Severe Acute Respiratory Syndrome Coronavirus 2 Vaccine Boosters: An Influenza Vaccine Perspective

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ABSTRACT Changes to severe acute respiratory syndrome 2 (SARS-CoV-2) vaccine guidance since their initial authorization may lead to confusion and hesitancy. Suggested recommendations for an annual SARS-CoV-2 vaccine naturally draw comparisons with the influenza vaccine program. Considering viral and vaccine characteristics between these pathogens provides an important perspective that can help increase vaccine confidence with SARS-CoV-2 vaccines.

Leaders from the U.S. FDA have recently advocated for an annual vaccine booster against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] The military population may be understandably confused as vaccination recommendations have been updated multiple times since messenger RNA (mRNA) vaccines were initially authorized by the FDA in December 2020; however, some understanding of mucosal viral pathogens and vaccine performance is an important perspective. Discussion regarding an annual or recurrent booster vaccine for SARS-CoV-2 naturally draws comparisons with influenza and its annual vaccine strategy, but differences between SARS-CoV-2 and influenza viruses and the vaccines used for each pathogen should be acknowledged that may provide increased confidence with coronavirus disease 2019 (COVID-19) vaccines.

The primary goal of all vaccines is to protect against severe disease and death. Despite waning immunity against infection secondary to decreasing titers of circulating neutralizing antibodies, COVID-19 vaccines have continued to demonstrate good protection against severe disease.[2] From multiple years of data, CDC estimates influenza vaccine effectiveness (VE) against severe disease at about 50% for adults aged 18-64 years,[3] whereas VE against severe disease for SARS-CoV-2 vaccines has consistently been higher.[2] The protection afforded by influenza vaccines has been utilized by the DoD for years. Influenza vaccine was first used across the military in the 1940s during World War II, and since the early 1950s, annual influenza vaccine requirements for all military personnel have been in place.[4]

Viral characteristics of SARS-CoV-2 and influenza prevent life-long sterilizing immunity and challenge vaccine efforts. Viruses that infect and replicate in the respiratory mucosa typically have shorter incubation periods. Additionally, antigen mutations and selection pressure help allow respiratory viral pathogens to evolve and evade neutralizing antibodies. Although high neutralizing antibodies can protect against infection, these antibody levels begin waning after 2-3 months. Memory T- and B-cells typically persist and play critical roles in protecting against severe disease, but reexposure to an antigen may take 3-5 days for these memory cells to respond. Thus, short incubation periods help viruses infect individuals despite prior immunity. The incubation period for influenza is 1-3 days,[5] whereas the median incubation period for SARS-CoV-2 is 4-5 days (although Omicron variants have possibly shorter median incubation periods of 3-4 days).[6] Increased incubating time allows memory cells to respond to an infection and prevent severe disease. Furthermore, severe COVID-19 with clinical deterioration typically occurs about 1 week after illness onset from SARS-CoV-2.[7] Comparatively, many hospitalizations secondary to influenza infection occur within the first week of symptoms.[8] For example, patients who develop viral pneumonia from influenza tend to deteriorate rapidly, within the first 3 days of sickness.[9]

SARS-CoV-2 vaccine characteristics also have advantages for protection against severe disease compared to influenza vaccines. For example, SARS-CoV-2 vaccines appear to generate stronger memory cell responses. High levels of bone marrow plasma cells (BMPCs) or memory B-cells are achieved after SARS-CoV-2 vaccination,[10,11] while BMPCs from influenza vaccination are short-lived and decline to near prevaccination levels within a year.[12] One strategy to induce memory cell immunity and increase antibody response with vaccines is the use of adjuvants. An adjuvant is a substance added to a vaccine to enhance the immune response and lower the quantity of antigen and the number of vaccine doses needed to provide protective immunity. No influenza vaccines approved in the United States for the military population contain adjuvants (Fluad contains an adjuvant but is approved for individuals aged $\geq$65 years in the United States).[13] Although mRNA SARS-CoV-2 vaccines do not contain classically recognized adjuvants, the lipid nanoparticles that encompass the mRNA and allow cellular entry have been shown to possess significant adjuvant activity.[14] A robust memory cell response and persistence is vital to sustaining protection against severe disease.

Decisions on future booster recommendations must continue to weigh risks and benefits. For example, the rates of

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severe adverse events for COVID-19 booster doses in a military population are a critical consideration (e.g., rates of myocarditis with additional COVID-19 vaccine doses). This risk/benefit balance may ultimately mean that the cadence of SARS-CoV-2 boosters could differ from influenza in either timing or age group recommendations, but at this time FDA regulators are targeting annual SARS-CoV-2 vaccine composition updates.[1]

Despite vaccine guidance after initial SARS-CoV-2 vaccine authorization changing multiple times and potentially causing confusion and hesitancy, many advantages are seen with vaccines against SARS-CoV-2 when compared to influenza. Viral and vaccine characteristics result in SARS-CoV-2 vaccines reaching higher protection against severe disease than traditional influenza vaccines, and these influenza vaccines have provided benefits to the U.S. military for decades. This is an important perspective that can help with vaccine confidence and booster uptake.

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CONFLICT OF INTEREST STATEMENT

None declared.

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