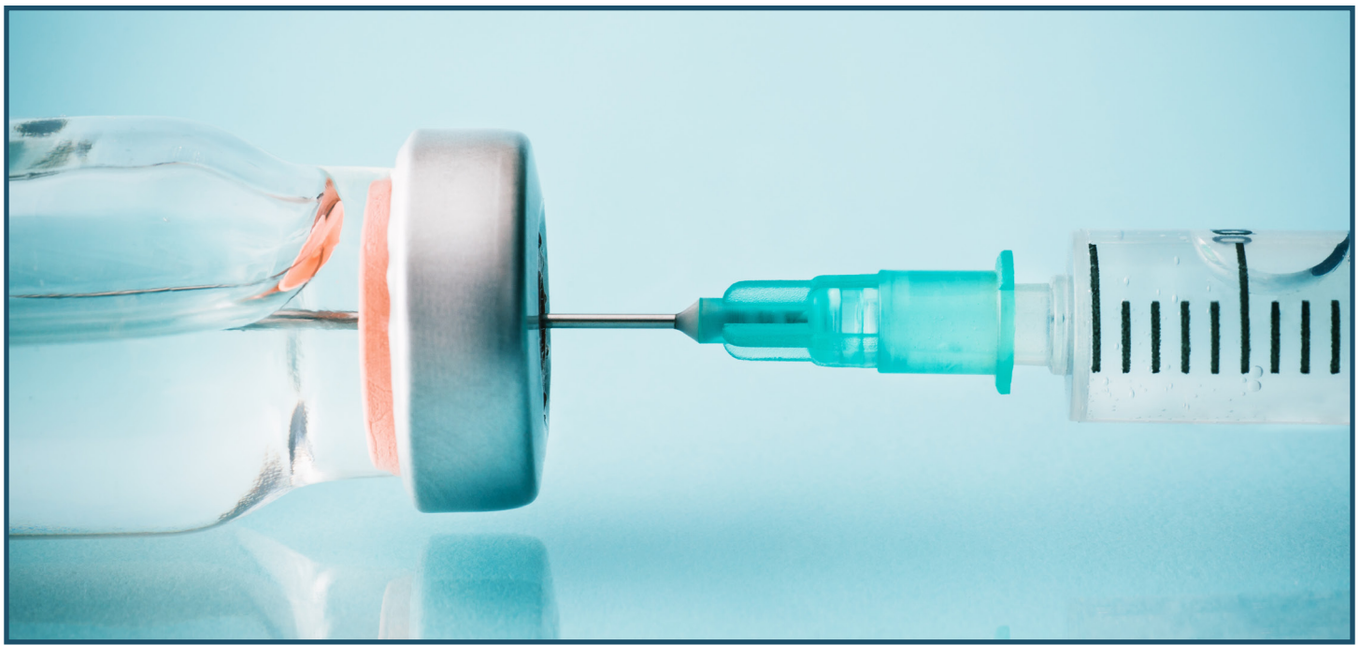

Understanding Vaccine Development & COVID-19

As the COVID-19 pandemic drags into summer, industry leaders, government agencies, and academics around the world continue to work tirelessly to push vaccine candidates through the development pipeline. Early in this unprecedented race to combat COVID-19, many candidates emerged from pre-clinical development in just weeks, and small Phase 1 trials have produced some early but promising results.

As the world hopes for an imminent breakthrough, there is still much work to be done, and experts continue to caution that a widely available vaccine could still be a year or more away. This is because it takes a significant body of evidence to ensure the safety and effectiveness of a vaccine (including an appropriate dose), and collecting, analyzing, and reviewing this evidence requires considerable time.

Types of Vaccines and How They Work

TRADITIONAL VACCINES

Vaccines induce their protective effect against pathogens by artificially exposing a person to a modified version of the pathogen, a part of the pathogen, or some toxin that it produces. The intent of this exposure is to provoke an adaptive, or memory-based, immune response that prevents future infection.

This immune response relies heavily on B lymphocytes, a type of immune cell that produces antibodies. Antibodies are produced in response to viruses, bacteria, or other foreign "invaders" and specifically bind to and neutralize antigens (i.e., surface molecules or structures) associated with them.

Most FDA-approved vaccines are one of the following types:

- **Live, attenuated** (e.g., chickenpox, MMR) – comprised of a whole virus that has been neutralized or weakened to prevent it from causing disease
- **Inactivated, killed** (e.g., polio) – made from dead viruses that are incapable of causing illness
- **Toxoid** (e.g., tetanus) – composed of inactivated bacterial toxins
- **Subunit/conjugate** (e.g., current influenza vaccine injections, hepatitis B) – made from a specific part of the virus, usually a key protein, either extracted from a live virus or manufactured using recombinant DNA technology

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DNA VACCINES

As vaccine technology has advanced in recent years, new vaccine types have been developed. DNA vaccines have emerged as particularly promising alternatives to traditional vaccines. Mechanisms differ, but most of these work by introducing the genetic sequence of a viral antigen into a host's cells and relying on the body to then transform (via transcription into mRNA and translation into protein) this genetic material into a viral subunit, which the body's B lymphocytes can target for adaptive immunity.

