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Clinical Outcomes Of A COVID-19 Vaccine: Implementation Over Efficacy

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ABSTRACT The global effort to develop a coronavirus disease 2019 (COVID-19) vaccine is on track to produce one or more authorized vaccines. We examine how different definitions and thresholds of vaccine efficacy, coupled with different levels of implementation effectiveness and background epidemic severity, translate into outcomes including cumulative infections, hospitalizations, and deaths. Using a mathematical simulation of vaccination, we find that factors related to implementation will contribute more to the success of vaccination programs than a vaccine's efficacy as determined in clinical trials. The benefits of a vaccine will decline substantially in the event of manufacturing or deployment delays, significant vaccine hesitancy, or greater epidemic severity. Our findings demonstrate the urgent need for health officials to invest greater financial resources and attention to vaccine production and distribution programs, to redouble efforts to promote public confidence in COVID-19 vaccines, and to encourage continued adherence to other mitigation approaches, even after a vaccine becomes available.

From the earliest stages of the coronavirus disease 2019 (COVID-19) pandemic, the development of safe and effective vaccines against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the viral cause of COVID-19, has been widely considered an essential component of any strategy to control the virus, the disease, and its effects. Since the publication of the SARS-CoV-2 viral sequence January 10, 2020, an unprecedented global collaboration among governments, vaccine manufacturers, and researchers has been mounted to develop COVID-19 vaccines.¹

In the United States this work is supported through billions of dollars in public investment and new entities such as Operation Warp Speed and the Accelerating COVID-19 Therapeutic Interventions and Vaccines public-private partnership.² Global coordination of vaccine research and development is provided by the Coalition

for Epidemic Preparedness and Innovation (CEPI); Gavi, the Vaccine Alliance; and the World Health Organization (WHO).³ According to CEPI, 321 COVID-19 vaccine candidates were in development worldwide as of September 2020.⁴ Of those, as of November 2020, more than fifty had progressed to clinical testing in humans, eleven of which were in Phase III clinical trials—the large-scale population-based testing capable of producing the safety and efficacy evidence required for regulatory approval.⁵ As of early November 2020 four Phase III COVID-19 vaccine clinical trials were under way in the United States, with preliminary results likely to be made available in the coming months and more complete results thereafter.⁶

Vaccine efficacy is a particularly critical outcome to be measured in these trials and subsequently evaluated by regulatory bodies such as the Food and Drug Administration (FDA) and its international counterparts. In a June 2020 guid-

ance document to vaccine manufacturers, the FDA adopted a broad definition of vaccine efficacy that encompasses both transmission effects (that is, the ability of the vaccine to prevent the spread of SARS-CoV-2 from an infected person to a susceptible person) and disease-modifying effects (that is, the ability of the vaccine to slow or prevent progression of illness, to speed recovery, to decrease the use of critical care resources, or to reduce mortality among people who have been vaccinated but who nonetheless become infected).⁷

Recognizing that vaccines can provide both direct protection (reducing susceptibility among the uninfected) and indirect protection (reducing viral spread in those who have been infected), the FDA guidance recommended both a transmission endpoint (confirmed SARS-CoV-2 infection with one or more COVID-19 symptoms) and a disease modification endpoint (evaluating whether a COVID-19 vaccine prevents severe disease among people who become infected).^{7,8} Regardless of how a manufacturer defined its efficacy endpoint, the FDA also established a minimum efficacy threshold, specifying a primary efficacy endpoint point estimate of at least 50 percent to ensure—in FDA’s view—that a widely deployed COVID-19 vaccine is effective.⁷

These definitions and thresholds are highly consequential, yet the FDA guidance document provides no justifications for either. The 50 percent efficacy threshold most closely resembles the typical effectiveness of vaccines against influenza, which is a less transmissible, morbid, and lethal disease than COVID-19.^{9,10} It is also a considerably lower efficacy standard than that for virtually all other approved and widely used vaccines.¹¹ But in the context of a global pandemic with ruinous economic and public health consequences, the FDA’s 50 percent threshold raises the following questions: Might policy makers settle for a vaccine with more modest effects, and if so, how modest? Conversely, what infection and mortality benefits could policy makers anticipate if recent, preliminary reports of vaccines with 90 percent efficacy are confirmed?^{12,13} Would a vaccine that has a limited impact on transmission but significantly reduces progression from infection to severe disease be acceptable—or even preferable? How might policy makers compare such a vaccine with one that lowers susceptibility to infection but has no impact on disease progression?

Recent work demonstrates that dramatically different epidemic trajectories result from changing assumptions about the strength and duration of adaptive immune response to SARS-CoV-2 and its interaction with vaccines and nonpharmaceutical interventions of varying

efficacy.¹⁴ Yet these biological factors—including vaccine efficacy as demonstrated through clinical trials—are only some of the many influences whose complex interaction will determine the real-world effectiveness of COVID-19 vaccination and its ability to alter the trajectory of the pandemic. How well a vaccine program “works” will also depend on how quickly it can be manufactured, how efficiently it can be distributed to locations in greatest need, how persuasive health messaging can be in promoting public acceptance, and how consistently the public can adhere to the many complementary prevention strategies (for example, masks, hand washing, distancing) to limit the spread of the virus.

