Report to the Boards of Health

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Viral Mutations and Vaccine Effectiveness

Below is a brief overview of viral mutation and how to determine if vaccines will still work against variants. The following video (https://youtu.be/bXgqZt9q6J4) from the Journal of the American Medical Association (JAMA) titled *Coronavirus Variants and Vaccines* gives an excellent overview regarding COVID-19 variants and determining vaccine effectiveness against these new variants. Note that the video is from April 2021 and focuses on earlier variants and vaccine considerations, yet the same ideas apply to our current variants and vaccine concerns. The video, coupled with the point below, will hopefully aid in your understanding of this complicated topic.

Viruses and Mutations

- Viruses are not living organisms. They take over the cells of living organisms, commandeering their resources to make them virus production facilities.
- In the case of COVID-19 and humans, it is estimated that between 300,000 to 300,000,000 infectious viral particles are made during the infection of *one* person.
- As a virus makes millions of copies of themselves, there will be mistakes. These mistakes make mutations. It is normal for all viruses to change through mutations and make new variants.
- In the case of COVID-19, it is estimated that out of every two or three people infected, one new mutation will happen. Currently, there are about 3 million cases per day globally - that's about 1 million new mutations occurring every day.
  - *The more COVID-19 infections, the more mutations that will occur.*
- Most of these mutations won't matter since they won't give the virus any survival benefit and may even make the virus worse at causing infection or reproducing. Plus, not every mutated virus will go on to infected someone new and continue to spread to others.
- Viruses follow the same process of evolution as other organisms. Mutations that allow a particular mutation in the virus to make more copies of itself, to stick better to cells, to hide from our immune system, or to otherwise do better than others will give it the advantage to survive and become dominate.
- The best prevention against newer variants is to reduce the number of infections.
  - The best prevention against COVID-19 infection is vaccination.
    - With new variants there are understandable concerns about how effective our vaccines will be.

