

COMMENTARY

What is the Definition of being Fully Vaccinated?

Should the Three-dose Vaccination with the mRNA Vaccines be the New Standard?

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Despite the availability of numerous clinically effective COVID-19 vaccines which have been approved and/or authorized for use in humans, mitigating morbidity and mortality associated with the exposure to or infection with SARS-CoV-2 virus remains an elusive global challenge. It is quite alarming that worldwide, over 5.2 million people have already died as a result of SARS-CoV-2 infection and over 8,000 continue to meet this tragic fate every day (1). In the US, over 790,000 have died as a result of COVID-19 and over 1,000 people are dying every day as a consequence of infection with SARS-CoV-2 (2).

In the US, three COVID-19 vaccines have been approved and/or authorized by the FDA and the CDC (Table 1). Using the currently recommended criteria, as of December 10, 2021, 60.5% (>200,000) of the U.S. population has been fully vaccinated (Table 1) and 71.5% have received at least one dose of the COVID-19 vaccine (2). It is perturbing that

multiple clinical studies have demonstrated the decline in vaccine protection against SARS-CoV-2 infection (3, 4). A large cohort study by Chemaitelly, *et.al.*, using subjects who received Pfizer vaccine showed that in the first two weeks after the first dose of the vaccine, vaccine effectiveness against the wild-type and any SARS-CoV-2 variant was undetectable (3). However, seven days later, it increased to 36.8%, peaking at 77.5% in the four weeks after the second dose. Interestingly, regardless of the age group, vaccine effectiveness against the wild-type SARS-CoV-2 and all its variants (including Delta) gradually decreased after one month, with the decline accelerating after month four, to only about 20% after five to six months following the second dose (3).

In Israel, Levin, *et.al.*, studied 4,868 vaccinated healthcare workers over the period of approximately six months (4). The subjects were tested monthly for anti-spike immunoglobulin G (IgG) and neutralizing antibodies against SARS-CoV-2. A

Table 1: FDA and CDC Approved and/or Authorized COVID-19 Vaccines in the United States

	Pfizer BioNTech (Comirnaty™)	Moderna	Jansen (Johnson and Johnson)
Type of Vaccine	mRNA	mRNA	Viral Vector
Primary Series of Immunization	Two (2) Doses 21 days apart	Two (2) Doses 28 days apart	One (1) Dose
Approved (age)	≥16 years	NO	NO
Authorized (age)	≥5 years	≥18 years	≥18 years
Booster or 3 rd Dose	≥16 years*	≥18 years*	≥18 years**
Current Definition of Fully Vaccinated	Two (2) weeks after 2 nd dose	Two (2) weeks after 2 nd dose	Two (2) weeks after 1 st dose

*At least six (6) months after completing the primary series of immunization

**At least two (2) months after receiving the first dose of the vaccine

very small cohort of healthcare workers (0.4%) were diagnosed as having a COVID-19 breakthrough infection. The mean IgG level during days four through 30 after two Pfizer vaccine doses was 29.3 as a sample-to-cutoff ratio. IgG concentrations fell substantially each month and had decreased by a factor of 18.3 after six months.

Similarly, neutralizing antibody titers dropped by a factor of 3.9 between the peak and the end of the study but declined more slowly from months 3 to 6. Expressed as a 50% neutralizing level, the mean concentration of neutralizing antibodies was 557.1 at the peak, decreasing to 119.4 by six months. Six months after the second dose, neutralizing antibody concentrations were much lower in men than in women (ratio of means [ROM], 0.64), those 65 years and older versus those 18 to 44 years (ROM, 0.58), and immunosuppressed vaccinees (ROM, 0.30). From the peak to the end of the study, substantially lower IgG levels were tied to older age, male sex, and the presence of at least two underlying chronic conditions (high blood pressure, diabetes, abnormal cholesterol levels, and heart, lung, kidney, or liver disease), autoimmune disease, and immunosuppression (4).

Given these clinical observations, the need for a booster dose of the COVID-19 vaccine was being seriously contemplated

by the scientists and the public policy experts. Israel was among the first country to initiate the booster dose of Pfizer vaccine for its citizens who were >60 years of age. Bar-On, *et al.*, evaluated over 1.1 million subjects over the age of 60 who had received the booster dose at least five months after completing the primary immunization with the Pfizer vaccine (5). Those who received the booster were approximately 19.5-fold less likely to develop severe COVID-19 as compared to a similar age-matched controls who had only received the two dose primary series of immunization. Interestingly, booster vaccination not only resulted in significant reduction in severe COVID-19, but also reduced (11.3-fold) SARS-CoV-2 infections (5). Similar results supporting the effectiveness of the third dose of the Pfizer vaccine in enhancing the protection against SARS-CoV-2 infections were also reported by Barda *et al.* (6).

