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Implementing COVID-19 Outbreak Control Measures: Disease-specific Requirements

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Executive Summary

In early 2020, just as the COVID-19 pandemic began, the Institute for Defense Analyses (IDA) published research that provided an analytical foundation for implementing measures to respond to outbreaks of contagious disease in an operational environment.[1] IDA researchers assessed the effect of response measures by the extent to which they collectively shifted disease transmission from R_0, defined as the mean number of infections that would be caused by an infected individual in an entirely susceptible population, to a lower value R, the mean number of infections caused per infected individual given some level of population immunity or control measures. From there, we posited that the primary objective of outbreak control measures is to cause R to fall below one. Once that point is reached, the outbreak will be controlled: the number of new cases will decline over time and the outbreak will wane and eventually end. We then established relationships between a set of disease and response parameters to determine the circumstances in which outbreak control measures can meet our objective, given the characteristics of a disease.

As the pandemic evolved, our IDA research team worked to extend our previous work to outbreaks of COVID-19. We closely monitored the emerging COVID-19 literature, and expanded the underlying methodology to account for unique aspects of this disease that force us to consider execution of control measures in ways not considered in our earlier research. Specifically, because of the extent of asymptomatic and pre-symptomatic transmission of COVID-19, we consider the potential role of diagnostic testing as a trigger for isolation and quarantine. In addition, in our earlier work, we assumed that compliance with vaccination or other pre-exposure prophylaxis would be universal in our population of interest; because we found vaccination to be successful in achieving $R < 1$ for the diseases we included, we did not consider vaccination in combination with other control measures. In our current assessment of COVID-19 control measures, we have added vaccine compliance as a parameter of interest, and developed a concept for assessing a progressively layered set of responses that begins with vaccination.

In this analysis, we discuss the requirements and opportunities for using medical countermeasures (in this case, vaccines), isolation, quarantine, and other forms of restrictions of

[1] Julia K. Burr, Robert L. Cubeta, Lucas A. LaViolet, and Sean M. Oxford, IDA P-10877, *Controlling the Spread of Contagious Disease in an Operational Environment* (Alexandria, VA: Institute for Defense Analyses), February 2020.

movement to control outbreaks of COVID-19. [2] We considered a layered approach, beginning with medical countermeasures and adding isolation, triggered by either symptom onset or as a result of diagnostic testing, and finally quarantine. The work described herein is part of IDA's ongoing program of work investigating operational chemical, biological, radiological, and nuclear (CBRN) medical issues for the U.S. Army Office of the Surgeon General (OTSG). Our body of work is intended to inform military planning and decision-making at the operational level; however, much of our analysis of COVID-19-specific outbreak control requirements is broadly applicable to outbreaks of this disease in any context.

Over the course of this analysis, we have engaged in persistent, ongoing review of the available literature to derive COVID-19-specific values for various parameters of interest. These include:

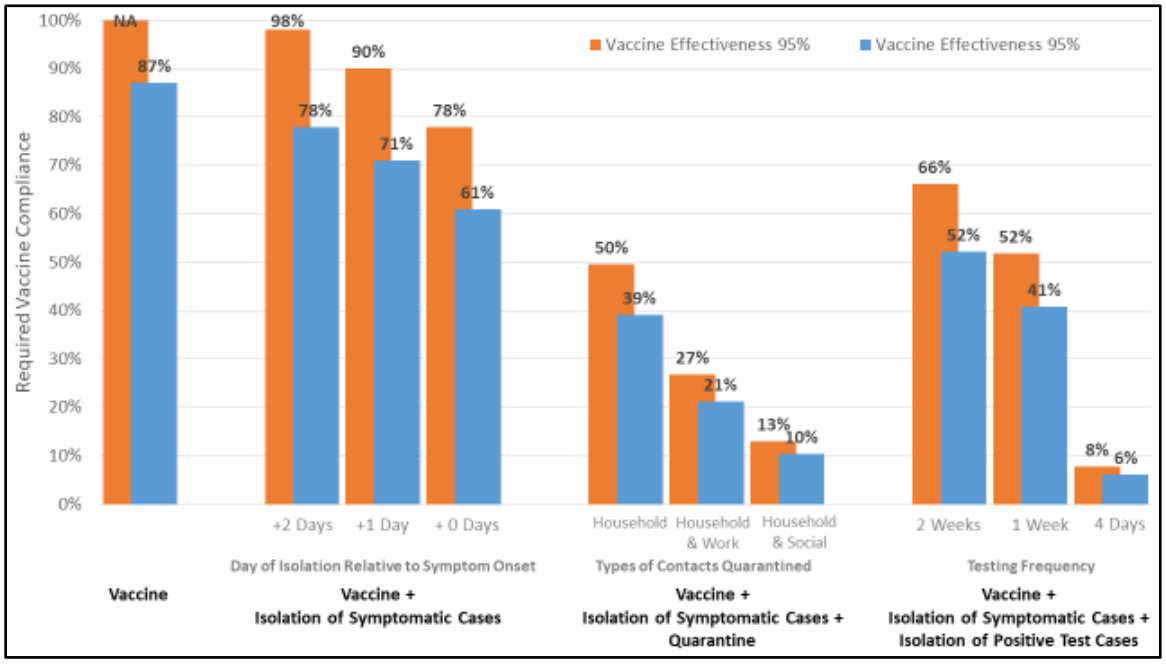
- R_0 = 5.9 (excursion value = 2.5)
- Mean time from exposure to symptom onset = 6 days
- Mean time from exposure to onset of contagiousness = 3 days
- Duration of contagious period = 12 days
- Percentage of asymptomatic cases = 30%
- Relative contagiousness of asymptomatic cases = .25

Our rationale for these parameter values is provided in Appendix A. In combination, they allow us to describe a mean individual profile of COVID-19 transmission over time, and to show when that transmission must be truncated to ensure that, on average, each individual infects less than one other person.

The results of our analysis of outbreak control measures are summarized in the following figure, which shows the rates of vaccine compliance within the population of interest needed to push R below 1, given the implementation of other control measures. These results assume our base-case R_0 where each contagious individual would infect, on average, 5.9 other individuals. Underlying all of these results are the major disease-specific challenges to containing outbreaks of COVID-19: pre-symptomatic transmission, asymptomatic transmission, and a high R_0 value. We estimate that 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

[2] Medical countermeasures are medical interventions—generally, pharmaceuticals—that diminish the susceptibility of personnel exposed to pathogens, or that treat illnesses resulting from such exposure. Isolation is the separation of contagious individuals from the healthy population. Quarantine is the separation of healthy but potentially exposed individuals, until those individuals either become contagious or are determined to be free of infection. For COVID-19, the distinction between these two responses is blurry because the disease is contagious prior to onset of symptoms. Both are forms of restrictions of movement, which could also include measures such as stay-at-home orders, or, in an operational context, limits on the physical contact between military units.

means that 40% of transmission overall cannot be prevented by outbreak control measures, such as isolation, that target sick individuals.



Effectiveness of Various Combinations of Outbreak Control Measures, Given Rate of Vaccine Compliance and R_0 = 5.9

While **vaccination** can be a very effective means of achieving $R < 1$, the vaccine efficacy required to do so is determined by the R_0 of the disease. Our COVID-19 base-case R_0 of 5.9 is quite high relative to other diseases, and therefore so too is the efficacy required for vaccination alone to control an outbreak: assuming universal compliance, the vaccine effectiveness required is 83%. In our base case, COVID-19 vaccines have demonstrated efficacy of 95% against most variants; this means that vaccines alone do indeed have the potential to cause an outbreak to wane. However, a 75% vaccine efficacy—chosen to represent the lower bound of demonstrated efficacy in preventing infection from variants of concern—is insufficient.

As vaccine compliance falls below 100%, an increasing fraction of the population will remain vulnerable to infection. Given a vaccine efficacy of 95%, at least 87% of the population must be vaccinated to control an outbreak. For the excursion vaccine effectiveness of 75%, even 100% compliance will be insufficient.

We found that **isolation of symptomatic individuals in concert with vaccination** will have a significant impact on the extent of vaccine compliance required; isolation of individuals at the time of symptom onset can substitute for approximately 25 percentage points of vaccine compliance. Yet, immediate isolation 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 required vaccine compliance, when isolation is implemented with delays of 24 and 48 hours after

onset of symptoms. Overall, we found that vaccine compliance rates would still need to be quite high for the outbreak to wane, particularly when isolation is delayed. Should the effectiveness of COVID-19 vaccines fall to 75%, the compliance rates required to achieve $R < 1$ (71% for 24 hours delay and 78% for 48 hours delay) could well prove prohibitive.

Next, we explored the utility of two additional measures: a **population-wide diagnostic testing regime** to identify and isolate asymptomatic and pre-symptomatic individuals, and **quarantine of specific contact groups**. We found that either of these measures could effectively augment vaccination and isolation. The use of population-wide diagnostic testing to facilitate isolation can reduce the required vaccine compliance rates by approximately 10% if conducted every two weeks, and by 20-25% if conducted weekly. Population-wide testing every three days could nearly eliminate the requirement for vaccination and make isolation alone an effective means of outbreak control.

Finally, we assessed the potential impact of quarantining rapidly identifiable subsets of individuals, to mitigate the time and labor challenges of detailed contact tracing. We found that at vaccine compliance rates of 50% or higher, quarantine of household contacts is sufficient to control an outbreak 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 1 day post-symptom onset, household and work contacts must be quarantined, and for isolation at 2 days post-symptom onset, household and social contacts must be quarantined. Alternatively, if quarantine is limited to household contacts and isolation occurs 2 days post-symptom onset, vaccine compliance rates must increase to 60% or 75%, depending on vaccine efficacy.

Based on our assessment of measures to control outbreaks of COVID-19, and our review of the available literature, we applaud the DOD's recent decision to mandate vaccination of service members. In addition, we have the following recommendations for OTSG, the Army (and other services), and the Department of Defense (DOD):

- DOD should enforce and execute its vaccine mandate as quickly as possible.
- DOD should continue to promote a culture in which sick individuals self-isolate ("if you're sick, stay home"), and ensure that such individuals have sufficient sick leave and appropriate medical support while in isolation.
- DOD should sustain surveillance of military populations for COVID-19, and ensure prompt reporting and tracking of cases, to include identification and tracking of variant strains within vaccinated and unvaccinated individuals.
- The Army should be prepared to sustain or resume public health measures such as social distancing and mask wearing in the event transmission of COVID-19 begins to increase, either within a particular unit, if the outbreak is localized, or among the Army population more broadly.

- The Army should be prepared to implement quarantine of residents of congregate housing in which cases of COVID-19 have been detected, and support quarantine of service members who are household contacts of identified cases.
- The Army and OTSG should procure and stockpile fast, simple COVID-19 tests that can be rapidly issued, and used as often as every three days to screen for asymptomatic and pre-symptomatic infections in units or organizations in which cases begin to increase.

The primary message of our analysis is that a combination of outbreak response measures can effectively cause COVID-19 outbreaks to wane when vaccine efficacy is 95% and population-wide vaccine compliance rates are perhaps 50-60%. Still, emergence and spread of variants against which vaccines are less effective continues to be a risk. As long as vaccine compliance rates remain low, 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, quarantine and/or testing can be used effectively to truncate transmission. While these measures are more burdensome than vaccination and isolation, they can be implemented in minimally onerous ways, through quarantine of readily identifiable household contacts, or screening tests administered weekly. The latter option in particular may avoid the disruption that comes from quarantine and other forms of restriction of movement.

For COVID-19, our understanding of disease transmission is primarily based on an observed relationship between viral load, as measured by Polymerase Chain Reaction (PCR) testing,[3] and the viability of virus in culture. In particular, this relationship has been used to establish the onset and duration of contagiousness and the role of asymptomatic and pre-symptomatic transmission. Yet, the laboratory work needed to derive this relationship was limited in scope and scale in the early months of the pandemic. In the future, an earlier, more systematic effort to establish a profile of disease transmission over time can support earlier, more effective implementation of outbreak control measures, and perhaps avoid some of the economic and social costs of a pandemic.

[3] PCR is a scientific method for making billions of copies of DNA, to provide sufficient quantities to allow further analysis.

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1. Requirements for the Implementation of COVID-19 Outbreak Control Measures

In early 2020, just as the 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.[4] The analysis documented three basic tenets:

- 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.
- 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.
- Meeting requirements for outbreak control measures will be challenging during military operations; the nature and magnitude of those challenges will vary by type of operation, as will the operational impact of meeting those challenges.

As the pandemic evolved, our IDA research team worked to apply these tenets to outbreaks of COVID-19. 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 continue to review the emerging COVID-19 literature, and have expanded the underlying methodology to account for unique aspects of this disease that force us to consider execution of response measures in ways not considered in our earlier research. Specifically, because of the extent of asymptomatic and pre-symptomatic transmission of COVID-19, we consider the potential role of diagnostic testing as a trigger for isolation and quarantine. We also consider the influence of vaccine compliance on requirements for implementing outbreak control measures we assess.

The results discussed herein are closely tied to our current understanding of this new disease, 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.

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[4] Julia K. Burr, Robert L. Cubeta, Lucas A. LaViolet, and Sean M. Oxford, IDA paper P-10877, *Controlling the Spread of Contagious Disease in an Operational Environment* (Alexandria, VA: Institute for Defense Analyses), February 2020.

As with the earlier research, this effort is part of IDA's program of work investigating operational chemical, biological, radiological, and nuclear (CBRN) medical issues for the U.S. Army Office of the Surgeon General (OTSG). Our body of work is intended to inform military planning and decision-making at the operational level; however, much of our analysis of COVID-19-specific outbreak control requirements is broadly applicable to outbreaks of this disease in any context.

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 focusses on four types of control measures: medical countermeasures, isolation, quarantine, and the restriction of movement between units or personnel within or between theaters of operation.

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. The public health community is just now beginning to quantify the population-level impact of these measures. Because of the nascent state of the data in this arena, our analysis does not formally address the requirements for or the effectiveness of measures such as these. However, we do discuss the potential for these measures to compensate for the limitations of the response measures we consider in our analysis.

Our earlier work defined functions that describe the effectiveness of medical countermeasures, isolation, quarantine, and restriction of movement,[5] which we could use to determine the circumstances in which the value of R would drop below one, causing the outbreak to wane. These functions incorporate the following parameters:

- The efficacy of medical countermeasures, if available
- The time delay from onset of symptoms (or other identifiable trigger) to isolation
- The probability that a contagious individual will be isolated
- The probability that infected individuals will be quarantined before they become contagious.

In this research, we introduce an additional parameter of interest: compliance with medical countermeasures, defined as the percentage of susceptible individuals within the population of interest who are no longer vulnerable to a given disease due to the use of medical countermeasures. Specifically, in this case we consider COVID-19 vaccine compliance. In our earlier work, we assumed that medical countermeasure compliance would be 100%. As of this writing, the United

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[5] Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, 47.

States has established a goal of achieving 70% vaccine compliance in the near term; however, vaccination rates have slowed and it now appears that at least in the near term, this goal will not be met. For reference, as of July 29, 2021, 57.1% of the U.S. population had received at least one dose of vaccine, and 49.3% were fully vaccinated.[6]

The range of values for these parameters that together lead to effective outbreak control are determined by a combination of disease characteristics. For the most part, these characteristics are static inputs, and cannot be readily changed or manipulated. Key disease characteristics are:

- ***R_0***. R_0 is the average number of infections a contagious individual would be expected to cause in a completely susceptible population, in the absence of response measures. The higher the value of R_0, the greater the challenge of forcing R below one.
- **Incubation period and latent period**. Incubation period is the time between exposure and onset of symptoms; latent period is the time between exposure and contagiousness. Because COVID-19 infections can be contagious prior to onset of symptoms, these two time periods are not the same for this disease.
- **Specificity of symptoms**. Many contagious diseases are mild and non-specific in their early stages, and thus in a clinical setting may be difficult to differentiate from common viral infections. Such diseases can inhibit effective outbreak response by confounding the development of situational awareness and sowing confusion and delay, particularly in the early stages of an outbreak. For COVID-19, this problem is significantly exacerbated by the significant percentage of cases that are asymptomatic—they never develop symptoms of disease—yet can still be contagious.

In the sections that follow, we discuss the requirements and opportunities for using medical countermeasures (in this case, vaccines), isolation, quarantine, and restrictions of movement to control outbreaks of COVID-19. We consider a layered approach, beginning with medical countermeasures and adding isolation, triggered by either symptom onset or as a result of diagnostic testing, and finally quarantine. This discussion postulates COVID-19-specific values for various parameters; these are summarized in Table 1. We provide our derivation of specific methodological parameter values from the available literature in Appendix A.

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[6] U.S. Centers for Disease Control and Prevention (CDC), "COVID-19 Vaccinations in the United States," Covid Data Tracker, https://covid.cdc.gov/covid-data-tracker/#vaccinations, accessed July 29, 2021. We have assumed that rates of vaccine compliance, the resulting spread of disease, and the total contribution of other control measures to reducing R can be defined for a population of interest, in this case, military units. We have not assessed the extent to which an outbreak can be controlled when our population of interest is routinely in contact with other populations in which vaccine compliance is different, or in which other control measures are implemented in different ways.

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

Parameter	Base-Case Value(s)[1]	Excursion Value(s)[1]
R_0	5.9	2.5
Vaccine effectiveness	95%	75%
Mean incubation period	6 days	
Mean latent period	3 days	
Period of symptomatic contagiousness	9 days	
Duration of contagious period[2]	12 days	
Time of peak contagiousness	One day prior to symptom onset	At symptom onset
% of transmission that occurs during pre-symptomatic period[3]	32.5%	25%
% of cases that are asymptomatic	30%	70%
Relative contagiousness of asymptomatic cases	.25	

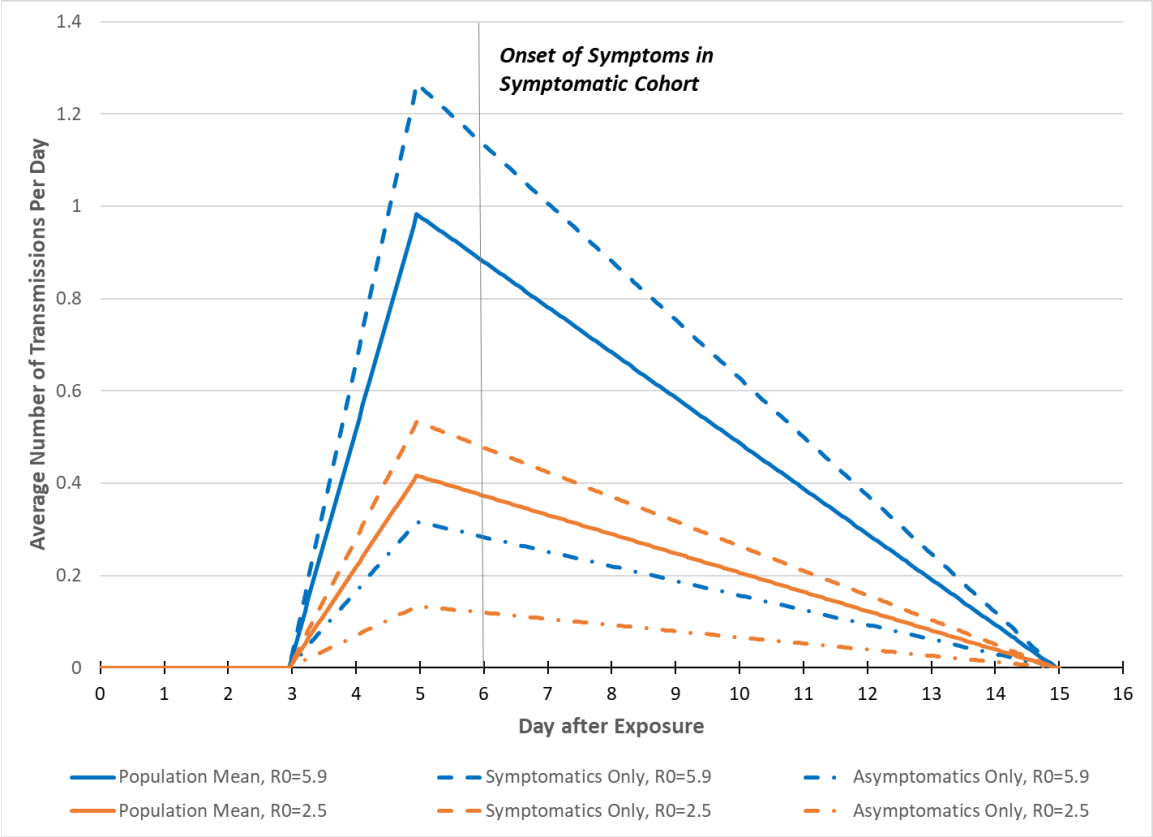
[1] See Appendix for sources and derivation of these values.

[2] Assumes that individuals are contagious for 3 days before onset of symptoms and 9 days after onset of symptoms.

[3] These values are calculated under the assumption that transmission is not truncated by isolation of contagious individuals.

In combination, these parameters allow us to represent a mean individual profile of COVID-19 transmission over time, and to show when that transmission must be truncated to ensure that, on average, each individual infects less than one other person. Figure 1 illustrates this profile, which further differentiates between overall mean transmission, and mean transmission from symptomatic and asymptomatic cases.[7]

[7] This figure is discussed at greater length in Appendix A. As noted there, given the paucity of data on asymptomatic transmission, we assume that the profile of transmission over time from asymptomatic cases will be the same as that of symptomatic cases. 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. Our approach to accounting for asymptomatic cases is described in Appendix B.



Source: Unless otherwise specified, IDA researchers generated all figures in this paper, using information derived from open source literature as described in Appendix A.

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

Figure 1 illustrates, a priori, 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.

For COVID-19, numerous epidemiological studies and laboratory analyses of factors related to immune response suggest that recovered individuals are protected against reinfection for at least several months, and reinfection is rare.[8] At the time of this writing, the U.S. Centers for Disease Control and Prevention (CDC) is engaged in several studies to monitor the percentage of the U.S.

[8] U.S. Department of Homeland Security (DHS), "Master Question List for COVID-19," Science and Technology Directorate (S&T), updated June 1, 2021: 8. This document also notes that the impact of emerging variants on the risk of reinfection is unclear, with the available evidence mixed as to whether specific variants are likely to challenge post-infection immunity.

population that has been infected with COVID-19. The most comprehensive set of data published to date from these studies, the Nationwide Commercial Laboratory Seroprevalence Survey, estimates that as of May 26, 2021, 22% of clinical blood specimens tested at commercial laboratories nationwide contained SARS-CoV-2 antibodies, indicating past infection or vaccination.[9] Since this study does not clearly differentiate between vaccinated and unvaccinated sample donors, the 22% value should be considered an upper bound of the possible rate of COVID-19 infection within the population. In the United Kingdom, where the cumulative confirmed cases of COVID-19 per million people are 67% of those in the United States,[10] the overall national seroprevalence rate among unvaccinated individuals was 9.8% as of February 8, 2021.[11] Based solely on the ratio of confirmed infections, this would imply that approximately 15% of unvaccinated individuals in the United States currently have antibodies to COVID-19 and some degree of immunity.

Because of the uncertainties regarding the durability of post-infection immunity, particularly with regard to emerging SARS-CoV-2 variants, and the lack of comprehensive data on its prevalence in the population over time, we have not formally considered the role that such immunity could play in outbreak control. However, as we evaluate the sufficiency of COVID-19 responses, where the resulting R is close to one, we assume that residual immunity in the unvaccinated population may be sufficient to make a difference and truncate transmission.

A. Medical Countermeasures

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.

In our earlier work, we considered three factors in our assessment of medical countermeasures: availability, effectiveness, and time to administration.

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9 CDC, Covid Data Tracker, https://covid.cdc.gov/covid-data-tracker/#national-lab, updated May 26, 2021.

10 Our World in Data, "United Kingdom: What is the cumulative number of confirmed cases?" Global Change Data Lab, United Kingdom. https://ourworldindata.org/coronavirus/country/united-kingdom?country=GBR~USA#what-is-the-cumulative-number-of-confirmed-cases, updated 15 June 2021.

11 Helen Ward et al., "REACT-2 Round 5: Increasing Prevalence of SARS-CoV-2 Antibodies Demonstrate Impact of the Second Wave and of Vaccine Roll-out in England," Imperial College London, 25 February 2021, https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/real-time-assessment-of-community-transmission-findings/.

- *Availability* is a condition that must be met before other parameters can be evaluated. Medical countermeasures do not exist for all diseases, and indeed, they were unavailable for COVID-19 until December 2020, nearly a year into the pandemic.
- *Effectiveness* is the probability that a medical countermeasure will have its desired effect within the real-world population of interest. COVID-19 vaccine clinical trials broadly focused on reducing severe disease and preventing death; as described in Appendix A, these vaccines have also demonstrated effectiveness in preventing COVID-19 infections. The latter is particularly important when assessing the ability of medical countermeasures to reduce *R*.
- *Time to administration* is the delay between a decision to use medical countermeasures and the successful delivery of them to a population. The time to administration depends on factors such as strategies for procurement, stockpiling, and distribution; the number of doses required; and the time needed to generate the desired physiological response after administration. This factor, in turn, determines the speed with which the impact of medical countermeasures on the course of an outbreak can be realized, and the number of cases that will occur in the meantime.

In this analysis, we have replaced consideration of *time to administration* with an alternative factor, *compliance*, defined as the percentage of the susceptible population that is vaccinated. In our earlier work, we assumed that vaccine compliance within a deployed military population would be near-universal (with some accommodation for counter-indications), and were interested in determining how quickly administration had to be accomplished to avoid levels of casualties that exceeded a postulated threshold above which military units would become operationally ineffective.

Although recently mandated, U.S. military populations are not yet fully vaccinated against COVID-19, and vaccination rates within the general population remain relatively low. Consequently, we have assessed 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. From our earlier work, the number of individuals whom a contagious individual can potentially infect is $(1 -$

ϵ_{MedCM}), where ϵ_{MedCM} is the effectiveness of the medical countermeasure, in this case vaccines.[12] To cause an outbreak to wane, the mean number of infections caused by a contagious individual, *R*, must fall below 1. Vaccines accomplish this by reducing the susceptibility in the uninfected population and limiting opportunities for a disease to spread. Therefore, the values of ϵ_{MedCM} that will lead to $R < 1$ are those that satisfy[13]

$$R = (1 - \epsilon_{MedCM})R_0 < 1$$

Given the R_0 value for the disease of interest, determining the value of ϵ_{MedCM} needed to ensure $R < 1$ is straightforward:[14]

$$\epsilon_{MedCM} > 1 - \frac{1}{R_0}$$

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 discussed in Appendix A, there are data that show current vaccines are less effective at preventing infection from some variants of COVID-19 than others,[15] suggesting that even with universal compliance, vaccination will need to be augmented by other types of outbreak controls should such variants become entrenched within the population. These calculations and discussion are summarized in Table 2.