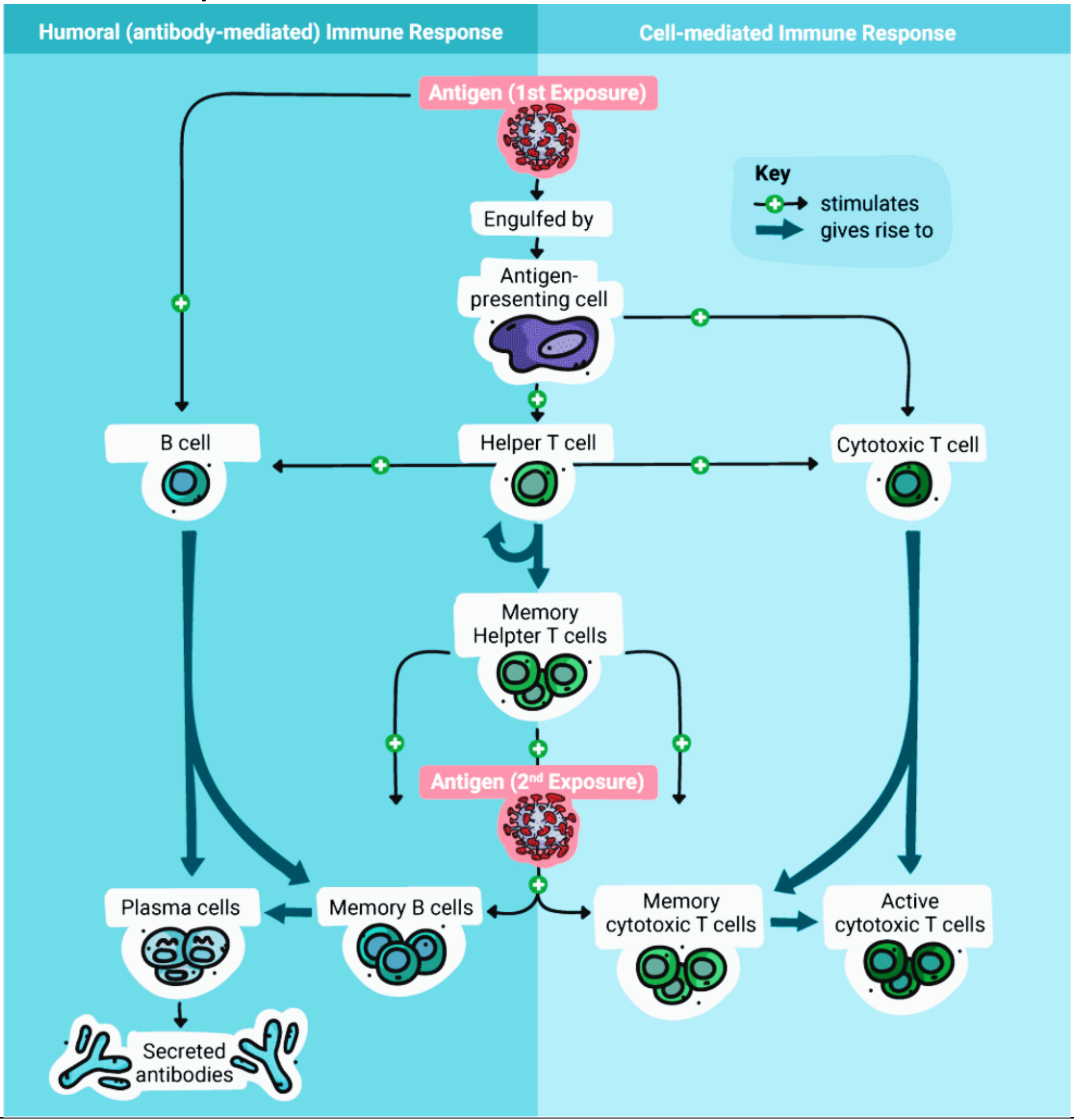
Mutations and Vaccination

- Multiple studies have found that, over time, vaccine protection against COVID-19 infection wanes (decreases). Protection against hospitalization and death wanes somewhat, but less than protection against infection.
- The best way to know if a vaccine is working is to study the number of infections, hospitalizations, and deaths in people that have and have not been fully vaccinated. In other words, study if the vaccine prevents illness and complications in real people.

- Studies have found that the primary mRNA vaccines and primary (monovalent) booster continued to do well against the earlier variants of COVID-19 at preventing hospitalization and death (as discussed in the [2021 JAMA video]).
- Against the Omicron variant and all its sublineages (BA.1, BA.2, BA.4, BA.5, etc.), effectiveness of the primary (monovalent) boosted against illness dropped after a few months and it was also lower against severe infections.
  - Because of the waning immunity and the drop in effectiveness against newer variants, a new bivalent mRNA booster was recommended, based on the BA.4 and BA.5 subvariants.

- Early when there is a brand-new variant, like XBB or XBB.1.5, there usually isn't enough information about infection rates to accurately know how effective the vaccines are.
- To try to get some ideas, scientists may look at antibodies in people who were vaccinated to try to determine if the vaccine will still work as well. Most often they study neutralizing antibodies, which are antibodies that bind to the virus in a way that would keep it from binding to our cells, blocking it from causing illnesses (see figure 1 for explanation of antibodies).
- The antibodies can be removed from the blood of someone that has been fully vaccinated, or even previously infected, and then combined with samples of the variant virus in the lab.
- There have been some early studies showing lower neutralizing antibodies to BQ.1, BQ.1.1, XBB, and XBB.1 subvariants in those fully vaccinated, including the bivalent vaccine, as well as those previously infected with other subvariants.
- However, there have already been several studies of past COVID-19 variants both after natural infection and after vaccination showing that having lower levels of neutralizing antibodies doesn't mean you will necessarily have a higher risk of illness, hospitalization, or death.
  - This is because antibodies are only one part of our immune response and neutralizing antibodies are not the only measure of vaccine protection.
- Vaccines and infections create different kinds of antibodies that do more than just neutralize viruses. They also activate cells and other processes to help fight infection. A simplified explanation is provided in figure 1, below. There are still more processes of our immune system than included in this figure.
  - Notice how much faster the response is after the second exposure to antigen. This is why you don't get sick or as severely sick if you've been vaccinated, as your immune system is ready to respond right away.

