mRNA Vaccines, Vaccine Hesitancy, and COVID-19: The Good, the Bad, and the Ugly

Minh-Thu Le, MD, FAAAAI, FACAAI, CoxHealth Allergy & Immunology

As a clinical immunologist, I have an intimate relationship with shots. I use immunotherapy daily in my allergic patients to retrain parts of the immune system to induce tolerance. Booster vaccines are my tools to determine which adaptive immunodeficiencies my patients may be suffering. Imagine my enthusiasm when immune mechanisms are now at the forefront of the COVID-19 pandemic and basic immunology is serving as the cornerstone for the vaccine candidates that will turn the tide of this pandemic!

There are many vaccine candidates on the horizon (Table 1), and many physicians are just as hesitant as the lay public about the mRNA vaccines, our newest candidate. They cite the speed of development, possible allergic and anaphylactic reactions of the early vaccinated groups which were not seen with the study groups, antibody dependent enhancement, "unknown" long-term side effects and general safety. However, as previous vaccines and our current studies on the mRNA COVID-19 vaccines would tell us, these concerns should not be stumbling blocks to be vaccinated if we look at the evidence. Recent media reports suggest that although 95% of physicians are being vaccinated, maybe only half of our nurses, medical assistants, and other medical professionals are.[2] We need to be able to address their concerns about vaccination.

Here, I'll address the common questions I've encountered:

Q. Are you worried about how fast the mRNA vaccines came about?

A. Absolutely not. mRNA technology has been in the works for over 20 years, and in vaccine technology for the past 15+ years. We have learned about what works and what doesn't through the first SARS CoV-1, Dengue fever, Zika virus, and multiple cancer treatments.[1] The Chinese genetically sequenced the virus (also called SARS CoV-2) in early January 2020. We determined the spike protein was the most immunogenic part of the virus and determined its sequencing early on. One of the advantages of mRNA is that it can be synthesized, not needing to be grown or cultured from cell lines, which takes more time.[3] Labs from all over the world shared information and published studies for anyone with an internet connection to glean. Billions of dollars were funneled from the public and private sectors to fund these studies, and there was a high burden of disease in the community that allowed determination of vaccine efficacy in record time. By doing safety and efficacy studies concurrently, we changed the paradigm on how to perform vaccine studies.