We sought to understand the interplay between these parallel considerations related to COVID-19 vaccines and vaccination: vaccine efficacy as determined through clinical testing and the design and execution of vaccination programs that follow. Specifically, we asked how vaccine-related changes in susceptibility to infection, progression of disease, and severity of illness might translate into population outcomes of interest such as cumulative infections, hospitalizations, and deaths. We explored how those downstream outcomes might vary in the face of alternative operational assumptions (for example, the pace of scale-up and the degree of public acceptance) and changes in the epidemiological context. We consider the implications of our results for ongoing efforts to hasten the development and deployment of COVID-19 vaccines in the months ahead.

Study Data And Methods

STUDY DESIGN We used a simple mathematical model to estimate the population benefits of a vaccine against COVID-19. We considered vaccines with varying degrees of preventive benefit (transmission effect) and disease-modifying benefit (progression and mortality effect). We considered different assumptions regarding the speed of manufacturing/distribution (pace) and the extent of vaccine delivery (coverage)—two implementation parameters that are independent of vaccine clinical trial results. We also considered different background epidemic severities, as measured by the reproduction number (R_t). Outcomes of interest—including total infections, deaths, and peak hospital or intensive care unit (ICU) use—were reported both on an absolute basis and as a percentage reduction from a “no vaccination” scenario during a six-month planning horizon. We initialized the simulation with a population size of 100,000 people, of whom 100 (0.1 percent) were exposed and 9,000 (9 percent) were recovered cases.¹⁵ The

model was implemented as a spreadsheet and parameterized and validated using population-average data inputs (see online appendix exhibit 1).¹⁶

COMPARTMENTAL MODEL The SEIR (susceptible-exposed-infectious-recovered) model is one of the simplest deterministic, mathematical frameworks for portraying the trajectory of an infectious disease through an at-risk population. Briefly stated, the SEIR framework treats the process of viral transmission and disease progression as a sequence of transitions among a finite number of health states (or “compartments”). Transitions are governed by mathematical equations that capture both the transmission dynamics of the virus and what is known about the natural history of disease.

We adapted the classic SEIR framework in two important ways (appendix exhibit 4).¹⁶ First, we divided the “infected” compartment into four distinct subcompartments to capture the increasing severity and resource use associated with more advanced COVID-19 disease: “asymptomatic,” “mild” (outpatient), “severe” (hospitalized), and “critical” (hospitalized in an ICU). Second, we introduced the possibility of vaccination by creating a parallel set of compartments to the ones described above. People receiving the vaccine moved from the “susceptible unvaccinated” state to the “susceptible vaccinated” state. From there, their progress to exposure, infection, recovery, and death was adjusted to reflect the transmission and disease-modifying benefits of the vaccine. This modeling device also permitted us to adjust the infectiousness of people who received an imperfect vaccine but who nevertheless became infected (that is, breakthrough infections).

VACCINE EFFICACY To capture the broad definition of vaccine efficacy in the FDA’s June 2020 guidance, we considered three different vaccine types (appendix exhibit 2)¹⁶: a preventive vaccine that decreases susceptibility to infection in uninfected people; a disease-modifying vaccine that improves the course of disease in infected people, slowing progression, speeding recovery, reducing mortality, and decreasing infectiousness; and finally, a composite vaccine that combines the attributes of both the preventive and disease-modifying vaccines. We set the efficacy for each of these attributes at 50 percent in the base case and examined ranges of 25–75 percent in sensitivity analysis. (For the recovery rate increase, the base-case value was 100 percent [that is, cutting recovery time in half] with a range of 75–150 percent.) We considered lag times between vaccine administration and when effects take hold ranging from fourteen days (representing a fast-acting, single-dose vaccine) to thirty

The challenges of vaccine development do not end once an effective vaccine is identified.

days in the base case (representing a two-dose vaccine with administration thirty days apart and partial efficacy after the first dose) and forty-two days (representing a two-dose vaccine with no efficacy after the first dose).^{17,18}

IMPLEMENTATION EFFECTIVENESS The challenges of vaccine development do not end once an effective vaccine is identified. The model includes two implementation measures: pace and coverage. Pace, the percentage of the population that could be vaccinated on a given day, is a measure of manufacturing and logistical preparedness. We assumed a base-case value of 0.5 percent for the pace parameter to approximate the daily rate of influenza vaccination in the US during the peak period of vaccination efforts each fall.¹⁹ This reflects our assumption that although a COVID-19 vaccine may need to be administered in two doses, the urgency of the pandemic may prompt sponsors to bring production and distribution to scale at twice the rate of the influenza vaccine. Given the uncertainty surrounding these assumptions, we considered alternative values ranging from 0.1 percent to 2 percent in sensitivity analysis. We defined coverage as the percentage of the population ultimately vaccinated—a measure of public acceptance and the success of public health efforts to make vaccines available to all who desire them. We used a base-case value of 50 percent (range, 25–75 percent), reflecting recent US polling data on vaccine acceptability.²⁰ At a daily pace of 0.5 percent, it would take $0.5/0.005 = 100$ days to achieve a 50 percent coverage goal.

