

## Are some COVID vaccines better than others? Interpreting and comparing estimates of efficacy in trials of COVID-19 vaccines

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Summary: COVID-19 vaccine trials provide valuable insight into the safety and efficacy of vaccines. Simple comparison of trial efficacy estimates, however, is problematic. When comparing efficacy results from COVID-19 vaccine trials, factors related to trial context and design must be considered.

## **Abstract**

COVID-19 vaccine trials provide valuable insight into the safety and efficacy of vaccines, with individually-randomized, placebo-controlled trials being the gold standard in trial design. However, a myriad of variables must be considered as clinical trial data are interpreted and used to guide policy decisions. These variables include factors such as the characteristics of the study population and circulating SARS-CoV-2 strains, the force of infection, the definition and ascertainment of endpoints, the timing of vaccine efficacy assessment, and the potential for performance bias. In this Viewpoint, we discuss critical variables to consider when comparing efficacy measurements across current and future COVID-19 vaccine trials.

**Keywords:** COVID-19, vaccine, efficacy, clinical trial, SARS-CoV-2

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## Viewpoint:

By the end of February 2021, the swiftly evolving global COVID-19 pandemic has led to more than 110 million SARS-CoV-2 infections and over 2.4 million deaths [1]. New preventive and therapeutic options are urgently needed to curb the spread of the infection and to mitigate the devastating consequences of COVID-19. At present, global demand for COVID-19 vaccines markedly exceeds available supply and distribution challenges abound. As countries grapple with a changing pandemic and viral evolution, a robust and complementary vaccination portfolio will be a critical tool in the fight against COVID-19.

To expedite the development, approval, and deployment of COVID-19 vaccines during this public health emergency, a U.S. government-initiated public-private partnership facilitated and accelerated the development, manufacturing and distribution of COVID-19 vaccines, therapeutics and diagnostics [2]. All vaccines in the U.S. in Phase 3 development are based on the spike glycoprotein of SARS-CoV-2 but vary in other attributes (Table 1). Results from the large phase 3 COVID-19 clinical trials for both the mRNA vaccines, BNT162b2 (Pfizer-BioNTech)[3] and mRNA-1273 (NIAID-Moderna) [4], demonstrate high efficacy against symptomatic infection and severe disease with an acceptable safety profile and are being distributed to prioritized population groups under Emergency Use Authorization (EUA). So far, large efficacy trials of a non-replicating chimpanzee adenoviral vector vaccine (ChAdOx1 nCoV19, Oxford-AstraZeneca) [5], a non-replicating adenovirus 26 vector vaccine (Ad26COV2S, Janssen) [6, 7], and an adjuvanted prefusion spike nanoparticle vaccine (NVX-CoV2373, Novavax) [8, 9] are underway in government-sponsored multicenter trials conducted in the U.S. and in other locales.

Vaccine efficacy data are now public for five of the above vaccines being studied in the U.S Phase 3 trials, through peer-reviewed publications, preprints, public regulatory or policy documents, or by press release [3-5, 10-12]. While the completeness and quality of the available data vary considerably, the availability of these new data have generated comparisons to the published results of the mRNA vaccines. Such comparisons of COVID-19 vaccine efficacy estimates must be made with careful consideration of numerous

potential differences in studies such as characteristics of the study population and circulating SARS-CoV-2 strains, force of infection, definition and discovery of endpoints, the precise window of vaccine efficacy measurement, and factors impacting performance bias. These parameters may not be fully available in press releases or early release publications (see Table 2) and some of these features, such as virus strain features, may be unknown even after the trial is published. Simple comparisons of point estimates of efficacy without contextualization could lead to incomplete or inaccurate conclusions on the value of COVID-19 vaccines and could undermine confidence in the products. Herein, we summarize critical variables to consider when evaluating vaccine trial outcomes.

