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Putting medical and nutrition news in historical, scientific, and just plain practical context.

Vaccines - History, Types, Safety & Efficacy

by Ann Gerhardt, MD September 17, 2020

Bottom Line at the Top: Don't hold your breath! Vaccine development is difficult, especially for SARS-CoV-2 (the virus that causes COVID-19), since some of the vaccine types in development are brand new.

History: A thousand years ago the Chinese ground up smallpox scabs and blew the dust into recipients' nostrils or scratched it into the skin to prevent smallpox. In the 1700's the practice of injecting fluid from smallpox blisters (called vesicles) to immunize became commonplace in Africa and Turkey, even as the disease ravaged Europe and the United States. After smallpox broke out in 1776, George Washington mandated smallpox inoculation of the entire Continental army.

About the same time, an English farmer used cowpox vesicle fluid to inoculate and protect his family from a village smallpox outbreak twenty years before the vaccine pioneer Edward Jenner did the same and published his results. All of this occurred prior to knowledge that disease is caused by infectious living organisms and that we have an immune system that fends off infection.

Cowpox vesicle fluid from cows clearly contained something that induced an inoculated recipient to avoid infection with human smallpox. This was the first proof of cross-reactivity, in which immunity to one entity confers immunity to another.

These injections were called variolation, after smallpox's causative agent, the variola virus. Over time vaccinations with vaccinia virus (from vaca, Latin for cow) became more common. Vaccinia virus is closely related to cowpox virus and causes minimal if any disease in normal humans. As scientists developed similar preventives for other infectious diseases, they all became known vaccines. Sort of like calling all tissues Kleenex.

Whatever the mechanism, variolation worked, 130 years before proof of the existence of viruses. Pasteur discovered bacteria in the late 1800s but could not find the germ causing rabies or other common viral diseases. Viruses are smaller than bacteria and scientists were unable to isolate them from blood or infected fluids. They felt the diseases were caused by contagious living fluid and named it "virus" from the Latin word for poison. By the time viruses were first viewed under an electron microscope in 1930, vaccines for rabies, as well as the bacteria causing typhoid fever, cholera and pneumococcal pneumonia, had been developed. Viral isolation then enabled polio, yellow fever, influenza and measles virus vaccine development over the next 30 years.

Knowing nothing about antibodies, Jenner couldn't have known whether cowpox vesicle fluid contained that which was protective or something that induced recipients to make the protective agent. **It was more than 100 years later before the discovery of antibodies in blood which proved that it was the latter mechanism.** With this discovery, doctors started to use immune sera (called antitoxin) to cure infected patients.

Until immunology was introduced to vaccinology, people just got a shot of something and hoped for a protective response. Using science to manipulate the immune system has revolutionized vaccines. However, vaccine development hasn't always been successful, as evidenced by two prominent failures - we have no vaccine for tuberculosis or the Human Immunodeficiency Virus (HIV, which causes AIDS). At least now we know more about immunological mechanisms that explain their failure.

Here are the basic mechanisms for and terminology related to how vaccines work. A foreign organism, the virus, or a part of it is introduced into the body via injection (most vaccines), inhalation (Flumist, an influenza vaccine nasal spray) or scratching it into the skin (smallpox vaccine). Our immune system recognizes as foreign various tiny sections of proteins called **antigens**. Whole proteins may have many sections that are **antigenic**, meaning they can trigger the immune system.

If the vaccine is not a whole virus, it is usually attached to something to carry it into the body, called a **vector**. It may also be accompanied by something that boosts our body's immune reaction to it. The booster may be the vector or something else. These are called **adjuvants**. (FLUAD is an influenza vaccine with an added adjuvant to boost response intensity). Some antigens induce more of an immune response than others, based on their chemical composition and the presence of adjuvant.

Once in the body, immune cells recognize the virus or vaccine as foreign and start an immune response. A non-specific attack degrades it but also triggers antigen-specific mechanisms that will enable faster future degradation and killing. The immune response can take the form of **antibodies** that circulate in the blood, **cellular immunity** that attacks in tissues or both. Cellular immunity isn't discussed much, because it's hard to quantify and most anti-viral immunity involves antibodies.

Five different antibody types have specific functions. Some bind a virus and engage other immune system components to kill it. Some physically block the ability of a virus to enter and reproduce inside cells. Some antibodies merely minimize damage from a virus, while some don't do anything useful at all.

How much antibody is produced is not the most critical factor, because it doesn't always correlate with quality or duration of desired outcome. **Just having measurable anti-viral antibody and/or reactive cells isn't enough** - the immune response must be effective at preventing subsequent infection with live virus. This requires **memory** cells that hang around for a long time in lymph nodes or other lymphoid tissue.

A memory response may be **short- or long-lived.** Antibodies have a half-life on average of only 26 days. Various immune cells circulating in the blood live only a few days or up to 5 weeks. Memory cells may survive five months or many decades, depending on the cell type. As memory cells die over time, response to infection wanes, leading to the need for booster injections. This is why we need a Tdap (tetanus, diphtheria & pertussis) shot every 10 years. Some vaccines, like Hepatitis A and B, need a booster series soon after the initial vaccine to get an adequate memory response.

We already know that natural antibody immunity acquired during infection with coronaviruses doesn't last long - three months for common cold coronaviruses, two years for SARS-CoV-1 and three years for MERS. The same is true for COVID-19 in animals.

Basics of vaccine development: A vaccine must be **immunogenic**, inducing **robust** and **durable** immunity of a type that **prevents or attenuates subsequent infection** by live virus, **without causing adverse effects**.

The most immunogenic vaccines, like pertussis, polio and smallpox, consist of whole inactivated viruses. Only a few companies are working on that type of vaccine for SARS-CoV-2, since there is concern that a manufacturing error might lead to infectious virus being injected.

Using non-live virus parts might fail as vaccines because 1) they are less immunogenic (inducing a less robust immune response) and/or 2) blocking just one viral component with antibody might not kill or inactivate the whole virus.

Some of the new vaccines entail a whole new paradigm of using viral genetic material for the proteins to which recipients should make antibodies. That's tough to comprehend and I'll try to describe them in future articles.

The vaccine must induce antibodies to a viral component that is **'conserved'**, meaning it must be present and identical in all SARS-CoV-2 strains. SARS-CoV-2, as an RNA virus, mutates over time. Already multiple mutated strains, with slightly different proteins, have been isolated. The most desirable vaccine would be one that induces immunity to a protein antigen present in all strains that is critical for infection.

The vaccine must be safe. It's not a good idea to prevent a viral disease by killing or incapacitating the human. Antibodies to SARS-CoV-2 might cross-react (bind) to damaged human tissue, causing disease unrelated to virus. This was described in three Chinese COVID-19 patients who made antibodies that cleared their infection but left them with other problems. Anti-SARS-CoV-2 antibodies might also initiate a cascade of inflammatory reactions called cytokine storm which is known to occur with COVID-19.

There are a lot of reasons why a vaccine may fail, which is why vaccine development usually takes years of trial and error. Just making sure that a vaccine protects against infection for the duration of the pandemic and has no long-term side effects can add months, if not years, to vaccine development.

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