EPIDEMIOLOGY AND NATURAL HISTORY We defined three epidemic severity scenarios: a base case with a reproduction number (R_t) of 1.8, a best case ($R_t = 1.5$) representing strict adherence to social distancing and other preventive best practices, and a worst case ($R_t = 2.1$) reflecting the higher risks associated with winter weather and greater indoor activity. We also report results for $R_t = 1.2$ in the appendix.¹⁶

Input data on the development and natural history of COVID-19 (including incubation

The effectiveness of a COVID-19 vaccine will be shaped by the success or failure of efforts to deliver a trusted vaccine quickly to the public.

times; likelihood of symptoms; and rates of progression, recovery, and fatality) were obtained primarily from modeling guidance issued by the Centers for Disease Control and Prevention (CDC) and the Office of the Assistant Secretary for Preparedness and Response in the Department of Health and Human Services, supplemented by published literature.²¹ We attempted to use the most current input data available. However, as clinical care and outcomes improve, as testing services magnify, and as the COVID-19 pandemic expands its demographic reach, our analysis will require adjustment and updating. Specifically, hospitalization and mortality rates are improving as the pandemic is controlled among the elderly and extends its reach to younger populations. Recognizing how quickly these statistics are evolving, we deliberately focused our attention in this analysis on infections, not deaths.

Appendix exhibit 1 documents all inputs and sources.¹⁶

LIMITATIONS Similar to any model-based analysis, our evaluation has important methodological limitations. First, we assumed a model of homogenous mixing. Although this simplified the underlying mathematics, recent evidence suggests that spikes in local positivity—and the resultant protective immunity—may be attributable to spatially correlated, small group gatherings. Vaccine hesitancy may also vary by setting and other demographics. Future refinements might consider more complex geospatial or age-based mixing assumptions.

Second, we did not stratify vaccine deployment or coverage scenarios across different at-risk and vulnerable populations, as suggested recently by the National Academies of Sciences, Engineering, and Medicine's Framework for Equitable Allocation of COVID-19 Vaccine.²² To some extent, sensitivity analyses on R_t might

serve as a surrogate for a stratified assessment of outcomes across communities with different epidemic severities. Furthermore, our framework did not allow for differential prioritization or uptake among groups at higher risk for hospitalization and death. Published data used to populate the model were necessarily taken from early in the pandemic course. Additional evidence (for example, age-adjusted outcomes, new strategies for COVID-19 clinical care, geographic case clustering, and patterns of vaccine hesitancy and acceptance among the public) may permit the model to be stratified by age or other dimensions and updated for risk for complications and death at the individual level.²³

Third, we assumed constant rates of transition from one model compartment to the next. This produced exponentially distributed residence times—time spent in a given state can be quite long, even if the mean duration is short—and could have biased the analysis against prevention and in favor of rapid implementation. As better data on the natural history of disease emerge, it may be possible to address the problem using multiple sequential compartments.

Finally, our base-case analysis restricted attention to a six-month horizon. Although we also report projections over the course of twelve months, this should be interpreted with caution, as waning immunity after disease and vaccine durability remain ongoing concerns.²⁴

A comprehensive description of the model, its parameters, governing equations, and input data values is in the appendix.¹⁶

Study Results

BASE CASE In a population of 100,000 and at a baseline reproduction number (R_t) of 1.8, the model projects 61,112 infections and 2,725 cumulative deaths over the course of six months without a vaccine. Introducing preventive, disease-modifying, and composite vaccines at baseline efficacy levels would result in 42,583, 39,767, and 31,625 cumulative infections and 1,896, 1,318, and 1,199 cumulative deaths, respectively (exhibit 1). Across all values of R_t , a 50 percent effective disease-modifying vaccine would have a greater impact on mortality and peak hospitalizations than a 50 percent effective preventive vaccine. The impact of both vaccines on total infections would be similar in a high-severity epidemic ($R_t = 2.1$), but the disease-modifying vaccine would have a more pronounced impact on total infections in a lower-severity epidemic ($R_t = 1.8$ and 1.5). The 50 percent effective composite vaccine, which combines the attributes of both the preventive and disease-modifying vaccines, would have the best

EXHIBIT 1

Output table for three SARS-CoV-2 vaccine types at six months with infections and deaths and three different reproduction numbers (R_t) (thirty-day delay to vaccine efficacy)