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[12] This formulation of f_{MedCM} is limited to describing the effect reducing population-wide susceptibility due to administration of a MedCM. The other potential benefits of MedCMs (e.g., aborting the infection of those incubating the disease or reducing the severity of disease progression) are not captured by this formulation.

[13] In our earlier work, we derived functions for *R* associated with individual response measures, so that $R_{response}$ was defined as some combination of R_{MedCM}, R_{iso}, $R_{quarantine}$, etc. In this paper, we discuss *R* with less formalism: *R* is always defined as the mean number of cases generated by a contagious individual at a given point in an outbreak, but the value of *R* changes over time due to overt implementation of outbreak control measures and adjustments in the population's behavior.

[14] Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, 15.

[15] Laith J. Abu-Raddad, Hiam Chemaitelly, and Adeel A. Butt, "Effectiveness of the BNT162b2 COVID-19 Vaccine against the B.1.1.7 and B.1.351 Variants," *The New England Journal of Medicine*, published May 5, 2021 online at NEJM.org: 1-3. DOI: 10.1056/NEJMc2104974. See the discussion of vaccine effectiveness in Annex A, pp. 34-36. Specifically, this study showed that while the Pfizer-BioNTech COVID-19 vaccine retained an extraordinarily high (97.4%) effectiveness in preventing severe, critical, or fatal disease, it was less effective in preventing COVID-19 infection from two specific variants: the B.1.1.7 variant, which originated in the UK (89.5% effective) and the B.1.351 variant, first identified in South Africa (75% effective). As of this writing, the B.1.1.7 variant is the dominant strain circulating in the United States, while the B.1.351 variant remains rare.

Table 2. Sufficiency of COVID-19 Vaccines in Achieving R<1, Assuming Universal Compliance

R_0	Required Vaccine Effectiveness	Vaccine Effectiveness = 95% (Baseline)	Vaccine Effectiveness = 75% (Excursion)
5.9	83%	Yes	No
2.5	60%	Yes	Yes

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.

The relationship between vaccine effectiveness and compliance is illustrated in Figure 2. In the figure, the areas above and to the right of the lines represent combinations of vaccine effectiveness and compliance that will 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 values associated with 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 3.

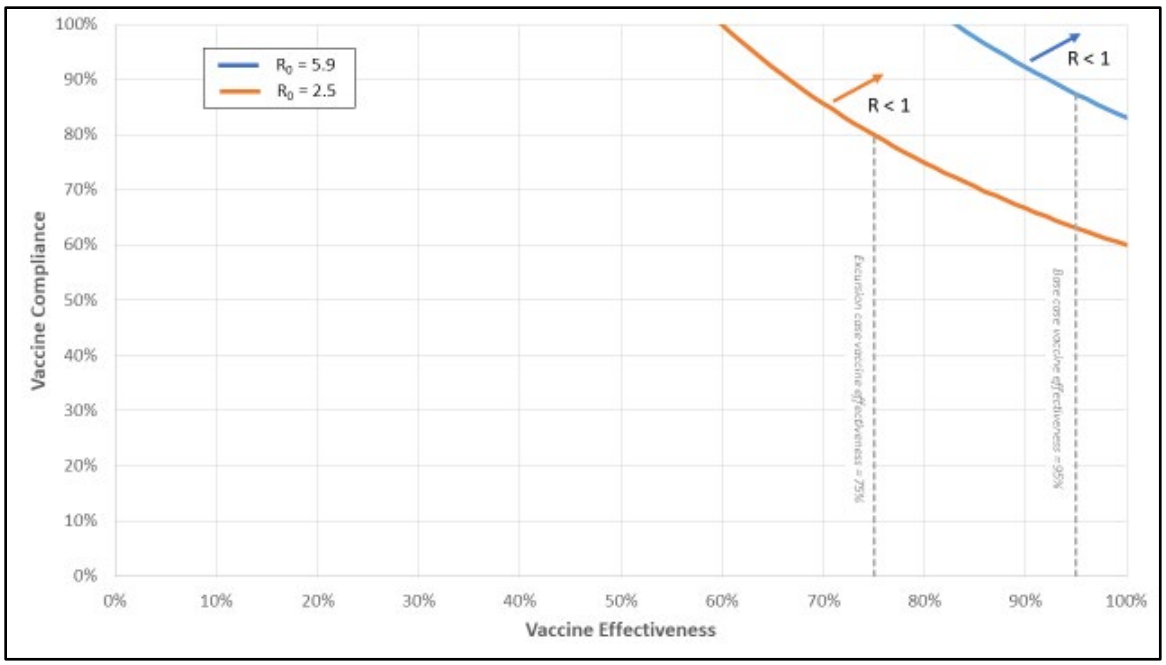

Figure 2. Relationship between COVID-19 Vaccine Compliance and Vaccine Effectiveness

Table 3. 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.[16] 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%.[17] Yet, while vaccines that are 95% effective in preventing infection can cause an outbreak to wane,

[16] U.S. Centers for Disease Control and Prevention, "Interim Clinical Considerations for Use of COVID-19 Vaccines Currently Authorized in the United States," July 16, 2021. Accessed 29 July at https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html#Contraindications.

[17] Kimberly G. Blumenthal, Lacey B. Robinson, Carlos A. Camargo, Jr., "Acute Allergic Reactions to mRNA COVID-19 Vaccines," *Journal of the American Medical Association* 325 no. 15 (2021): 1562.

should vaccine-resistant COVID-19 variants emerge, even mandatory vaccination could be insufficient to control an outbreak on its own.

B. 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, to retention in a hospital isolation ward, to 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."[18] 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 that 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.[19] 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.

In our earlier work, we posited that the isolation window of opportunity was determined by three main factors: the R_0 value for the disease in question; the duration of the contagious period; and the time of symptom onset relative to the onset of contagiousness. We then assessed the effectiveness of isolation based on its ability to cause an outbreak to wane, considering both who

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[18] Jane D. Siegel et al., *2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings (Updated)*, U.S. Centers for Disease Control and Prevention, October 2017: 66.

[19] See Appendix A and the discussion in the following sections for more specific information related to pre-symptomatic and asymptomatic transmission of COVID-19. In both our current and previous work, we assume that isolation, once implemented, is 100% effective. However, this assumption is highly optimistic for COVID-19. In our previous work, we also assumed that isolation would take place in a controlled environment where infection control practices would be well established. As the pandemic progressed, and cases increased, isolation in this form became impractical; cases that did not require hospitalization were isolated at home, where they could have continued contact with other members of their household. Moreover, because COVID-19 can be transmitted via aerosol, infection control measures beyond standard precautions must be used in medical settings to protect medical personnel and prevent nosocomial transmission. See https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html.

must be isolated (contagious individuals) and when (before they have the opportunity to infect others). To parameterize these factors, we defined the reduction in a contagious individual's transmission due to some isolation response capability as a function of two parameters:

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

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

$$R = f_{Iso}(\epsilon_{Iso}, D_{Iso})R_0 < 1$$

If we assume for the moment that all contagious individuals will be isolated, 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 3 shows how long isolation can be delayed 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. These include mean values for R_0, latent period, overall duration of the contagious period, and time of peak contagion.

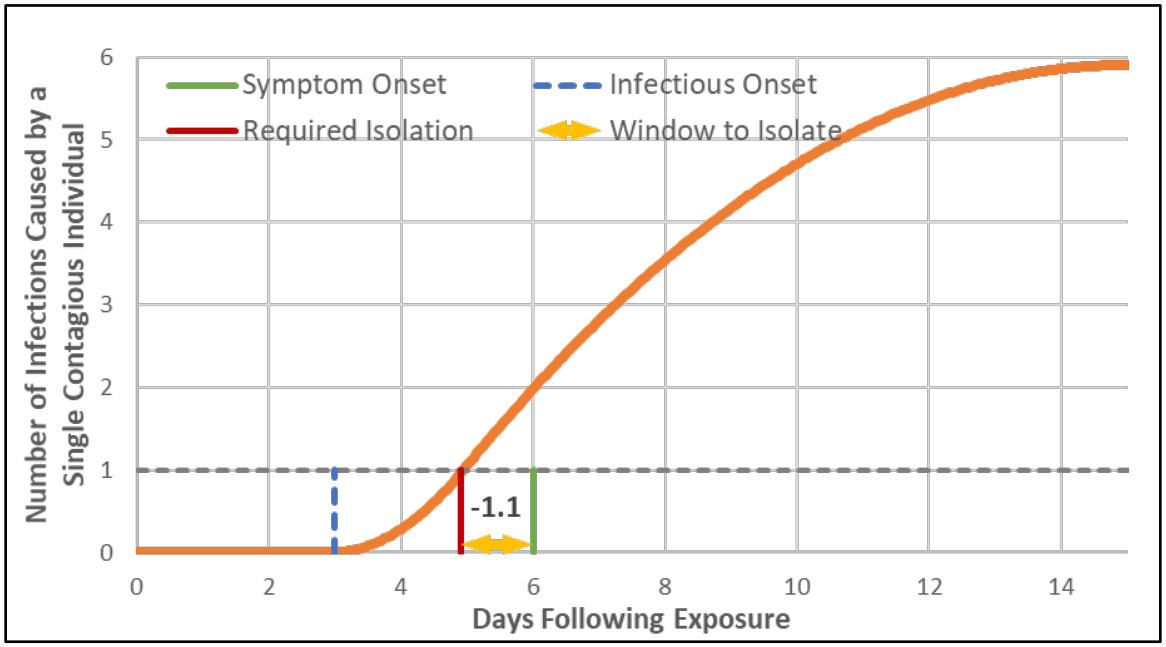

Figure 3. Mean Time Window for Isolation of an Individual with COVID-19 (Base-Case Parameter Values)

In Figure 3, the mean number of infections generated by a single contagious individual is determined by R_0 and our representation of contagiousness over time as a triangle function. We have assumed that transmission on average begins 3 days after exposure, peaks at 5 days after exposure (1 day prior to onset of symptoms), and continues for a total of 12 days. For these 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 R0 value, pre-symptomatic transmission, and a peak transmission time prior to onset of symptoms. Moreover, the requirement for isolation as shown in Figure 3 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 among those who have been vaccinated. Figure 4 shows our base-case 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.

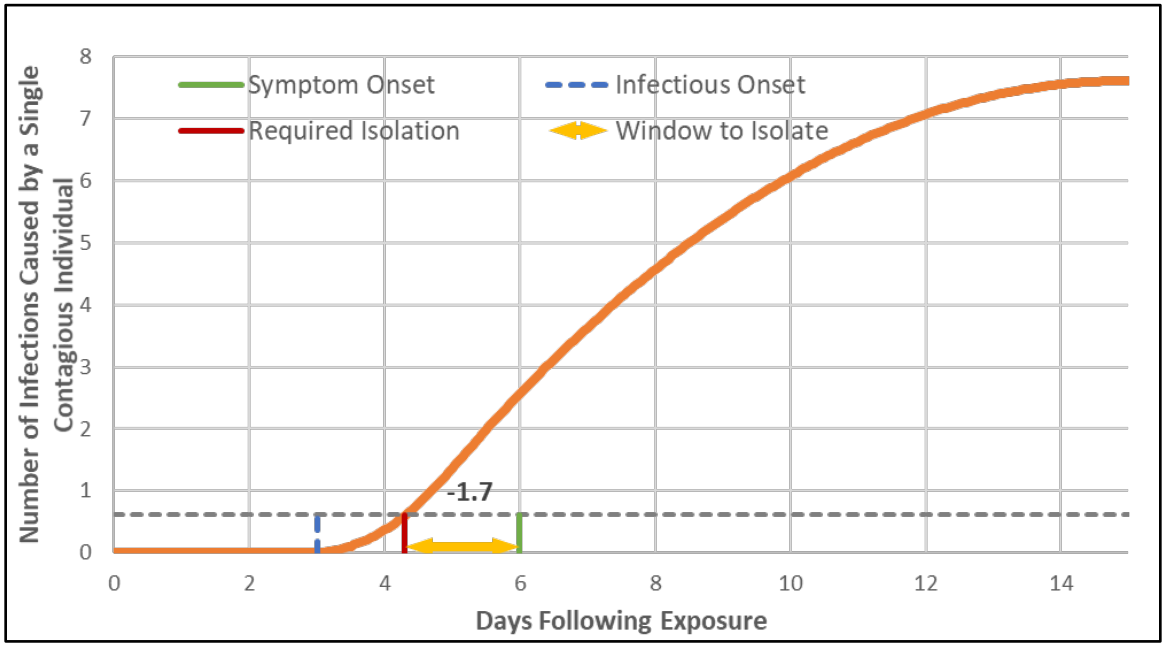

Figure 4. Mean Time Window for Isolation of Symptomatic Cases of COVID-19, Assuming Asymptomatic Transmission is Uncontrolled (Base-Case Parameter Values)

As seen in Figure 4, 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 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 4 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 4. 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, 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 3 days after exposure, and 2 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 less than 100% isolation (i.e. cases where $\epsilon_{Iso} < 1$). 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, as we did in our earlier work. 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.

C. 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.

For the base-case parameter values shown in Figure 4, we can see that at symptom onset on Day 6 following exposure, each symptomatic case would have infected an average of 2.5 other people. If all symptomatic cases are isolated immediately upon onset of symptoms—the best possible case for isolation when it is triggered by symptoms, even though transmission will have been ongoing during the pre-symptomatic portion of the contagious period—then the value of R for symptomatic cases will be reduced from 7.6 to 2.5, and the value of R for the combination of symptomatic and asymptomatic cases will be reduced to 2.3.[20] For an R_0 value of 2.5, the average number of cases infected by each symptomatic case at the time of symptom onset is 1.1 (not shown in the figure); isolation of all symptomatic cases at the time of symptom onset would then result in an overall R value of 1.3. This reduction in R due of isolation of symptomatic cases, from R_0 to something less than that, will in turn affect the requirements for vaccine effectiveness. For a given value of vaccine effectiveness, it will also change the requirements for compliance. Figure 5 illustrates the altered relationship between COVID-19 vaccine effectiveness and vaccine compliance given isolation of symptomatic cases immediately upon symptom onset.

[20] Recall that the overall R value is the weighted average of transmission from symptomatic and asymptomatic cases; for $R_0 = 5.9$ and isolation of symptomatic cases at symptom onset, $R = 0.7(2.5) + 0.3(1.9) = 2.32$.

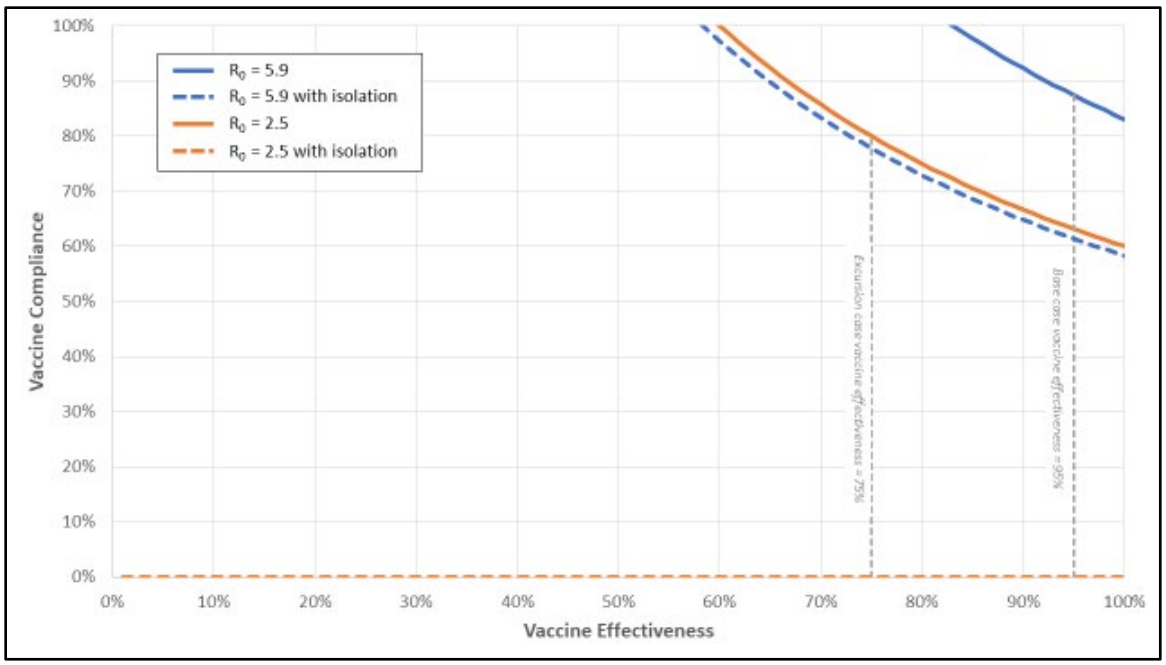

Figure 5. Impact of Isolation of Symptomatic Cases at Symptom Onset on the Relationship between Vaccine Effectiveness and Compliance

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.

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 24 and 48 hours after onset of symptoms. The resulting curves depicting this relationship are shown in Figure 6. The needed compliance rates, under various isolation regimes and given base-case and excursion values for vaccine effectiveness and R_0, are shown in Figure 7.

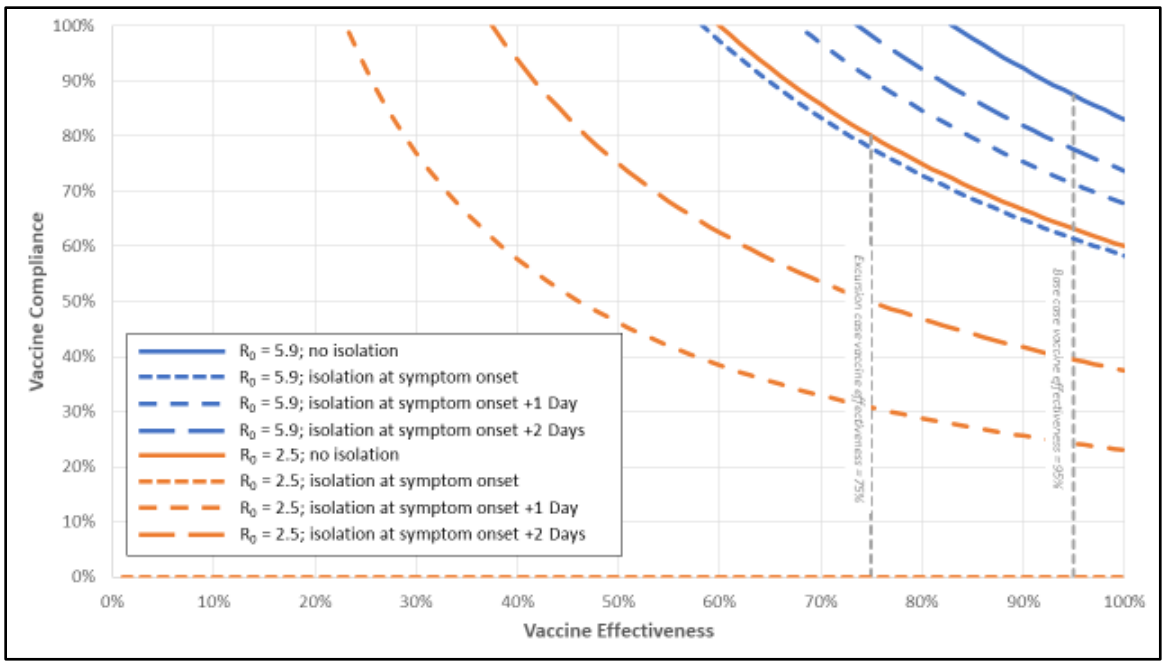

Figure 6. Impact of Delayed Isolation on the Relationship between Vaccine Effectiveness and Compliance

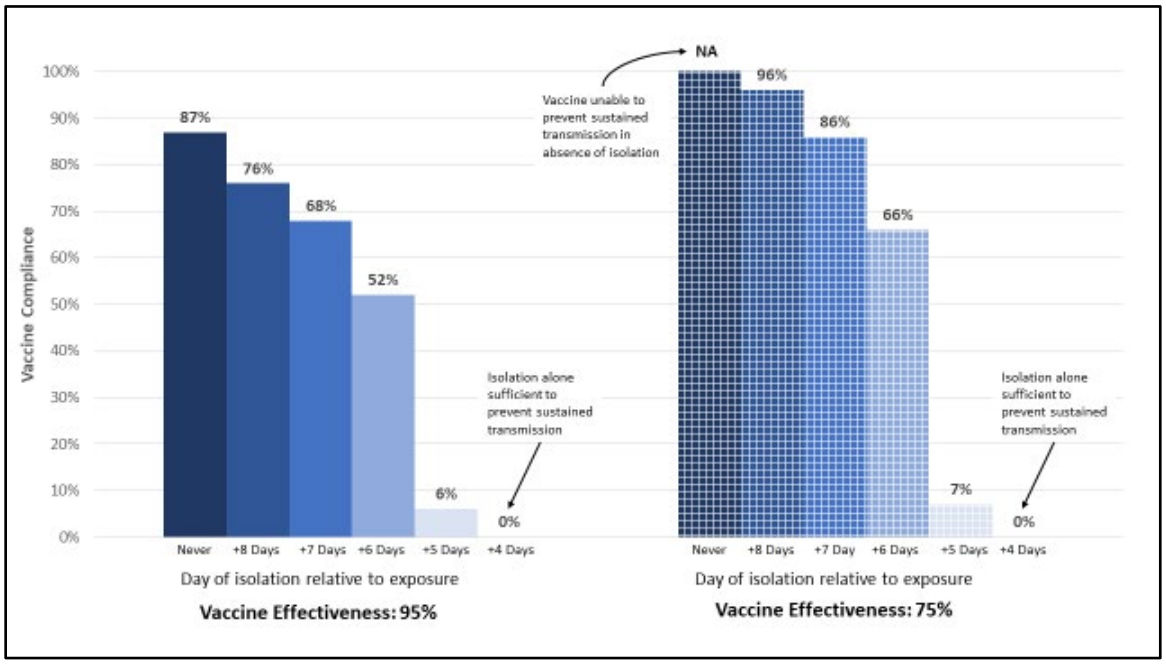

Figure 7. Vaccine Compliance Needed under Various Isolation Regimes (R_0 = 5.9)

As seen in Figure 6 and 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 unless vaccines become mandatory.

Yet, there is room for optimism: vaccines and isolation triggered by symptoms, together, 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.

A Note on Universal Isolation

In our earlier work, we posited that not only was isolation at symptom onset very unlikely, it was also unlikely that everyone who is symptomatic during a disease outbreak would be isolated. This concept is represented by the parameter ϵ_{Iso}, defined as the fraction of the contagious population that will be isolated. In our earlier discussion of isolation, we did not consider cases other than ϵ_{Iso}= 1, where everyone who is symptomatic is isolated, since even in that best case, isolation was unlikely to be effective.

Because of the complexity of the present analysis, we often chose to simplify the discussion by limiting the number of parameters or excursion cases included, or to consider specific values for things such as vaccine efficacy when those are generally known. Thus, when evaluating vaccines and isolation in combination in this portion of the analysis, we did not directly evaluate the consequences of ϵ_{Iso}< 1.

When establishing guidelines and procedures for isolation, however, one might question whether it is better to pursue immediate isolation, in the expectation that some individuals will be missed, or allow a more relaxed implementation, in the hope of encompassing a higher percentage. We can derive some understanding of the boundaries of this problem from our triangle function of transmission over time, and the difference in the area under the curve when transmission is truncated at specific time points. Thus:

- Isolating 100% of symptomatic individuals 1 day after symptom onset is equivalent to isolating 79% of symptomatic individuals at symptom onset and never isolating the remaining 21%;
- Isolating 100% of symptomatic individuals 2 days after symptom onset is equivalent to isolating 60% of symptomatic individuals at symptom onset and never isolating the remaining 40%.

D. Diagnostic Testing as a Trigger for Isolation

As discussed earlier in this analysis, transmission from individuals after onset of symptoms accounts for only about 60% of total COVID-19 transmission. 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 4). 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 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 vice symptom onset. We also assumed that 100% of the contagious population would be isolated.

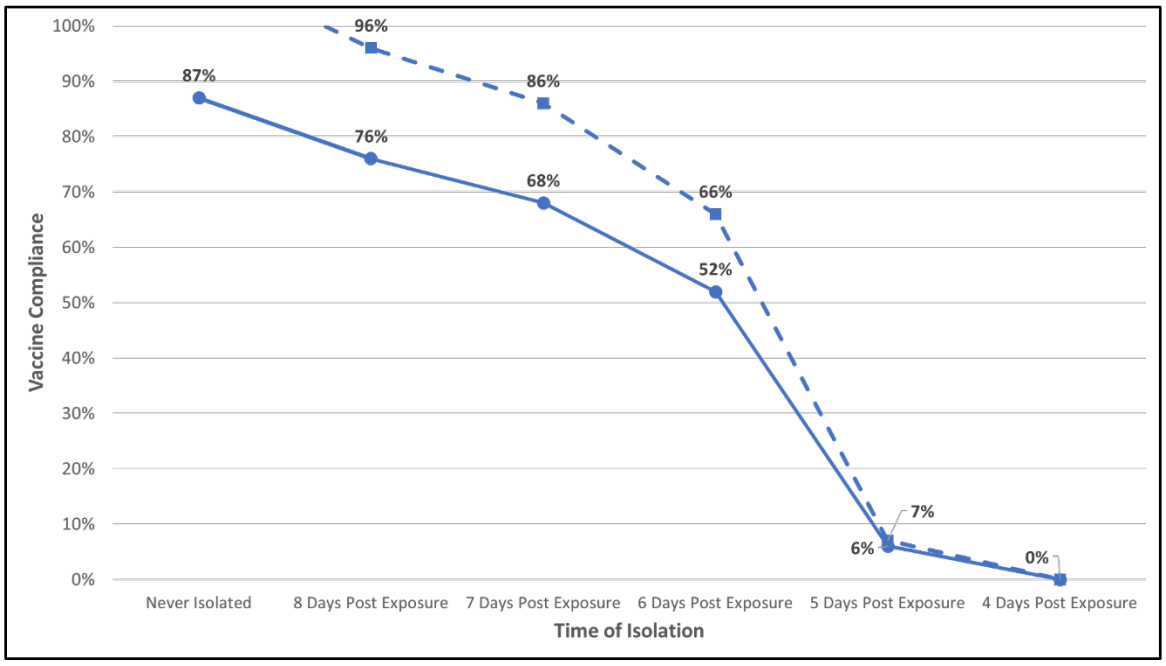

Figure 8. Vaccine Compliance Needed When Isolation Can Occur Before Symptom Onset (6 Days Post Exposure), R_0 = 5.9

For our base-case vaccine efficacy of 95%, at the mean time of symptom onset—6 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 efficacy 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. To do so, we developed a simple stochastic model to analyze the use of diagnostic testing as a trigger for isolation.[21] More specifically, we defined 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 $R < 1$.