### Characteristics of the study population

#### *Selection bias*

The choice of experimental population in any given clinical trial is based on several factors, including generalizability to the population in whom the intervention will be used, feasibility of follow-up to ensure uniform and high rates of study outcome ascertainment, and clinical equipoise. Differences in the presence of medical comorbidities and other social determinants of health may also affect overall efficacy results. Some trials may exclude participants with pre-existing conditions that could impact their response to either infection or vaccine, while another trial might include such participants. For example, Novavax reported a modest decline in vaccine efficacy against symptomatic disease in South Africa when HIV-infected individuals were included in the analysis [11]. Similarly, some trials enrolled fewer elderly participants, a population in which both immunosenescence and increased susceptibility to COVID-19 and severe disease must be considered. The original phase 3 ChAdOx1 nCoV19 trial, for example, demonstrated higher vaccine efficacy in study participants who received a half-dose in their initial immunization, but this cohort consisted of individuals only ages 18-55 years [5]. In the U.S., African American, LatinX, and Native American individuals have increased rates of COVID-19 and of severe disease in particular, which may be related to social determinants of health [13]. The variable inclusion of racial

and ethnic minorities across trials may, consequently, affect estimates of vaccine efficacy as a function of increased force of infection in these communities.

As more COVID-19 vaccines are approved, those at highest risk for becoming infected or for acquiring severe COVID-19 disease will have access to a vaccine through national allocation and distribution. The mRNA vaccine efficacy studies conducted by Pfizer-BioNTech and NIAID-Moderna occurred at a time when no vaccines against COVID-19 were available, and they enrolled relatively high percentages of participants 65 years of age and over [3, 4]. Emergency Use Authorizations issued in December 2020 and the current rollout of vaccines to priority populations of the U.S. will change the population available for ongoing and future vaccine efficacy trials. Randomization is intended to assure comparability of groups *within* trials but not *between* trials. While subgroup analyses, such as efficacy by age, may partly standardize comparisons, these cannot overcome the unmeasured differences in populations between trials.

#### *Serostatus of participants*

Baseline seropositivity for SARS-CoV-2 antibodies, consistent with prior exposure to SARS-CoV-2, will increase over time and may impact vaccine efficacy estimates. Individuals with preexisting anti-spike glycoprotein IgG are at significantly reduced risk of developing PCR-confirmed infection over a period of at least 6 months [14]. Beyond decreased baseline risk for SARS-CoV-2 reinfection, evidence has emerged demonstrating that seropositive participants have enhanced immune responses after a single dose of vaccine when compared to seronegative recipients [15]. The mRNA vaccine trials and the ChAdOx1 nCoV19 trial excluded participants in their primary analysis who were either seropositive at baseline or without baseline serologic results. Assessing vaccine efficacy in seropositive individuals after vaccination or infection will likely be factored into future trials, given the importance of this question clinically and increasing seropositivity rates globally.

## SARS-CoV-2 strains, prevalence, and transmission dynamics

Characteristics of the SARS-CoV-2 strains and evolving variants and the intensity of circulation will differ between COVID-19 vaccine clinical trials. The B.1.1.7 variant, first identified in the U.K. [16, 17], is associated with increased transmission, potentially increased virulence [18, 19], and is now the dominant variant in the U.K. and spreading quickly throughout the U.S. The B.1.351 variant, with more consequential changes to the spike glycoprotein than B.1.1.7, and also associated with increased transmissibility, was first identified in South Africa in October 2020 [20] and observed in the U.S. by the end of January 2021. The P.1 variant has recently emerged in Brazil in a high transmission setting and also has several consequential changes in the spike glycoprotein, with 3 mutations within the receptor binding domain [21]; the P.1 variant has also been identified in the U.S. and at least 20 other countries at the time of this writing [22].

