Vaccine Regimens and the Future of Covid-19 Boosters: Heterologous and Homologous Strategies of Vaccination

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1. Introduction

The human immune system is responsible for recognizing “self” and protecting it from “non-self.” It comprises two interlocking subsystems, the innate immune system and the adaptive immune system, which work in tandem to identify and destroy invading microbes. Innate and adaptive immunity are primarily distinguished by cellular lineages and the specific functions those cells perform in defending the body. In general, the innate immune system is responsible for the initial rapid, nonspecific response to an infection, and for alerting adaptive immune cells to the presence of an invading pathogen [1]. While the innate immune system is capable of clearing some infections without assistance from adaptive immune cells, it is unable to tailor its attack to specific targets, which can result in unintended damage to the host and evasion by evolutionarily efficient infections. The adaptive immune system exists, therefore, to provide both a pathogen-specific defense and as a storage repository for previous protection against repeat infections. Modern vaccines thus take advantage of the adaptive immune system to provide this powerful and lasting defense mechanism without the damage (and potential death) that can result from the immune challenge of a real infection.

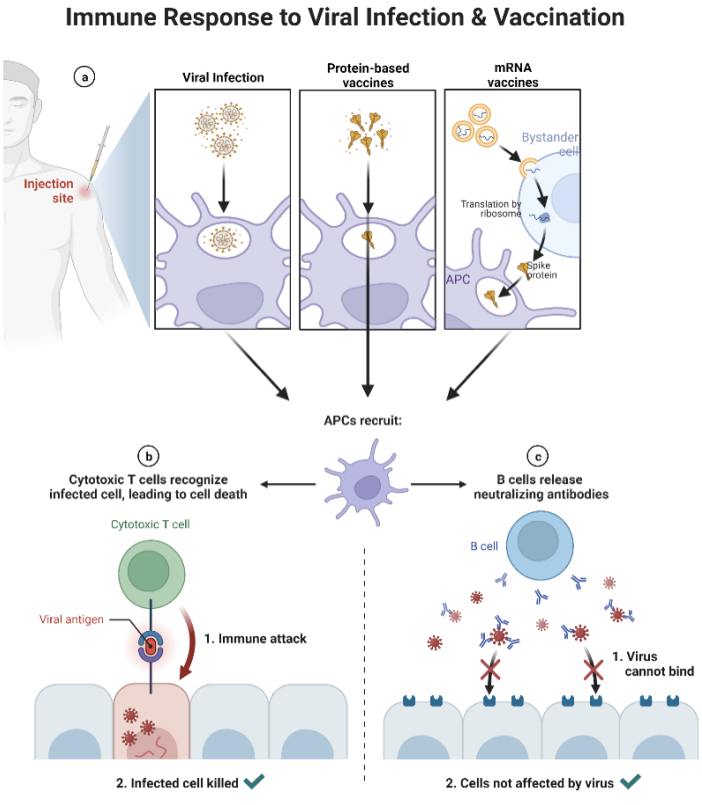
The immune system is incredibly complex, and immunology is a constantly evolving field of research; however, the science of vaccines is solid and relatively easy to understand at a surface level. In general, when a virus such as SARS-CoV-2 infects a human host, infected cells display a “not-self” signal on their surface, which is recognized by immune cells [Figure 1A]. These cells carry components of the virus, called “antigens,” through the lymphatic system and present them to adaptive immune cells called T cells. There are many types of T cells, but a

specific type—T helper cells (T_h)—have special receptors on their surface capable of recognizing a range of specific antigens. When the antigen is recognized, the T_h cell then presents it to another class of adaptive immune cells, called B cells (having originated in the bone marrow). B cells likewise have receptors on their surface that recognize specific antigens; because these receptors are formed by random combinations of genes, effectively every possible antigen has a corresponding B cell receptor in the body that can recognize it. When a B cell receptor binds to an antigen, this process “activates” the B cell, causing the B cell to recombine its receptor-specific DNA to improve binding to the antigen. When hyper-specific binding has been achieved, the B cell begins dividing. Most of the new B cells begin secreting a class of molecules called “antibodies” which, like the B cell receptor, bind to the target antigen with high specificity. These antibodies attack the invading pathogen, neutralizing its ability to infect cells and telling the rest of the immune system exactly where to attack to avoid damage to the self. A smaller population of the cells become memory B cells, which stay quiescent in the lymphatic system until the virus is reencountered, upon which they can immediately and rapidly divide to produce the necessary attacking antibodies that prevent the virus from mounting a full infection again [2,3].