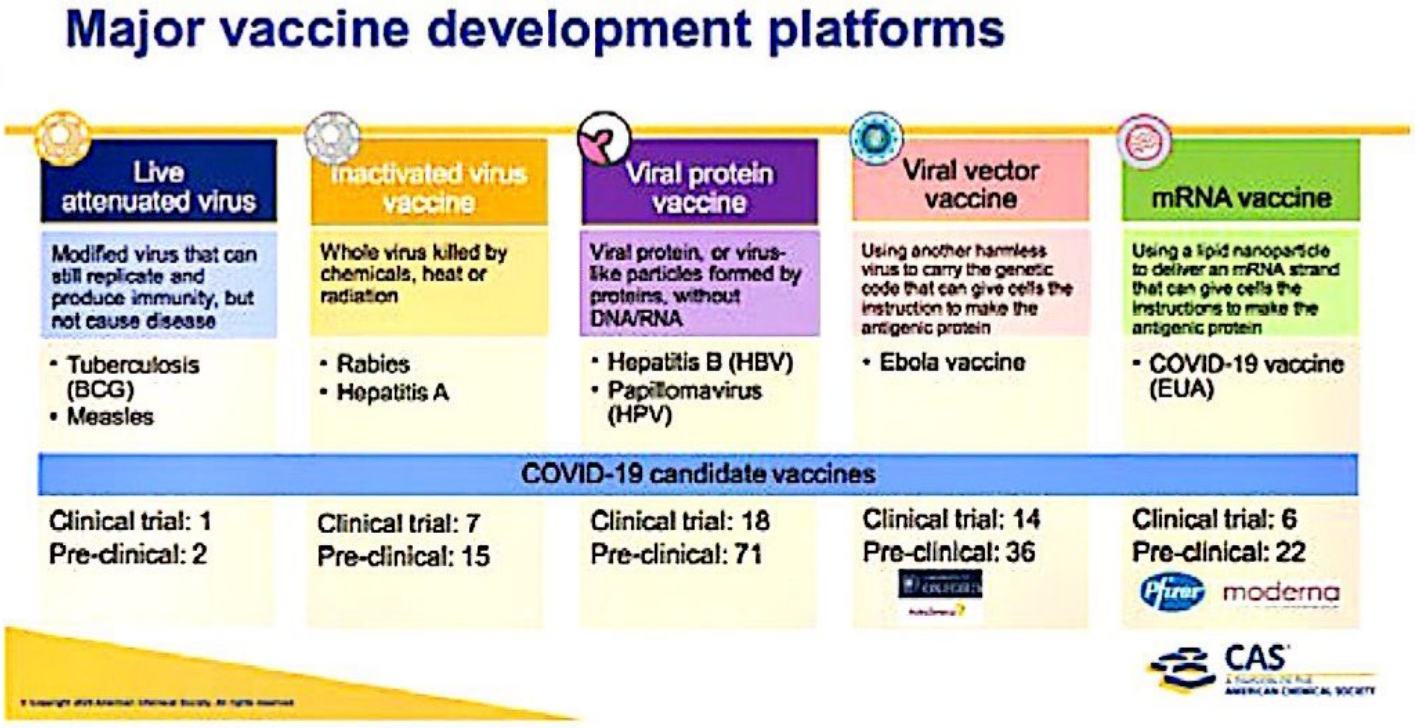

Table 1: Vaccine development platforms and COVID-19 candidate vaccines[1]

Our 100 years of previous vaccine research determined what safety mechanisms should be in place prior to enrolling the first patient. Also, with the specificity of vaccines now, there is a limited amount of extraneous proteins from viral particles that may harm people as it did with early vaccines and live vaccines.

Q. What about "antibody dependent enhancement"?[4]

A. This is a question that comes up because the Dengue fever vaccine (which was also mRNA based) had this phenomenon. This occurs when there are non-neutralizing antibodies produced that basically enhance the signal of the virus, making it easier to be infected and possibly more dangerous if infected. It is purely theoretical and not seen in the mRNA vaccines currently in production. We know there are neutralizing antibodies produced by mRNA vaccines, not non-neutralizing. This means that when these antibodies encounter a viral particle, they will neutralize it, destroy it, limiting infection in the host. If this was not the case, then there would have been more people infected in the vaccine groups than the placebo ones, which, as we know, did not happen.[5]

Key features of the COVID-19 vaccine frontrunners

	Pfizer/ BioNTech	Moderna	AstraZeneca/ Oxford	Janssen (Johnson & Johnson)
Type of vaccine	mRNA in lipid nanoparticles	mRNA in lipid nanoparticles	Non replicating adenovirus vector	Non replicating adenovirus vector
Dosage	2 doses 21 days apart	2 doses 28 days apart	2 doses 28 days apart	1 dose or 2 doses 56 days apart
Antibody detection	7 days after booster	14 days after booster	14 days after booster	14 days after booster
Efficacy	95%	95%	70%	N.A.
Planned production volume	50M (2020) 1.3B (2021)	20M (2020) 0.5-1B (2021)	3B (2021)	1B (2021)
Storage requirement	-70°C ± 10°C	-20°C	2-8 °C	2-8 °C
Shelf life once thawed	5 days	30 days	180 days	180 days
Phase III trial enrollment	43,000 (age 16-85)	30,000 (age 18+)	11,500 (age 18+)	Single dose 60,000 Two dose 30,000 (age 18+)
Percentage high risk population in phase III trial	40-50%	42%	N.A.	N.A.

Table 2: Key features of the COVID-19 vaccine frontrunners[15]

Q. Can mRNA change my DNA or cause sterilization?

A. Okay, I read this, and I think, "Duh! No!" But many of the public question this because they do not understand the basic science, and surprisingly, many doctors take this for granted and cannot convincingly allay these fears. This is how I would approach this question: DNA is found in the nucleus. Things can get out of the nucleus, but things cannot get in. There is no reverse transcriptase that allows mRNA to somehow get into the nucleus and make DNA. DNA makes RNA (and lots of other things), not the other way around. Viruses get into our cells and make mRNA to replicate themselves without being able to change our DNA. They do this in the order of millions, with multiple other proteins that get translated, wreaking more havoc than one mRNA strand which is degraded very quickly in the cytoplasm of the cell. For the sterilization issue, we can note that both the Pfizer and Moderna studies had people that became pregnant after they received the vaccines. Again, there no plausible cellular mechanism that mRNA could get into the DNA of eggs and sperm rendering them impotent. There are no placental proteins in the manufacturing of any mRNA vaccine, and there would never need to be since mRNA is synthesized in the lab. Furthermore, COVID-19 infection, itself, has been associated with infertility.[6] Because the vaccines cannot cause infection, it stands to reason that getting the vaccine would actually protect one from being infertile. Additionally, the American Society for Reproductive Medicine does not recommend withholding the mRNA vaccines for those planning to conceive, are pregnant, or lactating.[7]