In this model, we randomly characterized all individuals in our simulated population as belonging to one of two cohorts: asymptomatic or symptomatic. All individuals were subject to testing at randomly determined times and the timing of positive test results relative to their disease progression dictate when that individual is isolated. The number of new infections caused by each individual is determined by a Poisson distribution parameterized by the individual's expected number of new infections before the time of isolation, as determined by our representation of COVID-19 transmission over time (Figure 1). 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: 100% of tests were positive when administered during the contagious period, and 100% negative when administered outside the contagious period; test results were available without delay; and individuals were isolated immediately upon either a positive test result or onset of symptoms.

[21] A more detailed discussion of our model for simulating diagnostic testing is provided in Appendix B.

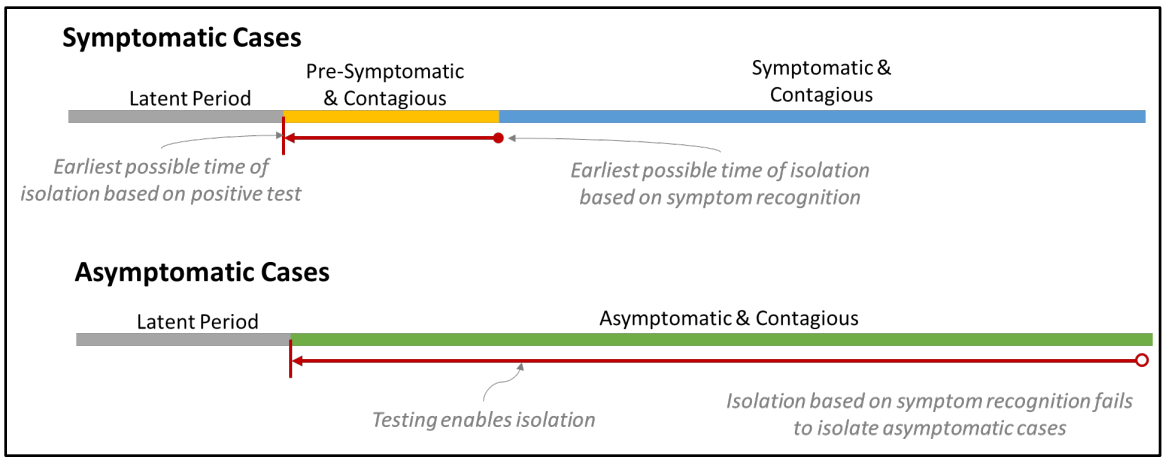

Figure 9. Diagnostic Testing Simulation Approach to Isolation of Symptomatic and Asymptomatic Cases of COVID-19

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. Again, these results assume that the entire population is subject to testing, all contagious cases are isolated, isolation is triggered by either a positive test result or onset of symptoms, whichever happens sooner, and isolation occurs on the same day as the trigger. As the figure shows, when vaccine efficacy is 95%, once vaccine compliance exceeds 60% testing no longer provides any benefit over vaccine and isolation along. When vaccine efficacy is 75%, testing ceases to be beneficial at compliance rates above 75%. Below these threshold values, once test frequency exceeds approximately 20 days, the marginal benefit quickly declines; at test frequencies of less than 3 days, diagnostic testing does not change the results, and isolation alone will be an effective response. Between these two boundaries, at intervals ranging from 3 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.

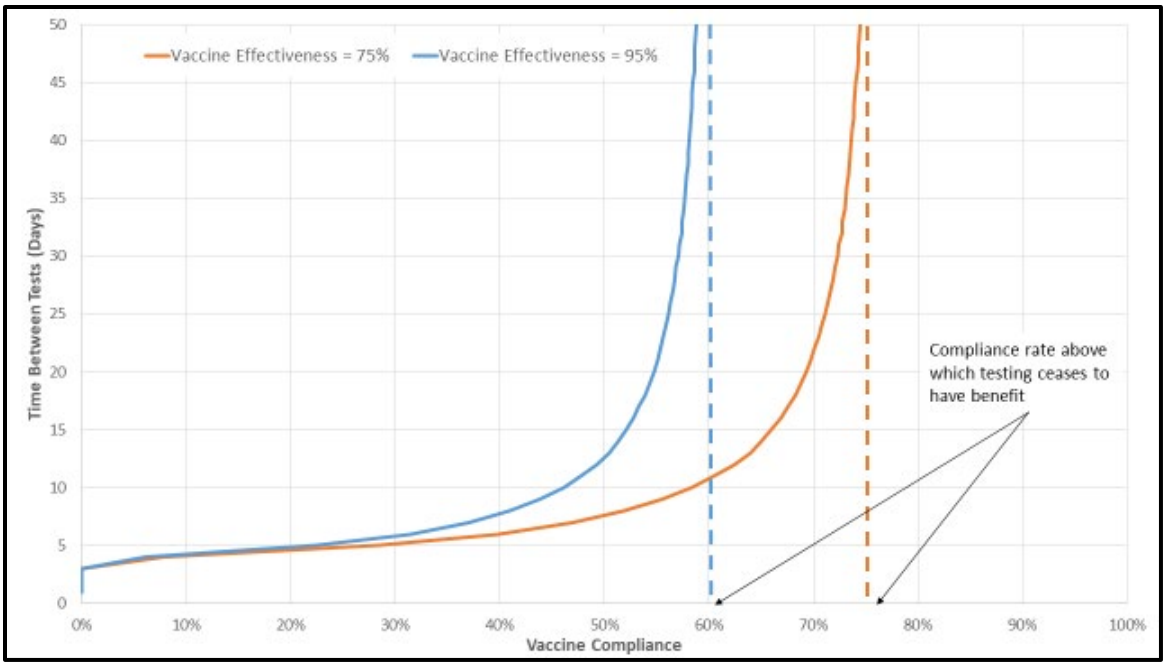

Figure 10. Frequency of Testing Needed to Trigger Isolation and Cause $R < 1$, Given Vaccine Compliance Rates, $R_0 = 5.9$

Point estimates of the vaccine compliance needed, given selected testing frequencies, are provided in Table 5 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 7 days or every 3 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 3 days could nearly eliminate the requirement for vaccination and make isolation alone an effective means of outbreak control.

Table 5. Impact of Diagnostic Testing on Vaccine Compliance Needed to Achieve $R < 0$

Testing Frequency	Compliance Needed if Vaccine Efficacy = 95%	Compliance Needed if Vaccine Efficacy = 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 localized surges in COVID-19 cases occur.

E. Isolation and Quarantine

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.[22]

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.

In our earlier work, we used the parameter ϵ_Q to describe the fraction of the infected individuals in quarantine, and subsequently isolated upon symptom onset, thus eliminating their opportunity to spread disease. As with other response measures, alone or in combination, enough infected individuals must be quarantined such that contagious individuals (both those in quarantine and those not in quarantine) infect, on average, less than one susceptible individual.

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[22] *ATP 4-02.84*: Appendix D. North Atlantic Treaty Organization, NATO STANAG 2461, *Allied Medical Publication 7.1 (AMedP-7.1): Medical Management of CBRN Casualties*, Edition A, Version 1 (NATO Standardization Organization, Brussels, Belgium), June 2018, 6-13; NATO STANAG 2873*, Allied Medical Publication 7.6 (AMedP-7.6): Commander's Guide on Medical Support to Chemical, Biological, Radiological, and Nuclear (CBRN) Defensive Operations*, Edition A Version 1 (NATO Standardization Organization, Brussels, Belgium), February 2018, 7-4; Headquarters, Department of the Army, Army Techniques Publication 4-02.84, *Multi-service Tactics, Techniques, and Procedures for Treatment of Biological Warfare Agent Casualties* (Washington, DC), November 2019.

One major question is how to achieve a given level of quarantine efficacy 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,[23] and can quickly be overwhelmed in a large outbreak.[24] For example, the Delaware Division of Public Health undertook a large-scale contact tracing effort to support isolation and quarantine within its state; this effort officially began in May 2020 when the Delaware National Guard was activated to assist.[25] Despite devoting substantial resources, the Delaware Division of Public Health found that on average, it took 3 days for them to receive a report of a confirmed COVID-19 case, and 5 additional days to conduct a contact tracing interview. Moreover, among those interviewed, 83% either refused to name contacts or could not recall them. When contacts were identified, the mean time from positive case interview to contact interview was 2 days.

Given that the mean latent period of COVID-19 is 3 days, however, 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.

The best data set that we have found on this subject comes from 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.[26] The objective of this study was to understand the proportion of asymptomatic carriers and transmission risk factors for COVID-19 among

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[23] One study of contact patterns in the United Kingdom found that the median number of close contacts per individual is 59; the authors predicted that on average, an index case would be able to identify 36 of these in support of contact tracing efforts. See Matt J. Keeling, T. Deirdre Hollingsworth, and Jonathan M. Read, "Efficacy of Contact Tracing for the Containment of the 2019 Novel Coronavirus (COVID-19)," *Journal of Epidemiology and Community Health* 74 (2020): 861-6.

[24] As the U.S. Centers for Disease Control and Prevention states in its contact tracing guidance document, *Operational Considerations for Adapting a Contact Tracing Program to Respond to the COVID-19 Pandemic in non-US Settings*: "Contact tracing, including case and source investigation, is a key component of controlling transmission of infectious diseases. Contact tracing for the current COVID-19 pandemic, however, is distinct from that undertaken for other diseases (e.g., Ebola, HIV, TB) because in nearly all countries the number of cases and contacts has outpaced the capacity of the public health system to quickly notify and quarantine all contacts and isolate all cases." https://www.cdc.gov/coronavirus/2019-ncov/global-covid-19/operational-considerations-contact-tracing.html.

[25] Florence A. Kanu et al., "Declines in SARS-CoV-2 Transmissions, Hospitalizations, and Mortality After Implementation of Mitigation Measures—Delaware, March-June 2020," *Morbidity and Mortality Weekly Report* 69 (November 6, 2020): 1-4.

[26] Oon Tek Ng et al., "SARS-CoV-2 Seroprevalence and Transmission Risk Factors among High-risk Close Contacts: A Retrospective Cohort Study," *Lancet Infectious Disease* 21 (2021), March 2021, 333-43.

contacts of various types; this study objective aligns closely with our own questions on stratification of contacts by risk of disease. Singapore is a small island nation with a population of 6 million; at the start of the COVID-19 pandemic, it promptly implemented a comprehensive outbreak response plan prepared as a follow up to the SARS epidemic; this plan included aggressive tracing and mandatory quarantine of all close contacts of confirmed cases of COVID-19.[27] As the authors note:

> "This closely monitored cohort of contacts provided a unique opportunity to determine attack rates on the basis of symptom-based PCR tests and follow-up serological surveys, coupled with questionnaires to determine the prevalence of asymptomatic infection. As unique index–contact pairs were known, individual-level exposure risk factors associated with SARS-CoV-2 infection could be determined by use of exposure-risk questionnaires to inform targeted community prevention strategies."[28]

The Singapore response plan defined close contacts as all household contacts, plus individuals who had contact for at least 30 minutes within a 2-meter distance from the index case. Ultimately, the study identified 7,770 such close contacts, of which 7,518 were included in the study, with 252 contacts excluded because of incomplete data. The study population included 1,779 household, 2,231 work, and 3,508 social close contacts. Other contacts who were within a 2-meter distance from the index case for 10-30 minutes were considered lower-risk contacts; these contacts were not quarantined but were placed under health surveillance by telephone. Individuals in quarantine who developed symptoms promptly underwent diagnostic testing, and isolated if their test was positive. All other contacts were asked to provide a blood sample for SARS-CoV-2 serology testing and to complete a risk factor questionnaire.[29]

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. Interestingly, lower-risk contacts were eventually excluded from the study because there were few infections in that group.

The Singapore data set does have limitations. Officials in that nation implemented their COVID-19 response plan immediately after the detection of their first case, so although the study

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[27] Ng et al., "SARS-CoV-2 Seroprevalence and Transmission Risk Factors among High-risk Close Contacts:" 341.

[28] Ibid, 334.

[29] Ibid, 335-6 and Figure 1.

period was early in the outbreak, transmission in Singapore was not unconstrained. Nonetheless, at this time, mask wearing was not mandatory and people were not constrained in their activities. Moreover, although quarantine was mandated and enforced, and identified cases were isolated in designated facilities, the mean time to isolation was 5 days from symptom onset.[30] As discussed earlier, isolation delays of this length will be of limited effectiveness in constraining transmission.

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.[31] The results are shown in Table 6.

Table 6. Estimated Fraction of Secondary Transmission by Contact Group

Contact Type	Number in Cohort	Estimated Number of Cases	Estimated Attack Rate	Fraction of Total Cases
Household	1779	196	11%	43%
Work	2231	89	4%	19%
Social	3508	175	5%	38%
Total	7518	460	6%	100%

Beyond the effort needed to identify close contacts on an individual basis, the implementation of quarantine itself presents numerous challenges. Unlike isolation, which only encompasses contagious individuals, quarantine affects healthy individuals who have some identified chance of becoming contagious. In addition, those who *will* become ill are a subset of those who *might* become ill, and that differentiation is impossible to determine a priori with current technology. To be effective, quarantine must encompass a number of individuals who will never become ill. In Singapore, while all of the identified close contacts were quarantined, only 6% were eventually contagious. This meant that for each secondary case successfully prevented from perpetuating transmission, 15 individuals who were not infected needed to be quarantined.

Using the information provided in Table 6, 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 11. 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 & work). The horizontal axis represents the portion of all contacts contained within a given group or

[30] Ibid, 337 and Table 1.

[31] This approach excludes both those infections that occur via random chance contact, and those that result from superspreader events. We have assumed here that, based on the Singapore data, the former are a very small fraction of the total, and that the latter would effectively be minimized by a regime of quarantine and isolation.

combined groups. The vertical axis represents the proportion of all transmission that occurred in the group. The dashed line is y = x and 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.

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.

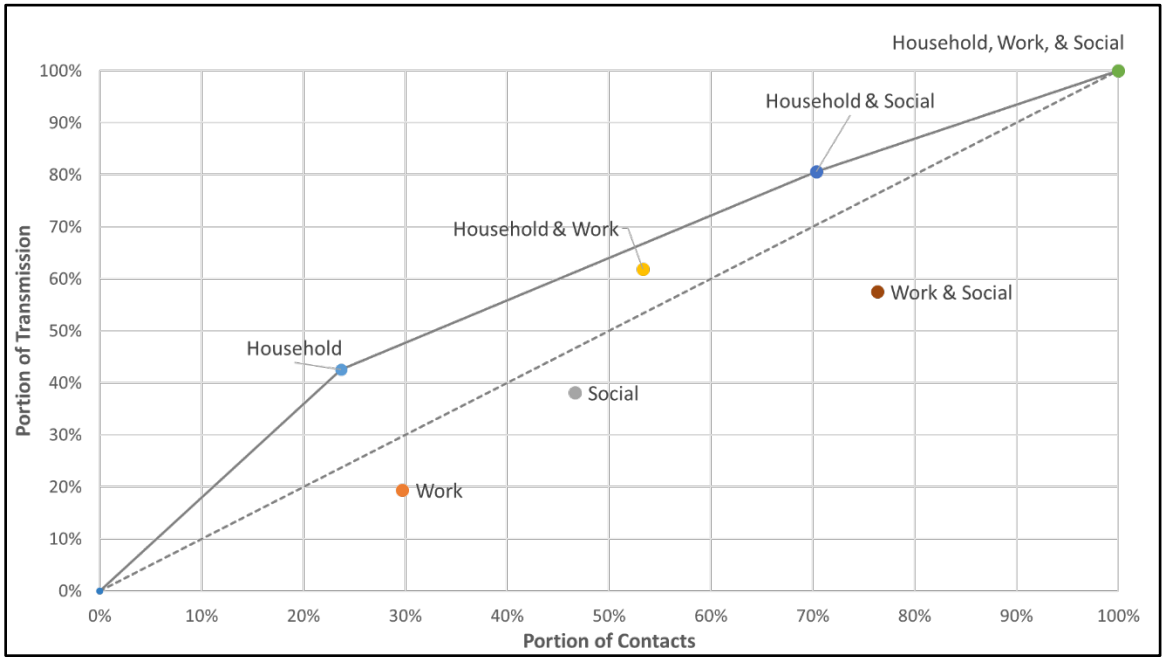

Figure 11. Percentage of Contacts that Must Be Quarantined to Avoid a Given Portion of Transmission

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.

Next, we assessed what the efficacy of quarantine, ϵ_Q, would need to be, given our base-case and excursion values for R_0 and the characteristics of other response measures. We began by extending our earlier work[32] to examine the relationship between quarantine efficacy and time to isolation triggered by symptom onset. In so doing, we assumed that quarantine was limited to the contacts of symptomatic individuals; secondary infections caused by asymptomatic individuals would be excluded from quarantine, and once their latent period ended would transmit disease without constraint. We also assumed, for purposes of bounding the problem, that all contacts would be quarantined before they had any opportunity to transmit disease. Figure 12 shows the fraction of infected individuals that would need to be quarantined for $R < 1$, given the time at which symptomatic individuals are isolated.

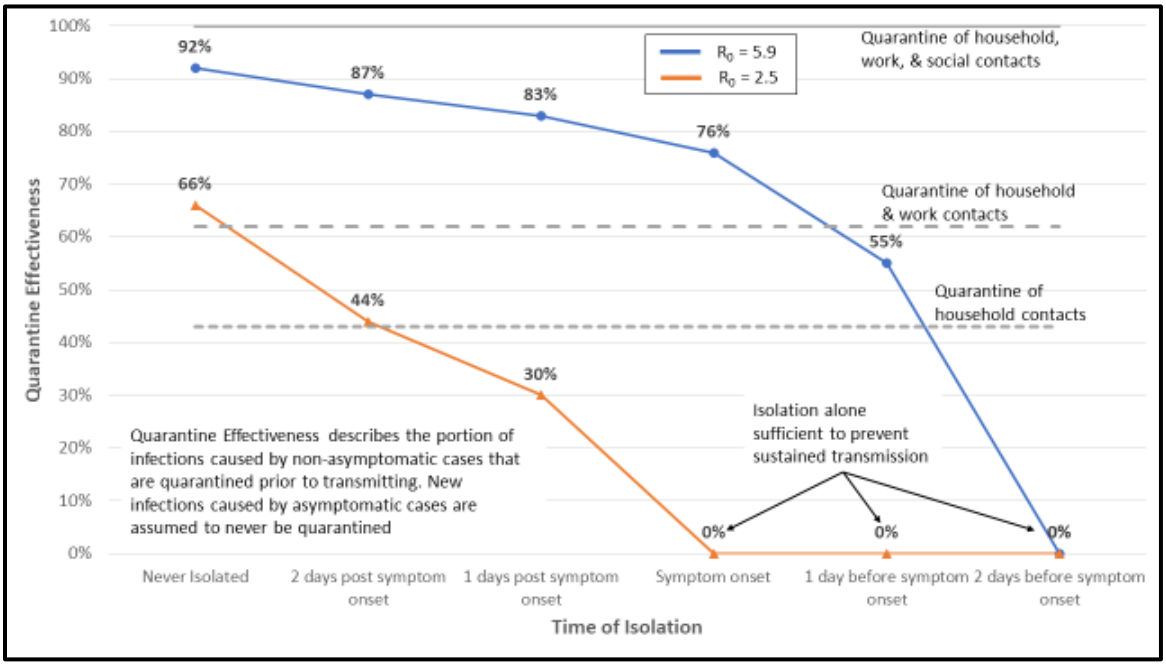

Figure 12. Quarantine Effectiveness Needed to Achieve $R < 1$, in Combination with Isolation Triggered by Symptom Onset

When we looked at the quarantine efficacy achievable through rapid quarantine of various contact groups, we see that for our base-case R_0 of 5.9, if symptomatic contacts are isolated at symptom onset, quarantine must encompass both household and social contacts to result in $R < 1$. If isolation takes place at any times after symptom onset, all contact groups would need to be

[32] Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, 36.

quarantined. For our excursion R_0 of 2.5, our results are much more optimistic: as discussed in previous sections, isolation at symptom onset is sufficient to achieve $R < 1$, and isolation at times up to two days after symptom onset can still be successful if household contacts are quarantined.

Finally, 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 efficacy and vaccine compliance is shown in Figure 13 for $R_0 = 5.9$.

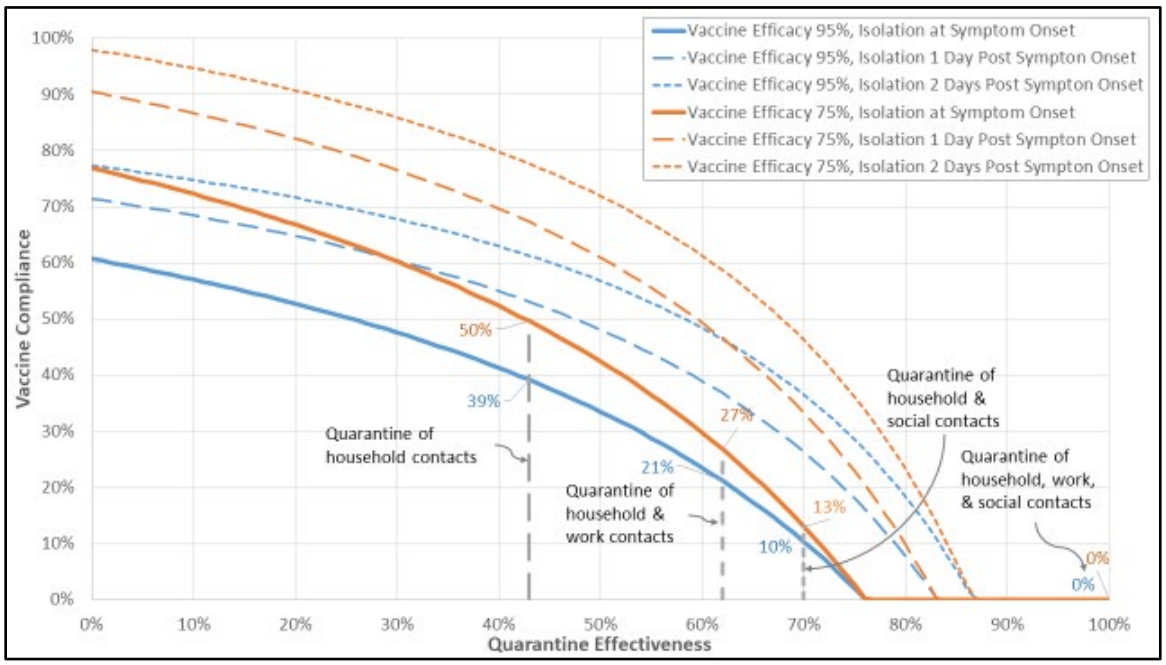

Figure 13. Relationship between Required Vaccine Compliance and Quarantine Effectiveness, Given Isolation of Symptomatic Individuals Only

We found that for both our base-case and excursion values for vaccine efficacy, 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 1 day post-symptom onset, household and work contacts must be quarantined, and for isolation at 2 days post-symptom onset, household and social contacts must be quarantined. Alternatively, if quarantine is limited to household contacts and isolation occurs 2 days post-symptom onset, vaccine compliance rates must increase to 60% or 75%, depending on vaccine efficacy.

F. Restrictions of Movement and the Protection of Disease-Free Units or Communities

In our earlier work, we postulated circumstances in which military commanders may wish to restrict contact between units or personnel that have not yet been affected by an outbreak and those that may have been affected, within or between theaters of operations. The objective of such restrictions of movement (ROM) is not necessarily to reduce the value of *R* but to prevent or delay the spread of disease to a particular population or unit to preserve immediate mission capability, prevent international spread of disease, and protect home nations. For example, ROM may be a viable option when critical military objectives must be accomplished in the immediate future by specific units, when other control measures are unavailable or ineffective, or when a stopgap measure is needed until other control measures can be brought to bear.[33]

The likelihood that a unit can remain disease-free for some period of interest is a function of the number of individuals who move into that population and the likelihood that those individuals will be incubating disease. This relationship can be used to determine the maximum daily movement of individuals that can be allowed before the probability of an asymptomatic or pre-symptomatic individual entering the disease-free population exceeds some threshold risk level.

We have described the probability of a unit remaining free of disease ($P_{No\ Disease}$) as:

$$P_{No\ Disease}(n, E, t) = (1 - E)^{nt}$$

where:

- *t* is the time period of interest, measured in days;
- *n* is the number of individuals who move each day, and
- *E* is the portion of the population in which disease is occurring that is not showing symptoms.[34]

In this formulation, we consider a population divided into two groups: 1) the unit or population that must be kept disease free, and 2) the remainder of the population, within which some fraction is currently ill. Movement between the two sub-populations is represented as a daily exchange of individuals, here defined by the parameter *n*. We assumed that symptomatic individuals will not move into the disease-free population, but that the movement of all asymptomatic and pre-symptomatic individuals is unconstrained.

The value of *E* is the fraction of asymptomatic and pre-symptomatic individuals in the population, given the fraction of symptomatic individuals in the population—information that can

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[33] Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, 41.

[34] For the mathematical derivation of this equation, see Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, Appendix A. For COVID-19, *E* will include both completely asymptomatic cases, and those that will become symptomatic.

be known to decision-makers. As outbreaks grow or wane, the value of this parameter will change, although it can remain stable during a given generation of disease transmission. We held the value of E constant in our assessment, meaning the results are valid only for short forecasts into the future.

For COVID-19, we assume a mean latent period of 3 days and a mean contagious period of 12 days, for both symptomatic and asymptomatic cases. The 70% of cases that will be symptomatic have a 3-day period of pre-symptomatic transmission, and over the course of their infection will spend 40% of their time without symptoms (6 of 15 days). The 30% of cases that are asymptomatic spend 100% of their time without symptoms. At any given time, 58% of infections can be expected to not show symptoms (30 + (70*.4)), while 42% will be symptomatic. This means that for each symptomatic infection that can be observed, there will be 1.38 asymptomatic infections (58/42). This means that if, for example, 2% of a population was symptomatic, the value of E would be 2.76.