Vaccines make use of this antigen recognition system to induce a memory B cell population capable of recognizing and attacking a specific virus while circumventing the damaging side effects of a primary infection [3].Vaccines are generally made from a weakened or dead virus, from critical viral proteins, or from mRNA (messenger RNA) that encodes a viral protein. By allowing the immune system to interact with components of a virus that cannot cause infection, the immune system is allowed to see and respond to the viral antigens it needs to learn and memorize an adaptive immune response [4].

The goal of vaccination is to thus mimic an immune response to a pathogen without inflicting actual illness. Vaccinology seeks to generate vaccines that induce the most effective, specific, long-lasting, and powerful response to a virus. While some vaccines can be administered once or twice and provide lifelong defense, other vaccines must be updated constantly to match the speed at which ever-evolving viruses, such influenza and SARS-CoV-2, mutate their antigens to avoid immune recognition. Vaccine regimens can thus be homologous—the same antigen injected one or more times—or heterologous—multiple injections of different versions of the same antigen or different antigens from the same virus. This review is an exploration of the different strategies of vaccination against common viral targets, and discusses the efficacy of homologous versus heterologous vaccine regimens, with a focus on the potential future of SARS-CoV-2 vaccination regimens as the disease becomes endemic across the globe.

2. Types of vaccines



Until the Covid19 global pandemic, the primary type of antiviral vaccine was composed of protein from a target virus. In general, genes are transcribed from DNA into messenger RNA, which then instructs cells to build a specific protein. Proteins are the basic functional building blocks of all life on earth, and viruses make use of proteins on the outer surface of their membranes to

enter cells [29]. Once inside, they hijack the host cell's machinery for replicating DNA and for translating mRNA into proteins, forcing cells to make viral proteins instead of functioning normally [30]. Protein subunit vaccines are generally made from surface proteins on the virus that are easily visible to the immune system during an infection; after injection, the immune system picks up the protein and presents it to B cells in a process similar but not identical to a genuine infection [Figure 1B] . However, these vaccines can be difficult to generate and do not necessarily mimic the viral mRNA-based course of an infection. The new class of mRNA vaccines, which are made of the messenger RNA responsible for encoding a target viral protein rather than the protein itself, more closely recapitulate the progression of an infection than a protein subunit vaccine. In part because proteins are often modified during translation in cells in ways not always predictable by scientists, mRNA vaccines can tell cells to generate a viral protein as they would during an infection [14,15][Figure 1C]. Although the cells are not infected, they can present a viral antigen as they would during an infection and trigger an adaptive immune response similar to that of a real infection [17,18]. The foreign mRNA is degraded by the cells soon after, leaving the body with protective antibodies in circulation and adaptive memory against the virus [16,19].

Figure 1: Mechanisms of viral and vaccine immune response in the human body. *(A) Viral infection, protein subunit vaccines, and mRNA result in antigen presenting cell (APC) activation. (B) Activated APCs induce effector T cell killing of cells that have been infected.*(C) *B cells antibody production is activated and neutralizing antibodies bind to the pathogen. Neutralizing antibodies slow down and control the spread of the infection in the body. Memory cells are created which are already prepared to fight off the same virus if encountered again [40].*

3. Vaccine Regimens and Vaccine Efficacy

For the most common infections, a single dose of protein subunit vaccine can provide a sufficient immune response against a target virus. However, a second dose can greatly increase that protection and the longevity of the immune response. Vaccine regimens can consist of multiple doses of the same antigen at different times, at the same or at increasing dosage levels (homologous), or can consist of different antigens against the same or mutated strain of the virus (heterologous) [20]. These regimens are virus-dependent; table 1 shows the various vaccine regimens for Measles, Mumps, Rubella, HPV, Influenza, Polio, and Ebola along with the vaccines' efficacy. As of 2023, SARS-CoV-2 is the only disease against which mRNA vaccine regimens are authorized in the United States [31].

