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Awaiting the Signal: Assessing the Efficacy of COVID-19 Vaccines

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The global campaign to identify effective vaccines against COVID-19 has entered the final stage of testing for regulatory approval—Phase III trials—for several promising candidates. Evaluation will be guided by criteria established by the Food and Drug Administration and the World Health Organization. The minimum threshold for efficacy is observed reduction of disease incidence of at least 50 percent, with high statistical confidence of efficacy above a minimum of 30 percent. Full safety reviews of the vaccine candidates may take several months, to ensure any adverse events are given sufficient time to become evident and then studied. For efficacy, however, statistically valid determinations can be made after approximately 150 confirmed cases of COVID-19 among trial participants, which may occur relatively quickly given the prevalence of the virus in many communities. Consequently, on the question of whether a vaccine works to prevent progression from the virus to the disease, a clear signal is likely to occur in a few months after the trial begins rather than over the longer time frames that may be necessary for evaluation of their safety profiles.

An intense global scramble is underway to identify and manufacture safe and effective vaccines against COVID-19. Social-distancing protocols, when implemented vigorously, can slow the transmission of the SARS-CoV-2 virus that causes the disease, but they are costly and therefore difficult to sustain over many months or years. In contrast, a strong vaccine would allow countries to resume more economic activities with less risk to human health.

Early in the pandemic, the US and other governments, along with key global nonprofits, recognized the potential importance of an accelerated vaccination effort to ending, or at least mitigating, the crisis. They deployed substantial resources to speed up the research and development of the leading candidates and scale up the manufacturing capacity of the companies sponsoring them. These early investments have worked; several vaccines have cleared the first two phases of the regulatory approval process and are now in or nearing the final stage—Phase III clinical trials involving tens of thousands of volunteers. Government funding also has allowed the manufacturers to begin stockpiling vaccines even before it is known if they work and can be approved.

Pronouncing on the efficacy of vaccine candidates is a matter of probability assessment, based on statistical methods. Trials with large numbers of volunteers speed up the process because, all other factors being equal, they shorten the time that must pass while waiting for the required number of

Table 1. OWS Vaccine Candidates in or near Phase III Trials

Vaccine Developer	Platform	# of Doses	Identifier	Start Date	Vaccine Arm #	Placebo Arm #	Trial Locations
NIAID/ Moderna	Genetic (mRNA)	2	NCT04470427	July 27, 2020	15,000	15,000	100 US
BioNTech/ Pfizer	Genetic (mRNA)	2	NCT04368728	July 27, 2020	22,000*	22,000*	113 US, Argentina, Brazil, and Turkey
Oxford-AstraZeneca	Viral Vector (adenovirus)	2	NCT04516746	August 17, 2020	20,000	10,000	62 US
Janssen/ J & J	Viral Vector (adenovirus)	1	NCT04505722	Expected September 2020	30,000	30,000	178 US, Brazil, Chile, Columbia, Mexico, Peru, Philippines, and Ukraine
Novavax	Protein Subunit	2	Not Available	Expected October 2020	Unknown	Unknown	Unknown

Note: *The sponsors have requested approval from the US government to expand the trial from 30,000 total volunteers to 44,000.
Source: World Health Organization; and ClinicalRegistry.gov.

confirmed cases of disease—likely under 200—to surface among the participants. Once that threshold is crossed, it will be possible to determine, within the acceptable boundaries, the efficacy of the candidate vaccines.[1]

The following provides a brief overview of the Phase III process, with a focus on the statistical considerations used to determine whether the vaccine candidates will work to protect sufficient numbers of people from developing the disease.

The Phase III Candidates

The World Health Organization (WHO) is tracking 180 COVID-19 vaccine candidates, of which 35 are in clinical trials involving human volunteers and nine are in Phase III (WHO 2020b).

Currently, the US has invested in six vaccines through its Operation Warp Speed (OWS) initiative (Capretta 2020). Four candidates are in Phase III (although one has not yet begun recruiting volunteers), and one more is readying its Phase III protocol. Table 1 summarizes the Phase III trial designs of these vaccine candidates.

