VIEWPOINT

Answering Key Questions About COVID-19 Vaccines

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Viewpoint

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The US government is investing in rapid development of vaccines against coronavirus disease 2019 (COVID-19), several relying on new technologies.[1] In the US, 4 vaccine candidates are in phase 3 studies with initial results expected soon. If studies succeed, 1 or more vaccines may become available within a few months. Clinicians are likely among the first to be offered COVID-19 vaccines and have a key role in helping patients make decisions about vaccination.[2] Providing evidence-based information will be particularly important in an environment of polarization and mistrust. This Viewpoint focuses on common questions patients are likely to ask about COVID-19 vaccines.

How Much Does a Vaccine Reduce the Risk of COVID-19 and Its Complications?

The US Food and Drug Administration (FDA) guidance set as an expectation for licensure that a COVID-19 vaccine would prevent disease or decrease its severity in at least 50% of people who are vaccinated.[3]

In reviewing the results of a study it is important to know there is a margin of error in estimating the percentage of cases or complications prevented. For example, a study might report a reduction in disease from 100 cases in the placebo group to 50 in those vaccinated. This difference would meet the standard of 50%, but it will be important to explain to patients the uncertainty surrounding that value. While the study showed a 50% reduction in illness, the confidence interval for the efficacy estimate might be 30% to 80%, meaning efficacy may be as low as 30% or as high as 80%. It will also be important to understand whether a vaccine reduces not only mild but also more severe disease, as well as hospitalizations and deaths. However, studies may have insufficient numbers of patients with severe outcomes to definitively evaluate those end points.

How Safe Is a Vaccine Candidate?

Clinicians will want to know how safety was evaluated, including whether studies have been completed, as planned, with 15 000 or more people vaccinated and followed up for time periods sufficient to detect most safety issues (eg, 2 months). It is also important for vaccine developers to present all safety data, including from outside the US.

It is likely that vaccination will be associated with mild adverse events like soreness at the injection site, fever, fatigue, and myalgias. While such symptoms may be unpleasant, so long as they are not severe and resolve quickly, and patients anticipate them, these symptoms are not usually worrisome, unless they lead to additional health care encounters.

More serious reactions, such as otherwise unexplained neurologic or inflammatory processes, would raise concerns. While patients need to understand that serious adverse events may occur coincidentally following receipt of a vaccine, these adverse events could be signals of a safety problem. Comparing rates of adverse events between vaccine and placebo recipients can help determine whether a signal is vaccine-related, but for small numbers of rare events it may be inconclusive.

Patients should understand that rare adverse events may only be detected as a vaccine is widely used. Patients will want assurance that the US has mobilized enhanced safety systems to monitor, evaluate, and communicate about the safety of COVID-19 vaccines after they are released.[4]

Will the Vaccine Be Effective for All Patients?

COVID-19 is more common and severe among individuals often underrepresented in clinical trials, including older individuals, people with chronic illnesses, and persons in racial/ethnic minority populations. Different groups may not have the same responses to vaccination. When results become available, it will be important to evaluate the characteristics of people included in the trial and determine whether they are similar to patients seen in the practice setting. A given vaccine may be more appropriate for some patients than others, and knowing those differences will be important.

Trials involving children and pregnant women will start once vaccine safety is demonstrated in others, making it unlikely vaccines will initially have FDA indications for these groups. In considering use of a vaccine in patients not within FDA indications, available evidence and recommendations from the CDC's Advisory Committee on Immunization Practices (ACIP) should be consulted.

Was Important Information Made Public and Reviewed by Independent Experts?

It is important to know whether all relevant information that might support or contradict the findings of a vaccine trial has been made public. For example, preliminary reports might not include all patients studied or might include only selected results. It must be clear if any information is missing and the reasons for that missing information should be provided.

In addition, it is important that the study has been reviewed by experts without personal or financial interests in the research, as done by major medical journals. Such review helps reduce the risk of errors or bias.