Q. How can you be sure the mRNA vaccines are safe?

A. We have seen a handful or reports of "anaphylaxis" after large scale roll outs of the Pfizer and Moderna vaccines. The fact is that true IgE-mediated vaccine anaphylaxis is rare. Per VAERS, it is about 1.3 per million.[8] However, these reactions may not actually be "anaphylaxis," as many are self-reported and have not undergone extensive workups (i.e., evaluation with an allergist, tryptase levels in the acute phase

of the reaction, etc.). Also, it seems that the recent reactions have been limited and highly responsive to treatment protocols in place for adverse or allergic reactions. It is highly contested, but potentially, the polyethylene glycol (PEG) component that stabilizes the lipid nanoparticle may be responsible. This is not true anaphylaxis, but by direct mast cell destabilization (anaphylactoid) like what we see in narcotic reactions, contrast media reactions, and NSAID or vancomycin (red man's syndrome) reactions.[9] This is not a reason to withhold the vaccine to high-risk individuals and front-line workers. No one has died or had a permanent adverse outcome from these reactions, and as an allergist, I would still recommend vaccination with close observation for 15-30 minutes, with treatment with epinephrine and drawing a tryptase level within 2-4 hours if anaphylaxis is suspected.

B. One reaction I will note: There were those with facial dermal fillers that had swelling after vaccination in the Moderna study.[5] This is an adverse reaction specific to these individuals which is still being studied. Again, a good dermatologist may be able to treat these post vaccination reactions and knowing they will occur and counseling patients will decrease anxiety and hesitancy. Also, other vaccines are coming which may be more suitable for these patients. From prior vaccine studies we can conclude that most serious vaccine reactions occur in the six weeks after vaccination, and with the studies going out to two months, we can be confident that these vaccines are safe. The last point that I'd make about vaccine safety is that mRNA vaccines, in general, are very clean and do not have any preservatives, animal or plant proteins associated with them. They are safer than other vaccines which may have other pre-manufacturing chemicals and preservatives as well as extraneous protein antigens that do not confer immunity. I've included a video link in my references that is very accessible to most people on the mechanism of mRNA vaccines.[10] I also like this analogy that my colleague in Texas uses with her patients:

Imagine your friend with multiple severe food allergies calls you and asks you to make a cake that is your specialty. You would like to make it for her, but worry that by making it in your kitchen, you may get some cross-contamination with other ingredients that she may be allergic. You may then just decide to give her your recipe so that she can go back to her allergy-free kitchen and make it safely there. That is what the mRNA vaccines are, the recipe that your own cells take up and use to make the spike protein to which your body will then mount an immune response.[11]

You can already see how much safer this would be than live virion overwhelming the immune system with multiple antigens, some of which are likely more harmful than just the spike protein and causing multiple sequelae that we are just beginning to understand.

Q. Will mutations in the COVID-19 virus make mRNA vaccines ineffective?

A. The headlines would have us believe that strains of the COVID-19 virus will make our vaccines ineffective. Luckily (or unluckily) the SARS CoV-2 virus is much more sophisticated than our flu viruses that mutate quickly and render past vaccines minimally effective.[12] COVID-19 may have a proofreading function that highly conserves its replication, much like eukaryotic cells do in our own body. The most recent strain noted in the UK is a deletion that changes 8-10 amino acids of the spike protein.[13] This is out of over 1700 amino acids specific to the spike protein. With the holidays, I've used this analogy: The spike protein is like a Christmas tree; we know what it looks like and can recognize it in any home. They are all decorated differently, but the basic shape and function of them is the same. Similarly, antibodies and immune cells still recognize the spike protein. Also, as more mutations occur, the virus will have to contend with changing its main pathway of getting into the cell, and it will be a delicate balance of evading our vaccines and continuing to be able to infect human cells effectively. And again, this is where mRNA has an advantage. We can quickly spin up a new vaccine using the newly sequenced RNA for the new variant spike protein if it does mutate to the point where current vaccines are rendered ineffective.