In addition to OWS-sponsored candidates, five additional vaccines are also in Phase III, as summarized in Table 2. Four of the non-OWS candidates are sponsored by companies based in China. The trials for these vaccines are being run entirely outside the US.

The Phase III process for vaccine approvals has been refined over decades and is governed primarily by the major regulatory agencies in advanced economies, including the US Food and Drug Administration (FDA) and European Medicines Agency. The WHO works to build uniformity across national regulatory agencies by providing guidance on how to assess vaccine safety and efficacy.

As the vaccine race heated up in the months after the pandemic began, both the FDA and the WHO chose to release documents stipulating the criteria they believed should be used to judge the safety and efficacy of vaccine candidates (FDA 2020 and WHO 2020a). The FDA's explanation of critical regulatory considerations is intended to guide decision-making about the licensure of

[1] Safety considerations also are paramount in the regulatory review process and an important function of large Phase III trials. Rare but problematic adverse reactions might become visible only when substantial numbers of volunteers are given a vaccine. While safety considerations are central to the regulatory review process, this report is focused on efficacy analysis.

Table 2. Non-OWS Vaccine Candidates in Phase III Trials

Vaccine Developer	Platform	# of Doses	Identifier	Start Date	Vaccine Arm #	Placebo Arm #	Trial Locations
CanSino Biological Inc.	Viral Vector (adenorvirus)	2	NCT04526990 NCT04540419	August 26, 2020	20,000	20,000	Pakistan
Gamaleya Research Institute	Viral Vector (adenovirus)	2	NCT04530396	August 31, 2020	30,000	10,000	19 Russia
Sinovac	Inactivated Virus	2	NCT04456595	July 2, 2020	4,435	4,435	12 Brazil
Wuhan Institute/ Sinopharm	Inactivated Virus	2	ChiCTR2000034780	July 2020	Unknown	Unknown	United Arab Emirates, Bahrain, Peru, Morocco
Beijing Institute/ Sinopharm	Inactivated Virus	2	ChiCTR2000034780	July 2020	Unknown	Unknown	United Arab Emirates, Bahrain, Peru, Morocco

Source: World Health Organization; and ClinicalRegistry.gov.

vaccines for use in the US or, potentially, an emergency authorization decision.[2] The WHO guidance is intended to help inform the regulatory bodies in many countries around the world.

In the US context, the FDA has an important role in ensuring the integrity of the manufacturing process to minimize the risk of compromised doses reaching vaccinees. It also outlines the data that must be collected to evaluate the safety profiles of the vaccine candidates. These and other considerations will be central to regulatory decisions.

Phase III trials for COVID-19 vaccines must follow the protocols of a high-quality randomized and blinded test. Volunteers will be divided into two basic groups: those getting the vaccine and those getting a placebo. Neither the vaccinees nor those administering the vaccines will know which volunteers are in which group. The process of assignment will be random to ensure a sound basis for statistical analysis.

The Primary Endpoint: Disease Incidence

Success or failure in clinical trials can be influenced by a number of factors; however, each trial has a primary endpoint that establishes the central objective for evaluating the vaccine candidate.

In terms of efficacy, the FDA and WHO agree it is permissible for the primary endpoint to be confirmed cases of COVID-19. More specifically, they believe the trials can measure vaccine efficacy by comparing the incidence of COVID-19 among the volunteers receiving the vaccine with those receiving the placebo, with a reduction in disease incidence of 50 percent being the minimum allowable for regulatory approval.

The regulatory agencies could have stipulated that the Phase III trials should target protection against viral infection as the primary objective of the candidate vaccines, as vaccines that are effective at preventing infection altogether would be ideal for halting the pandemic. However, making that the goal might rule out inoculations that are good at halting development of the disease but only after a person has become infected. Consequently, both the FDA and WHO have chosen to propose a minimum efficacy requirement focused on reducing the incidence of COVID-19 among the vaccinated population.

[2] The FDA recently announced it will soon issue a second document outlining more specifically the criteria for an emergency use authorization for COVID-19 vaccines.

