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

Novel mRNA COVID Vaccines - PrimeTime or Premature?

by Ann Gerhardt, MD December 1, 2020

I provided background information about vaccines in the last DrG'sMediSense article (Click Here). Here, I describe the science and development of two brand-new vaccine types that might (or might not) pull us out of the COVID-19 pandemic.

Basically, a vaccine meant to protect against an infectious organism stimulates a person's immune system to make antibody and immune cells that prevent subsequent infection by that organism. Traditional vaccines against viruses consist of one of three types. Two use the virus itself, in the form of killed intact virus or live virus altered so it causes minimal if any infection. The third type is a protein component of the virus, which alone cannot cause infection.

Most companies consider even killed or altered whole-virus vaccines to be too dangerous for SARS-CoV2, which causes COVID-19 disease. Only the Chinese have been gutsy enough to use an inactivated SARS-CoV-2 virus as a vaccine, with reported success. Most companies developing vaccines for the SARS-CoV-2 virus are playing it safe by using vaccine types based on viral protein to induce immunity.

Of the four SARS-CoV-2 viral proteins, spike protein is the major focus of COVID-19 vaccine efforts. After coronavirus attaches to a cell, spike protein initiates infection by boring a hole into it. While myriad research groups are using clever means to deliver intact spike protein as a vaccine, the two vaccines now garnering early attention, from Pfizer-BNT (Pfizer plus BioNTech) and Moderna-NIAID (Moderna plus the Vaccine Research Center at the National Institute of Allergy and Infectious Diseases) consist of mRNA (messenger RiboNucleic Acid),

which codes for spike protein (see below for how mRNA does this), rather than the protein itself. The major attraction of this vaccine type is that it is synthesized in a laboratory independent of live virus cultures, making it much easier to quickly scale production up to millions of doses.

Theoretically, mRNA makes little sense as a vaccine because our immune system recognizes and mounts responses to proteins, not mRNA. mRNA exists in cells to convert information in genetic material into functional proteins. mRNA transcribes the genetic material in a cell's nucleus and carries it to cellular machinery which translates mRNA coding and makes protein.

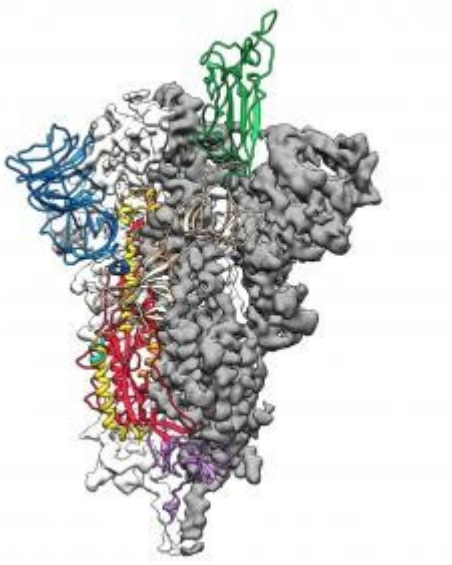
There has never been an approved mRNA vaccine for any infectious agent, despite development efforts since the 1990s. For an mRNA vaccine to work, there are a series of steps that must occur: 1) a cell must take up **intact** mRNA from outside the cell; 2) the cell's protein-making machinery must use the mRNA to make spike protein; 3) the cell must know to release the foreign, spike protein into surrounding blood or tissue; 4) that spike protein must stimulate the immune system; and 5) the antibody resulting from all this must kill SARS-CoV-2 virus or otherwise prevent infection. (Just showing that a vaccine can induce antibody production does not prove it will prevent COVID-19 infection.) It is surprising that those steps seem to have fallen into place for these vaccines.

Another problem is that mRNA is VERY unstable and easily degraded at room temperature. It needs a 'package' that can protect it. Both companies use a lipid (fat) nanoparticle-based shell to carry & protect the mRNA. mRNA degrades less easily at cold temperatures, hence the Pfizer-BNT vaccine's need for ultra-cold storage temperatures. Moderna-NIAID's vaccine only requires regular refrigeration, probably because of a less fragile lipid 'package.' This might present a problem for administering these vaccines: If the vaccine is not cooled properly prior to injection, the mRNA might have degraded and not work as a vaccine. The lipid shell can be chemically irritating and is probably responsible for the most common side effects of these vaccines, injection-site pain and fever.

No one could make an mRNA vaccine for SARS-CoV-2 without knowing the structure of spike protein. Chinese scientists identified the sequence of SARS-CoV-2's genome, and from that figured out the structure of SARS-CoV-2's spike protein. Using standard knowledge of the correlation between protein building blocks and RNA coding, scientists were able to make mRNA for spike protein. Spike protein takes two forms, one on the viral surface and a rearranged form after attaching to a target cell. Scientists at NIAID recreated spike protein's pre-cell-attachment structure and used that to make mRNA for Moderna's nanoparticle delivery platform. I cannot find information about the spike protein form used by BNT.

