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COVID-19 Vaccine Prospects

Introduction

As the COVID-19 pandemic smolders on, multiple vaccine trials are underway with some promising early results released in November – raising hopes for a new tool to prevent transmission. A successful vaccine would ideally be safe, effective, rapidly developed, and distributed as quickly as possible on a massive scale. Although the average vaccine takes 10-15 years to develop, current efforts are hoping to reduce this to as short as 1-2 years. Already a formidable logistical challenge, coronavirus' unique immunology adds uncertainty about the durability and potency of the immune response. Even if the scientific and logistical questions can be answered, vaccine effectiveness will depend on widespread adoption by the public. As hospitals look ahead to decide how they might immunize their staff, and as healthcare providers strategize how they might counsel their patients, we thought it would be useful to offer a glimpse into the current vaccine development pipeline.

Crash Course in COVID-19 Immunology

SARS-CoV-2, the virus responsible for COVID-19, emerged recently enough that immunologists are still exploring how the human body responds to the virus. It remains largely unknown why some individuals have mild or even asymptomatic disease, while others suffer life-threatening respiratory failure or even death. Early observations hint at a delicate balance between a protective versus an over-exuberant immune response.[1,2] For example, many asymptomatic or minimally symptomatic individuals appear to have low antibody titers and a rather tame immune response. In contrast, an overly aggressive immune response may be responsible for some of the later and more severe consequences of COVID-19 such as acute respiratory distress syndrome (ARDS), cytokine release syndrome (CRS), and multi-system inflammatory syndrome (MIS-C) in children.

Part of the natural immune response to SARS-CoV-2 involves the production of IgM and IgG antibodies, usually in the 1-2 weeks following infection. One of the main targets of these antibodies is the viral spike protein which binds to ACE-2 receptors and allows the virus to enter respiratory epithelial cells. While antibodies to spike protein can prevent viral entry into cells, the potency and durability of the immune response remains unknown. Until we understand SARS-CoV-2 better, immunologists have looked to similar viruses such as SARS-CoV (the virus responsible for the first severe acute respiratory syndrome outbreak in 2002) and Middle East Respiratory Virus (MERS from 2014). Unfortunately, immunity to these prior coronaviruses seems to wane within 1-2 years after infection – raising concern that protection may not be durable. Raising similar concerns for SARS-CoV-2, there have now been a handful of case reports in which individuals developed infection a second time.[3] Some researchers believe that an antibody-mediated response alone may not be sufficient to protect against SARS-CoV-2 and that cellular immunity (especially with CD8+ T cells) may also be needed.

There is also an important – though uncommon – phenomenon called antibody dependent enhancement (ADE). Best described in dengue virus, it occurs when a partly active (or partly cross-reactive) antibody can bind its target, but is not produced in sufficient quantities to neutralize the virus. In this case, virus may enter macrophages (a specialized immune cell which can ingest pathogens with IgG bound to their surface) where they can replicate and disrupt the immune response. Although there is no clear evidence that this occurs with SARS-CoV-2, researchers are watching carefully for any signal in the current vaccine trials.[1] So far, no related safety concerns have been reported.

Current Candidates

There are currently (as of November 2020) four large-scale phase 3 vaccine trials active in the United States. Three have released early results via press, and two are likely to be reviewed by the FDA for possible emergency use approval within the first week of December. All aim to trigger a strong IgG response against SARS-CoV-2's spike protein, but they each do so in slightly different ways.

The two with promising early results (at least via press release – formal peer reviewed data are not yet available) are both mRNA vaccines from Moderna and Pfizer/BioNTech/Fosun. mRNA vaccines are a new

approach which can be rapidly developed and do not involve live virus at all. Instead, the vaccine provides just the mRNA instructions for the hosts' own cells to make SARS-CoV-2 spike protein – in turn triggering both neutralizing antibodies and CD8 T cells. According to press releases, each appears to be 90-95% effective, and no significant short-term safety concerns. Both require 2 doses, and both require special refrigeration (-80°C) to prevent the mRNA from degrading.

In contrast, the Oxford/AstraZeneca and Johnson & Johnson vaccines rely on adenovirus vectors – essentially a weakened cold virus which cannot cause infection itself, but expresses the spike protein from SARS-CoV-2. Like the mRNA vaccines above, the Oxford/AstraZeneca vaccine requires 2 doses. The Oxford/AstraZeneca vaccine has also released early results via press, suggesting an average effectiveness of around 70%. Interestingly, two different doses were used – and the lower dose actually had higher effectiveness than high dose (90% vs 60%). The reason for this is not yet clear, but with the potential for lower dosing, and without any of the special refrigeration needs of the mRNA vaccines, the Oxford/AstraZeneca may still prove to be an important option for the large populations where refrigeration capacity limits distribution of the mRNA vaccines. Johnson & Johnson's results have yet to be released, but their vaccine is the only one with a single-dose regimen.

Notably, a few of these trials have periodically been paused due potential adverse events in trial volunteers. Temporarily halting enrollment while potential safety events are investigated is a standard process for any clinical trial. Although not all events will turn out to be related to the vaccine, trials are nonetheless paused until the cause for any adverse events can be verified and overall safety assured. Although such pauses do not typically make the news, they are a sign that the safety monitoring board is doing its job and assuring they have fully understood any potential adverse events before continuing the trial. As yet, no significant safety concerns have been identified.

How Effective Does a Vaccine Need to Be?

With long-term vaccine efficacy still unknown, researchers have used mathematical modeling to predict how good a vaccine needs to be to stem the tide of the COVID-19 pandemic. The threshold – not surprisingly – also depends on vaccine uptake among the public. In some simulations, vaccine efficacy as low as 60% could be adequate to prevent epidemic spread *if* 100% of the population took the vaccine. In contrast, if just 60% took the vaccine, it may have to be at least 80% effective.[4]

As with flu vaccine, it will be critical for frontline providers to know their vaccines, educate their patients, and encourage vaccine uptake (presuming a safe and effective vaccine becomes available). Hopefully with this primer, you'll be ready to follow results when the current candidate vaccine trials go to publication. Until then – and probably even for some time afterwards – stick to the 3 W's: hand washing, waiting (physical distancing), and wearing a mask!

References

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