It is perhaps surprising that while vaccine trials require large sample sizes, efficacy determinations are based on a relatively small share of the overall trial enrollment. The crucial variable is the number of volunteers who develop COVID-19 symptoms. For many diseases for which vaccines are desirable, the likelihood of becoming ill is low—perhaps 1 percent or less. This is true even during the current COVID-19 pandemic. The low risk of contracting the virus and developing the disease means that the sample sizes for the trials must be large to ensure a sufficient number of cases of disease emerge in a reasonable time frame to allow for efficacy assessments.

Once the number of cases of disease crosses a predetermined threshold, experts tapped to monitor the trial can compare the numbers who developed the disease after receiving the vaccine with those who developed the disease after receiving the placebo. If the number of cases among those who received the vaccine is substantially lower than the number of cases among those who received the placebo, then the vaccine will be deemed efficacious. In contrast, if the number of new cases in the arm that received the trial vaccine is too similar to the placebo group, then the candidate vaccine will fail to demonstrate efficacy and, as a result, is likely to fail the trial.

A statistical test determines whether there is a sufficient difference in the results across the two arms. As noted, the FDA guidance stipulated that the vaccinated arm must have no more than 50 percent of the number of confirmed COVID-19 cases as the control arm (its "efficacy rate"). In addition, based on the observed data, there must be no more than a small chance that the vaccine's true efficacy is below a 30 percent reduction in disease incidence. The WHO proposes that the trial's data point should ensure no more than a 2.5 percent chance that a vaccine with true efficacy of less than 30 percent will be approved. In other words, the 95 percent confidence interval for the true efficacy rate must exclude 30 percent.

These criteria reflect a balance between the desires to avoid erroneously approving an ineffective vaccine and avoid erroneously rejecting an effective one. The WHO guidance notes that the recommended criteria are consistent with a 10 percent probability that a vaccine with a true efficacy rate of 60 percent that is evaluated after 150 confirmed cases will fail to meet the statistical criteria and emphasizes that this risk of a false negative result appropriately balances the two potential errors.

Factors Influencing the Timing of Efficacy Evaluations

The need to satisfy both the 50 percent and 30 percent thresholds affects a number of decisions about the design of Phase III trials.

There is a trade-off between speed and confidence. More data points permit a more accurate signal of the vaccine's true efficacy, but acquiring them may mean a longer wait for an effective candidate vaccine to be approved.

For this reason, the criterion regarding the confidence interval is just as important as the observed efficacy rate, because it calibrates how confident regulators can be in estimating a candidate vaccine's true efficacy. Importantly, more cases of the disease increase confidence in the estimate of the true efficacy rate.

For instance, consider two trials each with a 50 percent observed efficacy rate and equal numbers of participants in the treatment and control groups. The first trial stops after 30 confirmed COVID-19 cases (i.e., 10 in the treatment and 20 in the control), and the second stops after 300 cases (100 vs. 200). In the second trial, the vaccine sponsors could more accurately predict the vaccine's true efficacy than in the first. Even if the vaccine had no effect whatsoever, a Phase III trial that concluded after 30 cases would produce an observed efficacy rate of at least 50 percent approximately 5 percent of the time due to random chance. After 300 observed cases, in contrast, the probability of observing a 50 percent efficacy rate if the vaccine had no effect is vanishingly small.

More disease cases also permit the analysis of "secondary" or "supportive" endpoints, in addition to the primary endpoint. For example, answering questions related to rarer COVID-19 outcomes—for example, whether a subject has a severe case of COVID-19 or dies from the virus—would require observing more overall COVID-19 cases than only examining whether a participant became sick with

Key Factors Affecting the Timing and Strength of Efficacy Signals

Sample Size. More participants in a trial mean that, for a given disease attack rate and fixed amount of time, there will be more observed cases of disease. Thus, the trial could conclude sooner, send a clearer signal of vaccine efficacy, or both.

Attack Rate. The frequency with which non-vaccinated individuals become sick also affects how long the trial will take to conclude. Higher attack rates mean that participants contract COVID-19 more quickly, decreasing the time required to observe a given number of confirmed cases.