Vaccines will likely perform differently against increasingly heterologous strains. In a press release, Novavax reported an overall vaccine efficacy of 89.3% against PCR-confirmed symptomatic COVID-19 from a trial in the U.K. where 50% of cases were attributed to the dominant B.1.1.7 variant (85.6% efficacy against U.K. variant). In comparison, a similarly designed trial in South Africa yielded an efficacy of 60% for the prevention of symptomatic COVID-19 disease among the population that was HIV-negative. In South Africa, during the trial, the B.1.351 variant was the predominant strain [11]. These observations are noted in the context of *in vitro* analyses of sera from vaccinees from the mRNA vaccine trials showing substantially lower virus neutralization titers to the B.1.351 variant when compared to the strain used to generate the vaccine [23, 24]. As the pandemic continues, new strains with mutations in the spike glycoprotein will emerge. Characterization of strain diversity as it affects transmission, virulence, and response to the vaccine will be a critical factor in the accumulation of endpoints and in determination of vaccine efficacy both within and between trials.

In addition to the viral strain, other factors affect transmission dynamics during a single trial or between trials. The intensity of the epidemic, for example, may have

contributed to the differences in efficacy estimates between countries. The number of infectious challenges to the host, and a higher inoculum of virus per challenge, may be present in settings where population density is greater and/or the epidemic is more intense. Large multicenter trials can control for some of these effects by enrolling participants at geographically diverse sites with varying transmission rates. Comparing attack rates in the placebo groups of different trials is one way to assess intensity of transmission during study conduct, and will be an important factor to compare, for example, when the Novavax data from the U.K. and South Africa are available in the peer-reviewed literature.

Nonpharmaceutical interventions aimed at reducing the force of infection, such as masking and restrictions on movement, may also impact trial endpoints. In the context of COVID-19, the imposition of mitigation measures has been associated with a decrease in transmission, while lifting of those restrictions is associated with increases in transmission [25]. The use of masks may reduce the viral inoculum to which the wearer is exposed, allowing wearers to mount an immune response to SARS-CoV-2 without causing clinically-significant disease [26]. As such, the effect of the vaccine in preventing COVID-19 may be difficult to differentiate from the effects of mitigation measures or naturally-derived immunity. None of the efficacy trials to date have consistently evaluated the application of nonpharmaceutical interventions across study sites nor personal adherence to those measures amongst study participants, although all participants were encouraged to use appropriate infection control measures.

## Vaccine Trial Design

### *Case ascertainment and endpoint definitions*

COVID-19 infections differ widely in their clinical manifestations with subsets characterized by asymptomatic/presymptomatic, mild, moderate, severe, and critical categories. The published phase 3 studies have focused on the assessment of any symptomatic SARS-CoV-2 infection as a primary outcome; however, definitions differ between trials [27]. Likewise, criteria for sample collection differ between trials. Testing on

the basis of milder symptoms will identify more cases, in contrast testing only those with more severe symptoms will reduce the number evaluated.

The case definitions and case ascertainment criteria are particularly relevant if vaccine efficacy estimates differ by vaccine severity, as indicated in early results from the adenoviral vector constructs [5, 12]. Prevention of severe disease is an important measure of public health impact for any COVID-19 vaccine and is the ultimate goal of most vaccination programs. While efficacy results have varied considerably for any symptomatic disease across trials, the efficacy results against severe disease have been more consistently robust. For the Oxford ChAdOx1 nCoV19 vaccine, efficacy of two doses of the vaccine was demonstrated at the interim analysis of 131 cases, which pooled data from Brazil and the U.K., to be 70.4% against symptomatic COVID-19 [5], which is lower than the mRNA point estimates. For the severity endpoint, from 21 days after the first dose, there were ten cases hospitalized for COVID-19, all in the control arm; two of the ten were classified as severe COVID-19 according to the World Health Organization's 10-point clinical progression scale [28], including one death [5]. While the Oxford ChAdOx1 nCoV19 cohort referred above was smaller, and hence the vaccine efficacy measurement is associated with wider confidence intervals, the vaccine efficacy approaches 100% in prevention of severe disease.