	No vaccine	Preventive vaccine			Disease-modifying vaccine			Composite vaccine		
		Total	Vaccinated		Total	Vaccinated		Total	Vaccinated	
			No	Yes		No	Yes		No	Yes
$R_t = 1.5$										
Total vaccinations	0	45,450	0	45,450	45,450	0	45,450	45,450	0	45,450
Total infections	39,685	15,985	12,641	3,344	12,894	9,182	3,712	9,348	7,912	1,436
Cumulative deaths	1,603	678	545	133	418	407	11	359	355	4
Peak hospitalizations	841	291	— ^a	— ^a	189	— ^a	— ^a	169	— ^a	— ^a
$R_t = 1.8$										
Total vaccinations	0	45,015	0	45,015	45,450	0	45,450	45,450	0	45,450
Total infections	61,112	42,583	34,074	8,509	39,767	28,639	11,128	31,625	26,338	5,287
Cumulative deaths	2,725	1,896	1,525	371	1,318	1,285	33	1,199	1,183	16
Peak hospitalizations	1,780	1,120	— ^a	— ^a	804	— ^a	— ^a	731	— ^a	— ^a
$R_t = 2.1$										
Total vaccinations	0	35,761	0	35,761	37,433	0	37,433	38,092	0	38,092
Total infections	71,199	59,064	49,325	9,739	59,142	45,553	13,588	51,652	44,102	7,551
Cumulative deaths	3,205	2,659	2,222	437	2,094	2,053	41	2,011	1,988	23
Peak hospitalizations	2,661	2,092	— ^a	— ^a	1,702	— ^a	— ^a	1,622	— ^a	— ^a

SOURCE Authors' assumptions. ^aNot applicable.

overall performance. However, its impact would be much less than the sum of the impacts of the other two vaccine types combined.

SENSITIVITY TO VACCINE EFFICACY To explore different possible clinical trial outcomes, we set vaccine efficacy variables to 25 percent, 50 percent, and 75 percent while holding all program implementation parameters constant (exhibit 2). We considered two implementation scenarios: a base case (scenario A) with pace at 0.5 percent and coverage at 50 percent, and more aggressive implementation (scenario B) with pace at 1 percent and coverage at 90 percent.

Greater vaccine efficacy always produced more favorable outcomes. In the case of preventive vaccines, the returns to increased efficacy were close to constant. For example, under base-case implementation assumptions (exhibit 2, scenario A) and $R_t = 1.8$, the incremental contribution to infections and to deaths averted from a preventive vaccine with efficacy of 25 percent, 50 percent, and 75 percent were 14 percent, 17 percent, and 17 percent and 14 percent, 17 percent, and 17 percent, respectively (see appendix exhibit 5 for results on deaths averted).¹⁶ Results with vaccine efficacy as high as 90 percent follow similar trends (see appendix exhibit 6).¹⁶ In contrast, there were markedly diminishing marginal returns to increased efficacy using disease-modifying and composite vaccines; these vaccines attained much of their full potential effect on outcomes at efficacy level 25 percent. For example, under the aggressive implementation

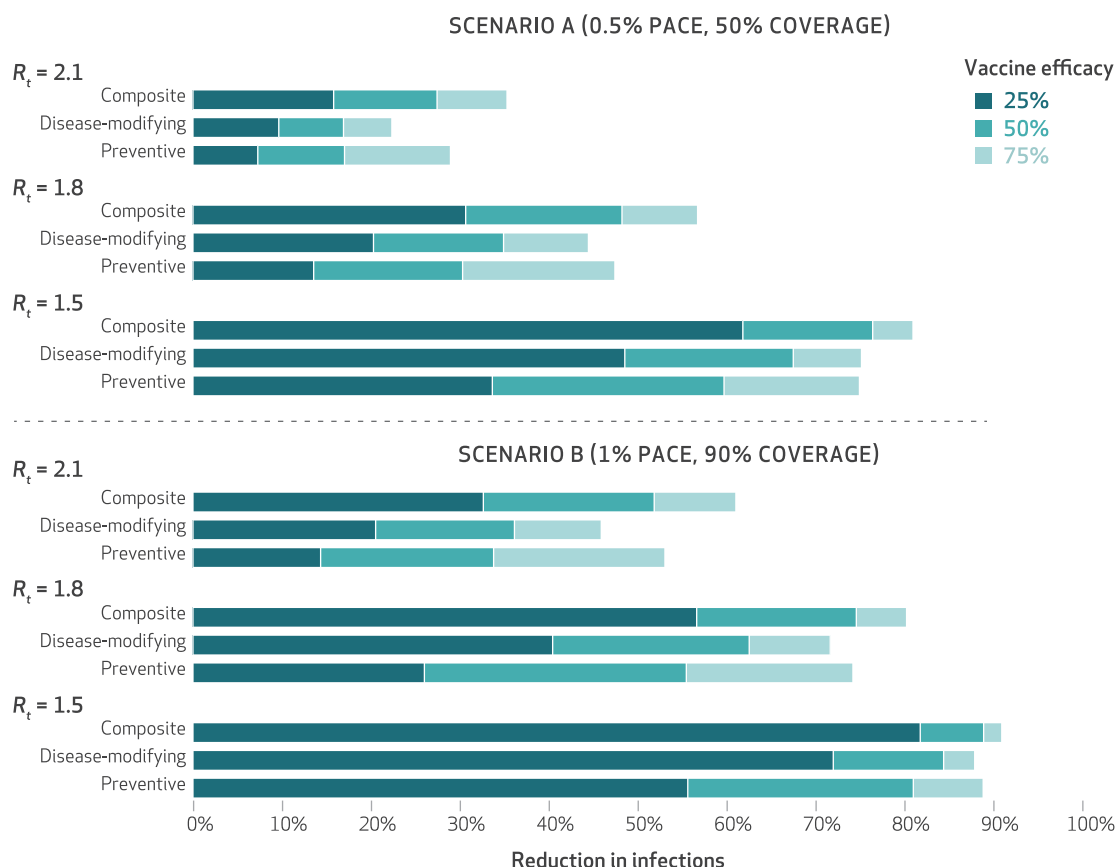
scenario (exhibit 2, scenario B) with $R_t = 1.8$, the incremental infections averted from a disease-modifying vaccine with efficacy 25 percent, 50 percent, and 75 percent were 40 percent, 22 percent, and 9 percent and incremental contribution to deaths averted was 62 percent, 15 percent, and 5 percent (appendix exhibits 5 and 6).¹⁶