Number of COVID-19 Cases. The required number of positive cases defines the power of the test to distinguish between effective and ineffective vaccines. More positive cases mean a clearer signal of vaccine efficacy. Fewer positive cases offer a less clear signal but permit the trial to conclude sooner. As such, there is a trade-off between confidence in the efficacy rate of the candidate vaccine and the speed at which an effective vaccine will be approved or a trial of an ineffective vaccine can be discontinued.

True Vaccine Efficacy. The true vaccine efficacy rate interacts with the sample size, required number of positive cases, and attack rate to determine how long the trial lasts and the probability that the trial succeeds. Unlike the sample size, which is fixed as a part of the trial protocol, and the attack rate, which can be estimated from existing data on disease rates, the true efficacy rate is unknown to the trial sponsor beforehand. But beliefs about vaccine efficacy are a major consideration when determining how many positive cases must be observed before evaluating the vaccine's effectiveness. Vaccines that are believed to be very effective require fewer positive cases to achieve a high level of confidence that the Phase III trial will be successful. Vaccines with efficacy rates that are believed to be marginally greater than 50 percent, in contrast, risk unlucky outcomes if the number of positive cases is too small.

Counterintuitively, higher vaccine efficacy also delays the end of a trial for a fixed number of endpoints by slowing the accumulation of positive cases in the treatment arm. As a result, if a trial sponsor believes the candidate vaccine is very effective and desires a speedy approval, the sponsor may prefer to limit the number of positive cases that must be observed before analyzing the vaccine's efficacy.

the disease. For similar reasons, testing the vaccine's efficacy on subpopulations—for example, the elderly or participants with comorbidities—requires more overall positive cases. While these data are secondary to the primary efficacy consideration, they can still be important to the regulatory process. The FDA will want to consider all aspects of the competing candidates' effectiveness profiles when deciding which vaccines should be used for which populations and under what conditions.

This balance between the desires to have an accurate estimate of a candidate vaccine's efficacy rate and a speedy signal of a vaccine's effectiveness explains why the FDA and WHO suggest that the trials should reach at least 150 confirmed cases of COVID-19 before reaching any final conclusions. As discussed below, with an observed vaccine efficacy rate of at least 50 percent after 150 observed cases, the results of the trial imply that the true efficacy rate indeed falls above 30 percent more than 97.5 times out of 100. Therefore, any trial that observes a vaccine efficacy rate of 50 percent or greater following 150 observed cases of disease satisfies both statistical criteria.

This does not mean, however, that a trial could not, at least in theory, end earlier than 150 confirmed cases and still satisfy the statistical efficacy criteria. But a trial with fewer cases would require a higher observed efficacy rate to produce a sufficiently convincing signal. If, for example, the trial concluded after 75 confirmed cases, an observed vaccine efficacy rate of 57 percent would be necessary to ensure that the true efficacy rate is over 30 percent with 97.5 percent confidence.

These four interrelated issues (summarized in the sidebar)—the number of participants in the trial ("sample size"), the number of positive cases

Table 3. 95 Percent Confidence Intervals Based on Case Counts and Observed Efficacy Rates

Case Counts	Observed Vaccine Efficacy Rates			
	40%	50%	60%	70%
50	(–8%, 68%)	(15%, 75%)	(28%, 81%)	(44%, 86%)
100	(11%, 61%)	(25%, 68%)	(39%, 75%)	(53%, 82%)
150	(17%, 57%)	(31%, 64%)	(44%, 73%)	(57%, 80%)
300	(25%, 53%)	(37%, 61%)	(49%, 69%)	(61%, 78%)

Source: Authors' calculations.

observed before evaluating effectiveness (the number of observed cases of disease, or "primary endpoints"), the likelihood for non-vaccinated participants to contract COVID-19 (the "attack rate") because of the virus' prevalence in the trial site communities, and the true effectiveness of the vaccine ("efficacy rate")—determine how quickly we should expect to see a vaccine approved and how effective we believe an approved vaccine will be.