Figure 14 shows the relationship between the percentage of symptomatic individuals within the population experiencing an outbreak and the number of people that can move each day from that population to a disease-free unit, with a $\geq$ 50% probability that the destination unit can remain disease-free for some defined period of time. In our example where 2% of the outbreak population is symptomatic, no more than 8.25 people could be allowed to move each day to have a 50% chance of keeping the destination unit free of COVID-19 for 3 days.

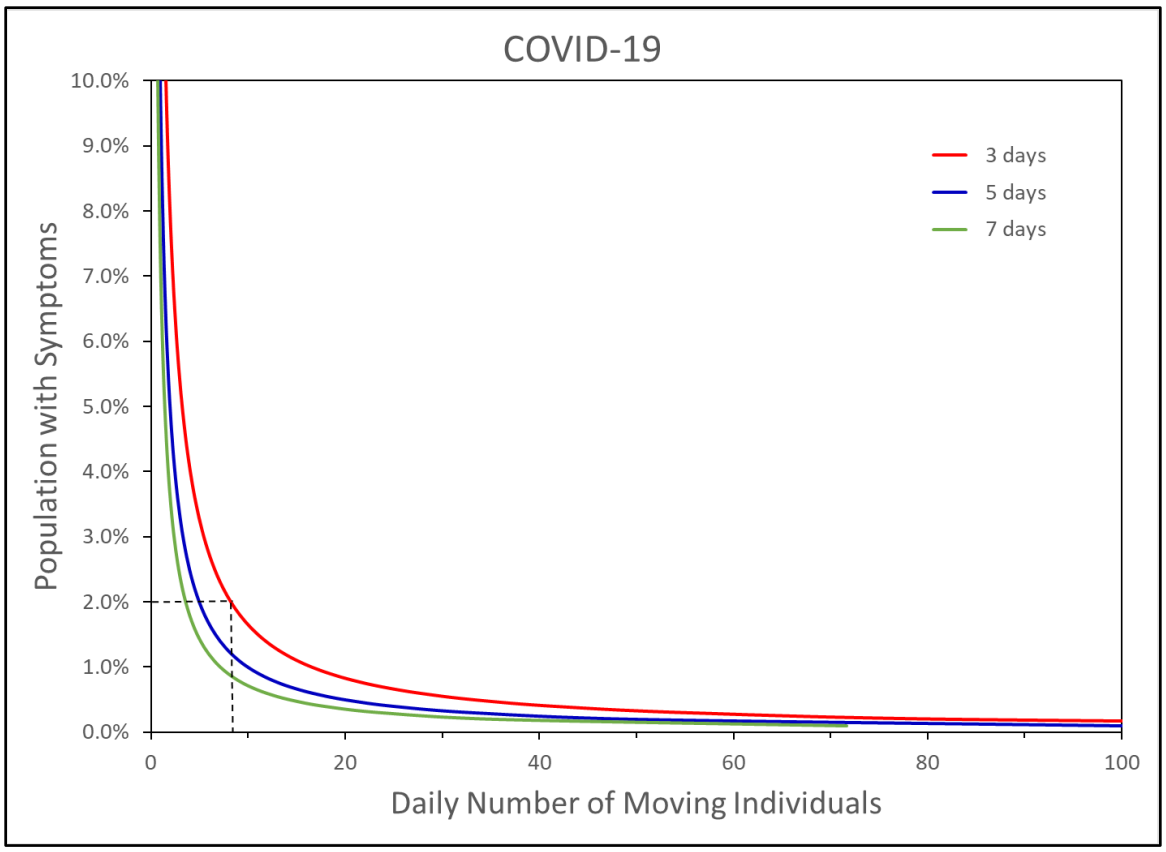

Figure 14. Maximum Movement of Personnel Allowed to Have a 50% Chance of Keeping a Unit Free of COVID-19 for a Period of Interest

Military personnel within a theater of operations are highly mobile: in an earlier study, we found that, on average, 20-25% of personnel deployed to Afghanistan changed location every day.[35] Restricting that movement will disrupt a force's ability to execute many aspects of modern military operations, such as tactical maneuver and just-in-time resupply. The extent of disruption depends on the degree to which movement is restricted; for example, cessation of all movement between units would have a greater impact than cessation of movement between units with contagious individuals and the unaffected units with which they have regular contact. Yet, as part of their ongoing assessment of operational risk, commanders may choose to restrict movement between units in circumstances where the immediate gains offset the costs. Table 7 shows the number of individuals that can be allowed to move, given background rates of infection, to have a 50%, 70%, or 90% chance of keeping a unit free of disease for 3, 5, or 7 days. Note that because this assessment is based on underlying rates of infection, versus numbers of cases, the results are independent of unit population.

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[35] Julia K. Burr et al., *Emerging Infectious Diseases Study*, IDA Paper P-5302, (Alexandria, VA: Institute for Defense Analyses), August 2016: 68

Table 7. Maximum Number of Personnel Allowed to Move Each Day to Have a 50%, 70%, or 90% Chance of Keeping a Unit Free of COVID-19 for a Period of Time

Population with Symptoms	3 Days			5 Days			7 Days		
	50%	70%	90%	50%	70%	90%	50%	70%	90%
0.1%	167	86	25	100	52	15	72	37	11
0.5%	33	17	5	20	10	3	14	7	2
1%	17	9	3	10	5	2	7	4	1
2%	8	4	1	5	3	1	4	2	1
3%	5	3	1	3	2	0	2	1	0
4%	4	2	1	2	1	0	2	1	0
5%	3	2	0	2	1	0	1	1	0
6%	3	1	0	2	1	0	1	1	0
7%	2	1	0	1	1	0	1	1	0
8%	2	1	0	1	1	0	1	0	0
9%	2	1	0	1	1	0	1	0	0
10%	2	1	0	1	0	0	1	0	0

As seen in the table, during an outbreak of COVID-19, almost no movement of personnel, from a population in which disease is circulating into a naïve population, can be tolerated to have a 90% chance of keeping units free of disease for any length of time. To have a better than 50% chance of keeping units free of disease, some degree of movement is possible when background rates of symptomatic infection are very low, but this too drops off quickly when those rates exceed 1-2%. In short, preventing the spread of COVID-19 among units will be very challenging for commanders, and could come at significant operational cost.

G. Other Outbreak Mitigation Measures: Shut-downs, Stay-at-Home Orders, and Masking

Governments at the national, state, and local levels have implemented several additional mitigation measures to reduce community spread of COVID-19, such as masking requirements, limits on the size of gatherings, closure of businesses of specific types, and stay-at-home orders. The effectiveness of such measures is difficult to quantify because they were implemented non-uniformly across communities, in various combinations, and at various times, relative both to the start of the pandemic and to the profile of ongoing disease transmission within the affected community. While the public health community is just now beginning to quantify the population-level impact of these measures, available evidence does suggest that such measures can substantially reduce the spread of COVID-19.

The CDC COVID-19 Response Team published a study in January 2021 that evaluated the impact of national-level mitigation measures on COVID-19 mortality in 37 European nations.[36] This study assessed the impact of the timing and stringency of mitigation policies, using available mortality data and a scoring system for COVID-19 response developed by the University of Oxford. This scoring system encompassed policies such as cancellation of public events, school closures, limits on the size of social gatherings, and stay-at-home orders, but excluded policies on mask wearing. The study found that nations that implemented earlier and more restrictive mitigation policies experienced reduced COVID-19 mortality compared to those that did not.[37]

Stay-at-home orders early in the pandemic appear to have substantially constrained disease transmission. For example, in Arizona, the 7-day moving average of new cases fluctuated between 154 to 443 from the time stay-at-home orders were first implemented on March 30 to when they were lifted on May 15; however, in the six weeks from the time those orders were lifted to when they were partially re-instated on June 29, the 7-day moving average of new cases increased dramatically from 443 to a peak of 4,377.[38] In Delaware during the spring of 2020, confirmed COVID-19 cases peaked 3 weeks after the institution of a mandated stay-at-home order, and declined precipitously thereafter until the order expired on June 1.[39]

Mask wearing appears to have been quite effective at the state level, reversing trends towards increased transmission and reducing mortality. In Arizona, local officials were permitted to mandate the use of masks on June 17, 2020, 12 days before the state's 7-day moving average of new cases peaked and before additional mitigation measures were implemented at the state level. As reported:

> "The number of COVID-19 cases stabilized and began to decrease approximately 2 weeks after local officials began mandating mask wearing (throughout several counties and cities) and enhanced sanitation practices. Additional declines in case counts were associated with implementation of statewide limitations and closures sustained throughout July and extended into August."[40]

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[36] James A. Fuller et al., "Mitigation Policies and COVID-19-Associated Mortality—37 European Countries, January 23-June 30, 2020," *Morbidity and Mortality Weekly Report* 70 (January 12, 2021): 1-5.

[37] Ibid, 2. More specifically, this study found that 1-unit increases in the assessed response score was associated with a decrease of 0.55 deaths per 100,000 in the affected population.

[38] M. Shayne Gallaway et al., "Trends in COVID-19 Incidence after Implementation of Mitigation Measures, Arizona, January 22—August 7, 2020," *Morbidity and Mortality Weekly Report* 69 (October 6, 2020): 2-3.

[39] Kanu et al., "Declines in SARS-CoV-2 Transmissions, Hospitalizations, and Mortality after Implementation of Mitigation Measures—Delaware, March-June 2020:" 2.

[40] Gallaway et al., "Trends in COVID-19 Incidence after Implementation of Mitigation Measures, Arizona:" 3-4.

More controlled evidence of the benefits of masking is described in a study of mask use in Kansas,[41] where the governor issued an executive order on July 3, 2020 requiring that masks be worn in public places. A law passed earlier in the summer permitted counties to opt out of such orders, and by 11 August, 24 counties had issued mask mandates and 81 had not. In both groups, the 7-day rolling average incidence increased each day from June 1 to July 2, although the growth in incidence was approximately three times greater in counties that ultimately mandated masks. In the period after the governor's executive order on July 3 through August 23, the 7-day rolling average incidence in mask-mandated counties fell slightly, from 17 new cases per 100,000 to 16 per 100,000, but doubled in counties where masking was not mandated, from 6 new cases per 100,000 to 12 per 100,000.[42] The authors also noted that 13 of the 24 counties with mask mandates had issued other recommended or mandated mitigations, such as limits on gatherings. Sensitivity analyses showed that "similar decreases in COVID-19 incidence after July 3 were observed among mandated counties with and without other strategies." They therefore concluded that while CDC guidance recommended the use of multiple mitigations, mask use mandates were particularly important tools for controlling the spread of disease.[43]

Evidence of the benefits of masking is further demonstrated in a study of COVID-19 hospitalization rates in states with mask mandates, during March 1-October 17, 2020.[44] This study found that relative to rates seen in the 4 weeks prior to the start of a mask mandate, hospitalizations fell among adults 40-64 years old starting within the first 2 weeks of a statewide mask mandate, and among those 18-39 years old after mask mandates had been in place for 3 weeks or longer. Statistically significant differences were not observed in those 65 and older, although the authors speculated this was due to a prevalence of mask wearing in this population even in the absence of a mandate.

We have not explicitly assessed the potential benefits of mitigation measures such as stay-at-home orders and mask mandates in reducing *R*. Such measures varied in scope, scale, time, and place, making it difficult to generalize, and the available literature is broadly indicative of trends in observed incidence of disease, rather than measured effects. As of this writing, we consider such measures as complements to isolation and quarantine, enhancing their effectiveness given the prevailing rate of vaccine compliance.

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[41] Miriam E. Van Dyke, "Trends in County-Level COVID-19 Incidence in Counties with and without a Mask Mandate—Kansas, June 1-August 23, 2020," *Morbidity and Mortality Weekly Report* 69 (November 20, 2020): 1-5.

[42] Ibid, 2.

[43] Ibid, 3.

[44] Heesoo Joo et al., "Decline in COVID-19 Hospitalization Growth Rates Associated with Statewide Mask Mandates—10 States, March-October 2020," *Morbidity and Mortality Weekly Report* 70 (February 5, 2021): 1-6.

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2. Summary, Conclusions, and Recommendations

A. Summary

In early 2020, just as the 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.[45] The research posited that the primary objective of outbreak control measures is to reduce R—the average number of infections caused by a contagious individual in any given outbreak—below one. We then established relationships between a set of parameters describing characteristics of both disease and response measures, to determine the circumstances in which the latter can be effective, given the former.

As the pandemic evolved, our IDA team worked to extend our previous research to outbreaks of COVID-19. We continue to review the emerging COVID-19 literature, and have expanded the underlying methodology to account for unique aspects of this disease that force us to consider execution of response measures in ways not considered in our earlier research. Specifically, because of the extent of asymptomatic and pre-symptomatic transmission of COVID-19, we consider the potential role of diagnostic testing as a trigger for isolation and quarantine. In addition, in our earlier work, we assumed that compliance with vaccination or other pre-exposure prophylaxis would be universal in our population of interest; because we found vaccination to be so successful in achieving $R < 1$ for the diseases we included, we did not consider vaccination in combination with other control measures. In our current assessment of COVID-19 control measures, we have added vaccine compliance as a parameter of interest, and developed a concept for assessing a progressively layered set of responses that begins with vaccination.

This analysis evaluates the sufficiency and requirements for implementation of five combinations of outbreak control measures: 1) vaccination alone; 2) isolation alone; 3) vaccination and isolation in combination; 4) vaccination, isolation of symptomatic cases, and isolation of positive test cases; and 5) vaccination, isolation, and quarantine. We have summarized our base-case results in Figure 15. Table 8 shows the value of various combinations of response measures in addition to vaccination, expressed in terms of the vaccine compliance required to achieve $R < 1$ when those measures are implemented.

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[45] Julia K. Burr, Robert L. Cubeta, Lucas A. LaViolet, and Sean M. Oxford, IDA P-10877, *Controlling the Spread of Contagious Disease in an Operational Environment* (Alexandria, VA: Institute for Defense Analyses), February 2020.

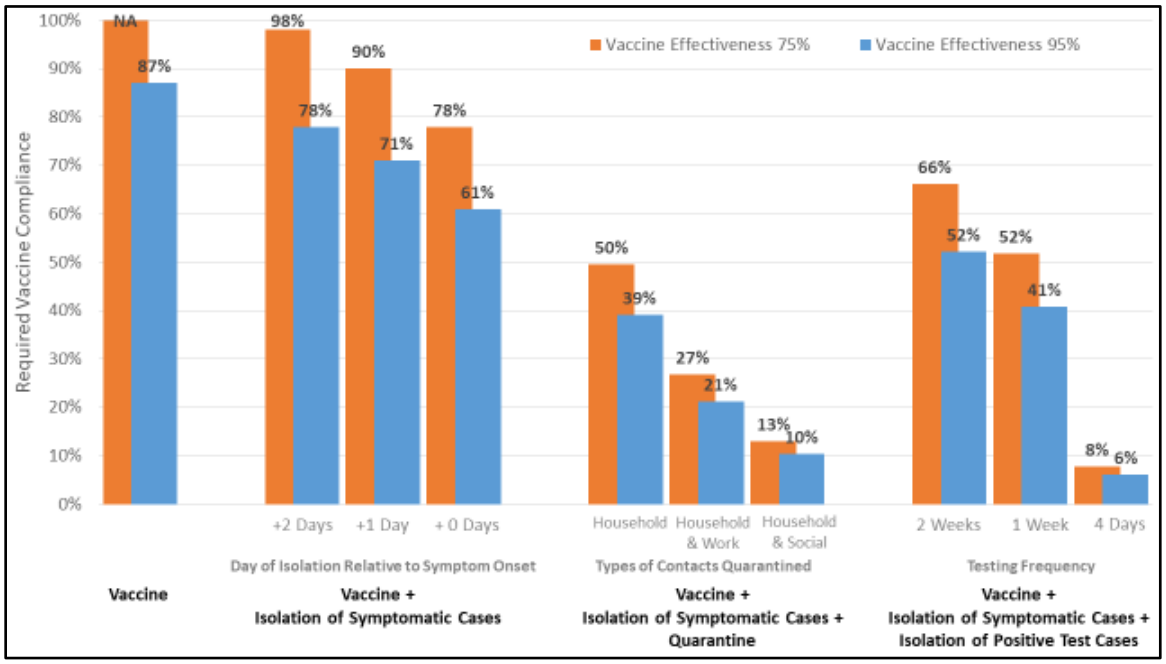

Figure 15. Effectiveness of Various Combinations of Outbreak Control Measures, Given Rate of Vaccine Compliance and R_0 = 5.9

Table 8. Benefit of Various Combinations of Control Measures, Expressed as the Change in Vaccine Compliance Needed to Achieve R < 1 Compared to Vaccines Alone

Control Measure	Implementation Rule	Reduction in Needed Vaccine Compliance, Vaccine Effectiveness = 95%	Reduction in Needed Vaccine Compliance, Vaccine Effectiveness = 75%
Vaccination+ Isolation of Symptomatic Cases	Isolation at Symptom Onset + 2 Days	9%	2%
	Isolation at Symptom Onset + 1 Day	16%	10%
	Isolation at Symptom Onset	26%	22%
Vaccination + Isolation of Symptomatic Cases + Quarantine	Household Contacts	48%	50%
	Household & Work Contacts	66%	73%
	Household & Social Contacts	77%	87%
Vaccination + Isolation of Symptomatic and Positive Test Cases	Testing Every Two Weeks	35%	34%
	Testing Every Week	46%	48%
	Testing Every Three Days	81%	92%

Vaccination. While vaccination can be a very effective means of achieving $R < 1$, the vaccine efficacy required to do so is determined by the R_0 of the disease. Our COVID-19 base-case R_0 of

5.9 is quite high relative to other diseases, and therefore so too is the efficacy required for vaccination alone to control an outbreak: assuming universal compliance, the vaccine effectiveness required is 83%. For the excursion R_0 value of 2.5, the vaccine effectiveness required is 60%. COVID-19 vaccines have demonstrated efficacy of 95% against most variants; this means that vaccines do indeed have the potential, in and of themselves, to cause an outbreak to wane in our base case. 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 efficacy—chosen to represent the lower bound of demonstrated efficacy in preventing infection from variants of concern—is insufficient.

As vaccine compliance falls below 100%, an increasing fraction of the population will remain vulnerable to infection. At a certain point, even completely effective vaccines would fail to control outbreaks. As shown in Figure 15, 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 control an outbreak. For the excursion vaccine effectiveness of 75%, even 100% compliance will be insufficient for an R_0 of 5.9. For the excursion R_0 value of 2.5, required compliance with a 95% effective vaccine is 63%, and 80% with a vaccine that is 75% effective.

Isolation. Before COVID-19 vaccines became available, and particularly early in the pandemic, isolation of sick individuals was the primary mechanism for preventing the spread of disease. Yet, COVID-19 creates numerous challenges to rapid isolation of contagious individuals:

- 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;
- the disease is contagious prior to symptom onset, so that a significant portion of transmission cannot be avoided in a regime where isolation is triggered by symptom onset; and
- a significant fraction of COVID-19 infections are asymptomatic yet still contagious to some extent.

We found that there were virtually no circumstances in which isolation of symptomatic individuals was, on its own, sufficient to cause an outbreak to wane. Consequently, we omitted this option from Figure 15.

Vaccination plus isolation. We found that isolation of symptomatic individuals can indeed have a significant impact on the extent of vaccine compliance required to control an outbreak. The magnitude of that difference depends on the value of R_0: at the higher base-case R_0 value of 5.9, isolation of individuals at the time of symptom onset can substitute for approximately 25 percentage points of vaccine compliance. However, as we have noted, immediate isolation 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 24 and 48 hours after onset of symptoms.

As seen in Figure 15, 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. This is particularly true when isolation is delayed by one or two days. Should the effectiveness of COVID-19 vaccines fall to 75%, the compliance rates required to end the outbreak could well prove prohibitive.

Vaccination plus isolation of symptomatic and positive test cases. 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. Using a simple stochastic model to simulate the probability and time at which contagious individuals—symptomatic, pre-symptomatic, and asymptomatic—would be isolated, we found that isolation triggered by a positive test could indeed be very beneficial. The addition of diagnostic testing to vaccination and isolation can reduce 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.

Vaccination, isolation, and quarantine. Given the limitations of vaccination and isolation in combination, 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. 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.

One major question is how to achieve a given level of quarantine efficacy 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 efficacy, 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 1 day post-symptom onset, household and work contacts must be quarantined, and for isolation at 2 days post-symptom onset, household and social contacts must be quarantined. Alternatively, if quarantine is limited to household contacts and isolation occurs 2 days post-symptom onset, vaccine compliance rates must increase to 60% or 75%, depending on vaccine efficacy.

Figure 15 showed our results for two specific values of vaccine effectiveness: 95% and 75%. Recall that in our work, the effectiveness of vaccines in preventing transmission is assumed to be measured by the extent to which they prevent infection and onward transmission. This definition of vaccine effectiveness is different than that used in clinical trials for vaccines approved for use in the United States, which focused on the prevention of severe illness and death. As discussed in Appendix A, clinical trials and early real-life assessments found that vaccines are generally 95% effective in preventing symptomatic disease and close to 100% effective in preventing severe illness and death, but that for some variants, protection against infection might be lower. Our excursion value of 75% represents a current lower bound of estimated effectiveness in preventing infection, and is associated with specific variants of the disease circulating at the time of this writing.

As COVID-19 variants continue to emerge and circulate, it is certainly possible that vaccine protection against infection and onward transmission could decline over time. Should that happen, additional outbreak control measures will need to be adopted to compensate for that decline. Figure 16 shows the combinations of outbreak control measures can result in $R < 1$, for a given combination of vaccine effectiveness and compliance.[46] 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.

[46] These boundaries are calculated by first determining the reduction in transmission, from R_0 to R, associated with each set of outbreak control measures. This new value of R is then used to calculate the requirements for vaccine effectiveness and compliance, as discussed in Section A above and illustrated in Figure 2.

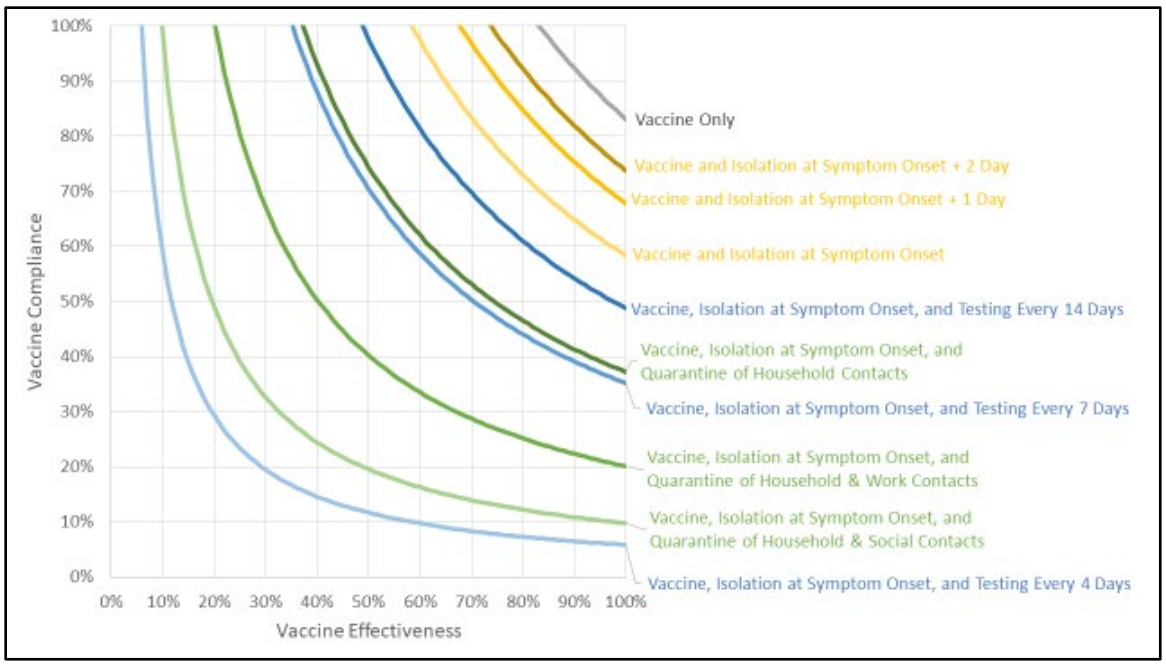

Figure 16. Outbreak Control Measures Needed to Achieve $R < 1$ for All Combinations of Vaccine Effectiveness and Vaccine Compliance

To illustrate, suppose that vaccine compliance is 70% in a population of interest, and the vaccine is 90% effective at preventing infection and onward transmission. In this case, a combination of vaccination and isolation at symptom onset would lead to $R < 1$, and the outbreak would be controlled. Now, suppose that vaccine effectiveness falls to 60%. At this point, vaccination and isolation at symptom onset must be augmented either by quarantine of household contacts or by population-wide screening tests administered every 7 days.

Development and administration of vaccine boosters is one possible solution to this problem, and we can envision an ongoing cycle wherein vaccine effectiveness repeatedly declines and is restored. Thus, while constructs such as that shown in Figure 16 can be used to determine which outbreak control measures should be added when vaccine effectiveness declines, they can also be used to determined which measures can be removed as either vaccine compliance or vaccine effectiveness increase.

B. Conclusions

Prevailing rates of vaccine compliance at the time of this writing would suggest that COVID-19 transmission can continue at the population level, despite current vaccine effectiveness in preventing infection from circulating variants in the United States. The primary message of our analysis is that outbreak control measures in combination can effectively cause COVID-19 outbreaks to wane at population-wide vaccine compliance rates of perhaps 50-60%. While the United States has yet to achieve that rate, removing 15% of the susceptible population from the equation based on their residual immunity could well make the difference. In addition, other

behavioral adaptations and remaining mitigation measures undoubtedly continue to suppress transmission, such that R is almost certainly much lower than R_0 in the United States at this stage of the pandemic.

Still, emergence and spread of variants against which vaccines are less effective continues to be a risk. As long as vaccine compliance rates remain low, 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, quarantine and/or testing can be used effectively to truncate transmission. While these measures are more burdensome than vaccination and isolation, they can be implemented in minimally onerous ways, through quarantine of readily identifiable household contacts, or screening tests administered weekly.