Exhibit 2 illustrates that the potential benefits of even the most optimistically effective vaccine are diminished if it is introduced into a more severe pandemic. For all three vaccine types, a 75 percent effective vaccine implemented in a population where $R_t = 2.1$ averted a smaller proportion of infections and deaths than a 25 percent effective vaccine implemented under less severe pandemic conditions ($R_t = 1.5$). The figure also illustrates that vaccination programs that confer higher levels of protection—even if for a smaller fraction of the target population—generally outperform strategies that confer lower protection on a broader population. For example, a 75 percent effective vaccine administered to 50 percent of the population bettered a 25 percent effective vaccine given to 90 percent. The findings presented here persisted for $R_t = 1.2$, for time horizons extending to twelve months, and for efficacy delays ranging from fourteen to forty-two days (see appendix exhibits 7A, 7B, 8A, and 8B).¹⁶

Exhibit 2 also illustrates the modest superiority of the composite vaccine. Although it achieved the greatest reduction in infections for any

EXHIBIT 2

Total SARS-CoV-2 infections: sensitivity to vaccine type



SOURCE Authors' model-generated results. **NOTES** This exhibit shows the fraction of infections averted with alternative vaccine types (preventive, disease-modifying, and composite) and at different background epidemic severities, represented by increasing values of the reproduction number (R_t). The different shades of each bar represent vaccine efficacies of 25 percent (darkest), 50 percent, and 75 percent (lightest). Scenario A represents an implementation scenario in which vaccination is scaled up in the population at 0.5 percent per day (pace) with a maximum of 50 percent coverage. Scenario B represents an implementation scenario in which the vaccination pace is 1 percent per day with 90 percent coverage.

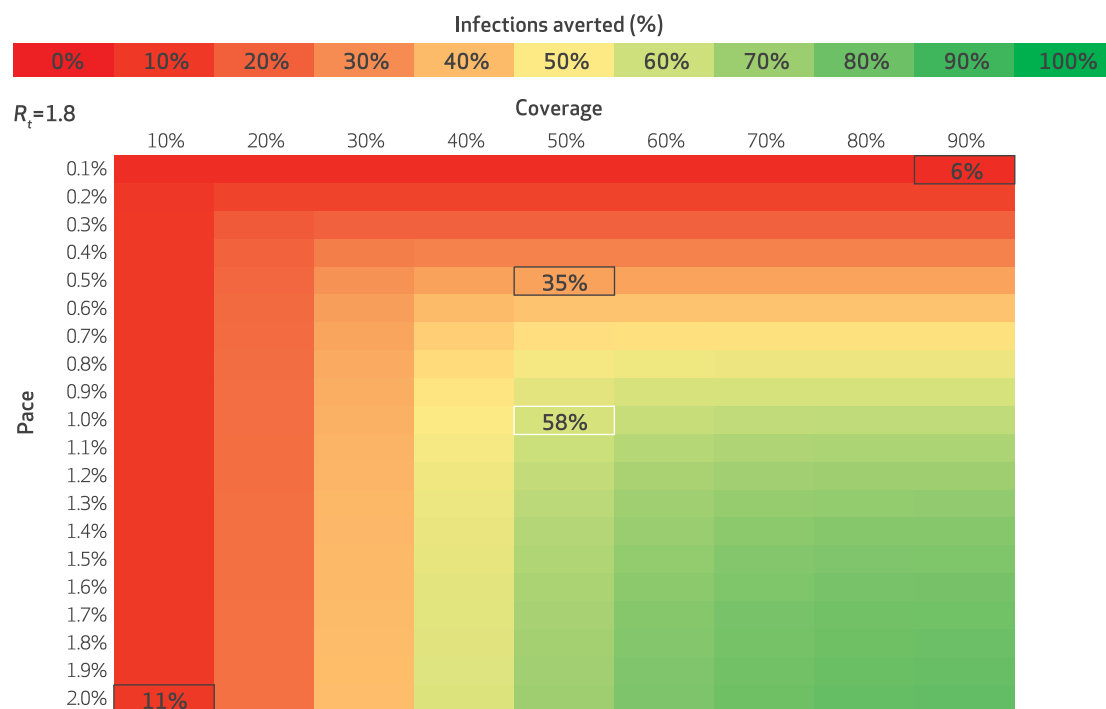
combination of pace and coverage, its impact was much less than the sum of the infections averted by the preventive and disease-modifying vaccines.