Modeling Phase III Efficacy Trials

Simulations of Phase III trial efficacy assessment provide useful insights into the interaction of the factors affecting the trial's length, the required observed efficacy rate, and the probability that a candidate vaccine satisfies the efficacy criteria. The modeling methodology used in these simulations is described in detail in the appendix and is divided into three parts, covering confidence interval and error rate calculations, duration analysis, and intermediate evaluations at lower numbers of confirmed cases.[3]

Table 3 reports the confidence intervals that are produced when the statistical analysis is assessed after various levels of confirmed cases and with varying rates of observed vaccine efficacy. (Intervals depicted in red would fail the test, while those in green would pass it.)[4]

As shown, if a candidate vaccine has an observed efficacy of 70 percent and the trial concludes after 50 cases, we would have 97.5 percent confidence that the true efficacy rate exceeds 44 percent, which satisfies the WHO criteria. In contrast, if a vaccine has an observed efficacy rate of 60 percent, 50 cases would not be enough, although 100 cases would be. Finally, for a vaccine with a 50 percent observed efficacy rate, 150 observed cases are sufficient to have 97.5 percent confidence that the true efficacy rate exceeds 30 percent. These results indicate that, so long as the trial concludes after 150 confirmed cases and the observed efficacy rate exceeds 50 percent, both statistical criteria will be satisfied. Finally, an observed efficacy rate of 40 percent will always fail the statistical test, due to the first statistical criterion, which requires that the trial results imply a true efficacy rate that is greater than 50 percent.

The preceding analysis demonstrates that the test's power to identify effective vaccines increases with the number of confirmed cases being analyzed. Trials that require fewer positive cases have a higher probability of mistakenly rejecting an effective vaccine. But trials that require fewer cases also end faster. For example, assuming a 30,000-person trial and three-month attack rate of 1 percent for the placebo arm, a trial for a vaccine with a 50 percent efficacy rate that requires 150 positive cases has a one in two chance of ending before two and a half months and more than a 99 percent chance of ending before three months. By comparison, the trial would observe 100 cases before two and a half months with near certainty.[5]

The overall number of participants in the trial and the candidate vaccine's true efficacy also affect the expected amount of time required to observe a sufficient number of positive cases. More participants mean more COVID-19 cases. For example, increasing the number of participants in the previous example by 50 percent would mean that the trial would reach 150 positive cases before two months more than 90 percent of the time. Perhaps counterintuitively, a higher true vaccine efficacy

[3] The code for the modeling is posted on AEI's Open Source Policy Center website.

[4] See Part I of the appendix for more detail on how these confidence intervals are derived.

[5] Part II of the appendix provides more detail on how these duration estimates are calculated.

rate slows the speed until a fixed number of positive cases are reached by slowing the accumulation of positive cases in the vaccinated arm. For instance, in a 30,000-participant trial for a vaccine with a 60 percent efficacy rate, the probability of reaching 150 positive cases before two and a half months drops to one in five. If the same trial were evaluating a vaccine with a 70 percent efficacy rate, that probability falls to less than one in 20.

Table 4. Case Counts at Interim and Final Efficacy Evaluation Stages for OWS Candidates in Phase III Trials

Evaluation Stages	Moderna	Pfizer/ BioNTech	Oxford/ AstraZeneca	Janssen/ J & J
First	53	32	75	*
Second	106	62	—	*
Third	—	92	—	*
Fourth	—	120	—	*
Final	151	164	150	154

Note: * Evaluation will be continuous (once per week) after four conditions are met, including at least 20 confirmed COVID-19 cases.
Source: Phase III protocols posted online by Moderna, Pfizer, AstraZeneca, and Johnson & Johnson.

The next set of analyses provides more detail on this trade-off between the power of the trial to identify effective vaccines and the number of observed cases before evaluating the candidate vaccine's efficacy. As noted previously, at 150 confirmed cases, a vaccine with a true efficacy rate of 60 percent has a nine in 10 chance of satisfying the statistical criteria. At only 100 cases, the probability of exceeding the required thresholds declines to three in four. At just 50 cases, the probability is closer to one in two.