RNA VACCINES

RNA vaccines are similar, but they only need to undergo translation to produce the requisite viral subunits for a memory-based immune response. In the past, RNA was regarded as difficult to work with because of its instability and tendency to degrade rapidly. Furthermore, many early RNA vaccines were ineffective at producing a robust immune response because they failed to properly integrate with the body's cells. Recent innovations, however, have sufficiently improved the "packaging" of mRNA such that it can be used in a vaccine. Advantages of this new technology are numerous, including the ability to be rapidly scaled up – something that may prove exceptionally important in light of the COVID-19 pandemic.

The Importance of Vaccine Dose

When consumers think about common drugs like ibuprofen or acetaminophen, the concept of dosing is easily understood from the packaging instructions. For example, take one pill every 4-6 hours as needed for pain. Most people know that drugs can be administered at higher dosages (up to the safety threshold) and that doing so may lead to a greater therapeutic effect.

The concept of vaccine dosing, however, may not seem so straightforward. When people head to the pharmacy or doctor's office for their annual flu shot, few stop to consider, "What dose of the vaccine am I receiving?" To be fair, vaccine dosing can vary from one vaccine to the next. In some cases, the same dose of a vaccine can be given to people and children of all sizes with similar results and in other cases, doses may be higher or lower for certain groups. Notably, the package insert for the annual flu vaccine advises a higher dose for children 6 months through 8 years of age, and a lower dose for individuals 9 years of age and older.

As vaccine efforts over the past several decades have made clear, dose is critically important for both efficacy and safety. While approved vaccines are overwhelmingly safe when administered according to published guidelines, accidental vaccine overdose can sometimes result in dangerous, hyperactive immune reactions. On the other hand, underdosing may fail to generate robust adaptive immunity, leaving under-vaccinated individuals potentially vulnerable to future infections. Both of these situations, however, represent only a tiny fraction of the billions of vaccine doses administered since the 1940s, but they do underscore the importance of getting the dose right, especially with a vaccine as highly sought after as the one for COVID-19.

When considering an appropriate dose, vaccine researchers are laser focused on the ability of the vaccine to grant immunity against the target pathogen. To this end, unlike most clinical trials for small molecules, which place an early emphasis on pharmacokinetics (i.e., how the drug is changed and moved through the body after dosing) before exploring effectiveness, vaccine trials are centered on pharmacodynamics (i.e., the changes that occur to the body in response to drug exposure) from the very beginning. Vaccine pharmacodynamics is most adequately quantified as the amount of circulating antibodies that the vaccine elicits and their antigen-specificity.

In COVID-19 vaccine trials, researchers have sought to identify antibodies from the blood of trial participants that can bind to and neutralize the SARS-CoV-2 virus. Trial sponsors are hopeful that by testing multiple vaccine doses, they will be able to narrow-in on a dose that produces an adequate number of neutralizing antibodies. If they succeed, then this dose will be tested in a larger, more diverse population of thousands of healthy volunteers. With a large enough study population, researchers will be able to determine whether the vaccine works against natural infection.

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This will be especially important as a "proof-of-concept" for mRNA vaccine candidates, as no RNA-based human vaccine has ever been approved.

Approaches for Determining Vaccine Effectiveness

The most accurate way to assess vaccine effectiveness involves observing how vaccinated people and the overall population interact with the virus after a sizeable percentage of the populace has been vaccinated. This sort of vaccine surveillance happens every flu season. While results of the flu vaccine vary year to year due to the ability of the virus to mutate and the long lead times necessary for producing flu vaccines, many virologists are hopeful that the SARS-CoV-2 virus is different.

The COVID-19 virus doesn't seem to mutate like the flu, and most vaccine candidates currently being developed are targeting a highly-conserved region of the virus known as the "spike protein." The spike protein is important because it enables the virus to attach to human cells and gain entry. By targeting a part of the virus that is unlikely to mutate, it is hoped that any such vaccine will be broadly effective at granting immunity without the need for creating additional vaccines every year.

In addition to the traditional approach for determining vaccine effectiveness through observation of natural infection events following vaccination, a more controversial approach has gained support in some circles in recent months. During this time, internet petitions have circulated in support of so-called "challenge trials" that could theoretically speed up the development of a COVID-19 vaccine.

Challenge trials work by dosing volunteers with a vaccine candidate and then, after enough time has passed to allow for antibody production (which can take weeks), intentionally exposing these individuals to the virus to see how they respond. There are numerous ethical challenges to this way of conducting clinical trials, and purposely infecting even the healthiest person with a virus that we are just beginning to understand is clearly not without risk.

Conclusions

Despite all the hope (and collective impatience) for a vaccine that can reliably prevent COVID-19, there are still many unknowns. Discovering a vaccine that enables the body to launch a memory-based immune response against the virus is only part of the puzzle; large-scale production, ensuring proper dosing for efficacy, and addressing potential safety concerns remain significant hurdles. Even after a vaccine is on the market and being distributed for use, research and surveillance efforts must continue to track virus persistence in the population, the potential for mutation, and the long-term effectiveness of the vaccine.

Nuventra is committed to doing our part in fighting this global pandemic by helping sponsors bring their COVID-19 vaccines and therapies to the general population as soon as possible. Our team has extensive experience in developing therapies for viral infections and we have former FDA staffers who are ready to help. Please contact us with any questions you may have related to developing your vaccine or anti-viral therapy.

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