Finally, we found that overall, even with asymptomatic and pre-symptomatic transmission, the challenge of COVID-19 could still be met with various response measures implemented in less than optimal ways when R_0 is 2.5; in other words, an outbreak could still be controlled even with low vaccine compliance, delays in isolation or isolation of less than 100%, limited or no testing, or limited or delayed quarantine. Unfortunately, the R_0 value of 2.5 estimated early in the pandemic is almost certainly too low, for a variety of reasons discussed in Appendix A.[47] For our base-case R_0 of 5.9, more responses are required and they must be implemented in a much more rigorous way: higher levels of vaccine compliance, isolation at symptom onset, and the addition of testing or quarantine. While R_0 itself cannot be readily manipulated, the prevailing value of R may be reduced by mitigation policies such as mask mandates and restrictions on the size of social gatherings can constrain transmission. Such policies can therefore enhance the effectiveness of more direct outbreak control measures such as those we have assessed.

C. Recommendations

Based on our assessment of measures to control outbreaks of COVID-19, and our review of the available literature, we applaud the DOD's recent decision to mandate vaccination of service members. In addition, we have the following recommendations for OTSG, the Army (and other services),[48] and the Department of Defense:

- DOD should enforce and execute its vaccine mandate as quickly as possible.
    - Rationale: Because COVID-19 is so transmissible, at least 87% of personnel must be vaccinated for an outbreak to be controlled, assuming is the vaccine is 95% effective in preventing infection (see Figure 2). At the time of this writing,

[47] For example, early estimates of R_0 did not account for asymptomatic cases or, typically, those that did not require hospitalization or demonstrate evidence of pneumonia. We now know that these severe cases represent a minority of the total.

[48] Because it is the sponsor of this research, we specified the Army in recommendations that would be implemented at the service level; however, unless these recommendations apply specifically to the Army in the execution of its executing agency functions, they can and should be extended to other services.

vaccination among service members has not achieved this level of compliance. Moreover, vaccines appear to be less effective in preventing infection from some COVID-19 variants, increasing the fraction of the population that must be vaccinated to achieve $R < 1$.

- DOD should continue to promote a culture in which sick individuals self-isolate ("if you're sick, stay home"), and ensure that such individuals have sufficient sick leave and appropriate medical support while in isolation.
    - Rationale: While isolation of symptomatic individuals will not, in and of itself, control an outbreak of COVID-19, when used in combination with other control measures it can be very effective, and can compensate to some extent for a lack of vaccine compliance (see Figure 5). The benefits of isolation are significantly greater the earlier in the course of the disease it can be implemented: even delaying isolation two days will nearly double the mean number of resulting infections compared to isolation at symptom onset (see Figure 4). Barriers to isolation at symptom onset include very mild, non-specific, and variable symptoms in the early course of illness, and organizational or financial imperatives to continue work. Throughout the pandemic, DOD and service organizations have instituted practices to rapidly identify symptomatic individuals, to prevent symptomatic individuals from reporting to work, and to provide tools to enable remote work where possible. Continuing these practices will limit the impact of future disease outbreaks on the health of DOD personnel, whether from COVID-19, other emerging diseases, or seasonal colds and influenza.
- The Army (and other services) should be prepared to sustain or resume outbreak control measures, to include public health measures such as social distancing and mask wearing, in the event transmission of COVID-19 begins to increase, either within a particular unit, if the outbreak is localized, or among the military population more broadly, if the outbreak is widespread.
    - Rationale: Prompt recognition of and response to local outbreaks is critical to ensure the outbreak is controlled before it spreads widely. Constructs such as provided in Figure 16 can be used to determine the most appropriate control measures, given vaccine effectiveness and compliance within the affected population.
- The Army (and other services) should sustain surveillance of military populations for COVID-19, and ensure prompt reporting and tracking of cases, to include identification and tracking of variant strains.
    - Rationale: Prompt recognition of and response to local outbreaks is critical to ensure the outbreak is controlled before it spreads widely. Laboratory analysis to

determine the prevailing virus strains is an important component of surveillance: those strains against which vaccines are less effective can lead to changes in recommended control measures.

- The Army (and other services) should be prepared to implement quarantine of residents of congregate housing in which cases of COVID-19 have been detected, and support quarantine of service members who are household contacts of identified cases.
    - Rationale: As shown in Figure 15, quarantine of those who may have been exposed to COVID-19 can be a very effective control measure, when used in combination with vaccination and isolation. Our analysis has shown that rapid quarantine of readily identifiable groups of individuals—starting with household contacts—will often be sufficient to control an outbreak (see Figure 13).
- The Army and OTSG should procure and stockpile fast, simple COVID-19 tests that can be rapidly issued, and used as often as every seven days to screen for asymptomatic and pre-symptomatic infections in units or organizations in which cases begin to increase.
    - Rationale: Routine testing can be used to screen a population of interest for cases of asymptomatic and pre-symptomatic COVID-19, expediting their isolation before symptom onset. Given the rates of vaccine compliance in the United States population at the time of this writing, and the continued effectiveness of the vaccine, testing need only be administered every two weeks to ensure that R remains below 1. As shown in Figure 16, should vaccine effectiveness decline in the future, testing will need to be conducted more frequently.

D. Limitations and Observations

The results of this analysis are closely tied to our current understanding of COVID-19, around which there remains significant uncertainty. At the time of this writing, for example, much about transmission from asymptomatic infections is largely speculative, including its duration, extent, and primary mechanisms. Because much of our work focuses on establishing relationships between parameters that describe characteristics of diseases and responses, we can readily update our results as the collective understanding of COVID-19 increases and our assumed parameter values change.

Emerging data does suggest that the most restrictive and onerous mitigation measures—business closures and stay-at-home orders—were highly effective in truncating transmission, but these were difficult to sustain. Our work suggests that isolation and quarantine, particularly in combination with vaccination, can be equally effective in achieving the same objective if implemented rigorously. We have not attempted to directly assess the burdens of outbreak control measures of various types, but do postulate that targeted measures limited to individuals known or suspected of being at risk are less burdensome than blanket measures that impact the population

as a whole. However, as we note repeatedly, successful implementation of targeted measures requires an understanding of COVID-19 transmission dynamics and clinical presentation. As described in our literature review in Appendix A, knowledge of those factors was not available when the pandemic began, and took several months to determine with sufficient certainty to enable the requirements for and effectiveness of control measures to be assessed.

The R_0 value of 5.9 that we used as a base case is significantly higher than the earliest estimates of the R_0 for SARS-CoV-2, which centered around 2.5. As discussed in Appendix A, we found that the early estimates of R_0 were driven by assumptions about the nature of the disease and its transmission that ultimately proved incorrect, and we found the arguments for the higher value to be compelling. As the pandemic has progressed, more transmissible SARS-CoV-2 variants have emerged and become dominant: the alpha variant, for example, is estimated to have an R_0 that is 40%-90% higher than earlier variants,[49] and by late July 2021, the CDC had estimated that the delta variant had an R_0 of approximately 8.5 and was as contagious as chickenpox.[50] The evolution in transmissibility of COVID-19 obviously increases the uncertainty surrounding our estimates of control measure effectiveness. Nonetheless, we believe that our recommendations remain valid. As transmissibility increases, so too does the speed with which control measures can be implemented. In our analysis, we found that either quarantine or isolation triggered by testing could be used in combination with vaccination and isolation triggered by symptoms to overcome low rates of vaccine compliance. Given high transmissibility variants, both of these measures may be needed.

For COVID-19, our understanding of disease transmission is primarily based on an observed relationship between viral load, as measured by PCR testing, and the viability of virus in culture. In particular, this relationship has been used to establish the onset and duration of contagiousness and the role of asymptomatic and pre-symptomatic transmission. Yet, the laboratory work needed to derive this relationship was limited in scope and scale in the early months of the pandemic. In the future, as SARS-CoV-2 variants and other novel diseases emerge, an earlier, more systematic effort to establish a profile of disease transmission over time can support earlier, more effective implementation of outbreak control measures, and perhaps avoid some of the economic and social costs of a pandemic.

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[49] Nicholas G. Davies et al., "Estimated Transmissibility and Impact of SARS-CoV-2 Lineage B.1.1.7 in England," *Science* 372 no. 149 (9 April 2021): 1-9. https://doi.org/10.1126/science.abg3055.

[50] Yasmeen Abutaleb, Carolyn Y. Johnson, and Joel Achenbach, "'The War has Changed': Internal CDC Document Urges New Messaging, Warns Delta Infections Likely More Severe," *The Washington Post*, July 29, 2021. https://www.washingtonpost.com/health/2021/07/29/cdc-mask-guidance/.

Appendix A. Parameter Value Sources and Selection

This analysis defines parameters that can be used to evaluate requirements for implementation of disease outbreak response measures; the values assigned to these parameters are mostly disease-dependent. Not unexpectedly, COVID-19 presented a number of challenges to our efforts to determine the best values to use to populate the parameters in our analysis. The magnitude of the scientific and medical community effort to understand COVID-19 has generated a staggering amount of relevant published data and analysis. As a result, our understanding of this new disease has expanded and evolved, and continues to do so. Yet, there remains significant uncertainty in many of the disease characteristics directly relevant to our assessment of outbreak response requirements. At the same time, the behavior of COVID-19 within the human population has expanded the complexity of response and led to the use of some measures, such as diagnostic testing, in ways unforeseen in our original work.

Over the course of our current efforts, from March 2020 through March 2021, we monitored published and preprinted COVID-19 literature, and reviewed available data describing specific characteristics of interest, such as the estimated R_0 value and latent period of the disease. While by necessity we needed an endpoint for the selection of parameter values, we sought to ensure that our work could be readily updated should consensus around any of these values change with time.

Broadly speaking, COVID-19 literature can be divided into three main categories: 1) laboratory test data and patient case studies; 2) epidemiological investigations; and 3) population-level outbreak modeling studies. We have observed a growing consensus over certain COVID-19 characteristics, such as the likelihood of pre-symptomatic spread of disease, as it has been supported by observations and conclusions in all three of these categories. When selecting parameter values, to the extent possible we have sought those that reflect this coalescence of multiple types of data and analysis.

The key disease parameters used in our assessment of outbreak control measures are provided in the main body of this analysis and in Table A-1, together with base-case and excursion values for COVID-19. The base-case values reflect what we believe the evidence suggests is most reasonable, given current knowledge of this disease. In many instances, a strong case can be made for the use of different values, and we include these as excursions. However, the uncertainty surrounding these values is not formally addressed in our analysis, and the values used should not be considered the full range of possibility. The degree of confidence in and consensus around our selected values is discussed qualitatively in the sections that follow.

Both the U.S. Centers for Disease Control and Prevention (CDC) and the U.S. Department of Homeland Security (DHS) have published and regularly updated parameter values for biological and epidemiological characteristics of COVID-19 on their websites, respectively entitled "COVID-19 Pandemic Planning Scenarios" and "Master Question List for COVID-19."[51] The stated goal of these documents is to synthesize the enormous and continually growing body of available literature and to support COVID-19 response decision-making across the federal government.

The DHS values have been updated weekly, and the CDC values were updated for a final time on 19 March 2021. Together with their associated reference lists and rationale, these two sets of values served as a major point of departure for our literature review. In many cases, our base-case parameter values are consistent with those published by these two organizations; where we have deviated from them, we used the DHS or CDC "best estimate" as our excursion value.

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

Parameter	Base-Case Value(s)	Excursion Value(s)
R_0	5.9	2.5
Vaccine effectiveness	95%	75%
Mean incubation period	6 days	7 days
Mean latent period	3 days	
Period of symptomatic contagiousness	9 days	
Duration of contagious period	12 days	
Time of peak contagiousness	One day prior to symptom onset	At symptom onset
% of transmission that occurs during pre-symptomatic period (calculated)	32.5%	25%
% of cases that are asymptomatic	30%	70%
Relative contagiousness of asymptomatic cases	.25	

[51] CDC, "COVID-19 Pandemic Planning Scenarios," https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html, accessed 25 May 2021; and DHS, "Master Question List for COVID-19 (caused by SARS-CoV-2)," https://www.dhs.gov/publication/st-master-question-list-covid-19, accessed 25 May 2021. To reinforce the challenges of selecting COVID-19 parameter values, and the limits of any insights derived therefrom, the CDC web site notes: "New data on COVID-19 are available daily, yet information about the biological aspects of SARS-CoV-2 and epidemiological characteristics of COVID-19 remain limited, and uncertainty remains around nearly all parameter values."

Basic Reproduction Number (R_0)

R_0 is the average number of infections a contagious individual would be expected to cause in a completely susceptible population. This value is determined by a combination of disease characteristics, such as mode of transmission and duration of the contagious period, and social factors, such as population density and contact patterns. R_0 describes disease transmission unconstrained by outbreak control measures, adaptive changes in population behavior, growing herd immunity, or any other mitigations.

The parameter R_0 can be contrasted with the effective reproduction number, defined in our work as the parameter R: the mean number of infections caused by a contagious individual in a population where transmission is constrained for various reasons.[52] At a basic level, disease outbreaks grow when R is greater than one and each contagious individual, on average, infects more than one other individual. Outbreaks wane when R is less than one and each contagious individual, on average, infects less than one other individual.

When outbreaks of contagious disease begin, the value of R can be considered approximately equal to the value of R_0, but will decline over time as populations naturally adjust their behavior, as immunity within the population grows, and as active outbreak response measures are implemented to prevent the spread of disease. This concept is at the heart of our analysis: we assess the extent to which outbreak response measures, individually and in combination, will cause the value of R to fall from R_0 to below one. From there, we can establish the requirements for implementation that will allow response measures to achieve that desired end. The higher the value of R_0, the more difficult it will be to successfully control an outbreak of a given disease.

Despite the prevalence of the concept,[53] R_0 has generally proven difficult to estimate. Observations of disease transmission within an outbreak reflect the value of R at any point in time; as noted, R can change over time, and will generally approach R_0 only in the early phases of an outbreak. Yet, the data needed to estimate R_0 are unlikely to be widely available either in real time or retrospectively. Impediments to early and accurate data collection abound: case definitions, case reporting, active disease surveillance, and epidemiological investigations take time to develop and execute. Moreover, there are numerous methods available to calculate R_0, using different inputs and assumptions and generating different values.[54] Finally, there really is no true, single value for the R_0 of a given disease. Because disease transmission is heavily influenced by socio-economic

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[52] This parameter is often referred to as R_a in the literature. Since our earlier paper defined this parameter simply as R, we have retained that convention here for consistency.

[53] "The basic reproductive ratio, R_0, is one of the fundamental concepts in mathematical biology…R_0 has been widely used as a measure of disease strength to estimate the effectiveness of control measures and to form the backbone of disease-management policy." Jing Li, Daniel Blakely, and Robert J. Smith, "The Failure of R_0," *Computational and Mathematical Methods in Medicine*, Volume 2011, May 2011, doi:10.1155/2011/527610, 1.

[54] Li et al., "The Failure of R_0," 2.

factors that vary from country to country or region to region, R_0 too will likely vary by location.[55] Estimates based on data from one location may not reflect the dynamics of disease transmission in another.

Estimating a value of R_0 for COVID-19 has been particularly challenging.[56] Early documentation of cases and epidemiological investigations to track disease transmission—key inputs to the calculation of R_0—were hampered by a lack of understanding of key disease characteristics, including the wide range of clinical manifestations of disease, the predominance of mild cases, and the potential contribution of asymptomatic cases to the spread of disease. At the start of the pandemic in Wuhan, China, case reporting was focused on hospitalized individuals diagnosed with "novel coronavirus-infected pneumonia," detected via China's program for surveillance of pneumonia of unknown etiology. Initial working case definitions were fairly narrow, requiring both fever and pneumonia, and were based on those of other novel coronavirus diseases, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS).[57] Diagnostic tests needed to confirm cases of COVID-19 and the protocols to use them had only recently been developed.[58]

In the spring of 2020, an early consensus emerged from the literature that the value of R_0 for COVID-19 early in the epidemic in Wuhan was likely between 2 and 3. Liu et al. reviewed a dozen early estimates of R_0 for COVID-19 published between 1 January and 7 February 2020.[59] The estimates, based primarily on reported cases in Wuhan early in the epidemic, "ranged from 1.4 to 6.49, with a mean of 3.28, a median of 2.79 and interquartile range (IQR) of 1.16." Observing that the more recent of the estimated R_0 values—which may have benefitted from improved data quality and availability—tended to stabilize between 2 and 3, the authors concluded that the R_0 for

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55 For discussion of how social factors may influence the R_0 for COVID-19, see (for example): Benjamin Rader, Anjalika Nande, Ben Adlam, et al., "Crowding and the Epidemic Intensity of COVID-19 Transmission," medRxiv 2020.04.15.20064980; doi: https://doi.org/10.1101/2020.04.15.20064980; and Karla Therese L. Sy, Laura F. White, and Brooke Nichols, "Population Density and Basic Reproductive Number of COVID-19 across United States Counties," medRxiv 2020.06.12.20130021; doi: https://doi.org/10.1101/2020.06.12.20130021.

56 Katarina Zimmer, "Why R_0 is Problematic for Predicting COVID-19 Spread," *The Scientist*, July 13, 2020, accessed online at https://www.the-scientist.com/features/why-r0-is-problematic-for-predicting-covid-19-spread-67690.

57 Tim K. Tsang, Peng Wu, Yun Line, Eric H.T. Lau, Gabriel M. Leung, and Benjamin J. Cowling, "Effect of Changing Case Definitions for COVID-19 on the Epidemic Curve and Transmission Parameters in Mainland China: A Modelling Study," *The Lancet Public Health*, 5 (May 2020): e291.

58 Qun Li et al., "Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia," *The New England Journal of Medicine*, 31 January 2020, DOI: 10.1056/NEJMoa2001316.

59 Ying Liu et al., "The Reproductive Number of COVID-19 is Higher Compared to SARS Coronavirus," *Journal of Travel Medicine* 27, no. 2 (13 February 2020): 1-4, https://doi.org/10.1093/jtm/taaa021.

COVID-19 early in the epidemic in Wuhan likely falls within that range. This conclusion is generally consistent with subsequent investigations of early disease transmission in China.[60]

Several studies analyzing the spread of COVID-19 outside China also reported values for R_0 that were largely consistent with the likely range for Wuhan. Estimated values of R_0 based on data from the Diamond Princess cruise ship (2.28),[61] Japan (2.5),[62] and Iran (2.7)[63] fell within that range, while estimates based on data from the Republic of Korea (2.6 or 3.2) and Italy (2.6 or 3.3) were within or just above that range, depending on the assumed start date of exponential growth in cases in each country.[64]

The current CDC best estimate of the R_0 for COVID-19 is 2.5, with a range from 2.0 to 4.0;[65] the DHS Master Question List for COVID-19 states "estimates of human transmissibility (R_0) range from 2.2 to 3.1."[66] These estimates continue to reflect the early consensus on the value of R_0 in the literature: the ranges provided by the CDC represent the upper and lower bounds of the widest confidence intervals calculated by Li et al. in their study of early COVID-19 transmission dynamics in Wuhan.[67]

There is substantial reason to believe these early estimates of R_0 are low. They are based predominantly on analysis of confirmed cases in China through January 2020, at which time confirmation was achieved through diagnostic testing (PCR or whole-genome sequencing) of suspected cases, narrowly defined as symptomatic individuals from Wuhan, with fever and

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60 Qun Li et al., "Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia," op cit.; Zhanwei Du et al., "Risk for transportation of 2019 novel coronavirus disease from Wuhan to other cities in China," *Emerging Infectious Diseases* 26, no. 5 (May 2020): 1049–52, https://dx.doi.org/10.3201/eid2605.200146; and Tao Zhou et al., "Preliminary prediction of the basic reproduction number of the Wuhan novel coronavirus 2019-nCoV," *Journal of Evidence-based Medicine* 13, no. 1 (12 February 2020): 3–7, https://doi.org/10.1111/jebm.12376.

61 Sheng Zhang et al., "Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis," *International Journal of Infectious Diseases* 93 (2020): 201–204, https://doi.org/10.1016/j.ijid.2020.02.033.

62 Sugishita et al., "Preliminary evaluation of voluntary event cancellation as a countermeasure against the COVID-19 outbreak in Japan as of 11 March, 2020," medRxiv (16 March 2020), https://doi.org/10.1101/2020.03.12.20035220.

63 Ahmad Khosravi et al., "The basic reproduction number and prediction of the epidemic size of the novel coronavirus (COVID-19) in Shahroud, Iran," medRxiv (8 April 2020), https://doi.org/10.1101/2020.04.04.20052308.

64 Zian Zhuang et al., "Preliminary estimating the reproduction number of the coronavirus disease (COVID-19) outbreak in Republic of Korea and Italy by 5 March 2020," medRxiv (10 March 2020), https://doi.org/10.1101/2020.03.02.20030312.

65 https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html, accessed 1 Mar 2021.

66 https://www.dhs.gov/publication/st-master-question-list-covid-19, p. 4, accessed 1 Mar 2021.

67 Qun Li et al., "Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia," op cit.

radiographic evidence of pneumonia.[68] Case definitions established by China early in the outbreak, when understanding of COVID-19 was limited, led to significant under-reporting of cases. One study estimates that before January 23, 2020, 92% of cases in China went undetected.[69]

Subsequent analyses of the outbreak in its early period in China have calculated estimates of R_0 that are somewhat larger than these initial estimates of R_0 in Wuhan. A systematic review of 23 studies estimating the R_0 for COVID-19 in China, published in March 2020,[70] generated a pooled R_0 estimate of 3.32; the R_0 estimate provided in these studies ranged from 1.90 to 6.49. One of these studies included a reanalysis of an early study of data from China by the original authors generated a revised R_0 estimate approximately 50% higher than their original value.[71]

One such analysis conducted by a group of researchers at Los Alamos National Laboratory,[72] estimated the median R_0 value for COVID-19 in China to be 5.7.[73] This analysis sought to reduce the dependency of R_0 on the reporting of cases in Wuhan, which could be "confounded by reservoir spillover events, stochasticities in the initial phase of the outbreak, and low surveillance intensity."[74] Instead, the growth of cases in Wuhan was inferred by combining information on COVID-19 cases in Chinese provinces other than Hubei, where Wuhan is located, with the reported rates of travel between Wuhan and those provinces. This study is cited in the CDC Planning Scenarios document[75] as a noteworthy example of the uncertainty surrounding R_0 and an indication that the value may be higher than previously thought.

When the outbreak of COVID-19 in China spread to other countries, researchers began to estimate R_0 for the disease in other parts of the world. Recognizing the challenge of under-reporting, some of this work adopted methods to derive R_0 from reported COVID-19 fatalities, as

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68 Tim K. Tsang, Peng Wu, Yun Line, Eric H.T. Lau, Gabriel M. Leung, and Benjamin J. Cowling, "Effect of Changing Case Definitions for COVID-19 on the Epidemic Curve and Transmission Parameters in Mainland China: A Modelling Study," *The Lancet Public Health*, 5 (May 2020): e291.

69 Tsang, et al., "Effect of Changing Case Definitions for COVID-19": e294.

70 Yousef Alimohamadi, Mrayam Taghdir, and Mojtaba Sepandi, "Estimate of the Basic Reproduction Number for COVID-19: A Systematic Review and Meta-analysis," *Journal of Preventive Medicine and Public Health* 53 (2020):151-7, https://doi.org/10.3961/jpmph.20.076.

71 Tao Liu et al., "Transmission dynamics of 2019 novel coronavirus (2019-nCoV)," bioRxiv (26 January 2020), https://www.biorxiv.org/content/10.1101/2020.01.25.919787v1 reported an R_0 of 2.9, whereas the newer study (Tau Liu et al., "Time-varying transmission dynamics") reported an R_0 of 4.4 for Wuhan. The original analysis was included in the review by Ying Liu et al., "The reproductive number of COVID-19."

72 Steven Sanche et al., "High contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2," *Emerging Infectious Diseases* 26, no. 7 (7 April 2020), https://doi.org/10.3201/eid2607.200282.

73 Sanche et al., "High Contagiousness and Rapid Spread:" 1475.

74 Sanche et al., "High Contagiousness and Rapid Spread."

75 https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html, accessed 1 Mar 2021.

the most reliable reflection of transmission rates. Studies using this approach estimated R_0 values of 5.2 for Turkey[76] and 6.94 for the United Kingdom.[77]

Population-level estimates of R_0 are typically derived from serial interval values,[78] defined as the time between symptom onset in an index case and symptom onset in a secondary case in a transmission pair. Longer contagious periods are associated with longer serial intervals and higher R_0 values. However, serial intervals are determined not just by the characteristics of disease but on the behavior of the population, and will change with time as transmission is truncated by various means. In the early days of the outbreak, the restrictive case definition for COVID-19 used in Wuhan meant that transmission generally ceased when patients were isolated in a hospital, and was otherwise unabated from less severe cases in the population. Over time, measures such as quarantine and lock-downs served to truncate transmission, and hence reduce the serial interval. The body of COVID-19 literature reports a wide range of serial intervals, and are one explanation for the variability of R_0.

As the pandemic progressed, so too did the broad communal understanding of COVID-19 presentation and transmission dynamics. One critical characteristic of the disease, unknown in the early weeks of the outbreak in China, is the extent of pre-symptomatic transmission. The existence of pre-symptomatic transmission lengthens the estimated contagious period of the disease and results in longer mean serial intervals and higher estimated values for R_0.[79]

The group of researchers at Los Alamos[80] referenced above developed an approach to estimating the value of R_0 in the United States and eight European countries that accounted for pre-symptomatic transmission and incorporated a serial interval of 6-8 days. This study inferred transmission dynamics from confirmed case counts and COVID-19 deaths reported by March 31, 2020. Combining estimates of national-level epidemic growth rates and detection probability with consensus values for latent period and contagious period, the group estimated an R_0 value of 5.9 for the United States, and values ranging between 3.5 and 6.4 for the European countries assessed.

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76 Ibrahim Halil Aslan et al., "Modeling COVID-19: Forecasting and Analyzing the Dynamics of the Outbreak in Hubei and Turkey," medRxiv (15 April 2020), ttps://doi.org/10.1101/2020.04.11.20061952

77 Greg Dropkin, "COVID-19 UK Lockdown Forecasts and R_0," *Frontiers in Public Health* (29 May 2020), https://doi.org/10.3389/fpubh.2020.00256.

78 R. Ke, E. Romero-Severson, S. Sanche, and N. Hengartner, "Estimating the Reproductive Number R_0 of SARS-CoV-2 in the United States and Eight European Countries and Implications for Vaccination," *Journal of Theoretical Biology* (2021): 9; doi: https://doi.org/10.1016/j.jtbi.2021.110621.

79 Ke et al., "Estimating the Reproductive Number R_0 of SARS-CoV-2 in the United States and Eight European Countries:" 10.