Another way of considering this same trade-off is by examining what the true efficacy rate of a vaccine must be to achieve a 90 percent probability of success at various case counts. At 100 confirmed cases, the true vaccine efficacy rate needs to be at least 66 percent, and at just 50 cases, it must be at least 73 percent.[6]

This discussion also underscores an important difference between statements related to beliefs about the efficacy of a vaccine and beliefs about the probability of passing a Phase III trial. A claim that a candidate vaccine has a three in four chance of satisfying the criteria for regulatory approval in a trial with 150 confirmed cases, for example, is consistent with a claim that the vaccine has a 55 percent expected efficacy rate. In contrast, a claim that a candidate vaccine has an expected efficacy rate of 75 percent is consistent with a belief that the vaccine has less than a one in 20,000 chance of failing to satisfy the statistical criteria in a trial with 150 confirmed cases.

Multiple Endpoints and Early Signals

One way to balance the trade-off between the quality of the signal and the duration of the trial is to permit evaluation of vaccine efficacy at a series of intermediate case counts. The WHO, for instance, recommends that the trial be evaluated after 50, 100, and 150 confirmed cases, with vaccine efficacy thresholds of 76 percent, 59 percent, and 50 percent, respectively, at each stage.

Table 4 provides a summary of the intermediate evaluation points selected by the sponsors of the four ongoing Phase III trials of vaccine candidates in the OWS portfolio. As shown, Moderna's Phase III trial similarly includes intermediate evaluations at 53 and 106 cases, before a final evaluation at 151 cases, and requires an observed efficacy rate of 74 percent to demonstrate efficacy after 53 cases (Moderna 2020). Pfizer's trial includes four intermediate evaluation stages—the first after just 32 cases—and a final evaluation at 164 cases. To demonstrate efficacy after 32 cases, however, Pfizer's observed efficacy rate would need to exceed 77 percent (Pfizer 2020). This methodology ensures that only highly effective vaccines satisfy the regulatory criteria after just 50 positive cases, whereas vaccines with efficacy rates closer to 50 percent are more likely to require at least 150 observed cases before receiving approval.

The progressively weaker efficacy requirements across the three evaluation stages are consistent with the desire to identify an effective vaccine as quickly as possible while retaining the power of

[6] Part I of the appendix provides more detail on the methodology used to make these power calculations.

the statistical test. If, instead, we applied the same criteria at each intermediate stage as the criteria that we apply to the final analysis, we would approve too frequently vaccines with efficacy rates lower than 50 percent because each evaluation stage would offer another opportunity for an insufficiently effective vaccine to satisfy the statistical criteria by random chance.

The effect of permitting multistage evaluation on the expected duration of the trial, however, depends largely on the vaccine's true effectiveness. A trial for a vaccine with a true efficacy rate of 55 percent that evaluates the vaccine at 50, 100, and 150 positive cases using the WHO-recommended criteria will, on average, require 130 positive cases. More than six times in 10, the trial would continue to its 150-case conclusion. In contrast, if the candidate's true efficacy rate is 75 percent, then just 78 positive cases would be required, on average, to demonstrate its effectiveness, and the trial could end early nearly 99 times out of 100. Thus, an "early peek" at the data is not likely to make a difference in the trial's duration if, as trial sponsors claim, there is around a three in four chance of eventual approval of the vaccine based on its strength against the targeted disease.[7]

Table 5 provides an overview of the probabilities of vaccines with varying true efficacy rates meeting both of the efficacy threshold requirements (50 percent observed efficacy and high confidence of at least 30 percent efficacy) at intermediate counts of confirmed COVID-19 cases. For instance, for a vaccine with true efficacy of 80 percent, it will be found to meet both efficacy threshold requirements at 50 confirmed cases in 68 percent of Phase III trials, and, if not found efficacious at that point, it would be found efficacious after 100 cases in nearly all of the 32 percent of occasions in which it failed at 50 cases. It would be very rare (less than a 1 percent probability) that such a vaccine would not be found efficacious at either 50 or 100 confirmed cases (thus necessitating 150 cases to confirm its efficacy). After 150 confirmed cases, it would be even more rare for a such a vaccine to fail to meet for a third time the efficacy assessment criteria.