SENSITIVITY TO IMPLEMENTATION EFFECTIVENESS To understand how imperfect implementation might affect vaccination program success, we held the vaccine efficacy parameter at its base value (50 percent) and simultaneously varied the two program uptake parameters, pace and coverage (exhibits 3–5). With $R_t = 1.8$ (exhibit 3), a disease-modifying vaccine that attained even 90 percent coverage only averted 6 percent of infections at a pace of 0.1 percent; that same vaccine averted only 11 percent of infections at coverage 10 percent, even when it attained a pace of 2.0 percent. Bringing both coverage and pace up to their base case levels (50 percent and 0.5 percent) averted 35 percent of infections (see black outlined cells in the figure). The ob-

served pattern persisted for $R_t = 1.5$ (exhibit 4) and $R_t = 2.1$ (exhibit 5). It was also observed across all vaccine types (appendix exhibit 9A) and all lag-time assumptions (appendix exhibits 9B and 9C).¹⁶ Sufficient pace and coverage function as complements, not substitutes, and both are necessary for a vaccination program to produce large reductions in infections. High performance on one implementation measure cannot fully compensate for low performance on the other.

The impact of a vaccine dissipates dramatically as the severity of the epidemic (that is, R_t) increases. For example, a disease-modifying vaccine with 50 percent coverage and 1.0 percent pace averted 82 percent, 58 percent, or 35 percent of infections with $R_t = 1.5$, 1.8, or 2.1 (see white outlined cells in exhibits 3–5). All other things being held equal, the proportional power of any vaccine to reduce infections, deaths, and

EXHIBIT 3

Total SARS-CoV-2 infections: sensitivity to implementation factors, $R_t = 1.8$ 

SOURCE Authors' model-generated results. **NOTES** This heat map depicts the performance of a disease-modifying vaccine at baseline efficacy (50 percent) with a background epidemic severity level of reproduction number (R_t) = 1.8. The figure considers a range of vaccination coverage levels (horizontal axis, 10–90 percent) and scale-up paces (vertical axis, 0.1–2 percent per day). The color spectrum represents the proportion of infections averted: green averts the greatest number of infections and red the smallest number.

peak hospitalization was greatest at lower values of R_t .

Although shorter efficacy lag times invariably resulted in more favorable vaccine outcomes, the qualitative findings highlighted here for the thirty-day efficacy lag were similar to those for vaccines with efficacy lags of fourteen and forty-two days (appendix exhibits 9B and 9C).¹⁶

The results of additional sensitivity analysis are reported in the appendix.¹⁶

Discussion

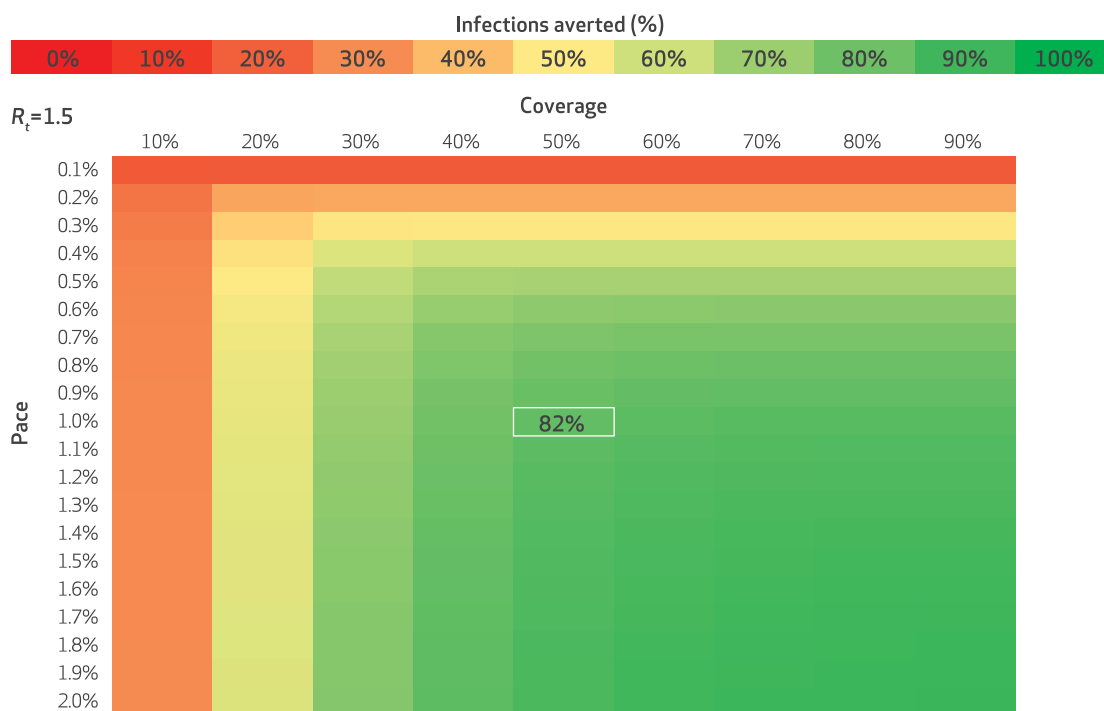
Our results demonstrate that the benefits of any COVID-19 vaccine, whether highly, moderately, or modestly efficacious by any trial-defined outcome, will depend at least as much on how swiftly and broadly it is implemented and the epidemiological environment into which it is introduced as it will on the vaccine's physiological properties, as shown through clinical trials. Although these latter vaccine-specific characteristics are fixed, the medical, public health, and government communities can productively intervene with respect to the contextual considerations that would increase the benefits of a vaccine up-

on its introduction.