Is a Vaccine Licensed or Provided Under an Emergency Use Authorization?

FDA has a long track record of licensing vaccines that have protected individuals against diseases like measles, polio, and pneumonia. FDA has stated it will apply its usual high standards to COVID-19 vaccines.[5] These standards mean clinicians can have confidence in what is known about the safety and efficacy of a licensed vaccine.

However, FDA could make an as-yet unapproved vaccine available through an Emergency Use Authorization (EUA). Rather than proven safety and effectiveness, EUAs

only require FDA determine a product "may" be effective and that benefits are likely to outweigh risks.

In some circumstances an EUA may be appropriate. For example, substantial data demonstrating safety and efficacy may be available, but it may take additional months for the developer to submit all documentation to FDA or for FDA to review data required for licensure but unrelated to safety or efficacy. Or early results may document convincing safety and efficacy, but it may be months until final data on all enrolled patients are available.

FDA officials have stated,[6] and affirmed in recent guidance,[7] that they would only issue a COVID-19 vaccine EUA with substantial evidence of safety and efficacy. Nonetheless, there is widespread concern a vaccine might be prematurely authorized under political pressure.[8] Clinicians will want to know that any EUA is based on science, with supporting data publicly available, and that those issuing an EUA have not been pressured to do so.

If a vaccine is released under an EUA, clinicians should inform patients that the vaccine is not FDA licensed. Key questions will include why the vaccine is not licensed and what information FDA may be waiting for. If clinical trials have not been completed, there will be questions about how much confidence exists regarding estimated efficacy. Other important considerations include whether adequate safety data from all participants have been analyzed, and whether FDA has ensured the vaccine meets manufacturing and quality standards.[3,7]

FDA has indicated that prior to any decision it will bring potential EUAs or approvals to an advisory committee, allowing outside expert input and enhancing transparency of the evaluation.[3] Furthermore, after FDA makes its determination, CDC and ACIP normally provide recommendations about who should receive a vaccine. If these steps are not followed, or if, in an unprecedented action, the secretary of the Department of Health and Human Services or White House, rather than FDA, were to issue an EUA, it should be apparent. If so, the foundation of scientific expertise and integrity that clinicians rely on to make recommendations to patients would be compromised, and use of a vaccine would need to be carefully considered in that harsh light.

Will All COVID- 19 Vaccines Be the Same?

Different vaccines are likely to perform and be used differently. Clinicians will need to be aware of any differences between vaccines including dose numbers and schedules, as well as safety and efficacy. Importantly, some vaccines may be preferred for certain populations. Clinicians should understand the basics of how different vaccines perform and, if more than one is available, be able to recommend the best for a given patient.

Can Vaccinated People Stop Worrying About COVID-19?

While a vaccine will help protect individual patients and those around them, a large proportion of the population must be immunized and protected before transmission is substantially reduced. Especially for 2-dose regimens, this will take months. No vaccine will be 100% effective and a vaccine that protects against developing clinical illness may not prevent transmission to others. Also, the duration of naturally occurring immunity to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is unknown and may wane with time.[9] Therefore, the likely duration of protection by new COVID-19 vaccines is unknown.

For these reasons, even after vaccines become available, SARS-CoV-2 will be a continuing concern. Effective public health measures, such as social distancing, limiting the size of gatherings, and wearing masks, will be needed for at least several more months, and potentially longer.

Conclusions

Many individuals are hesitant about receiving COVID-19 vaccines. Reasons include the novelty and rapid development of the vaccines, as well as the politicization of the pandemic and inconsistent messages from scientists and government leaders. It is critical that clinicians stay well informed about emerging data so that they can help patients make sound decisions about the vaccines needed to help end the pandemic.

ARTICLE INFORMATION

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Additional Information: Dr Goodman reported that he served as the chief scientist of the FDA from January 2009 to March 2014.

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