An additional example of increasing efficacy by increasing level of severity can be inferred by the limited results available in a press release for the single dose Janssen Ad26COV2S trial conducted in the U.S. and seven other countries. Overall, the level of protection for the combined endpoint of moderate-to-severe disease was 66%, with variation from 57% in South Africa to 72% in the United States [10, 12]. Importantly, the efficacy against severe disease, defined as laboratory-confirmed SARS-CoV-2 plus evidence of severe systemic illness, respiratory failure, shock, significant organ dysfunction, hospital intensive care unit admission or death, was 85% across geographies. Five COVID-19-related deaths were reported in the placebo group, and none in the vaccine group. Having the data presented in a peer-reviewed journal will aid in fully interpreting the results [12].



Even when applying the same definition of severe disease, as was done in the mRNA vaccine trials, the ascertainment of the endpoints differed between the trials. How symptoms are monitored and collected during a trial, such as the comprehensiveness and specificity of symptom monitoring, may alter the timing of when cases are evaluated or whether they meet severity criteria. For example, participants with COVID-19 in the NIAID-Moderna trial recorded their oxygen saturations at home, while participants in the Pfizer-BioNTech trials did not, a potential explanation for the additional number of cases classified as “severe” as defined only by an O<sub>2</sub> saturation of  $\leq 93\%$  in the Moderna study ([3, 4] see Supplementary appendices). Hence, comparing the rates of severe COVID-19 across trials requires examination of the definitions used within each trial and an understanding of how those definitions were ascertained during the trial.

#### *Time period of vaccine efficacy assessment*

The precise window in which vaccine efficacy is measured impacts the interpretation of the results. If endpoints are collected starting from day 1 of vaccination the host will not have developed a specific immune response to the vaccine and individuals may be in the incubation period for SARS-CoV-2 infection. For example, the estimate of efficacy between the first and second dose of the Pfizer-BioNTech COVID-19 vaccine is 52.4% against any protocol-defined COVID-19 disease, but the efficacy estimate increased to 92.6% if cases were only counted between day 15 and 21 [29]. Many of the early COVID-19 diagnoses likely occurred in participants in the incubation period of infection, and/or before the development of an adaptive immune response. Additionally, measurements of vaccine efficacy beginning 2 weeks following the second dose, and extending for the next few months, may differ from measurements of efficacy with case accrual extending over longer periods of time. When the duration of time over which vaccine efficacy is measured is significantly extended, waning immunity, additional infectious challenges from mutated viruses, or both could lead to lower efficacy measurements. Emerging data about the durability of vaccine-induced immunity may influence the timepoints chosen in future trials.

Standardization of the observation periods and the definitions of disease across future trials would facilitate optimal comparison of vaccine benefits.

*Performance bias: availability of COVID-19 preventives and therapeutics*

In the U.S. and other developed countries, increasing availability and use of therapies such as corticosteroids and remdesivir in hospitalized patients and of monoclonal antibodies in non-hospitalized patients may confound interpretation of vaccine trial endpoints such as severe disease and death as these therapies reduce mortality [30], time to recovery and hospital discharge[31, 32], and rates of hospitalization [33]. Standards of care and available preventative medications and therapeutics may differ widely depending on region. As the standard of care for the treatment of COVID-19 changes to reflect emerging data about therapeutic interventions in inpatient and outpatient settings, future trials are likely to skew toward less severe disease, and comparison of efficacy data across vaccine trials should consider this difference.

Considerations beyond vaccine efficacy

The ultimate success of vaccination programs is measured by the ability to prevent disease, not the ability to achieve a high point estimate of efficacy in an individually-randomized clinical trial. For example, the highly efficacious two-dose mRNA vaccines require stringent cold chain distribution and storage conditions, a minimum number of doses per shipment, and availability of medical management for anaphylaxis [34]. Therefore, an mRNA vaccine program is not feasible in many settings. Vaccines that are moderately efficacious against disease, and able to reach large segments of the population because of greater supply, single dose formulations, improved delivery characteristics, or greater acceptability will yield substantial public health gains (Table 1).

