Understanding COVID-19 vaccine efficacy

By Marc Lipsitch and Natalie E. Dean

The elderly and people with comorbidities are at greatest risk of severe coronavirus disease 2019 (COVID-19). A safe and effective vaccine could help to protect these groups in two distinct ways: direct protection, where high-risk groups are vaccinated to prevent disease, and indirect protection, where those in contact with high-risk individuals are vaccinated to reduce transmission. Influenza vaccine campaigns initially targeted the elderly, in an effort at direct protection, but more recently have focused on the general population, in part to enhance indirect protection. Because influenza vaccines induce weaker, shorter-lived immune responses in the elderly than in young adults, increasing indirect protection may be a more effective strategy. It is unknown whether the same is true for COVID-19 vaccines.

For COVID-19, age-structured mathematical models with realistic contact patterns are being used to explore different vaccination plans (1, 2), with the recognition that vaccine doses may be limited at first and so should be deployed strategically. But as supplies grow large enough to contemplate an indirect protection strategy, the recommendations of these models depend on the details of how, and how well, these vaccines work and in which groups of people. How can the evidence needed to inform strategic decisions be generated for COVID-19 vaccines?

Phase 3 vaccine trials are designed to assess individual-level efficacy and safety. These trials typically focus on a primary endpoint of virologically confirmed, symptomatic disease to capture the direct benefit of the vaccine that forms the basis for regulatory decisions. Secondary endpoints, such as infection or viral shedding, provide supporting data, along with analyses of vaccine efficacy in subgroups. Nonetheless, unanswered questions about COVID-19 vaccine characteristics are likely to remain even after trials are completed. First, trials are typically not powered to establish subgroup-specific efficacy, yet the performance of the vaccine in high-risk groups affects the success of a direct-protection strategy. Second, can vaccines prevent infection or reduce contagiousness? This matters for achieving indirect protection. Expanding ongoing efforts or planning new studies may generate the data needed to address these questions.

For estimating subgroup-specific efficacy, randomized controlled trials can provide early estimates, yet these will have wide confidence intervals, leaving substantial uncertainty about true effects in high-risk subgroups. This uncertainty would be greater in interim analyses that are based on the number of events across the whole trial population and may be exacerbated if high-risk participants are more cautious and have lower exposure to infection, reducing their contribution to the efficacy estimates.

There are several strategies to address subgroup-specific efficacy, some of them already in place. Ensuring that high-risk adults are well represented in the trial population can be achieved by setting minimum enrollment targets for older adults and/or adults with comorbidities. Another consideration relates to the stopping rules for interim analyses in trials. Vaccine trials with early interim analyses that are planning to discontinue randomization and vaccinate placebo participants after declaring efficacy are most prone to subgroup uncertainty. To improve the precision of efficacy estimates in high-risk subgroups, regulators could insist that interim analyses be performed only after a certain number of confirmed disease cases occur in these subgroups, in addition to existing monitoring of the overall number of events in the study.

Trials that maintain blinded follow-up to assess long-term efficacy and safety may also generate more-reliable evidence on age-specific effects. For example, the World Health Organization’s Solidarity Vaccines Trial will preserve placebo-controlled follow-up through month 12 or when an effective vaccine is deployed locally (3). However, depending on where the trials are being done and whether the vaccine becomes rapidly available in sufficient quantities after emergency-use authorization in the population undergoing the trial, it may become unethical and/or impractical to ask participants in some subgroups to forego access to an available vaccine. For vaccine candidates evaluated in multiple trials, such as the Oxford-AstraZeneca vaccine being studied in the United Kingdom, South Africa, Brazil, and the United States, meta-analyses can synthesize results across locations to improve precision of subgroup-specific effect estimates.

Ideally, the phase 3 trials in progress will identify more than one safe, effective vac-
Vaccines that reduce disease severity can also reduce infectiousness by reducing viral shedding and/or symptoms that increase viral spread (e.g., coughing and sneezing). A worst-case scenario is a vaccine that reduces disease while permitting viral shedding; this could fail to reduce transmission or conceivably even increase transmission if it suppressed symptoms.

To assess a vaccine’s impact on infectiousness, some phase 3 trials examine the amount or duration of viral shedding in laboratory-confirmed, symptomatic participants in the United Kingdom for the Oxford-AstraZeneca vaccine trial is testing individuals that test negative for the virus weekly regardless of symptoms, but not in other trials for which protocols have been released. Even weekly testing will not give detailed information about the effect of the vaccine on viral shedding, and the relationship between viral loads and infectiousness is unknown; nonetheless, this approach is likely to provide some evidence if viral loads are on average lower among vaccinated people. Human challenge vaccine studies, in which individuals in a randomised controlled trial are deliberately exposed to the virus, could generate high-quality data on the effect of vaccines on viral shedding (9).

Other approaches exist to directly estimate infectiousness without the need to extrapolate from viral load. Add-on household studies can supplement efficacy trials. Investigators can follow household members or other close contacts of infected participants to assess the vaccine’s effect on infectiousness, as has been implemented for the respiratory disease pertussis (also called whooping cough) (10). Viral sequencing could be used within the trial to link infector-infectee pairs and better estimate indirect effects (11). Another strategy is to design cluster-randomized trials in which indirect effectiveness is a primary outcome. In influenza vaccine trials, health care workers at nursing homes were cluster-randomized to be offered vaccine or not, and the endpoints were mortality, influenza-like illness, or influenza infection in the patients they cared for (12).