80 Ke et al., "Estimating the Reproductive Number R_0 of SARS-CoV-2 in the United States and Eight European Countries."

As shown in Table A-1, we chose an R_0 value of 5.9 for our base case, following the Los Alamos study and a value of 2.5 as an excursion, based on early estimates from Wuhan. While on the higher range of published estimates, we found the approach and input values used to generate the Los Alamos estimate to be compelling and well-supported. Moreover, epidemiological studies and more geographically focused analysis of case reports in the United States have found effective reproductive numbers—estimates of transmission that are by definition smaller than R_0—to be significantly higher than 2.5.[81] For example, one study of COVID-19 surveillance data collected by the Georgia Department of Public Health estimated that prior to implementation of a statewide shelter-in-place order, the effective reproductive number reached as high as 6 in 2 of the 5 counties examined, and was 2 or less in only one county.[82] Finally, future outbreaks of COVID-19 may well be caused by more transmissible variant strains of the virus, such as those that are becoming dominant in the current pandemic. For example, the transmissibility of the B. 1.1.7 variant that emerged in the United Kingdom is estimated to be 60%-71% higher than other circulating variants in various regions of that country.[83] Consequently, when evaluating response measures for future outbreaks of COVID-19, it is reasonable to consider relatively high estimates of transmissibility.

Effectiveness of Medical Countermeasures

Medical countermeasures are medical interventions—generally pharmaceuticals—that diminish the susceptibility of personnel exposed to pathogens, or that treat illnesses resulting from such exposure. At the time of this writing, there are three vaccines authorized in the United States to prevent COVID-19: the BNT162b2 messenger RNA vaccine manufactured by Pfizer-BioNTech; the mRNA-1273 messenger RNA vaccine manufactured by Moderna; and the JNJ-78436735 viral vector vaccine manufactured by Janssen Pharmaceuticals Companies of Johnson & Johnson.[84]

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[81] See, for example, Karla Therese L. Sy, Laura F. White, and Brooke Nichols, "Population Density and Basic Reproductive Number of COVID-19 across United States Counties," medRxiv preprint doi: https://doi.org/10.1101/2020.06.12.20130021, and Benjamin Rader et al., "Crowding and the Epidemic Intensity of COVID-19 Transmission," medRxiv preprint doi: https://doi.org/10.1101/2020.04.15.20064980.

[82] Max S. Y. Lau et al., "Characterizing Superspreading Events and Age-Specific Infectiousness of SARS-CoV-2 Transmission in Georgia, USA," PNAS 117 no. 36 (September 8, 2020): 22431, https://www.pnas.org/cgi/doi/10.1073/pnas.2011802117.

[83] Nicholas G. Davies et al., "Estimated Transmissibility and Severity of Novel SARS-CoV-2 Variant of Concern 202012/01 in England," medRxiv preprint doi: https://doi.org/10.1101/2020.12.24.20248822. See also Eric Volz et al., "Evaluating the Effects of SARS-CoV-2 Spike Mutation D6114G on Transmissibility and Pathogenicity," *Cell* 184 (January 7, 2021): 64-75, https://doi.org/10.1016/j.cell.2020.11.020.

[84] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html, accessed 26 May 2021.

In clinical trials:

- the Pfizer vaccine was 95% effective in preventing laboratory-confirmed COVID-19 illness;
- the Moderna vaccine was 94% effective in preventing laboratory-confirmed COVID-19 illness; and
- the Johnson & Johnson Janssen vaccine was 66% effective in preventing laboratory-confirmed COVID-19 illness.[85]

The CDC and other government agencies continue to evaluate the effectiveness of these three vaccines in real-world conditions and against new variants of COVID-19. The CDC's most recently published interim estimates of vaccine effectiveness in real-world conditions come from an ongoing study of U.S. health care personnel who have the potential for exposure to SARS-CoV through direct patient contact or indirectly via contact with contagious materials.[86] The study considers both the Pfizer and Moderna messenger RNA vaccines and has so far found them to be 94% effective in preventing symptomatic illness, consistent with the effectiveness observed in clinical trials.[87] The CDC web site also states that "early data show that vaccines help keep people with no symptoms from spreading COVID-19."[88]

The CDC also continues to investigate reported SARS-CoV-2 infections among fully vaccinated individuals ("breakthrough infections") to determine incidence and to identify the virus variants involved.[89] As of April 30, 2021:

- Among the approximately 101 million individuals in the United States fully vaccinated against COVID-19, a total of 10,262 breakthrough cases had been reported from U.S. states and territories;
- 27% of the reported cases were asymptomatic;
- 10% of the reported cases were hospitalized, 29% of them for reasons unrelated to COVID-19;

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85 https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines.html, accessed 26 May 2021.

86 Tamara Pilishvili et al., "Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health Care Personnel—33 U.S. Sites, January- March 2021," *Morbidity and Mortality Weekly Report* 70 no. 20 (May 21, 2021): 753-8.

87 Pilishvili et al., "Interim Estimates of Vaccine Effectiveness:" 754.

88 https://www.cdc.gov/coronavirus/2019-ncov/vaccines/keythingstoknow.html, accessed May 27, 2021.

89 CDC COVID-19 Vaccine Breakthrough Case Investigations Team, "COVID-19 Vaccine Breakthrough Infections Reported to CDC—United States, January 1-April 30, 2021," *Morbidity and Mortality Weekly Report Early Release* 70 (May 25, 2021): 1-3.

- 160 of the reported cases died; the median age of fatal cases was 82 and 18% of them were asymptomatic or died from a cause unrelated to COVID-19.[90]

The authors do note that the number of reported cases is likely undercounted, as individuals with asymptomatic or mild illness may not seek testing once they have been fully vaccinated.

This study also notes that among the 5% of reported cases where genomic sequencing information was available, the proportion of breakthrough infections attributed to variants of concern is similar to the proportion of these variants circulating in the United States.[91] While preliminary, this limited data set suggests that the available vaccines are as effective against variants of concern as they are against other variants.

In contrast, a recently published correspondence from researchers in Qatar[92] found that the effectiveness of the Pfizer vaccine was somewhat reduced against two specific variants: the B.1.1.7 variant that originated in the United Kingdom and currently is responsible for nearly 70% of cases in the United States; and the B.1.351 variant first identified in South Africa, but in limited circulation (<1%) in the US.[93] These two variants currently are the dominate variants in Qatar, accounting for nearly all cases in which virus was sequenced after March 7, 2021. Qatar began a mass vaccination campaign with the Pfizer vaccine in late December 2020, and as of March 31, 2021, 265,000 people were fully vaccinated. In a study similar to that used by the CDC to estimate overall vaccine effectiveness, the Qatar researchers found that the Pfizer vaccine was 97.4% effective in preventing severe, critical, or fatal disease. However, it was somewhat less effective in preventing any documented COVID-19 infection: 89.5% against the B.1.1.7 variant and 75% effective against the B.1.351 variant.[94]

For our analysis, we have assumed a baseline vaccine effectiveness of 95% in preventing cases of COVID-19 that are capable of transmitting disease. To account for the possibility of reduced effectiveness against virus variants of concerns, we have considered an excursion with vaccine effectiveness set to 75%.

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90 CDC COVID-19 Vaccine Breakthrough Case Investigations Team, "COVID-19 Vaccine Breakthrough Infections Reported to CDC:"1.

91 CDC COVID-19 Vaccine Breakthrough Case Investigations Team, "COVID-19 Vaccine Breakthrough Infections Reported to CDC:"2.

92 Laith J. Abu-Raddad, Hiam Chemaitelly, and Adeel A. Butt, "Effectiveness of the BNT162b2 COVID-19 Vaccine against the B.1.1.7 and B.1.351 Variants," *The New England Journal of Medicine*, published May 5, 2021 online at NEJM.org: 1-3. DOI: 10.1056/NEJMc2104974.

93 https://covid.cdc.gov/covid-data-tracker/#variant-proportions, accessed May 27, 2021.

94 Abu-Raddad, Chemaitelly, and Butt, "Effectiveness of the BNT162b2 COVID-19 Vaccine against the B.1.1.7 and B.1.351 Variants:" 1.

Contagious Period

As described in the main body of this analysis, the objective of control measures is to prevent the spread of disease either by generating immunity within the susceptible population, or constraining the opportunities for contagious individuals to spread disease to others. Understanding the duration of the contagious period and the presentation of the disease during that time is key to identifying contagious individuals and establishing requirements for measures to prevent disease transmission.

Symptom onset is a key time point in efforts to control outbreaks of contagious disease, as typically it is the most readily observable mechanism for identifying and isolating contagious individuals; prior to the onset of symptoms, individuals who are incubating disease are difficult to differentiate from others who may have been exposed but are not incubating disease. In general, the contagious period is measured relative to symptom onset, as the latter is an observable point in the progression of disease.

The time of symptom onset can be difficult to detect, especially when early symptoms are very mild and not specific to any particular disease. COVID-19 is no exception, as early symptoms are highly variable and very mild, similar to common colds or allergies. In many cases, symptoms could persist for some time before an individual even realizes he/she is ill. As discussed in the main body of the analysis, this creates challenges for responses that rely on symptom onset as a trigger.

For many diseases, individuals become contagious at or shortly after the onset of symptoms (plague, smallpox, SARS), and the contagious period is often equal to the symptomatic period of illness. This is in part because symptoms themselves are an important mechanism for disease transmission: for example, coughing and sneezing expel pathogen-laced droplets or aerosols that are then inhaled by others. Some diseases, however, can be contagious prior to symptom onset (influenza). COVID-19 is relatively unique in that a significant fraction of its contagious period, and perhaps even peak contagiousness, occurs prior to symptom onset. As discussed in the main body of this analysis, this creates challenges for controlling the spread of disease from these individuals.

Incubation Period

Incubation period is defined here as the time from exposure to symptom onset. The DHS Master Question List for COVID-19 states that on average, symptoms develop 5 days after exposure with a range of 2-14 days.[95] The document states that there is a general consensus that the incubation period of COVID is between 5 and 6 days, although it notes that "more recent

[95] https://www.dhs.gov/publication/st-master-question-list-covid-19: 6.

estimates using different models calculate a longer incubation period."[96] The CDC COVID-19 Pandemic Planning Scenarios document provides a mean time from exposure to symptom onset of 6 days.[97]

The DHS document references a systematic review of published literature by Wei et al.,[98] while the CDC references a contemporaneous review of the literature conducted by McAloon et al;[99] both reviews encompassed published or pre-print studies available through April 2020 that estimated the COVID-19 incubation period from case reports and epidemiological investigations. The review conducted by Wei et al.[100] estimated an incubation period with a median of 5.8 days and a mean of 6.9 days, while that conducted by McAloon et al.[101] estimated an incubation period with a median of 5.1 days and a mean of 5.8 days.[102] The DHS document further referenced exemplar studies[103] that estimated incubations periods with 1) a median of 5.1 days and a mean of 5.5 days;[104] 2) a median of 5.4 or 6 days, depending on the distribution assumed;[105] and 3) a median of 7.76 days and a mean of 8.29 days.[106]

The distribution of the COVID-19 incubation period is skewed to the left, with the preponderance of cases occurring early. The distribution calculated by McAloon et al., for

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96 https://www.dhs.gov/publication/st-master-question-list-covid-19: 6.

97 https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 6.

98 Yongyue Wei et al., "A Systematic Review and Meta-analysis Reveals Long and Dispersive Incubation Period of COVID-19," medRxiv preprint posted June 22, 2020, https://doi.org/10.1101/2020.06.20.20134387.

99 Conor McAloon et al., "Incubation Period of COVID-19: A Rapid Systematic Review and Meta-analysis of Observational Research," *BMJ Open* 10 (July 2020), doi:10.1136/bmjopen-2020-039652.

100 Wei et al., "Long and Dispersive Incubation Period of COVID-19:" 9.

101 McAloon et al., "Incubation Period of COVID-19:" 8.

102 Note that the McAloon review was limited to studies providing estimated mean, variance, and confidence intervals for estimated distributions, while the Wei review had broader criteria for inclusion, including raw data on identified transmission pairs. It is not clear whether identification of transmission pairs at this time would have accounted for the possibility of transmission from contact occurring prior to symptom onset; if such contact resulted earlier-than-recognized exposure, the resulting incubation period would be longer than originally reported.

103 The first of these three studies was included in both Wei et al. and McAloon et al., the second was included in Wei et al., and the third was not considered by Wei et al., and deliberately excluded from McAloon et al. because of the methods used.

104 Stephen A. Lauer et al., "The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application," *Annals of Internal Medicine* 172 no. 9 (May 5, 2020), https://doi.org/10.7326/M20-0504.

105 Lin Yang et al., "Estimation of Incubation Period and Serial Interval of COVID-19: Analysis of 178 Cases and 131 Transmission Chains in Hubei Province, China," *Epidemiology and Infection* 148 (June 2020): 2-3, https://doi.org/10.1017/S0950268820001338.

106 Jing Qin et al., "Estimation of Incubation Period Distribution of COVID-19 using Disease Onset Forward Time: A Novel Cross-sectional and Forward Follow-up Study," *Science Advances* 6 (14 August 2020).

example, estimated that while 97.5% of cases would experience symptom onset within 13.60 days of exposure, in 75% of cases, symptom onset would occur within 7.15 days of exposure.[107] This accounts for the difference between the estimates of the median and mean time to onset reported in the literature.

To be consistent in our selection of parameter values throughout our work, we use an estimated mean value for time to onset, vice median value. The two systematic reviews used as primary references by the CDC and DHS provided mean estimates of incubation period of 6 and 7 days, respectively. Since, all things being equal, shorter incubation periods could prove more challenging from a response perspective, we chose to use 6 days as our baseline incubation period, and 7 days as an excursion value.

Transmission after Onset of Symptoms

The DHS Master Question List for COVID-19 states: "A systematic review of published studies on SARS-CoV-1, SARS-CoV-2, and MERS-CoV found none that reported isolation of infectious virus from COVID-19 patients beyond 9 days from symptom onset, despite high viral loads by genetic tests."[108] Multiple studies have assessed viral shedding over time from various types of clinical specimen;[109] while shed virus can generate a positive COVID-19 test result, its presence does not, alone, indicate contagiousness. Rather, the viability of the virus is key. The DHS-referenced review by Cevik at al.[110] identified eight studies that attempted to isolate live virus from clinical samples. While all of these studies successfully cultured viable virus from respiratory samples taken within the first week of illness, most were unable to do so after 8 days, and none after 9 days.[111] Individuals can continue to shed detectable virus for many days, weeks, or even months after the onset of symptoms,[112] however the detected virus has not proven viable

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[107] McAloon et al., "Incubation Period of COVID-19:" 7.

[108] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 6.

[109] He et al., "Temporal Dynamics in Viral Shedding"; Kelvin Kai-Wang To et al., "Temporal profiles of viral load in posterior oropharyngeal saliva samples and serum antibody responses during infection by SARS-CoV-2: an observational cohort study," *Lancet Infectious Diseases* 2020, https://www.sciencedirect.com/science/article/pii/S1473309920301961, updated 23 March 2020; Ivan Yu Jun Seah et al., "Assessing Viral Shedding and Infectivity of Tears in Coronavirus Disease 2019 (COVID-19) Patients," *Ophthalmology* 2020, https://www.sciencedirect.com/science/article/pii/S0161642020303110, updated 24 March 2020; Joshua L. Santarpia et al., "Transmission Potential of SARS-CoV-2 in Viral Shedding Observed at the University of Nebraska Medical Center," *medRxiv* 2020, https://www.medrxiv.org/content/10.1101/2020.03.23.20039446v2, updated 26 March 2020.

[110] Muge Cevik et al., "SARS-CoV-2, SARS-CoV, and MERS-CoV Viral Load Dynamics, Duration of Viral Shedding, and Infectiousness: A Systematic Review and Meta-Analysis," Lancet Microbe (November 19, 2020), https://doi.org/10.1016/S2666-5247(20)30172-5.

[111] Cevik et al., "Viral Load Dynamics:" 5.

[112] Cevik et al., "Viral Load Dynamics:" Figure 2, 4,

and therefore cannot be transmitted to others. Based on the Cevik review, we considered the post-symptomatic period of contagiousness to be 9 days.

The studies that established the duration of post-symptomatic contagiousness based on isolation of viable virus collectively have had significant impact on the emerging understanding of—and response to—COVID-19 beyond this particular parameter value. Critically, they established the threshold concentration of viral load in samples needed for successful isolation, and by extension, allowed estimation of which and when individuals would be contagious. One of the earliest and most widely referenced of these studies, by Wolfel at al.,[113] found that samples containing $<10^6$ viral RNA copies/mL never yielded an isolate. As reported in the Cevik review, other studies using RT-PCR to quantify viral load found that virus could not be isolated from samples with cycle threshold (Ct) values higher than 24, at the lower bound, or 34 at the upper bound.[114] In a study published subsequent to the Cevik review, researchers at Johns Hopkins University[115] reinforced the lower of these bounds: of 131 PCR-positive samples they attempted to culture, 47 were successful; only three of these had Ct values higher than 24.[116] They also demonstrated that the relationship between Ct values and successful culture is probabilistic: the probability of successful culture was 76.7% for those with Ct values between 10 and 20, compared to 24.1% of those with Ct values between 20 and 30, and only 2.9% for those between 30 and 40.[117] From a public health and outbreak control perspective, this correlation between viral load and successful isolation is among the most critical scientific findings from the study of COVID-19, and has since been extended to assess and support hypotheses regarding pre-symptomatic and asymptomatic transmission of disease.

Transmission before Onset of Symptoms

For many diseases, individuals become contagious at the onset of symptoms (SARS), or at some point thereafter (plague, smallpox), usually when more serious or distinctive symptoms emerge; the contagious period is therefore equal to, or a subset of, the symptomatic period of

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[113] Roman Wolfel et al., "Virological Assessment of Hospitalized Patients with COVID-2019," *Nature* 581 (28 May 2020), https://doi.org/10.1038/s41586-020-2196-x. This study tested numerous types of clinical samples using RT-PCR and attempted to isolate virus from all that were positive. Urine and blood samples never tested positive, and stool samples never generated a virus isolate. The authors generally found high viral loads and successful isolation in oro- and naso-pharyngeal and throat swab specimens and in sputum (p. 466).

[114] Cevik et al., "Viral Load Dynamics:" 5.

[115] Victoria Gniasdowski et al., "Repeat COVID-19 Molecular Testing: Correlation of SARS-CoV-2 Culture with Molecular Assays and Cycle Thresholds," Accepted Manuscript, *Clinical Infectious Diseases*, published online 27 October 2020, https://doi.org/10.1093/cid/ciaa1616

[116] Gniasdowski et al., "Correlation of SARS-CoV-2 Culture with Molecular Assays and Cycle Thresholds:" Figure 2.

[117] Gniasdowski et al., "Correlation of SARS-CoV-2 Culture with Molecular Assays and Cycle Thresholds:" 12.

illness. Some diseases, however, can be contagious prior to symptom onset (influenza).[118] Because the causative agent of COVID-19 is closely related to that of SARS, and because the severe presentation of both diseases appeared similar, the public health community initially assumed that COVID-19 would share many of the characteristics of SARS, including transmission mechanisms and dynamics, and could be controlled in much the same way. As the pandemic progressed into the spring of 2020, however, anecdotal evidence and more extensive epidemiological research began to support the hypothesis that COVID-19, like influenza, could be contagious in its pre-symptomatic period. This meant that some common public health guidelines and measures—such as "if you are sick, stay home"—might be insufficient to halt the spread of disease.

In late spring 2020, researchers affiliated with the Singapore Ministry of Health conducted a review of all 243 cases of COVID-19 confirmed in that nation through March 2020 to determine whether pre-symptomatic transmission was likely to occur.[119] The research team identified 10 individual cases and 7 epidemiologic clusters of COVID-19 in which pre-symptomatic transmission was likely, with transmission found to have occurred 1-3 days before symptom onset in the source patient.[120]

In this same time period, He et al.[121] conducted a two-pronged study, using both clinical sample test data and epidemiological data to understand the contagiousness profile of COVID-19. This group of researchers collected cycle threshold (CT) values from RT-PCR analysis of clinical samples from 94 COVID-19 patients hospitalized in Guangdong, China. They also collected information on 77 COVID-19 transmission pairs identified from publicly available information in mainland China and Hong Kong, where there was a clear epidemiological link between infector and infectee, and where other known potential sources of infection, such as travel to Wuhan, were absent. By fitting a distribution of serial interval—the time between successive cases in a transmission chain—to the transmission pair data, combining it with estimates of incubation period found elsewhere in the literature, and conducting a range of sensitivity analyses, they were able to infer that contagiousness began 2-3 days before symptom onset, and peaked at 0.7 days post-symptom onset. From their fitted distribution, they further calculated that 44% of transmission had occurred before symptom onset.[122]

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[118] Burr et al., *Controlling the Spread of Contagious Disease in an Operational Environment*, 26.

[119] Wycliffe E. Wei et al., "Presymptomatic Transmission of SARS-CoV-2—Singapore, January 23-March 16, 2020," *Morbidity and Mortality Weekly Report* 69, April 1, 2020.

[120] Wei et al., "Presymptomatic Transmission of SARS-CoV-2," 2.

[121] Xi He et al., "Temporal Dynamics in Viral Shedding and Transmissibility of COVID-19," *Nature Medicine*, published online 15 April 2020, https://doi.org/10.1038/s41591-020-0869-5.

[122] He et al., "Temporal Dynamics."

He et al. did not use their clinical sample data in this portion of the analysis, but they did observe a pattern of results they found consistent with pre-symptomatic transmission, with high viral loads detected at symptom onset that steadily decreased over time. Similar results were observed by Wolfel et al. in their virological assessment of COVID-19 cases in Germany: "In general, the concentrations of viral RNA were very high in initial samples. In all patients except one, the concentration of viral RNA in throat swabs seemed to be already on the decline at the time of first presentation." [123]

While clinical sample analyses such as these were suggestive of transmission prior to onset of symptoms, they did not include samples from individuals who subsequently developed symptoms and hence were not conclusive. Then in late March 2020, Kimball et al. published initial results of systematic point-prevalence survey testing of the resident population in a skilled nursing facility in King County, Washington, instituted immediately following its first confirmed case of COVID-19 in early March 2020.[124] More complete results of the systematic testing at this facility were subsequently published by Arons et al. in May 2020.[125] During the study period, this facility experienced very rapid spread of infection among residents, even though it rapidly instituted an infection prevention and control process that included symptom screening and immediate isolation of symptomatic individuals and the routine use of personal protective equipment by health care providers.[126]

Nursing staff conducted symptom screening and collected clinical samples for RT-PCR testing in 76 of the 82 residents of this facility. The initial round of testing found positive results for 23 individuals, only 10 of whom were symptomatic. When reassessed one week later, 10 additional individuals had developed symptoms in the intervening period and were re-categorized by the study team as pre-symptomatic at the time of testing.[127] Ultimately, 48 of the 76 participating individuals tested positive for COVID-19 in either initial or follow-on rounds of testing. Of these, 21 were symptomatic at the time of testing, 24 were asymptomatic at the time of testing but became symptomatic thereafter, and 3 remained asymptomatic during the study period.[128]

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[123] Wolfel et al., "Virological Assessment of Hospitalized Patients with COVID-2019," 467.

[124] Anne Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections in Residents of a Long-term Care Skilled Nursing Facility—King County, Washington, March 2020," U.S. Department of Health and Human Services Centers for Disease Control and Prevention, *Morbidity and Mortality Weekly Report* 69 (March 27, 2020).

[125] Melissa M. Arons et al., "Presymptomatic SARS-CoV-2 Infections and Transmission in a Skilled Nursing Facility," *The New England Journal of Medicine* 382 no. 22 (May 28, 2020).

[126] Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 1-2.

[127] Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 2.

[128] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2083.

Neither study found significant differences in mean Ct values among samples from individuals with symptomatic, pre-symptomatic, and asymptomatic infections.[129] Overall Ct values ranged from 13.7 to 37.9; the median value for pre-symptomatic cases was slightly lower (23.1) than those for asymptomatic cases (25.5) and for typical and atypical symptomatic cases (24.8 and 24.2, respectively).[130]

In addition, positive cultures were obtained from RT-PCR-positive samples taken from 13 of 17 symptomatic individuals, from 17 of 24 pre-symptomatic individuals, and from 1 of 3 asymptomatic individuals.[131] All 31 of the positive cultures were obtained from samples with Ct values below 35—the upper bound of the threshold for viability reported in the Cevik et al. review—and 24 of these had Ct values of 24 or less, the lower bound of the reported threshold for viability.[132]

Considering these test results in combination with the failure of control measures focused on symptomatic individuals, Arons et al. concluded, "Transmission from asymptomatic residents infected with SARS-CoV-2 most likely contributed to the rapid and extensive spread of infection to other residents and staff. Symptom based infection-control strategies were not sufficient to prevent transmission after the introduction of SARS-CoV-2 into this skilled nursing facility."[133]

In addition to epidemiological studies and laboratory test data, population-level modeling studies in this period also concluded the pre-symptomatic transmission of COVID-19 was taking place, and sought to determine its extent. These studies used distributions of COVID-19 incubation period and serial interval estimated from contact tracing efforts or more formal epidemiological studies to assess the time frame over which pre-symptomatic transmission occurred and/or the proportion of transmission that occurred during this period.

While both incubation period and pre-symptomatic transmissibility are characteristics of a disease, serial interval is determined both by transmissibility over time and contact patterns within a population. Hospitalization of contagious individuals, for example, will truncate their opportunity for transmission and—by limiting the period of time in which they can transmit disease—reduce the associated serial interval. As the COVID-19 pandemic progressed, isolation of symptomatic individuals and quarantine of their contacts would lead to a greater proportion of

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[129] Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 2, and Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2085.

[130] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2086.

[131] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2086.

[132] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2086, and Cevik et al., "Viral Load Dynamics:" 5. Of the samples from the three positive individuals who remained asymptomatic, all had Ct values below 35, and one had a Ct value below 24.