## Conclusions and future directions

In the past year, the world has suffered extreme clinical, social and financial consequences of the COVID-19 pandemic. The vaccine development response to this critical need has been historic in terms of speed, product diversity, and robustness of clinical and regulatory evaluation. Thus far, efficacy estimates against symptomatic illness for both mRNA vaccines tested in the U.S. have far exceeded the FDA minimum criteria of 50%. While these high point estimates of efficacy are impressive, the most important measures of vaccine impact from the public health standpoint are number of cases, and severe cases, prevented. Peer-reviewed data from U.S. studies of non-mRNA vaccines are pending, although data available from other countries or through press release strongly suggest that spike glycoprotein based constructs will markedly reduce severe disease outcomes.

Variant strains have been recognized since early in the pandemic and emerged before introduction of vaccines. The cross-protective effects of vaccination as measured by early immunogenicity and disease outcomes are reassuring, albeit imperfect [11, 23]. How vaccines will affect future virus evolution is unknown. Moore and Offit propose several steps in response to emergence of variants, including establishment of an active sequencing and surveillance system; isolation and characterization of virus from individuals who are fully vaccinated and develop serious disease; and a central repository of serum samples from vaccinated individuals to allow testing against future emerging strains [35]. The emergence of variant strains further emphasizes the need to quickly control viral replication and transmission, through public health practices of masking, social distancing and testing, and by vaccinating the global population as rapidly as possible. Several manufacturers have announced their intention to develop and manufacture vaccines based on variant strains.

Multiple manufacturers are needed to meet the enormous global demand for COVID-19 vaccines and to achieve high global vaccine coverage. As additional vaccines are studied, examination of how point estimates of efficacy were determined, in what epidemiologic setting, and against what endpoints, will contextualize the significance of the raw numbers. Importantly, results must be clearly communicated to policymakers to inform vaccine recommendations and prioritization, and to the public to maintain confidence and maximize vaccine uptake. Emphasizing prevention of severe disease is one such important message. While for illustrative purposes this perspective focused on U.S. vaccine trials, a global response is the only path forward in ending this pandemic.

### **Potential Conflicts of Interest**

K.N. reports grants from NIH to participate in overall organization of COVID vaccine trials and participation in vaccine trials. K.N. also reports grants from Pfizer to conduct clinical trials on COVID vaccines. K.N. receives no salary support on this grant. E.H. reports personal fees from the University of Oxford, outside the submitted work. E.H. serves as a co-investigator for the phase 3 COVID-19 vaccine trials sponsored by Novavax and Moderna but received no financial support for these activities. E.H. also serves on the Endpoint Adjudication Committee for the phase 3 COVID-19 vaccine trial sponsored by Oxford-AstraZeneca and receives an hourly fee. R.R. is a co-investigator on COVID-19 vaccine trials sponsored by NIAID-Moderna, Pfizer, and Novavax and has volunteered as an endpoint assessor for the Oxford-AstraZeneca vaccine trial.

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**Table 1:** Product attributes and clinical trial design variables for COVID-19 vaccines in Phase 3 efficacy testing in the United States, as of February 26, 2021