Observational studies may also be helpful, but, in general, measuring indirect effects of vaccines is even harder than detecting direct effects. It is urgent, therefore, to obtain evidence on how each candidate vaccine affects infectiousness either before approval or soon after, when scarcity may justify randomized distribution of a vaccine.

Other open questions about the rapidly developed COVID-19 vaccines include long-term safety (indicating the critical need for pharmacovigilance activities), the duration of vaccine protection, the efficacy of a partial vaccination series or of lower doses (13), the vaccine’s level of protection against severe infection and death, efficacy by baseline serostatus, and the potential for the virus to evolve to escape vaccine-induced immunity. The answers to such questions inform the optimal use of any vaccine.

Availability of a COVID-19 vaccine will initially be limited, and so several expert
Enhancing host cell infection by SARS-CoV-2

Neuropilin-1 binds the furin-processed spike protein of SARS-CoV-2 to promote virus entry

By Margaret Kielian

The current global pandemic of coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A critical initial step of infection is the interaction of the virus with receptors on host cells. In the case of SARS-CoV-2 and other coronaviruses, this receptor binding occurs through the spike (S) protein on the virus surface. Both SARS-CoV-2 and the related SARS-CoV, which caused an outbreak in 2003, bind to angiotensin-converting enzyme 2 (ACE2) on human cells. However, the observed differences in tissues that are infected by these two viruses (tropism) suggest that additional host factors may be involved. On pages 861 and 856 of this issue, Daly et al. (1) and Cantuti-Castelvetri et al. (2), respectively, show that the membrane protein neuropilin-1 (NRP1) promotes SARS-CoV-2 entry and explain how NRP1 interacts with the SARS-CoV-2 S protein. The results suggest the S protein–NRP1 interaction as a potential antiviral target.

Coronaviruses are enveloped RNA viruses that can cause human diseases that range from the common cold to severe and fatal respiratory infections. It is thought that both SARS-CoV-2 and SARS-CoV bind to ACE2 on the host cell surface, are internalized by endocytosis, and fuse with the endolysosome membrane to deliver the viral genome for replication in the host cell (3, 4) (see the figure). The viral S protein mediates this key membrane fusion reaction, but its activity requires several processing steps. S is synthesized as a large membrane protein that is cleaved into two components, S1 and S2, which remain noncovalently associated (5, 6). Cleavage is required for infection and can occur during virus particle production or virus entry into the target cell. The S1 protein forms the “head” of the molecule and mediates binding to ACE2. The S2 protein is anchored in the virus membrane and mediates membrane fusion. S2, like the fusion proteins of influenza virus and HIV-1, inserts a hydrophobic fusion peptide at its amino terminus into the cell membrane and then folds back to merge the host and virus membranes (7). The S2 protein needs a further proteolytic step to “liberate” its fusion peptide, and this is carried out by transmembrane protease serine 2 (TMPRSS2) or other proteases (8).

A potentially important difference between SARS-CoV-2 and SARS-CoV is the mechanism of S protein cleavage into S1 and S2. In SARS-CoV, this is caused by host cell proteases called cathepsins, which are located within endocytic compartments. However, the sequence of the SARS-CoV-2 S protein contains a series of basic amino acids at the S1-S2 junction. Such polybasic sites can be substrates for furin, a protease that is present in the secretory pathway and endocytic compartments (8). Studies with SARS-CoV-2 show that its S protein is cleaved by furin during virus production and that this cleavage promotes subsequent virus infection (3, 6). Thus, a notable difference between the S proteins of these two coronaviruses is the protease that carries out the S1-S2 cleavage reaction. Furin cleavage also produces a potentially important remnant: the polybasic site that remains at the carboxyl terminus of SARS-CoV-2 S1 after cleavage.

Neuropilins are a family of membrane proteins that were originally identified because of their involvement in angiogenesis (blood vessel formation) and axon guidance (9). The neuropilins are co-receptors for molecules such as vascular endothelial growth factors (VEGFs) and semaphorins, and recent studies have demonstrated their up-regulation during tumor angiogenesis and their potential as anticancer targets. Both NRP1 and NRP2 can bind the carboxyl-terminal sequences generated by furin processing of molecules such as VEGFs, with the sequences fitting into a pocket on the b1 domain of the NRP (9). Detailed studies of such NRP1-peptide interactions show that binding to the b1 pocket requires the sequence Arg/Lys-XX-Arg/Lys (R/K-XX-R/K, where X can be any amino acid) at the carboxyl terminus of the protein or peptide (10). This “C-end rule,” or CendR, can thus predict whether a protein is a candidate for binding to NRPs.

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ACKNOWLEDGMENTS

M.L. receives funding from cooperative agreement 1U19CA251277 from the U.S. National Institutes of Health. N.E.D. receives funding from NIH/NIAID R01 AI139281. We thank R. Venkayya and N. Gradly for helpful comments. M.L. receives honoraria and consulting fees from Merck, Affinigen, Sanofi Pasteur, and Antibody Discovery; receives research funding (institutional) from Pfizer; and provides unpaid scientific advice to Janssen, Astra-Zeneca, and Dovaax (United Biomedical).

REFERENCES AND NOTES

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Science 370 (6518), 763-765.
DOI: 10.1126/science.abe5938 originally published online October 21, 2020

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