early variants, the fraction of the population that

was vaccinated grew. While the point on the plot associated with the new combination of vaccine compliance and effectiveness shifted upwards and to the left, the combinations of control measures that would be effective remained the same.

We can envision an ongoing cycle wherein vaccine effectiveness repeatedly declines and is restored. The construct shown in Figure 13 can be used to determine which outbreak control measures should be added when vaccine effectiveness declines, and they can also be used to determined which measures can be removed as either vaccine compliance or vaccine effectiveness increase.

F. Conclusions

The unique characteristics of COVID-19 present significant but not insurmountable challenges to the implementation of effective outbreak control measures. Given the disease's high level of contagiousness, prevalence of transmission from non-symptomatic individuals, and the continuing emergence of new variants; vaccination alone may be inadequate to control outbreaks. Instead, a layered combination of response measure is needed. Here, we demonstrate that IDA's previously developed analytical methodology for assessing outbreak response measures is able to characterize requirements for isolation, diagnostic testing, and quarantine given prevailing rates of vaccine efficacy and compliance within a population.

The utility of the methodology depends on the availability of accurate information on certain disease characteristics, namely: the contagiousness of the disease, as measured by R_0, and the timing of the contagious period relative to symptom presentation. Additionally, the effectiveness of vaccine at preventing infection and transmission against circulating variants must also be known. While a scientific consensus on these factors was emerging when we completed our analysis, uncertainty persists. However, the flexibility of the methodology presented here enables parametric consideration of multiple possible transmission profiles and levels of vaccine performance.

The successful adaptation of our existing methodology for consideration of COVID-19 response measures suggests the approach may be useful for informing the response to future emerging infectious diseases. However, our analysis highlights the need for laboratory researchers and epidemiologists to rapidly characterize critical attributes of a newly emerging disease. These research efforts should be supplemented by comprehensive case reporting, analysis, and information sharing both across the United States and the global scientific community. Timely access to this information will help ensure efficient response measures that effectively curtail disease spread while not being overly disruptive to the lives or mission of a population.

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H. List of Acronyms

CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus disease 2019
IDA	Institute for Defense Analyses

I. List of Descriptors

Coronavirus disease 2019
COVID-19
disease transmission
contagious disease
outbreak control measures
outbreak response
isolation
quarantine
restrictions of movement
vaccination
vaccine compliance

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14. ABSTRACT

In this document, we discuss the requirements and opportunities for using various measures to control outbreaks of COVID-19, and in particular explore the relationship between vaccine compliance rates in a population and the requirements for implementing other control measures. We begin by developing a profile of mean individual COVID-19 transmission over time, accounting for both pre-symptomatic and asymptomatic transmission, to allow us to determine the impact of timing on control measure effectiveness. We consider a layered use of control measures, beginning with vaccination and adding isolation, triggered by either symptom onset or as a result of diagnostic testing, and finally quarantine. Our work shows that COVID-19 outbreaks cannot be controlled solely through isolation of symptomatic individuals, given the high transmissibility of COVID-19 combined with asymptomatic and pre-symptomatic transmission. Vaccines can overcome this challenge if they are sufficiently effective, and if compliance rates are sufficiently high. Yet, if vaccine compliance rates remain low in certain regions, or if the effectiveness of vaccines is compromised by the emergence of variants, transmission of COVID-19 may continue or even increase. Should that be the case, our assessment shows that—assuming prompt isolation of symptomatic individuals continues—implementation of quarantine and/or population-wide diagnostic testing can cause an outbreak to wane.

15. SUBJECT TERMS

COVID-19, vaccine effectiveness, vaccination, compliance, outbreak control, outbreak response, isolation, quarantine

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