We already know that for many, COVID-19 is fatal, for others, it can be debilitating for months and maybe even years. The "shadow" of COVID-19 is far reaching, and vaccines can decrease not only the active infection, but in turn, decrease its sequelae (i.e. MIS-C, DM type I, long-COVID syndrome, and psychosis).[14] The vaccine frontrunners (Table 2) will all be here shortly.[15] Arming ourselves with the expertise to allay the fears and hesitancy of our patients, staff, colleagues, friends and family members will allow us to finally recover from COVID-19 as a community and as a nation.

References:

1. COVID-19 Vaccines— American Chemical Society. Webinar slides and discussion: file:///Users/minh-thu/Downloads/2020-12-22- -vaccines-cas-final%20(3).pdf

2. Large Numbers of Healthcare And Frontline Workers Are Refusing Covid-19 Vaccine. https://www.forbes.com/sites/tommybeer/2021/01/02/large-numbers-of-health-care-and-frontline-workers-are-refusing-covid-19-vaccine/?sh=128afd713c96

3. Pardi, N., Hogan, M., Porter, F. et al. mRNA vaccines — a new era in vaccinology. Nat Rev Drug Discov 17, 261–279 (2018). https://doi.org/10.1038/nrd.2017.243

4. In the Pipeline. Antibody-Dependent Enhancement. https://blogs.sciencemag.org/pipeline/archives/2020/12/18/antibody-dependent-enhancement

5. FDA Review of Efficacy and Safety of Moderna Vaccine Emergency Use Authorization Request, https://www.fda.gov/media/144585/download

6. Khalili MA, Leisegang K, Majzoub A, Finelli R, Panner Selvam MK, Henkel R, Mojgan M, Agarwal A. Male Fertility and the Pandemic: Systematic Review of the Literature. World J Mens Health. 2020 Oct;38(4):506-520. doi: 10.5534/wjmh.200134. Epub 2020 Aug 14. PMID: 32814369; PMCID: PMC7502312

continued on page 24

Le, continued from page 14

7. American Society for Reproductive Medicine (ASRM) Patient Management and Clinical Recommendations During the Coronavirus (COVID-19) Pandemic, UPDATE No. 11 – COVID-19 Vaccination. December 16, 2020. https://www.asrm.org/globalassets/asrm/asrm-content/news-and-publications/covid-19/covidtaskforceupdate11.pdf

8. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016.J Allergy Clin Immunol. 2019 Apr;143(4):1465-1473. doi: 10.1016/j.jaci.2018.12.1003. Epub 2019 Jan 14. PMID: 30654049; PMCID: PMC6580415

9. Pseudo-anaphylaxis to Polyethylene Glycol (PEG)-Coated Lipoomes: Roles of Anti-PEG IgM and Complement Activation in a Porcine Model of Human Infusion Reactions. ACS Nano 2019, 13, 8, 9315-9324. Publication Date:July 26,2019. https://doi.org/10.1021/acsnano.9b03942

10. How mRNA vaccines work to fight COVID-19 https://www.youtube.com/watch?v=LcTEmHlvY10

11. Personal communication with Lukena Karhanis, MD.

12. Sanders W, Fritch EJ,Madden EA, et al. Comparative analysis of coronavirus genomic RNA structure reveals conservation in SARS-like coronaviruses. Preprint. bioRxiv. 2020;2020.06.15.153197. Published 2020 Jun 16. doi:10.1101/2020.06.15.153197

13. Andrew Rambaut1, Nick Loman2, Oliver Pybus3, Wendy Barclay4, JeffBarrett5, Alesandro Car-abelli6, Tom Connor7, Tom Peacock4, David L Robertson8, Erik Volz4, on behalf of Genomics Consortium UK (CoG-UK)9. Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. Pre-print.https://virological.org/t/preliminary-genomic-characterisation-of-an-emergent-sars-cov-2-lineage-in-the-uk-defined-by-a-novel-set-of-psike-mutations/563

14. Pollard, A.J., Bijker, E.M. A guide to vaccinology: from basic principles to new develop-ments. Nat Rev Immunol (2020). https://doi.org/10.1038/s41577-020-00479-7

15. Zhou, Angela. Top 5 vaccine questions answered. cas.org/blog/covid19-vaccine-questions ◆

GREENE COUNTY MEDICAL SOCIETY

– a voice for physicians!

If you would like to volunteer for a leadership position, please contact the GCMS Office.