The influenza regimen is heterologous with a 10 to 60% efficacy; however, there is a trend toward decreasing efficacy each year [9,32]. One of the reasons is the mutability of the influenza virus: every year, vaccinologists work to generate a vaccine that will be efficacious against the predicted dominant viral strain. However, this strain prediction is imprecise, and the vaccine is less protective against that year's dominant influenza virus as a result [33]. The MMR two-dose vaccine regimen is heterologous as well, with a 93% efficacy against measles and an 88% efficacy against mumps. The vaccine is a live-attenuated virus, which can cause an active infection after administration; however, this is extremely rare and the MMR vaccine is consistently effective in the population against infection [10]. The polio vaccine is similarly effective, with a four-dose, homologous vaccination regimen resulting in 99% efficacy. There are two forms of the polio vaccine, consisting either of an inactivated, injectable polio virus (IPV) or a weakened virus administered orally (OPV); both forms are effective, but the IPV form of

administration is more common in first world countries 12]. Likewise, the two-dose homologous HPV vaccine regimen is highly efficacious (97%) and protects against both the viral infection and against viral cervical cancer, which is caused by virally induced mutations in cervical cells during infection [11, 34].

Table 1: Standard vaccine regimens and efficacy for common viral infections [9,10,11,12,13].

Virus	Vaccine Type	Dose Schedule	Regimen Type	Vaccine Efficacy
Measles	Live-attenuated vaccine	Two doses, second dose at least one month after the first dose	Heterologous	One dose of MMR: 93% successful against measles, 97% successful against rubella, 78% successful against mumps Two doses of MMR: 97% successful against measles, 88% successful against mumps
Mumps	Live-attenuated vaccine	Two doses, second dose at least one month after the first dose	Heterologous	One dose of MMR: 93% successful against measles, 97% successful against rubella, 78% successful against mumps Two doses of MMR: 97% successful against measles, 88% successful against mumps
Rubella	Live-attenuated vaccine	Two doses, second dose at least one month after the first dose	Heterologous	One dose of MMR: 93% successful against measles, 97% successful against rubella, 78% successful against mumps Two doses of MMR: 97% successful against measles, 88% successful against mumps
HPV	Subunit vaccine	Two doses: second dose 6-12 months after first dose, Three doses: second dose 1-2 months after, third dose 6 months after	Homologous	HPV vaccine has a 97% rate in stopping cervical cancer from the HPV virus
Influenza	Viral vector vaccine	One dose each year	Heterologous	The influenza vaccine is 10%-60% effective
Polio	Inactivated vaccine	Four doses: one dose at 2 months old, second dose at 4 months old, third dose 6-18 months old, fourth dose at 4-6 years old	Homologous	Two doses of Polio are 90% effective, three doses are 99% effective
Ebola	Viral vector vaccine	Two doses: second dose 8 weeks later	Heterologous and Homologous	The Ebola vaccine is 70%-100% successful

4. Vaccinating against Covid-19

Currently, there are three approved vaccines targeting SARS-CoV-2 in the United States: two mRNA vaccine series, and one (single dose) protein-based vaccine. The mRNA vaccines, manufactured by Moderna or Pfizer-BioNTech, have an initial vaccination series consisting of a primary shot, a second dose 1-2 months later, and a booster 3-6 months following the second

shot [25]. Additional boosters have been approved for various populations at different dosage levels, and variant-specific vaccines are approved in ongoing clinical trials [35]. Both Moderna and Pfizer-BioNTech's initial homologous vaccine series were 95% effective in preventing earlier variants of Covid-19 [27].

In a study from the *National Library of Medicine* comparing homologous versus heterologous boosters in Covid-19, boosters heterologous to the initial dosage against the virus were more beneficial than homologous boosters [21]. Those immunized with a heterologous vaccine regimen—in this case, some combination of the Moderna, Pfizer, or Johnson & Johnson (which is a weakened, adenovirus virus vaccine rather than an mRNA vaccine [41]) booster series, all of which target the SARS-CoV-2 spike protein in slightly different ways—had a lower infection and disease rate than those immunized with the vaccines from the same manufacturer (homologous) [21]. All the heterologous testing groups were 100% seropositive at day 28 [21]. This suggests that heterologous booster regimens result in more antibody production against the target virus than homologous booster regimens [42].

More antibodies does not necessarily mean greater protection against infection; however, heterologous boosting also stimulated a stronger immune response and increased the amount of neutralizing antibody titers in the body [21]. While all antibodies bind to some component of a virus to alert the immune system to its presence, neutralizing antibodies are also capable of functionally inhibiting the target they bind to; they can therefore slow or stop pathogens from attacking healthy cells altogether to control the spread of the infection [22].