In contrast, for a vaccine with true efficacy of 50 percent, it would be rare—a 1 percent chance—to meet the efficacy requirements with just 50 confirmed cases. At 100 cases, such a vaccine would be found efficacious 20 percent of the time, and at 150 cases, 34 percent of the time. These probabilities indicate that a vaccine with a true efficacy of just 50 percent would be found insufficiently effective after 150 confirmed cases of disease in around half of the occasions that such a vaccine was tested in a Phase III clinical trial. Put another way, in the trial of such a vaccine, its observed efficacy in the trial would be less than its true efficacy with sufficient frequency that the vaccine would fail the trial around one out of every two times it was tested.

Table 5. Probability of Meeting Efficacy Thresholds at Various Counts of Confirmed Cases

	True Vaccine Efficacy Rates			
Case Counts	**50%**	**60%**	**70%**	**80%**
50	1%	6%	25%	68%
100	20%	53%	68%	32%
150	34%	33%	7%	<1%

Source: Authors' calculations.

Conclusion

The COVID-19 global pandemic has disrupted normal life in all corners of the world. There is wide recognition that the economic costs of social-distancing protocols are such that they cannot be sustained indefinitely; the world needs a solution that does not involve mass unemployment.

The vaccines under development provide reason for optimism. Multiple candidates have shown promise in early-stage clinical trials and now have entered into the final step of the regulatory approval process. Administering these vaccines to tens of thousands of volunteers in Phase III trials should give regulatory agencies the data they need to fully assess their safety and effectiveness.

Because of the urgency of the moment, there is a worry that governments may be too quick to approve vaccines before they have fully demonstrated their worth. That is certainly an argument for not rushing

[7] Part III of the appendix provides more detail on the methodology used to calculate these trial duration and case count estimates.

the trials; some safety concerns may take months before becoming evident.

In terms of efficacy, however, valid statistical determinations likely can be made rather quickly, taking approximately three months once a trial is at full enrollment rather than half a year or longer. That is due mainly to the prevalence of COVID-19, which increases the likelihood that trial participants will be exposed to the virus in their communities. If a candidate vaccine is truly effective at halting progression to COVID-19, that will be known soon enough by observing the presence of the disease primarily among those receiving the placebo. If a vaccine does not work, that too should be known rather quickly, as the disease will be nearly equally present among those randomly assigned to both arms of the Phase III trial.

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Appendix

The following provides an overview of the key assumptions and statistical methodology used to produce the estimates in this report.[8] A full replication of the coding is available through the Open Source Policy Center.

Of note, several statistical methods can be used to evaluate uncertainty concerning estimates of vaccine efficacy. The analysis here, which relies on a combination of exact probabilities derived from binomial distributions and numerical estimates based on Monte Carlo simulations, may differ slightly from analyses published elsewhere.

Part I: Confidence Intervals and Error Rates. Confidence intervals and power analyses are based on the cumulative distribution function and quantiles of the binomial distribution.

For example, the probability that a vaccine with true vaccine efficacy rate VE satisfies the criteria after N observed cases is defined in the following manner. Let

$$X_1 \sim B(N, \frac{RR}{1+RR}),$$

which is the distribution of the number of cases observed in the vaccinated arm given N total cases with the probability of any individual case being in the vaccinated arm equal to

$$\frac{RR}{1+RR}.$$

Let x_1^* be the maximum permissible number of cases in the vaccinated arm. The probability of success, then, is equal to

$$P(X_1 \leq x_1^*).$$

The confidence interval for VE conditional on the observed efficacy rate ($\widehat{VE}$) is derived similarly. Specifically, let $q(X_1, Q)$ be Qth quantile of the number of cases in the vaccinated arm out of N observed cases, where

$$X_1 \sim B(N, \frac{\widehat{RR}}{1+\widehat{RR}}) \text{ and } \widehat{RR} = 1 - \widehat{VE}.$$