	<b>Pfizer-BioNTech**</b>	<b>NIAD-Moderna*</b>	<b>ChAdOx1 nCoV19*</b>	<b>Janssen*</b>	<b>Novavax*</b>
<b>Platform</b>	mRNA	mRNA	Chimpanzee adenovirus vector	Human adenovirus vector	Recombinant protein + Matrix M adjuvant
<b>Target protein</b>	Pre-fusion stabilized full length S glycoprotein	Pre-fusion stabilized full length S glycoprotein	Full length S glycoprotein	Pre-fusion stabilized full length S glycoprotein	Pre-fusion stabilized full length S glycoprotein
<b>Stability and Storage Requirements***</b>	<ul style="list-style-type: none"> <li>• 6 months @ -70 C</li> <li>• 2 weeks @ -25 to -15 C</li> <li>• 5 days @ 2-8 C [36]</li> </ul>	<ul style="list-style-type: none"> <li>• 6 months @ -20 C</li> <li>• 30 days @ 2-8 C</li> </ul>	<ul style="list-style-type: none"> <li>• 6 months @ 2-8 C</li> </ul>	<ul style="list-style-type: none"> <li>• 2 years @ -20 C</li> <li>• 3 months @ 2-8 C</li> </ul>	<ul style="list-style-type: none"> <li>• Stored @ 2-8 C</li> </ul>
<b>Status of Clinical Trials in the U.S.</b>	Phase 3 in ages 12+ ongoing	Phase 3 in ages 18+ years ongoing	Phase 3 in adults 18+ years ongoing	Phase 3 of 1- and 2-dose regimens in adults 18+ years ongoing	Phase 3 in adults 18+ years ongoing
<b>Approval status</b>	EUA granted Dec 2020 for ages 16+ years	EUA granted Dec 2020 for ages 18+ years		EUA application submitted	
<b>Timing of Primary Efficacy Assessment****</b>	7 days after second dose [3]	14 days after second dose [4]	14 days after second dose [37]	ENSEMBLE [6] 14 and 28 days after vaccination ENSEMBLE2 [38]: 14 days after second dose	7 days after second dose [8]
<b># doses, interval</b>	2 doses, 21 days apart	2 doses, 28 days apart	2 doses, 28 days apart	ENSEMBLE: 1 dose ENSEMBLE2: 2 doses, 56 days apart	2 doses, 21 days apart
<b>Primary Endpoint Definition</b>	Any COVID-19 disease in seronegative participants; COVID-19 in all participants	Any COVID-19 disease in seronegative participants	Any COVID-19 disease in seronegative participants	Moderate-severe/critical COVID-19 disease in seronegative participants	Any COVID-19 disease in seronegative participants
<b>Definition of COVID-19 for Endpoint Analysis</b>  PCR or NAAT confirmation of SARS-CoV-2 infection plus:	<ul style="list-style-type: none"> <li>•1+: FDA criteria ## for mild COVID-19, shortness of breath, anosmia, or ageusia</li> </ul>	<ul style="list-style-type: none"> <li>•1+: cough, shortness of breath, pneumonia <b>OR</b></li> <li>•2+: fever (<math>\geq 38^{\circ}\text{C}</math>), chills, myalgia, headache, sore throat, anosmia or ageusia</li> </ul>	<ul style="list-style-type: none"> <li>•1 day of fever, dyspnea or shortness of breath <b>OR</b></li> <li>•2+ days of: chills, cough, myalgia, fatigue, headache, vomiting, diarrhea, anosmia, ageusia, sore throat, congestion, runny nose</li> </ul>	<ul style="list-style-type: none"> <li>•1+: respiratory symptoms, DVT <b>OR</b></li> <li>•2+: FDA criteria ## for moderate COVID-19, anosmia or ageusia, red or bruised looking feet or toes ("COVID toes")</li> </ul>	<ul style="list-style-type: none"> <li>•1+ Fever, cough <b>OR</b></li> <li>•2+: FDA criteria ## for mild COVID-19, shortness of breath, anosmia, or ageusia</li> </ul>
<b>Definition of Severe Disease</b>	FDA criteria for severe or critical	FDA criteria for severe or critical	FDA criteria for severe or critical	FDA criteria for severe or critical COVID-19	FDA criteria for severe or critical