[133] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2087.

early transmission, and by extension a shorter serial interval. Thus, assessments of the proportion of transmission occurring prior to symptom onset could be used to evaluate both the effectiveness of isolation as implemented within a given population, and its upper bound. One of the earliest such efforts, by Yang Liu and colleagues,[134] used estimated distributions of incubation period and serial interval derived from a large dataset on COVID-19 cases and their contacts from Shenzhen, China, published by Bi et al.,[135] with sensitivity analysis performed using similar but less extensive data from other sources. This study estimated that "without active case finding to accelerate isolation in Shenzhen," 12-28% of transmission occurred before onset of symptoms; with active case finding, that percentage increased to 21-46% as more individuals were isolated sooner, and the total number of secondary cases was reduced 35-60%.[136]

The Liu study did not estimate the duration of the pre-symptomatic transmission period. However, a subsequent meta-analysis and systematic review of COVID-19 incubation period and serial interval estimates conducted by Casey et al.[137] found that transmission was most likely in the day before symptom onset, although some of the included studies estimated that the mean time of transmission was even earlier, 2-3 days before symptom onset.[138]

The DHS Master Question List for COVID-19 states that individuals may be contagious for 1-3 days before symptom onset, citing both the Wei and Arons studies.[139] It also states that peak contagiousness may be during the incubation period, one day before symptoms develop, citing He et al.[140] Estimates of the percentage of combined pre-symptomatic transmission—which as noted above depends on the prevalence of control measures such as isolation of sick individuals—and asymptomatic transmission—discussed in the next section—range from 51% to 76%.[141]

The CDC COVID-19 Pandemic Planning Scenarios document does not provide estimates of the start of the contagious period relative to onset of symptom, or of the time of peak

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[134] Yang Liu, Centre for Mathematical Modelling of Infectious Diseases nCoV Working Group, Sebastian Funk, and Stefan Flasche, "The Contribution of Pre-symptomatic Infection to the Transmission Dynamics of COVID-2019," *Wellcome Open Research*, 1 April 2020, https://doi.org/10.12688/wellcomeopenres.15788.1.

[135] Qifang Bi et al., "Epidemiology and Transmission of COVID-19 in 391 Cases and 1286 of their Close Contacts in Shenzhen, China: A Retrospective Cohort Study," *Lancet Infectious Disease* 2020 (April 2020), https://doi.org/10.1016/S1473-3099(20)30287-5.

[136] Liu, Funk, and Flasche, "The Contribution of Pre-symptomatic Infection to the Transmission Dynamics of COVID-2019:" 5.

[137] Miriam Casey et al., "Pre-symptomatic Transmission of SARS-CoV-2 Infection: A Secondary Analysis using Published Data," medRxiv preprint, June 11, 2020, https://doi.org/10.1101/2020.05.08.20094870.

[138] Casey et al., "Pre-symptomatic Transmission of SARS-CoV-2 Infection:" 12.

[139] https://www.dhs.gov/publication/st-master-question-list-covid-19: 4.

[140] https://www.dhs.gov/publication/st-master-question-list-covid-19: 6.

[141] https://www.dhs.gov/publication/st-master-question-list-covid-19: 4.

transmissibility. It does include estimates of the percentage of transmission occurring prior to symptom onset, ranging from 30% to 70%, with a current best estimate of 50%. The lower CDC estimate is the lower bound of the 95% confidence interval of the percentage of pre-symptomatic transmission calculated by He et al.; the higher CDC estimate is based on the studies included in the Casey et al. review, and the CDC best estimate is the geometric mean between the two bounding estimates.[142]

In summary, it is now widely accepted in the community that pre-symptomatic transmission of COVID-19 occurs. The literature contains two major approaches to describing pre-symptomatic transmission: 1) the time period during which transmission can occur before and after symptoms, to include the time of peak transmissibility, and 2) the percentage of transmission that occurs before and after symptom onset. Because the first approach is based on the temporal dynamics of disease progression, and is not influenced by efforts to prevent symptomatic individuals from transmitting disease, it is more suited to our purposes.

As discussed earlier, and as reflected in the DHS Master Question List, it appears that individuals can begin to transmit disease approximately 3 days prior to symptom onset, and that transmissibility peaks at or slightly before symptom onset. We therefore represented disease transmission over time as a triangle function, starting 3 days before symptom onset and continuing for 9 days after symptom onset, for a total contagious period of 12 days. We further assumed that peak transmission occurred one day before symptom onset, and considered an excursion case where peak transmission occurred at the time of symptom onset.

Asymptomatic Cases and Asymptomatic Transmission

Asymptomatic infections are those in which individuals can test positive for a disease but not experience any signs or symptoms. For many diseases, a significant portion of infected individuals will be asymptomatic. For example, nearly 60% of Q fever infections are asymptomatic,[143] and estimates of the asymptomatic fraction of influenza cases range from 4% to 28%.[144] Yet, as noted previously, the public health community initially assumed that SARS-CoV-2 would behave similarly to SARS-CoV-1, and documented asymptomatic cases of SARS are extremely rare.[145]

Early in the COVID-19 pandemic, the existence and prevalence of asymptomatic infection was very uncertain, and virtually nothing was known about whether those with asymptomatic infections could further spread disease. As the pandemic spread and more data—and more types of data—has become available, the existence of widespread asymptomatic infection has been well

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[142] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 5-6.

[143] M. Maurin and D. Raoult, "Q Fever," *Clinical Microbiology Reviews* 12, no. 4 (October 1999): 532.

[144] Nancy H. L. Leung et al., "The Fraction of Influenza Virus Infections that are Asymptomatic: A Systematic Review and Meta-Analysis," *Epidemiology* 26 (no. 6), November 2015: 4.

[145] Harold K.K. Lee et al., "Asymptomatic Severe Acute Respiratory Syndrome-associated Coronavirus Infection," *Emerging Infectious Diseases* 9 (no. 11), November 2003.

documented. Yet, many questions remain about the prevalence of asymptomatic infection, the variability of asymptomatic infection rates by age group, and most importantly, the contribution of asymptomatic infections to ongoing disease transmission.

Existence and Prevalence of Asymptomatic COVID-19 Infection

Suspected asymptomatic infection were identified and described in the literature by March 2020, but such cases were typically asymptomatic at the time of testing, and follow-up was often limited, making it difficult to know if the identified cases were truly asymptomatic, or pre-symptomatic. Recall that at the time, prevailing case definitions included radiographic evidence of pneumonia,[146] and the dominance of mild presentation of disease was not well understood. Individuals who tested positive for COVID-19 but never developed pneumonia or required hospitalization were generally not tracked and may well have been categorized as asymptomatic.

Mizumoto et al.[147] generated one of the earliest estimates of the prevalence of asymptomatic cases, in a study of COVID-19 transmission aboard the Diamond Princess Cruise ship in February 2020. This study highlights many of the challenges and uncertainties in generating such an estimate. During a two-week quarantine period, over 3,000 COVID-19 tests were administered to the 3,711 passengers and crew of the ship; testing strategies prioritized symptomatic or high-risk groups on board, with some individuals being tested multiple times and others not at all. A total of 634 individuals tested positive, with 306 symptomatic and 328 asymptomatic cases at the time of testing.[148] All of these individuals were removed from the ship to medical facilities in Japan, and data on clinical progression—to include the development of symptoms in individuals who were asymptomatic at the time of testing—was not available to the research team.[149] Since direct observation of cases was not feasible, the authors used a statistical model to estimate the prevalence of truly asymptomatic cases. This model combined a distribution of COVID-19 incubation period

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[146] Tsang, et al., "Effect of Changing Case Definitions for COVID-19 on the Epidemic Curve and Transmission Parameters:" e291.

[147] Kenji Misumoto, Katsushi Kagaya, Alexander Zarebski, and Gerardo Chowell, "Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases on Board the Diamond Princess Cruise Ship, Yokohama, Japan, 2020," *Euro Surveillance* 25 (no. 10), March 12, 2020.

[148] Misumoto et al., "Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases:" 1.

[149] Data on the clinical course of disease for 96 of the Diamond Princess cases who were asymptomatic at the time of testing and removed to a hospital in Japan was subsequently published in August 2020. See Aki Sakurai et al., "Natural History of Asymptomatic SARS-CoV-2 Infection," Correspondence, *New England Journal of Medicine* 383 (August 27, 2020). Of the 96 cases directly managed by the authors, 84 remained asymptomatic. This article further notes that overall, of 410 cases of infection that were asymptomatic at the time of testing, a total of 79 eventually developed symptoms. This article does not provide a number of symptomatic cases at the time of testing, and the number of identified asymptomatic cases is not the same as that reported by Misumoto et al. Nonetheless, if the proportion of pre-symptomatic and asymptomatic cases published by Sakurai et al. is extended to the Misumoto data, the proportion of asymptomatic infections overall among the Diamond Princess passengers and crew would be 42%, much higher than that estimated by Misumoto.

taken from the available literature with data on the proportion of asymptomatic cases among positive test results over time. While the authors found their results to be highly sensitive to incubation period, they assumed a mean incubation period of 6.4 days—consistent with the value of 6 that we chose for our work—and estimated that, consequently, 17.9% of the positive Diamond Princess cases would ultimately turn out to be truly asymptomatic.[150]

On January 31, 2020, the nation of Iceland commissioned a SARS-CoV-2 testing program targeting individuals considered at high risk for COVID-19, primarily because of travel history; on March 13, 2020, the program was expanded to include broader population screening to generate metrics for evaluating outbreak control measures.[151] Although somewhat mixed, the results of this program provided an early indication that asymptomatic COVID-19 infection could be prevalent. Through April 4, some 13,080 individuals were tested in the population screening portion of the program, 10,797 of whom were volunteers and 2,283 were solicited at random. To qualify, participating individuals had to be either symptom-free or have "mild symptoms of the common cold." Within this population, 100 individuals tested positive, with 57% symptomatic. In their published results, the Icelandic researchers stated, "Notably, 43% of the participants who tested positive reported having no symptoms, although symptoms almost certainly developed later in some of them."[152] With no documented follow-up, the true rate of asymptomatic infection was impossible to determine, yet the reported 43% rate was assuredly high for that population. Yet at the same time, the researchers noted that the presence of mild symptoms could well have been a motivating factor for those who volunteered under the population screening test protocol: overall, 33% of those who volunteered for testing reported experiencing mild symptoms, while only 12% of those who were randomly selected reported any symptoms. This suggested that the percentage of asymptomatic cases within the test population could have been artificially deflated by study design, and not reflective of that experienced among the population overall.

As described in the previous section, the work by Kimball[153] and Arons[154] in a skilled nursing facility in Kings County, Washington was among the first published reports of systematic testing of a defined population at discreet time intervals, with follow-up on clinical outcomes. All assenting residents of this facility were tested on March 13, 2020, and those who were negative, who had atypical symptoms of COVID-19, or who were positive but asymptomatic were tested

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[150] Misumoto et al., "Estimating the Asymptomatic Proportion of Coronavirus Disease 2019 (COVID-19) Cases:" 2. The authors reported a 95% credible interval of 15.5%-20.2%, and further found their estimate to be highly sensitive to input data used to represent incubation period.

[151] D. F. Gudbjartsson et al., "Spread of SARS-CoV-2 in the Icelandic Population," *The New England Journal of Medicine*, NEJM.org, April 14, 2020, 1-14. DOI: 10.1056/NEJMoa2006100.

[152] Gudbjartsson et al., "Spread of SARS-CoV-2 in the Icelandic Population:" 4-13.

[153] Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections."

[154] Arons et al., "Presymptomatic SARS-CoV-2 Infections."

again on March 19-20, 2020.[155] Of the 48 positive cases, 27 were asymptomatic at the time of testing, but 24 of these 27 developed symptoms within 7 days. Only 3 of the 48 positive cases remained asymptomatic.[156]

In an often-cited study published online in June 2020, Lavezzo et al.[157] assessed the results of systematic COVID-19 RT-PCR testing of the population of Vo', Italy in late February 2020 and then two weeks later in early March. The primary objective of this study was to assess the prevalence of COVID-19 infections in the population immediately before imposition of lock-down infection control measures, and again after those measures had been in place for two weeks. This was an extensive experiment: of the 3,275 residents of Vo', 2,812 (85.9%) were tested in the first round, with 73 positive results; 2,343 (71.5%) were tested in the second round, with 29 positive results overall and 8 new cases.[158] The authors stated:

> "Notably, a total of 29 out of the 73 participants (39.7%; 95% CI: 28.5-51.9%) who tested positive at the first survey were asymptomatic (that is, did not show symptoms at the time of swab sampling nor afterwards)…A similar proportion of asymptomatic infection was also recorded at the second survey (13 out of 29, 44.8%; 95% CI: 26.5-64.3%); of the eight new cases, five were asymptomatic."[159]

The definition of "symptomatic" in the Vo' study was fairly broad: "a participant who required hospitalization and/or reported fever and/or cough and/or at least two of the following symptoms: sore throat, headache, diarrhea, vomit, asthenia, muscle pain, joint pain, loss of taste or smell, or shortness of breath."[160] This contrasts with the much more restrictive case definitions for COVID-19 established just weeks before, at the outset of the pandemic, and demonstrates the rapid evolution of understanding of this disease.

The CDC COVID-19 Pandemic Planning Scenarios document provides estimates of the percent of infections that are asymptomatic ranging from 15% to 70%, with a "current best estimate" of 30%.[161] The lower bound approximates the lower 95% confidence interval bound estimated in a systematic review and meta-analysis of the literature on asymptomatic COVID-19

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[155] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2082.

[156] Arons et al., "Presymptomatic SARS-CoV-2 Infections:" 2083.

[157] Enrico Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak in the Italian Municipality of Vo'," *Nature* 584 (20 August 2020).

[158] Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak:" 426.

[159] Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak:" 427.

[160] Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak:" Methods Annex.

[161] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 4.

published through July 2020 conducted by Byambasuran et al.;[162] the upper bound approximates the upper 95% confidence interval in a study by Poletti et al.[163] that quantified the probability of symptoms and severe disease among RT-PCR confirmed cases of COVID-19 in Lombardi, Italy, between February and April 2020. The "current best estimate" is the midpoint of the range of estimates.

The Byambasuran review generated a pooled estimate of asymptomatic cases from 13 selected studies (including those described previously), which described a total of 663 RT-PCR-positive cases of which 111 (17%) were asymptomatic.[164] The Poletti study evaluated 5,484 close contacts of confirmed COVID-19 cases and identified 2,824 infections among that group, by RT-PCR testing, antibody testing, or both. Among these, some 69% were found to be asymptomatic.

As noted in the CDC document, "current peer-reviewed and preprint studies vary widely in follow-up times for re-testing, or do not include re-testing of cases. In addition, studies vary in the definition of a symptomatic cases, which makes it difficult to make direct comparisons between estimates."[165] Indeed, both of the studies cited by the CDC are indicative of the variability in the definition of "symptomatic" or "asymptomatic." Poletti et al. themselves noted that published estimates of asymptomatic COVID-19 infection were highly dependent on the symptoms included in case definitions, then went on to restrict the definition of "symptomatic" to those with respiratory symptoms or fever in excess of 37.5°C, thus categorizing the dominant mild forms of illness as asymptomatic.[166] Moreover, Poletti et al. also stated that "cases were followed up for symptoms throughout the study period," but details as to methods, duration, and outcomes of that follow-up are not provided.[167] While the Poletti study was not included in the Byambasuren review, the latter identified the acceptability of case definition as the greatest potential source of risk of bias in the 13 studies it did include, with 9 of the 13 studies having a moderate or unclear risk.[168]

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[162] Oyungerel Byambasuren et al., "Estimating the Extent of Asymptomatic COVID-19 and its Potential for Community Transmission: Systematic Review and Meta-Analysis," *Official Journal of the Association of Medical Microbiology and Infectious Disease Canada* 5 no. 4 (December 2020): 223-34.

[163] Piero Poletti et al., "Probability of Symptoms and Critical Disease after SARS-CoV-2 Infection," arXiv preprint, 22 June 2020.

[164] Byambasuren et al., "Estimating the Extent of Asymptomatic COVID-19:" 229, Figure 3. For inclusion in this review, studies had to demonstrate that asymptomatic cases were followed up for a sufficient period of time to confidently differentiate between cases that were pre-symptomatic at the time of testing and those that were truly asymptomatic. At the time the review was conducted, there were only a limited number of studies that met this criterion.

[165] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 5.

[166] Poletti et al., "Probability of Symptoms and Critical Disease after SARS-CoV-2 Infection:" 3.

[167] Poletti et al., "Probability of Symptoms and Critical Disease after SARS-CoV-2 Infection:" 4.

[168] Byambasuren et al., "Estimating the Extent of Asymptomatic COVID-19:" 230, Table 3.

Another systematic review of literature published before June 2020 by Diana Buitrago-Garcia and colleagues[169] evaluated 80 separate studies that included estimates of the prevalence of asymptomatic COVID-19 infection. These estimates were derived in multiple ways, including epidemiological investigations of single-family clusters of illness, larger contact tracing studies, screening of defined groups, and inferred estimates from modeling studies (specifically, the Misumoto study of COVID-19 cases aboard the Diamond Princess). The authors accepted the definitions of "symptomatic" and "asymptomatic" from the included studies, but noted that—as in the Byambasuren review—the main risk of bias came from the selection of people with asymptomatic infection and "mismeasurement of asymptomatic status because of absent or incomplete definitions."[170] Across all of the included studies, the overall estimate of asymptomatic infection prevalence was 20%, a value that is consistent with the results of the Byambasuran review. When looking only at the subset of studies (n=7) where cases were detected through screening of all people in a defined population the summary estimate of asymptomatic infection prevalence was 31%.[171] In their summary discussion, the authors noted that they'd found significant heterogeneity between studies that were typically conducted for purposes other than investigating asymptomatic infection, and that "serological tests, in combination with virological diagnostic methods, might improve ascertainment of SARS-CoV-2 infection in asymptomatic populations."[172]

Indeed, as the pandemic progressed and researchers began to understand the timing and magnitude of COVID-19 antibody development over the course of an infection, seroprevalence studies became a viable means of estimating whether an individual had previously had a COVID-19 infections. Rather than testing individuals to determine if they were currently infected, researchers could look backwards and determine who had been infected, and therefore could estimate both the prevalence of undocumented COVID-19 cases and the proportion of them that were asymptomatic.

Two systematic, comprehensive studies of seroprevalence have been conducted at the national level over the course of the pandemic, in Spain and in England. A recent systematic review

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[169] Diana Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections: A Living Systematic Review and Meta-Analysis," *PLOS Medicine* 17 no. 9 (September 22, 2020). https://doi.org/10.1371/journal.pmed.1003346.

[170] Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 9.

[171] Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 9-10. In general, we would consider population screening to be a more rigorous and comprehensive approach to estimating the prevalence of asymptomatic infections than other data collection efforts represented in this review; presumably the authors extracted these screening studies and reported on them separately for the same reason.

[172] Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 16.

of the literature on asymptomatic COVID-19 infections by Oran and Topol[173] characterized these two studies as the highest-quality evidence of the prevalence of asymptomatic infection, because of the scale and because antibody testing provides the retrospection needed to differentiate between asymptomatic and pre-symptomatic infection.

The first of these two studies took place in late spring 2020 in Spain.[174] From April 27 to May 11, the Seroepidemiological Survey of SARS-CoV-2 Virus Infection in Spain (ENE-COVID) tested over 61,000 individuals, selected via a random sampling scheme that controlled for geographic location and municipality size, using both point-of-care antibody tests and more sensitive laboratory immunoassay testing for each individual. The ENE-COVID study found that 5% of the tested population was positive by the point-of-care test and 4.6% by immunoassay; it estimated seroprevalence in the population overall to be between 3.7% (both tests positive) and 6.2% (either test positive).

Participants in the ENE-COVID study were also given questionnaires regarding their history of symptoms compatible with COVID-19, much like that used to estimate asymptomatic cases in the Vo' study: fever, chills, fatigue, sore throat, cough, shortness of breath, headache, nausea, and loss of taste or smell. The proportion of the seropositive population reported to be asymptomatic ranged from 21.9% (both tests positive) to 35.8% (either test positive). The asymptomatic proportion of seropositive cases was 32.7% from the point-of-care test alone, and 28.5% from the laboratory assay alone.[175]

The second phase of the Real-time Assessment of Community Transmission (REACT2) study in England, commissioned by the Department of Health and Social Care, was the second major study of COVID-19 seroprevalence within a large population.[176] The REACT study team provided self-administered immunoassay tests to a total 365,104 adults across three separate cross-sectional surveys conducted at six-week intervals between June and September 2020.[177] The objectives of this study were to document seroprevalence among the population, and to track the persistence of antibodies over time. Participants in the study were solicited via invitations sent to individuals randomly selected from the National Health Service patient list; the first two rounds

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[173] Daniel P. Oran and Eric J. Topol, "The Proportion of SARS-COV-2 Infections that are Asymptomatic: A Systematic Review," *Annals of Internal Medicine* 274 (2021): 659.

[174] Marina Pollan et al., "Prevalence of SARS-CoV-2 in Spain (ENE-COVID): A Nationwide, Population-based Seroepidemiological Study," *Lancet* 396 (July 6, 2020): 535-44.

[175] Pollan et al., "Prevalence of SARS-CoV-2 in Spain:" 539.

[176] For information on the REACT series of studies conducted at the population level in England, see https://www.imperial.ac.uk/medicine/research-and-impact/groups/react-study/.

[177] Helen Ward et al. for the REACT study team, "Declining Prevalence of Antibody Positivity to SARS-CoV-2: A Community Study of 365,000 Adults," medRxiv preprint, October 27, 2020. https://doi.org/10.1101/2020.10.26.20219725.

of testing each comprised 125,000 participants, and the third comprised 195,000 participants. In addition to the test itself, participants completed a survey questionnaire upon completion of their self-test; among other things, this questionnaire asked participants 1) if they knew or suspected they'd had COVID-19, 2) if so, whether they'd had symptoms and how severe they were, and 3) if they'd had symptoms, which ones they'd experienced.[178]

Overall, the REACT2 study found that COVID-19 seroprevalence in England was 6.0% in June 2020 and fell to 4.4% by September, suggestive of antibody waning over time after infection, to levels below the documented sensitivity of the immunoassay test used in the study.[179] More importantly for our purposes, the percentage of participants with positive tests who reported no symptoms of infection was remarkably consistent in each round of testing: 32% in Round 1, 33% in Round 2, 32% in Round 3, and 32% overall.[180] Based primarily on these two studies, Oran and Topol concluded that "it seems that the asymptomatic fraction of SARS-CoV-2 infection is at least one third."[181] The DHS Master Question List for COVID-19 document, referencing Oran and Topol, states that "approximately 33% of individuals will remain asymptomatic after SARS-CoV-2 infection."[182]

The U.S. Marine Corps' COVID-19 Health Action Response for Marines (CHARM) study took yet another approach to investigating the risk of COVID-19 transmission among Marine recruits. This study, conducted from May 12 through July 15, 2020, used a combination of quantitative PCR (qPCR) testing and phylogenetic analysis to both identify COVID-19 cases and to identify clusters of disease with common origins.[183] The latter supported epidemiological investigation to characterize transmission dynamics within the recruit population. This allowed the Marine Corps to identify residual sources of risk when a wide range of outbreak control measures were in place, such as universal mask wearing, social distancing, enhanced sanitation, and limited contact with outsiders.

During the CHARM study period, 3,467 new recruits entered the Marine Corps, 1,848 of whom volunteered to participate in the study. All new recruits at this time were required to quarantine at home for two weeks, and then spent two weeks in supervised quarantine with enforced public health measures in place, prior to the start of basic training. Study volunteers were

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[178] https://www.imperial.ac.uk/media/imperial-college/institute-of-global-health-innovation/200608-Study-5-Testing-ANTIBODY-Round-1-User-Survey.pdf

[179] Ward et al., "Declining Prevalence of Antibody Positivity:" 7, 11.

[180] Ward et al., "Declining Prevalence of Antibody Positivity:" Table 3, 12.

[181] Oran and Topol, "The Proportion of SARS-COV-2 Infections that are Asymptomatic:" 659.

[182] https://www.dhs.gov/publication/st-master-question-list-covid-19: 7.

[183] Andrew G. Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine," *The New England Journal of Medicine*, published online at NEJM.org November 11, 2020. DOI: 10.1056/NEJMoa2029717.

tested for COVID-19 upon arrival at their quarantine location, Day 0, and again on Days 7 and 14 of quarantine.[184] Of those recruits tested upon arrival, 16 were positive; of these, 12 recruits remained asymptomatic for the entirety of their quarantine period. An additional 24 recruits tested positive on Day 7, and 16 of those remained asymptomatic through the remaining week of quarantine; all 11 positive cases on Day 14 were asymptomatic.[185] While the clinical course of disease for these positive cases was not described in the published CHARM study, given the COVID-19 incubation period, it is very likely that those asymptomatic cases identified on Day 0 (75%) were truly asymptomatic, as are the large majority of those identified via testing on Day 7 (66%). In the absence of follow-up information, it cannot be determined how many of those who were positive on Day 14 remained asymptomatic.

In summary, the CHARM study documented high rates of asymptomatic infection among recruits, of whom 83.5% were young adults between 18 and 20 years old. The observed rate of asymptomatic infection was significantly higher than those documented in the seroprevalence studies in Spain and England, in the Vo' study, or in the work of Kimball and Arons, raising questions about the age-dependence of asymptomatic infection.

Based on the seroprevalence testing studies in Spain and England, we assume for our base case that 30% of COVID-19 cases are asymptomatic. The CHARM study has been an outlier, with 70% of the positive cases very likely to have been asymptomatic for the duration of their infection. However, because of the possible variability in asymptomatic infection rates by age, and because the overwhelming majority of the study population—healthy young adults between 18 and 20 years old—is of interest to our work, we have included an asymptomatic infection rate of 70% as an excursion.

Asymptomatic Transmission of COVID-19

While the potential for transmission of disease from asymptomatic infections is generally accepted, the relative contagiousness of these infections and their contribution to COVID outbreaks overall remains unclear. An early scoping review of the literature[186] on the relative contagiousness of asymptomatic cases, through April 2020, found very little information available on which to base an assessment; at that time, only six studies addressed the subject and their

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[184] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" Figure 1.

[185] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" Supplementary Appendix, Figure S1. All individuals who tested positive for COVID-19 during quarantine were placed in isolation. The Marine Corps conducted a separate but related study of infected recruits, involving more frequent testing during isolation. The results of this study—to include the clinical course of disease within these recruits—were not reported by Letizia et al. and are not yet publicly available.

[186] David McEvoy et al., "The Relative Infectiousness of Asymptomatic SARS-CoV-2 Infected Persons Compared with Symptomatic Individuals: A Rapid Scoping Review," medRxiv preprint, 1 August 2020. https://doi.org/10.1101/2020.07.30.20165084.

findings were very heterogeneous. Although the authors called for further study of the potential for asymptomatic transmission as a matter of urgency, a survey of virologist, epidemiologist, immunologists, and evolutionary biologists conducted a year later identified the role of asymptomatic infection in disease transmission as one of the top remaining questions about COVID-19.[187]

As noted in the outset of this section, the role of asymptomatic infections in the ongoing transmission of COVID-19 is not yet fully understood by the public health community. The CDC COVID-19 Pandemic Planning Scenarios document describes some of the challenges: the difficulty in identifying true asymptomatic infections, in observing and quantifying transmission from those cases, and in differentiating the latter from pre-symptomatic transmission. Yet, to the extent that these cases do contribute to the spread of disease, they must be accounted for in the implementation of outbreak control measures.