Based on $q(X_1, Q)$, we derive 95 percent confidence intervals for VE:

$$[1 - \frac{q(X_1, 0.975)}{N - q(X_1, 0.975)}, 1 - \frac{q(X_1, 0.025)}{N - q(X_1, 0.025)}]$$

Part II: Duration Analysis. We assume that the three-month COVID-19 attack rate for the non-vaccinated arm (AR_0) is 1.0 percent, consistent with the WHO (2020).[9] The attack rate in the vaccinated arm (AR_1) is the attack rate in the non-vaccinated arm multiplied by the relative risk (RR), which is equal to 1 minus the true vaccine efficacy rate (VE). Thus, $AR_1 = AR_0 \cdot RR = AR_0 \cdot (1 - VE)$. We also assume that the attack rates in both arms of the trial do not vary with the time elapsed since administration of the vaccine or placebo.

We simulate the waiting time until a fixed number of cases (N) have been observed across the two arms based on 100,000 simulations. In each simulation, the time to infection for each participant is drawn from an exponential hazard function. Consistent with WHO guidance, we discard all observations that occur in the first 14 days of the trial.

Part III: Intermediate Evaluations. We use the methodology proposed by the WHO (2020a) to define the acceptance and rejection criteria conditional on the number of observed cases when the trial is evaluated at intermediate case counts.

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[8] For a step-by-step description of a similar binomial methodology, see Chan and Bohidar (1998).

[9] Other sources predict different attack rates. Pfizer's Phase III trial protocol, for example, predicts an attack rate of 1.2 percent per year in the non-vaccinated arm, which would imply a slower accumulation of positive cases than the estimates reported here.

We calculate the probability of demonstrating efficacy at an intermediate case count and the expected total number of observed cases conditional on VE using a Monte Carlo simulation. Specifically, each simulated trial is represented by a sequence of N Bernoulli random variables with probability of success equal to

$$\frac{RR}{1+RR}.$$

That is,

$$X_{i,b} = B\left(1, \frac{RR}{1+RR}\right),$$

where $i \in \{1, \ldots, N\}$ indicates whether the ith observed case is in the vaccinated arm in simulated trial b. In each simulated trial, we then calculate the observed efficacy rate after n trials—that is, $\widehat{VE}_{n,b}$.

$$\widehat{VE}_{n,b} = 1 - \frac{\sum_{i=1}^{n} X_{i,b}}{n - \sum_{i=1}^{n} X_{i,b}}$$

In each simulated trial, we end the trial at an intermediate case count if the observed efficacy rate is too high or too low. The WHO recommends intermediate observations at 50 and 100 cases, before a final analysis at 150 observations. At 50 observations, the vaccine demonstrates efficacy if the observed efficacy rate is at least 76 percent and is deemed ineffective if the observed efficacy rate is less than or equal to –14 percent. At 100 observations, the vaccine demonstrates efficacy if the observed efficacy rate is at least 59 percent and deemed ineffective if the observed efficacy rate is less than or equal to 32 percent.

Of note, the probability that a vaccine with a true efficacy rate of 55 percent has a trial conclude early because there are too many cases in the vaccinated arm is less than one in 200 and is vanishingly small for a vaccine with a true efficacy rate of 75 percent.

We thus calculate the expected number of cases as:

$$50 \cdot P\left(\widehat{VE}_{50} \notin (-.14, 76)\right) +$$

$$100 \cdot P\left(\widehat{VE}_{100} \notin (32, 59) | \widehat{VE}_{50} \in (-.14, 76)\right) P\left(\widehat{VE}_{50} \in (-.14, 76)\right) +$$

$$150 \cdot P\left(\widehat{VE}_{100} \in [32, 59] | \widehat{VE}_{50} \in (-.14, 76)\right) P\left(\widehat{VE}_{50} \in (-.14, 76)\right)$$

where the probabilities of establishing efficacy or ending the trial due to ineffectiveness at intermediate case counts are estimated from 100,000 simulated trials.

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