First, the effects of any COVID-19 vaccine are highly dependent on the effective reproductive number of the virus (R_t) at the time a vaccine is deployed. In our model, R_t functions in part as a proxy for the success of efforts to promote widespread, sustained adherence to risk mitigation strategies such as masking, physical distancing, and limitations on large gatherings.²⁵ When R_t is comparatively low (1.5), indicating that viral circulation is being controlled through these non-pharmaceutical measures, vaccines with low efficacy (25 percent) are capable of producing larger reductions in the fraction of infections and deaths than vaccines with much higher efficacy (75 percent) that are introduced at times when R_t is significantly higher (2.1). Furthermore, the additional benefit of a vaccine with 25 percent versus 75 percent efficacy very much depends on the background R_t ; in cases of outbreak control ($R_t \leq 1.5$), a vaccine with 25 percent efficacy might well have a substantive impact. Even the effects of a vaccine with 90–95 percent efficacy, as Pfizer/BioNTech and Moderna have characterized the performance of their vaccines in preliminary press statements, relies heavily

EXHIBIT 4

Total SARS-CoV-2 infections: sensitivity to implementation factors, $R_t = 1.5$



SOURCE Authors' model-generated results. **NOTES** This heat map depicts the performance of a disease-modifying vaccine at baseline efficacy (50 percent) with a background epidemic severity level of reproduction number (R_t) = 1.5. The figure considers a range of vaccination coverage levels (horizontal axis, 10–90 percent) and scale-up paces (vertical axis, 0.1–2 percent per day). The color spectrum represents the proportion of infections averted: green averts the greatest number of infections and red the smallest number.

on the background R_t at the time of its introduction.^{12,13}

The complexity of infectious disease transmission dynamics accounts for what may be a counterintuitive result—one that goes against the usual finding in clinical needs assessment that efforts should be targeted where severity is greatest. For a highly infectious disease, even a vaccine with seemingly adequate efficacy, pace, and coverage may be insufficient to alter the fundamental population dynamics that produce high disease prevalence. Mathematical modeling has shown that differences in steady-state prevalence and the marginal steady-state impact of vaccine effectiveness are typically inversely proportional to the reproduction number.²⁶ The same is true in prevention interventions such as syringe exchange, which is more effective against HIV than against hepatitis C, given differences in R_t .²⁷

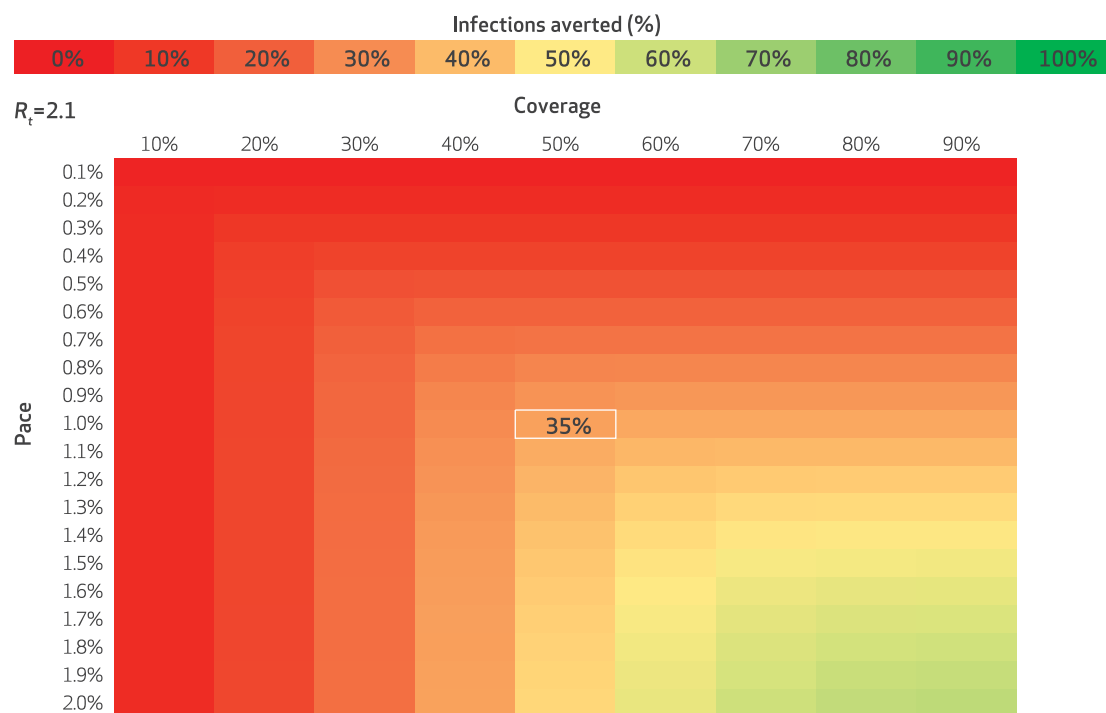
Managing and reducing R_t requires a sustained commitment to the public health practices and tools known to reduce the spread of COVID-19. Investment in these activities remains imperative not simply until the arrival of a vaccine but throughout the likely prolonged period

during which a vaccine is being deployed.