There are multiple ways to approach this problem. Epidemiological investigations and contact tracing studies have been able to identify asymptomatic cases as the most likely source of infection in a number of instances. Large-scale studies of this type have focused on evaluating transmission in relatively controlled settings, such as households during lockdowns, and found disparities in attack rates—the proportion of susceptible individuals who become ill—between those with symptomatic and asymptomatic sources of infection. As discussed in following sections, studies of this type have been used to generate the estimates of relative infectivity provided in the DHS Master Question List for COVID-19. Alternatively, observed viral loads in asymptomatic cases and the correlation of viral load with contagiousness can also be combined to generate estimates of the relative contagiousness of asymptomatic cases; this is the approach used to inform estimates in the CDC COVID-19 Pandemic Planning Scenarios document. Finally, population-level modeling studies have estimated the overall percentage of transmission caused by asymptomatic infections; since these studies typically use assumptions about asymptomatic infection prevalence and relative contagiousness as inputs, and generate outputs that are highly dependent on assumptions regarding outbreak control measures in place, these studies are not well suited to our purposes and are no longer considered here.[188]

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[187] Helen Branswell, "We Know a Lot about COVID-19; Experts Have Many More Questions," *STAT*, April 20, 20021, https://www.statnews.com/2021/04/20/we-know-a-lot-about-covid-19-experts-have-many-more-questions/. The impact of nonpharmaceutical interventions—the IDA's team's primary focus—is another of the key questions identified in this survey.

[188] For a representative, well-constructed study of this type, see Michael A. Johansson et al., "SARS-CoV-2 Transmission from People without COVID-19 Symptoms," *JAMA Network Open*, January 7, 2021. doi:10.1001/jamanetworkopen.2020.35057.

Epidemiological Investigations

The first published case of presumed asymptomatic transmission of COVID-19 was reported by Yan Bai and colleagues investigating a familial outbreak cluster in Anyang, China in January 2020.[189] The presumed index case (Patient 1) was a young woman who lived in Wuhan, China and traveled to Anyang where she visited with relatives from 10-13 January. Five of those relatives developed symptomatic, RT-PCR confirmed cases of COVID-19 between 17 and 26 January. Despite being asymptomatic, the index case herself was tested for COVID-19 because of her association with the family cluster of disease; her test results were mixed, with negative results on 26 January, positive results on 28 January, and negative results again on 5 and 8 February. The study team considered it likely that Patient 1's first test result was a false negative, and concluded that she was the most likely source of infection because "none of the patients had visited Wuhan or been in contact with any other people who had traveled to Wuhan (except patient 1)."[190]

In their work at the Washington state skilled nursing facility, Kimball and Arons were able to document the existence of pre-symptomatic and asymptomatic cases of COVID-19. Furthermore, based on Ct values associated with these cases, culture results, and the ineffectiveness of symptom-based control measures, they concluded that pre-symptomatic and asymptomatic cases, collectively, contributed to the spread of disease among the residents of a skilled nursing facility. However, given the conjugant living environment with established, widespread disease, they were unable to quantify the contributions of pre-symptomatic or asymptomatic cases to onward transmission.

In the Vo' study, Lavezzo et al. evaluated the overall impact of lockdown measures in reducing the spread of disease, to include estimation of the relative risk of infection for household contacts of isolated cases. During their epidemiological investigation, they discovered that two of the new cases detected during the second testing phase had an asymptomatic case as a likely source of infection.[191]

In the CHARM study, phylogenetic analysis and epidemiological investigations combined to provide even stronger evidence of asymptomatic transmission. The study team was able to obtain

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[189] Yan Bai et al., "Presumed Asymptomatic Carrier Transmission of COVID-19," Research Letter, *Journal of the American Medical Association*, published online February 21, 2020. doi:10.1001/jama.2020.2565. As noted in the letter (p. E1), "To our knowledge, transmission of the novel coronavirus that causes coronavirus disease 2019 (COVID-19) from an asymptomatic carrier with normal chest computed tomography (CT) findings has not been reported."

[190] Yan Bai et al., "Presumed Asymptomatic Carrier Transmission of COVID-19:" E2. Subsequent epidemiological investigations and modeling studies have suggested that transmission outside of Wuhan was taking place in China in this period (see, for example, Sanche et al., "High Contagiousness and Rapid Spread."); in retrospect, it seems equally likely—and perhaps better supported by RT-PCR test results—that this cluster of illness had an alternative source and that the presumed asymptomatic carrier was herself infected during her stay in Anyang.

[191] Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak:" Extended Date Figure 3.

more than 95% complete viral genomes from 32 of the 51 positive recruits.[192] Phylogenetic analysis identified six independent clusters of disease, indicative of local transmission during quarantine. This analysis further identified three potential index cases for specific clusters of illness, including the two largest; two of these cases tested positive on Day 0, the third on Day 7. All remained asymptomatic throughout the quarantine period.[193]

Beyond demonstrating the existence of asymptomatic transmission, several epidemiological studies have observed attack rates within households or among close contacts of individuals with symptomatic and asymptomatic presentation of COVID-19. These studies suggest that asymptomatic cases are generally less contagious than symptomatic cases. Citing the Buitrago-Garcia review referenced previously and epidemiological studies by Tan,[194] Bi,[195] and Li,[196] the DHS Master Question List for COVID-19 states that "asymptomatic individuals transmit SARS-CoV-2 less often than symptomatic individuals, causing 66% fewer secondary cases."

The study by Li et al. is the specific reference for the 66% value in the DHS document, but this appears to be a misreading of the information provided. This very large study retrospectively assessed all laboratory-confirmed or clinically confirmed cases and all laboratory-confirmed asymptomatic infections identified in Wuhan, China between December 2, 2019 and April 18, 2020, together with their household contacts. The overall purpose of the study was to estimate the probability of transmitting COVID-19 within households, and to determine factors that influenced the infectivity of cases and the susceptibility of their household contacts. Altogether, Li et al. obtained data on 27,101 households with 29,578 primary cases, which in turn had 57,581 household contacts and generated 10,367 secondary infections.[197] The study used a two-pronged approach: it calculated an observed secondary attack rate directly as the proportion of secondary infections among all household contacts, and it used a regression model to assess individual- and

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[192] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" 6. Interestingly, the authors report that most of the SARS-CoV-2 variants circulating within the United States at the time were detected among the recruits, consistent with the geographic diversity of the participants.

[193] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" 8. Ultimately, the study determined that for the recruit population in quarantine, the primary risk factors for disease transmission were shared rooms and shared platoon membership.

[194] Fen Tan et al., "Viral Transmission and Clinical Features in Asymptomatic Carriers of SARS-CoV-2 in Wuhan, China," *Frontiers in Medicine* 7 Article 547 (August 2020).

[195] Qifang Bi et al., "Household Transmission of SARS-CoV-2: Insights from a Population-based Serological Survey," medRxiv preprint, November 4, 2020. https://doi.org/10.1101/2020.11.04.20225573.

[196] Fang Li et al., "Household Transmission of SARS-CoV-2 and Risk Factors for Susceptibility and Infectivity in Wuhan: A Retrospective Observational Study," *Lancet Infectious Disease* 21 (January 18, 2021): 617-28.

[197] Li et al., "Household Transmission of SARS-CoV-2 and Risk Factors for Susceptibility and Infectivity in Wuhan:" 620.

household-level risk factors, such as household size and contact age.[198] In both cases, the assessment excluded the approximately 10% of households with multiple primary cases, and hence was limited to the 24,985 households with a single primary case.

Both approaches found that asymptomatic individuals were much less contagious than those who were symptomatic. The regression model estimated an odds ratio of 0.34 for asymptomatic transmission versus patients with mild and moderate disease. The observed secondary attack rate model estimated an odds ratio of 0.42 for asymptomatic versus symptomatic individuals before February 1, 2020, and an odds ratio of 0.21 thereafter.[199] The authors noted that as of February 1, 2020, disease reporting requirements in Wuhan changed and subsequently mandated reporting of asymptomatic infections; for this reason, they believed the estimated relative infectivity after February 1 was more accurate. Consequently, the Li study concluded that asymptomatic infections were 80% less likely to infect others than symptomatic infections.[200]

The Buitrago-Garcia review found five epidemiological studies that provided enough data to calculate the relative infectivity of asymptomatic index cases.[201] The authors generated a pooled risk ratio of 0.35 for transmission from asymptomatic versus symptomatic cases. This value is consistent with that calculated using the Li study's regression model. However, the underlying data is highly variable, with the asymptomatic versus symptomatic transmission risk ratios calculated for individual studies ranging from 0.06 to 0.78.[202] In another study referenced by DHS, Bi et al. conducted a serological survey of residents of Geneva, Switzerland and found that seropositive household members who did not report symptoms had 0.25 times the odds of infecting another household member compared to those reporting symptoms.[203] Finally, in a study of 12 asymptomatic individuals with laboratory-confirmed COVID-19 at the People's Hospital of Wuhan University, Tan et al. determined that only 1 of those 12 cases was found to have transmitted disease to a household contact.

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[198] Li et al., "Household Transmission of SARS-CoV-2 and Risk Factors for Susceptibility and Infectivity in Wuhan:" 619.

[199] Li et al., "Household Transmission of SARS-CoV-2 and Risk Factors for Susceptibility and Infectivity in Wuhan:" 623. The odds ratio of 0.34 calculated from this study's regression model appears to be the source of the DHS Master Question List for COVID-19 statement that asymptomatic infections cause 66% fewer infections that symptomatic infections.

[200] Li et al., "Household Transmission of SARS-CoV-2 and Risk Factors for Susceptibility and Infectivity in Wuhan:" 626.

[201] Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 14.

[202] Buitrago-Garcia et al., "Occurrence and Transmission Potential of Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 14, Figure 3.

[203] Bi et al., "Household Transmission of SARS-CoV-2: Insights from a Population-based Serological Survey:" 5.

A recently published communication from the Singapore Ministry of Health[204] describes a study of all individuals in Singapore who had been quarantined as a consequence of contact tracing between August 1 and October 11, 2020, and who had also undergone serology testing. The study's authors found that among the 3790 individuals in quarantine, the incidence of COVID-19 was 3.85 times higher among close contacts of a symptomatic case than for close contacts of an asymptomatic case.

Viral Load in Asymptomatic Cases

From the preceding discussion, it appears that epidemiological studies have begun to coalesce around the conclusion that asymptomatic infections are approximately 25% as contagious as symptomatic infections. Yet, evidence to directly support that conclusion from studies of viral load dynamics, to include the differentiation between viable and inert virus—remains elusive.

The CDC COVID-19 Pandemic Planning Scenarios document estimates the contagiousness of asymptomatic individuals relative to symptomatic as ranging from 25% to 100%, with a "current best estimate" of 75%.[205] The document states that "the current best estimate is based on multiple assumptions. The relative contagiousness of asymptomatic cases to symptomatic cases remains highly uncertain, as asymptomatic cases are difficult to identify, and transmission is difficult to observe and quantify. The estimates for relative contagiousness are assumptions based on studies of viral shedding dynamics."[206] The ranges provided in the document are derived from numerous published studies of viral loads and duration and amounts of viral shedding in asymptomatic and symptomatic cases, some of which found the dynamics to be the same, and some of which found them to be significantly different.

The CDC cited a study by Lee et al.[207] among the evidence that viral load does not vary significantly between symptomatic and asymptomatic infections. This study is among the most comprehensive treatments of this topic found in the literature, in terms of both the overall number of RT-PCR tests performed and the average number of tests per individual. Lee and colleagues conducted a retrospective cohort study of 303 RT-PCR-confirmed cases of COVID-19 who were isolated in response to a positive RT-PCR screening test within a community treatment center in Cheonan, Republic of Korea, from March 6 to March 26, 2020. Of these 303 cases, 110 were asymptomatic at the time of isolation, and 89 remained so for the duration of their stay. Regardless

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[204] Andrew A. Sayampanathan et al., "Infectivity of Asymptomatic versus Symptomatic COVID-19," *The Lancet* 397 (January 9, 2021): 93-4.

[205] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 5.

[206] https://www.cdc.gov/coronavirus/2019-ncov/hcp/planning-scenarios.html: 6.

[207] Seungjae Lee et al., "Clinical Course and Molecular Viral Shedding among Asymptomatic and Symptomatic Patients with SARS-CoV-2 Infection in a Community Treatment Center in the Republic of Korea," *JAMA Internal Medicine*, 180 no. 11 (August 6, 2020): 1447-52.

of symptom status, all patients were tested on days 8, 9, 15, and 16 of isolation, and could be tested on days 10, 17, 18, and 19 at the discretion of the attending physician. The mean number of tests was 6.4 per asymptomatic case and 6.2 per symptomatic case. Altogether, 1,886 RT-PCR tests were performed, 567 for asymptomatic cases and 1,319 for symptomatic cases.[208] The authors found that overall, viral load as measured by Ct values in asymptomatic patients was similar to those in symptomatic patients.[209]

Some of the studies discussed in previous sections provide similar results on a somewhat smaller scale. Both in the Vo' study and in the work of Kimball and Arons, researchers found that viral loads did not vary significantly between symptomatic, pre-symptomatic, and asymptomatic cases.[210]

Yet in other studies, the findings were contrary to those of Lee and colleagues, and showed significant differences in viral load between symptomatic and asymptomatic cases of COVID-19. One such study, by Zhou et al.[211] and cited by the CDC, examined the results of serially administered RT-PCR tests of 31 individuals isolated in Guangzhou Eighth People's Hospital from January 23 to March 3, 2020. All 31 individuals were asymptomatic upon admission; 22 of them eventually became symptomatic and 9 remained asymptomatic for the duration of their isolation. In all cases, the Ct values for the symptomatic cases—both in their pre-symptomatic and symptomatic phases of illness—were higher than those observed in the asymptomatic cases.[212] Of the latter, none had Ct values lower than 35, the upper bound of the reported threshold for viability.[213]

The Marine Corps CHARM study also reported that viral load, as measured by Ct value, was on average approximately four times as high in recruits who were symptomatic at the time of testing as in those who were asymptomatic, although some asymptomatic recruits did indeed have high viral loads.[214] For example, of the 12 asymptomatic recruits who tested positive on Day 0, 5

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[208] Lee et al., "Clinical Course and Molecular Viral Shedding among Asymptomatic and Symptomatic Patients with SARS-CoV-2 Infection:" 1448-9.

[209] Lee et al., "Clinical Course and Molecular Viral Shedding among Asymptomatic and Symptomatic Patients with SARS-CoV-2 Infection:" 1452.

[210] Lavezzo et al., "Suppression of a SARS-CoV-2 Outbreak:" Extended Date Figure 3, and Kimball et al., "Asymptomatic and Presymptomatic SARS-CoV-2 Infections:" 2. Note also that Lavezzo et al. found that viral load peaked on or before symptom onset and declined thereafter, supporting both the existence of pre-symptomatic transmission and the time of peak infectiousness used in our analysis in the main body of this paper.

[211] Rui Zhou, "Viral Dynamics in Asymptomatic Patients with COVID-19," *International Journal of Infectious Diseases*, 96 (2020): 288-90.

[212] Zhou, "Viral Dynamics in Asymptomatic Patients with COVID-19:" 289.

[213] Zhou, "Viral Dynamics in Asymptomatic Patients with COVID-19:" 290, Figure 2.

[214] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" 4.

had Ct values of 24 or less,[215] the lower bound of the reported threshold for viability. The relatively low Ct values in asymptomatic cases compared to symptomatic cases was contrary to that found in other studies, again raising questions about the variability in the nature of COVID-19 infection in different age groups.

We found it difficult to choose parameter values to represent the relative contagiousness of asymptomatic cases. On the surface, it is difficult to reconcile the epidemiological evidence that asymptomatic infections are far less likely to transmit disease with the uniformity in viral loads between asymptomatic and symptomatic cases observed in the largest studies of that type. This is particularly true as we have relied on Ct value thresholds as a surrogate for contagiousness when making assumptions about pre-symptomatic transmission, as discussed previously. Still, epidemiological studies provide the most direct observation of the behavior of disease among a population, and these studies have consistently concluded that asymptomatic cases are not as contagious as symptomatic cases. Therefore, based on the increasing convergence among studies of this type, we have assumed that asymptomatic cases are 25% as contagious as symptomatic cases.

Disease Transmission over Time

Our representation of COVID-19 transmissibility over time is shown as a triangle function in Figure A-1, for both our base-case R_0 of 5.9 and our excursion value of 2.5. The area of the triangles is equal to R_0, and the peak number of transmissions per day is calculated.

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 are symptomatic will, on average, cause four times as many infections as those individuals who remain asymptomatic; 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%. As illustrated in Figure A-1, and accounting for both of these factors, 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.

[215] Letizia et al., "SARS-CoV-2 Transmission among Marine Recruits during Quarantine:" Supplementary Appendix, Figure S1. See Section 3.b. above for a discussion of the relationship between Ct value and the viability of virus in culture.

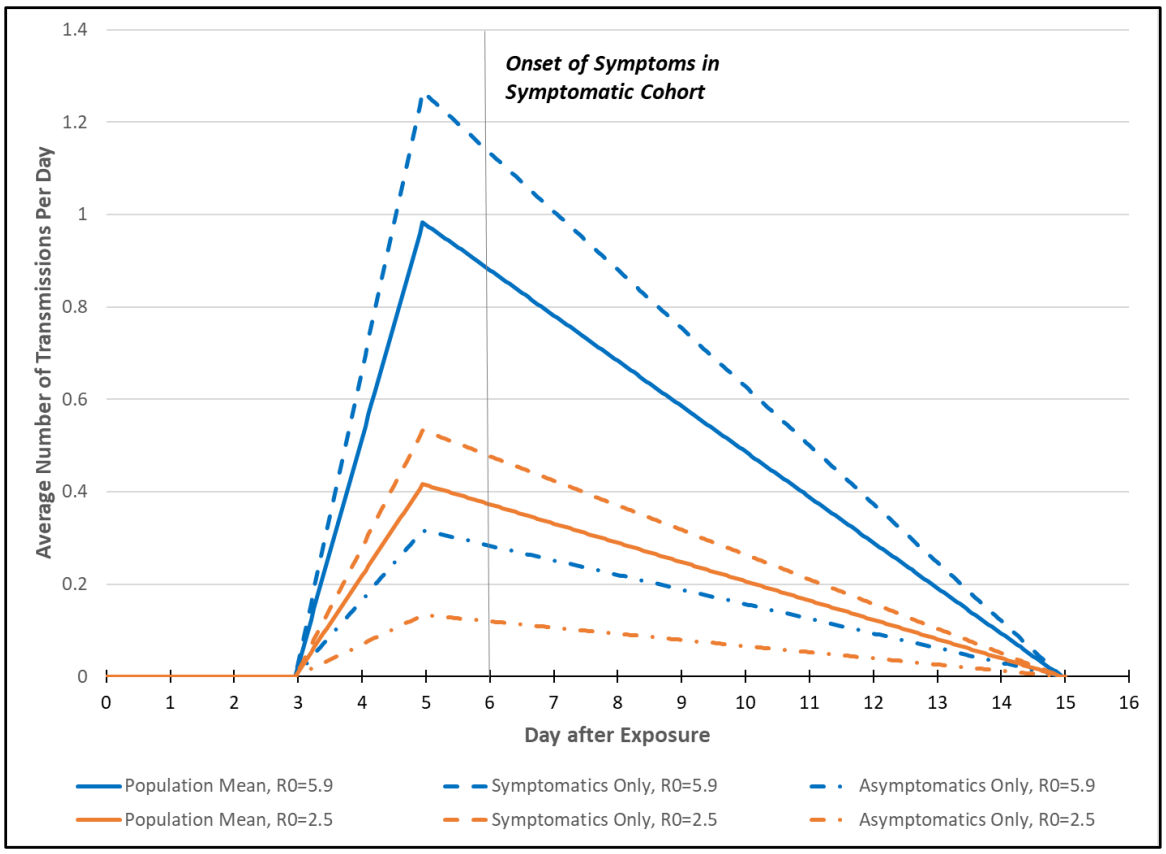

Figure A-1. Representation of COVID-19 Transmission over Time from Various Cohorts, with Peak Transmission on Day 5 after Exposure

In this representation, the percentage of transmission that would occur before and after onset of symptoms can be calculated based on the portion of the triangle that falls within the pre-symptomatic period. When peak transmission occurs one day before symptom onset, 32.5% of transmission would take place before onset of symptoms. 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 the population-level modeling studies conducted by Lui et al. and He et al., and cited in the CDC Planning Scenarios Document.

Given the paucity of data on asymptomatic transmission, we have assumed that the profile of transmission over time from asymptomatic cases will be the same as that of symptomatic cases. 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.

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Appendix B. Extension of Original Analytic Methodology to Account for COVID-19-Specific Characteristics

Accounting for Asymptomatic Cases

The original methodology derived for IDA Paper P-10877 represents the transmission of disease averaged across an entire population. However, the transmission of COVID-19 can be characterized by the dynamics of two distinct cohorts of infected individuals—those who never develop symptoms (called asymptomatic for our analysis) and those that develop symptoms after a brief pre-symptomatic contagious period (called symptomatic for our analysis). To account for this dynamic, we expanded our original methodology to include these two cohorts.

We introduce a new parameter, α, that describes the proportion of cases that are asymptomatic and consider the population-level transmission of the disease as the weighted average of the transmission from asymptomatic and symptomatic cases

$$R_0 = (1-\alpha)R_s + \alpha R_a$$

where R_s and R_a are the average number of new infections caused per symptomatic and asymptomatic individual respectively.

From this new starting point, we can incorporate the impact of various response measures by reducing transmission from either one specific cohort or both. For example, the impact of vaccines on disease transmission applies equally to both cohorts. As a result, we can express the average number of new infections per contagious individual given a vaccine with effectiveness ϵ_{vax} and compliance c_{vax} as

$$R_{vax} = (1 - c_{vax}\,\epsilon_{vax})[(1-\alpha)R_s + \alpha R_a].$$

In comparison, isolation triggered by the appearance of symptoms will only impact the transmission of individuals in the symptomatic cohort. As a result, we can express the average number of new infections per contagious individual given some isolation regime as

$$R_{Iso} = f_{Iso}(\epsilon_{Iso}, D_{Iso})(1-\alpha)R_s + \alpha R_a$$

where $f_{Iso}(\epsilon_{Iso}, D_{Iso})$ is the same function representing the reduction in transmission due to isolation that was derived in the original analysis.

We assume that only the contacts of symptomatic individuals would be quarantined. As a result, we only reduce the transmission form symptomatic individuals when we account for

quarantine. As in the original analysis, we characterize quarantine by a single parameter, ϵ_Q, that describes the fraction of infected individuals who are quarantined and subsequently isolated such that they do not transmit the disease. In the present analysis, this only applies to the infections caused by symptomatic individuals. As a result, the average number of new infections per contagious individual given some quarantine regime is

$$R_Q = \left(1 - \epsilon_Q\right)(1 - \alpha)R_s + \alpha R_a.$$

Finally, to consider quarantine and isolation in use together, we simply incorporated the corresponding factors from the isolation and quarantine formulation as follows

$$R_{Iso,Q} = \left(1 - \epsilon_Q\right)f_{Iso}(\epsilon_{Iso}, D_{Iso})(1 - \alpha)R_s + \alpha R_a.$$

As in the original analysis, we assessed various response measures by their ability to reduce the average number of new infections per contagious individual to less than one, $R < 1$. By converting the above equations into inequalities, we can determine the parameter values needed for a given response to prevent sustained disease transmission.

Methodology for Simulating Population-Wide Testing

We developed a simple stochastic model to analyze the use of diagnostic testing as a trigger to isolate contagious individuals. 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 and the timing of positive test results relative to their disease progression dictate when that individual is isolated. The total number of new infections caused per individual is determined based on when they are isolated. A large number (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 disease progression for asymptomatic individuals is as follows: a 3-day latent period followed by a 12-day contagious but non-symptomatic period. Individuals who are characterized as being symptomatic have the following disease progression: a 3-day latent period followed by a 3-day pre-symptomatic contagious period, which is followed by a 9-day symptomatic contagious period. To reiterate, the classification of an individual as being either asymptomatic or symptomatic is randomly determined, however once classified, their disease progression is deterministic. 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 transmissibility of individuals is governed by the triangle functions shown in Figure 1.

Diagnostic testing and isolation were simulated under the following assumptions:

- All individuals are subject to diagnostic testing.

- Diagnostic tests are assumed to have a 100% probability of detection during the contagious period (regardless of the presence of symptoms) and a 0% probability of detection otherwise.
- The time it takes to conduct the test negligible.
- Individuals are isolated at the time of either their first positive test result or symptom onset, whichever occurs first.
- The expected number of new infections caused by an individual is equal to the area under the corresponding triangle function (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.

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Appendix C. Illustrations

Figures

Tables

Appendix D. References

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Appendix E.Abbreviations

CBRN	Chemical, Biological, Radiological, and Nuclear
CDC	US Centers for Disease Control and Prevention
CHARM	COVID-19 Health Action Response for Marines
COVID-19	Coronavirus Disease of 2019
Ct	Cycle Threshold
DHS	Department of Homeland Security
DoD	Department of Defense
ENE-COVID	Seroepidemiological Survey of SARS-CoV-2 Virus Infection in Spain
IDA	Institute for Defense Analyses
MedCM	Medical Countermeasures
MERS	Middle East Respiratory Syndrome
mRNA	Messenger Ribonucleic Acid
OTSG	U.S. Army Office of the Surgeon General
PCR	Polymerase Chain Reaction
qPCR	Quantitative Polymerase Chain Reaction
REACT	Real-time Assessment of Community Transmission
RNA	Ribonucleic Acid
ROM	Restriction of Movement
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-1	Severe Acute Respiratory Syndrome Coronavirus 1
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

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14. ABSTRACT

In this presentation, 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 that accounts for both pre-symptomatic and asymptomatic transmission. We then use that profile to determine the point in time, relative to both exposure and mean symptom onset, when an individual would, on average, transmit COVID-19 to one other person. Next, we assess the requirements for implementing control measures such that they would, collectively and on average, truncate transmission at or before that point in time. We consider a layered approach, 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, disease transmission, contagious disease, outbreak control measures, outbreak response, isolation, quarantine, restrictions of movement, vaccination, vaccine compliance

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