In a separate study from the *International Journal of Environmental Research and Public Health*, heterologous boosting was also found to result in higher vaccine efficacy than homologous boosting in terms of preventing infection (heterologous-96.10%,

homologous-84.00%), severe symptoms (heterologous-56.80%, homologous-17.30%), and hospitalization (heterologous- 97.40%, homologous-93.20%) [28]. In general, however, both types of booster regimens were effective and safe when it came to preventing Covid19 [28]. Interestingly, those immunized with heterologous booster shots reported more post-vaccination side effects, including higher fever, fatigue, and muscle pain when compared to those immunized with homologous boosters [28]. While these side effects are unpleasant, they are also indicative of a stronger adaptive immune response to immune challenge [36].

On a similar note, one study from the *New England Journal of Medicine* compared overall off-target effects of homologous versus heterologous boosters in Covid-19 vaccination [23]. Although the majority of people immunized with mRNA vaccines had no lasting side effects, it was found that both heterologous and homologous boosters resulted in similar levels of negative side effects post vaccination [23,24]. This suggests that heterologous and homologous boosters trigger around the same level of adverse effects after vaccination. Another study from *The Lancet* found that individuals administered the heterologous booster had a higher rate of off-target immunogenic effects than individuals administered the homologous booster. Heterologous boosters resulted in more post vaccination effects (17.9%) compared to homologous boosters (13.2%). Despite minimal adverse effects, both heterologous and homologous regimens were shown to be safe and effective against Covid-19 virus, and every approved vaccine regimen prevents hospitalization and severe effects during breakthrough infections. Overall, both heterologous and homologous boosters are safe and highly effective in preventing severe infection; heterologous vaccination appears to be slightly more protective at the expense of a slightly increased risk for (temporary) negative side effects than homologous regimens [37].

It is likely that a variant-specific booster against Covid-19 will become a part of standard health care practices similar to the yearly flu vaccine. The booster, like the yearly influenza vaccine, will target a specific strain of Covid due to the constantly mutating nature of coronaviruses. However, scientists have been trying to create a universal Covid-19 vaccine which could be effective against multiple strains of coronavirus. This vaccine will likely combine the chimeric spikes of different coronaviruses, which will increase the range of immunity upon vaccination. Nanoparticle vaccines, which target vulnerable regions of the viral spike protein, are also in development. Due to the viral mutation rate and the speed of mRNA vaccine development, however, future Covid-19 boosters and coronavirus vaccination will most likely be variant-specific mRNA vaccines [38].

5. Future outlook

Several studies have shown that heterologous vaccine booster regimens are more effective in preventing the spread of infection viruses like influenza and SARS-CoV-2 when compared to homologous booster regimens [21,28]. Heterologous boosting also results in higher vaccine efficacy than homologous boosting in preventing severe side effects and hospitalization for breakthrough SARS-CoV-2 cases [28]. This because the heterologous, varied antigens induce a stronger immune response than repeated exposure to identical homologous booster antigens, resulting in the production of more neutralizing antibodies against the virus and its mutant strains [21,22]. Although homologous boosting still has a high efficacy rate in the case of Covid19, heterologous booster regimens have been demonstrated to be more effective against newer strains [21,28].

There is evidence that heterologous have a greater potential for unfavorable vaccine side effects [28,37]. However, these side effects—fevers, chills, muscle aches, etc.—are generally temporary and non-life threatening, and are also indicative of a stronger immune response to the vaccine and more protection against real viral infection [36]. And despite temporary side effects, heterologous and homologous boosting are both safe and effective in preventing the severity and infection of Covid-19 [28].

With the advent of mRNA vaccines, the potential for rapid vaccine generation in response to constantly mutating viruses like SARS-CoV-2 has been greatly increased. Although research is ongoing, it is clear that all existing, FDA-approved heterologous and homologous vaccination regimens are safe and effective in preventing infection [28,38]. Heterologous boosters appear to have a higher efficacy at preventing severe symptoms and controlling the spread of infection when compared to homologous regimens and have been shown to induce greater amounts of neutralizing antibodies that slow pathogenic spread [21, 22, 28]. These data suggest that in the future, a yearly, strain-specific heterologous Covid-19 booster shot should (and likely will) become a part of standard healthcare practices.

6. Works Cited

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