Second, our results show that the effectiveness of a COVID-19 vaccine will be shaped by the success or failure of efforts to deliver a trusted vaccine quickly to the public. The pace of vaccination—how quickly the vaccine is introduced—will be determined by a combination of manufacturing capacity, the development of distribution systems and infrastructure, the creation of mass vaccination clinics in diverse locations, and related logistical considerations. The vaccine benefit also depends on how many doses are required. Most vaccines currently in large-scale clinical trials are two-dose series, including those from Pfizer/BioNTech and Moderna most likely to be authorized first.⁵ A two-dose vaccine that takes twenty-eight to forty-two days to achieve efficacy, where maximum efficacy may be reached during the coming winter months with a higher R_t , should be expected to have diminished impact when compared with a one-dose vaccine with only a fourteen-day delay to efficacy.

Vaccination coverage—the percentage of the population that ultimately receives a vaccine—is dependent on efforts that foster widespread

EXHIBIT 5

Total SARS-CoV-2 infections: sensitivity to implementation factors, $R_t = 2.1$ 

SOURCE Authors' model-generated results. **NOTES** This heat map depicts the performance of a disease-modifying vaccine at baseline efficacy (50 percent) with a background epidemic severity level of reproduction number (R_t) = 2.1. The figure considers a range of vaccination coverage levels (horizontal axis, 10–90 percent) and scale-up paces (vertical axis, 0.1–2 percent per day). The color spectrum represents the proportion of infections averted: green averts the greatest number of infections and red the smallest number.

public enthusiasm for vaccination and address sources of hesitancy for vaccines in general and COVID-19 vaccines in particular.^{28,29} It also requires efforts to ensure that vaccines are accessible to all communities, particularly underserved groups for which long-standing disparities in vaccination coverage have been observed.^{30,31} This includes racial and ethnic minority groups, among whom the effects of COVID-19 have been disproportionately felt.^{32,33} Delivering the vaccine to as many people as possible as quickly as possible can result in large reductions in infections and death, even at higher R_t . Conversely, a slow pace of vaccination or low vaccination coverage dramatically reduces the benefits of vaccines even with moderate or high efficacy.

Some of the activities associated with accelerating vaccine production, distribution, and deployment, such as the advance manufacturing of vaccine doses while clinical trials remain under way and planning for robust postauthorization vaccine safety monitoring, have received considerable attention and investment from Operation Warp Speed and various federal agencies. But many other components of vaccination

planning are at much earlier stages of development, even as vaccines rapidly approach potential FDA authorization and as mass vaccination efforts are expected to begin virtually immediately thereafter. Among the issues for which considerable work remains are the detailed design of what will be exceedingly complex and unprecedented vaccine supply-chain strengthening and distribution activities in communities (for example, medical records and lot documentation to track dual-dose vaccine administrations and investments in ultra-low-temperature cold-chain capacity) and companion culturally sensitive and evidence-based communication to promote vaccine acceptance and convey the continued need for other prevention practices even after a vaccine becomes available.

State and local health officials expected to design and carry out much of the on-the-ground work related to COVID-19 vaccination have stated since spring 2020 that they lack sufficient funds to do so successfully.^{34,35} In September 2020 the CDC director concurred, telling Congress that an additional \$6 billion in federal funding to states was required for their role in vaccine distribution and related public out-

reach.³⁶ The need for those funds—an amount representing only half of the approximately \$12 billion committed to COVID-19 vaccine development to date—was disputed by other federal health officials, and Congress had not acted on this request as of early November 2020.³⁷

Overall, our results suggest that the significant public optimism regarding the potential value of vaccines in reducing the burden of COVID-19 is warranted, even if vaccines in development are shown to be only moderately efficacious. Not surprisingly, vaccine-associated benefits increase with greater levels of efficacy against infection, infectiousness, disease progression, and mortality. But even vaccines below the 50 percent efficacy threshold established in the June 2020 FDA guidance document could make valuable contributions to COVID-19 prevention and response.

But the efficacy of the COVID-19 vaccines currently being studied in Phase III trials and soon

to be reviewed by the FDA, although important, will be only one contributor to the overall effectiveness of the vaccination programs of which they may eventually be part. The ultimate success of COVID-19 vaccination efforts will depend on embracing a wide range of vaccine efficacy profiles at the time of authorization or approval, managing expectations regarding how a vaccine will contribute to public health responses in tandem with the continued use of nonpharmaceutical interventions, and investing substantially and rapidly in efforts to rapidly deliver vaccines to as large a portion of the population as possible and to quickly identify and respond to sources of vaccine hesitancy. Such a strategy would maximize the individual and population benefits of any authorized or approved COVID-19 vaccines and increase the likelihood that they approach the very high expectations placed on them. ■

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NOTES

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