Moderna-NIAID's mRNA-1273 vaccine was the first to enter human trials in the United States. Phase I and II dose-

finding, safety and efficacy trials in limited numbers of people showed that two monthly injections of either a low or high-ish (100 µg) dose were 'reasonably' tolerated. The high dose induced more marked side effects and better antibody levels. For reference, SARS-CoV-2 vaccine investigators use recovering COVID-19 patients' antibody levels as their goal. (See below for Phase I, II and III trial definitions.)



SARS-CoV-2 Spike Protein

mRNA-1273's Phase III, placebo-controlled trial enrolled 30,000 people older than 18 years from all demographic groups. Participants received 2 of the 100 µg dose injections 28 days apart by October 22, 2020. On November 15 (that is scary "Warp Speed") the independent data and safety monitoring board reported that the vaccine was safe and effective. Ninety-five cases of COVID-19 disease were diagnosed, only 5 of which were in vaccine recipients. All eleven severe COVID-19 cases occurred in placebo recipients.

The Pfizer-BNT vaccine followed a similar timeline, except their Phase 3 trial started sooner. BioNTech studied multiple mRNA vaccine possibilities but found that BNT162b2 led to adequate antibody response with fewer severe side effects. The mRNA is mutated slightly to make the resulting spike protein's stimulation of the immune system more potent. Young people, with generally stronger immune systems, were the only ones who experienced severe and longer-duration side effects. People older than age 65 years had less injection site pain and fever, but also made less antibody.

Pfizer-BNT started their Phase III, multi-national vaccine trial on July 27, 2020, enrolling close to 44,000 participants from all demographics who were older than age 15 years. They received two injections of either placebo or 30 µg vaccine 21 days apart. Only 41,135 received both injections by the time of trial 'completion' on November 18. All data have not been analyzed yet, but the company announced their positive results. After the second dose, 170 people contracted COVID-19, all but 8 of whom received placebo. This represents 95% protection, assuming all participants had equal exposure to potential disease. Of ten severe cases, only one occurred in a vaccinated subject. Disease prevention was reportedly equal across demographic groups, including elderly and other high-risk people. Side effects were assessed in a subset of 8000 people. Severe side effects of fatigue and headache occurred in up to 3.8% of subjects.

Here are my concerns with these early reports:

1. The reports that the vaccine protected 90% or 94.5% of vaccine recipients, based on the percent of people who developed disease, assume that all people were exposed equally, which might not have been the case.
2. Using the mRNA-1273 (Moderna) vaccine dose that caused the most marked side effects in earlier studies seems problematic.

3. This is too soon to evaluate a large vaccine trial for two reasons: The Food & Drug Administration requires at least 2 months post-treatment observation for delayed adverse effects. Follow-up of two months does not tell us how long immune protection against SARS-CoV-2 will last.
4. mRNA vaccines have no track-record from which to extrapolate and we know from other coronavirus infections that antibody levels tend to wane rapidly.
5. Both Moderna and Pfizer deny any obligation, other than what is required by law, to update "forward-looking" statements or predictions (about results, side effects and future vaccine production) contained in their November results announcements. I believe we should know about all developments and revisions to results as they become known to the company.

Based on their early, positive results, both companies have applied to the Food & Drug Administration for Emergency Use Authorization (EUA). EUA enables early vaccine production for health care providers and others who are high risk before we have reassurance about the above issues. If the vaccine's immune protection is short-lived and people who think they are immune stop social-distancing and wearing masks, people will get sick and die.

I find the funding sources for these vaccines' development to be interesting: Funding for Moderna's mRNA-1273 vaccine came largely from the U.S. government, plus multiple lesser university and private foundation donors (including Dolly Parton). BioNTech developed the BNT-162b2 vaccine (to which Pfizer purchased rights to provide finance, clinical trial management and manufacturing) with funding from non-U.S. government sources, in order to prevent politically motivated interference in the vaccine's development by Trump's "Operation Warp Speed". The U.S. government has only helped Pfizer pay for vaccine distribution in the U.S.

In summary, these mRNA vaccines represent exciting new technology, but we need more than a few interim results to feel confident that they will be safe and effective for a clinically meaningful time period.

Drug/vaccine/treatment Trial Descriptions:
Phase I trials: Small number healthy people to make sure the intervention is **tolerable**. Often helps to determine best dose and route of administration.
Phase II trials: Hundreds of people at risk for the disease tested using the dose and route determined to be best in Phase I. Checking for **efficacy and safety**.
Phase III trials: Thousands of all types of people at risk for disease are tested to **compare** the safety and efficacy of the intervention versus placebo.

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