Figure 1: Adaptive Immune Response



- **Antigen:** any foreign substance that causes the body to make an immune response; in the case of COVID-19, it is either infection or vaccine
- **Antigen-presenting cell:** (may be called a phagocyte or "cell that eats") engulf invading particles and cells and break them up into small pieces called antigens and then transport the pieces to the lymph nodes and present them on their surface, starting the process of identifying specific antigens
- **B cell:** in charge of humoral immunity, which is immunity through antigen-specific antibodies. When a B cell is activated by an antigen, the B cell proliferates and produces two types of cells: antibody-secreting plasma cells and memory B cells.
- **Helper T cell:** recognize the antigens presented by antigen-presenting cells and activate the other cells of the adaptive immune system, including the Killer T, B cells, and macrophages (a phagocyte)
- **Cytotoxic (Killer) T cell:** can directly target and destroy both invading microorganisms and cells that have already been infected by viruses/microorganisms
- **Memory Cytotoxic (Killer) and Helper T cells:** Once the infection is cleared, most T cells triggered for that infection die; however, a few will remain as memory T cells that become activated again if they encounter the same antigen
- **Plasma cells:** B cells that produce antibodies; each plasma produces only one specific antibody to one specific site (epitope) on an antigen
- **Memory B cells:** "remember" pathogens you've encountered before. These cells live a very long time and quietly circulate in the body. If they encounter the pathogen that caused their production in the first place, they will quickly trigger the adaptive immune response to the invader, and antibody production will begin much more quickly than it did the first time.
- **Secreted antibodies:** proteins that can target and bind to specific antigens. There are different types of antibodies that have different functions. Some swarm and block the ability of pathogens to interact with cells (called neutralizing antibodies). Others will flag the pathogens or infected cells for destruction by other immune cells and proteins (called opsonization).

For more detailed information about the immune system, see "BiteSized Immunology" at the British Society for Immunology at https://www.immunology.org/public-information/bitesized-immunology

- For comparison, influenza is another RNA virus, like COVID-19, that mutates often. Every year, scientists around the world study the virus to decide the best four strains of virus to use for the yearly influenza vaccine. They look at several things, including:
  - Which viruses were circulating the last season and in different parts of the world, studying the genetics of the viruses for any changes.
  - Vaccine effectiveness studies performed in the prior season to see how well that vaccine worked to protect against multiple things such as illness, hospitalization, ICU admission, death, and how the vaccine worked in people of different ages and risk factors.
  - Predictions of which flu viruses will circulate the next season based on prior data.
  - What parts of the virus (which antigens) create the best antibody response.
  - How well do the antibodies produced work against the virus.

References

- Sender, Ron, et al. "The total number and mass of SARS-CoV-2 virions." Proceedings of the National Academy of Sciences 118.25 (2021): e2024815118. https://www.pnas.org/doi/10.1073/pnas.2024815118
- Edwards, K., Orenstein, W. COVID-19: Vaccines. UpToDate. 2022.
- Wang, Qian, et al. "Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants." *Cell* (2022).
- Ardeuengo, M. 2020. Antibodies, Immunity and Vaccines: A Short Primer on the Adaptive Immune Response. Promega Connections. https://www.promegaconnections.com/antibodies-immunity-and-vaccines-a-short-primer-on-the-adaptive-immune-response/
- CDC. Selecting Viruses for the Seasonal Influenza Vaccine. https://www.cdc.gov/flu/prevent/vaccine-selection.htm