	COVID-19	COVID-19	COVID-19		COVID-19, acute stroke, acute thrombotic event
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**Table 1 Legend:** S=spike; \* = U.S. Government Public-Private Partnership; \*\* = Company sponsored and financed; \*\*\*= Data collected from reference [39] unless otherwise noted; \*\*\*\*= Listed with key references to manuscript or protocol; gray shading denotes continued reference to associated protocol or manuscripts for rows below in column. ##: FDA criteria as noted in reference [40], summarized as follows regarding symptoms and clinical signs. All definitions of COVID-19 require PCR or NAAT confirmation. Mild-COVID-19: Mild symptoms such as fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, without shortness of breath or dyspnea. Moderate COVID-19: Any mild symptoms as well as shortness of breath with exertion. Clinical signs include respiratory rate  $\geq 20$  breaths per minute, saturation of oxygen (SpO<sub>2</sub>)  $> 93\%$  on room air at sea level, heart rate  $\geq 90$  beats per minute. Severe COVID-19: Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress. Clinical signs include respiratory rate  $\geq 30$  per minute, heart rate  $\geq 125$  per minute, SpO<sub>2</sub>  $\leq 93\%$  on room air. Critical COVID-19: Evidence of critical illness, defined by one of the following: Respiratory failure defined based on resource use requiring Endotracheal intubation and mechanical ventilation, oxygen delivered by high flow nasal cannula at flow rates  $> 20$  L/min, noninvasive positive pressure ventilation, ECMO, or clinical diagnosis of respiratory failure (e.g. would require above resources but unavailable); shock, or multi-organ dysfunction.

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**Table 2:** Clinical trial variables with potential effects on point estimates of efficacy

Factor	Potential effect on efficacy estimate	Example from current trials
Study population	<p>A higher prevalence of older age, chronic conditions or frailty within a population could lead to lower immunogenicity and lower efficacy overall.</p> <p>Certain populations may be more likely to develop severe disease. If efficacy varies by severity, this could contribute to efficacy differences between trials.</p>	Novavax trial, inclusion of HIV-infected individuals in analysis led to slightly lower efficacy estimates [11]
Virus characteristics	The efficacy of vaccine may be diminished if the predominant virus strain does not match the vaccine strain.	Janssen ENSEMBLE trial, relatively lower vaccine efficacy noted in S. Africa, where 94.5% of vaccinees were infected with the B.1.351 lineage, while efficacy of 72% was observed in the U.S.[10]
Force of infection	Higher force of infection may overwhelm vaccine induced immunity and decrease efficacy estimates.	Attack rates are higher in the placebo group in Janssen ENSEMBLE trial compared to the placebo group in the Pfizer-BioNTech trial in the primary interim analysis [3, 10]
Definition and ascertainment of endpoint	<p>If efficacy varies by severity, this could contribute to efficacy differences between trials.</p> <p>Even comparing similar endpoints (e.g. severe disease) between trials will be biased by varying definitions of severity.</p>	NIAID-Moderna trial criteria for severe COVID-19 could be characterized by features of SpO <sub>2</sub> ≤93% on room air [4], see protocol for detail; while the ChAdOx1 nCoV-19 trial defined severe COVID-19 by a WHO clinical progression scale score of 6 or greater, requiring at minimum respiratory support of high-flow oxygen or non-invasive positive pressure ventilation [5].
Timing of vaccine efficacy assessment	<p>Longer period of follow-up assesses a more durable immune response and a longer period of vaccine efficacy</p> <p>Effect of vaccine may be diluted by counting cases early on, prior to development of an effective adaptive immune response</p>	Pfizer trial, efficacy 52.4% against any protocol-defined COVID-19 disease between 1 <sup>st</sup> and 2 <sup>nd</sup> dose; estimate increases to 94.8% if cases are counted between day 15 and 21 [29]
Performance bias: Availability of treatments	Differential use of prophylactic or therapeutic treatments will affect number of severe cases and outcome of cases and could affect efficacy estimates	This data has not been reported with trial results thus far