Based on these and similar clinical observations which provided unequivocal evidence underscoring the effectiveness of a booster dose of COVID-19 vaccines in enhancing protection against SARS-CoV-2 infection, on August 12, 2021, FDA authorized a 3rd dose of Pfizer and/or Moderna vaccine for certain immunocompromised individuals (7). This authorization was limited to solid organ transplant recipients or those who are diagnosed with conditions that are considered

to have an equivalent level of immunocompromise. On November 19, 2021, CDC modified the authorization allowing booster dose for all adults ages 18 years and older who received a Pfizer-BioNTech or Moderna vaccine at least six months after their second dose (8). Emergency authorization for Pfizer-BioNTech COVID-19 Vaccine was further modified by the FDA on December 09, 2021, for the Pfizer-BioNTech COVID-19 vaccine allowing the use of a single booster dose for administration to individuals 16 and 17 years of age at least six months after completion of primary vaccination with the Pfizer-BioNTech COVID-19 vaccine (9).

The recent identification of Omicron (5.1.1.529) variant of SARS-CoV-2 from southern African nations and its rapid spread across the globe has alarmed the scientific community and the public health experts (10-12). This has also called to question the efficacy of the existing COVID-19 vaccines in affording protection against this variant. A team of scientists from the Africa Health Research Institute tested 14 plasma samples from 12 participants, with 6 having no previous history of SARS-CoV-2 infection and all were previously vaccinated with two doses of Pfizer/BioNTech vaccine (13). The results showed a 41-fold decline in antibodies generated by the Pfizer vaccine to neutralize the Omicron variant as compared to the Delta variant of SARS-CoV-2. Interestingly, antibodies in the blood from the six volunteers who had previous SARS-CoV-2 infection and were subsequently vaccinated were better able to neutralize the virus (13).

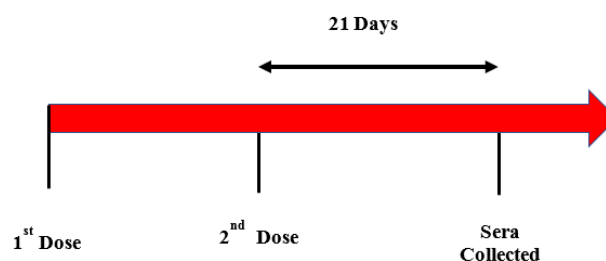
The possibility of immune evasion by the Omicron variant has also been predicted by artificial intelligence models that have been extensively validated (14). Based on 132 three-dimensional structures of antibody-receptor binding complexes, it was suggested that Omicron may be twice more likely to escape current vaccines as compared to the Delta variant. In an independent study, Pfizer has claimed that three doses of Pfizer-BioNTech COVID-19 vaccine (Group B, Figure 1) effectively neutralized the Omicron variant while two doses (Group A, Figure 1) showed significantly reduced neutralization titers (15). Additionally, the data also indicated that the third dose of the Pfizer/BioNTech COVID-19 vaccine increased the neutralizing antibody titers by 25-fold as compared to two doses against the Omicron variant.

From the foregoing scientific evidence, we conclude that to afford effective protection against various variants of the SARS-CoV-2, at a minimum three doses of Pfizer or Moderna and two doses of Jansen vaccine would be required. In fact, we had previously argued that the Pfizer/BioNTech or Moderna COVID-19 vaccines should have been authorized by the FDA as a three dose primary vaccination series. Likewise, we had also previously suggested that Jansen COVID-19 vaccine should have been a two dose primary vaccination series. **Considering the available data, we are also**

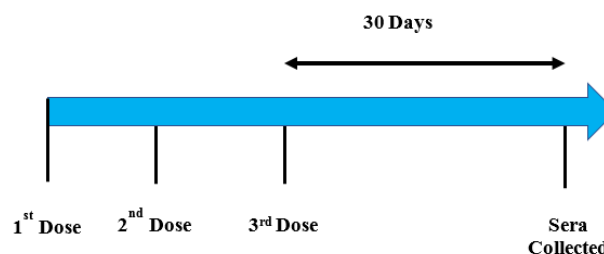
recommending that booster dose should be authorized for children 5-15 years of age ensuring that they are also protected against the SARS-CoV-2 variants. Lastly, we are also recommending that the definition of FULLY VACCINATED be revised to include three doses of Pfizer/BioNTech or Moderna and two doses of Jansen COVID-19 vaccines. It is not entirely inconceivable that in the very near future, we may require additional doses of COVID-19 vaccine that has been tailored to neutralize evolving SARS-CoV-2 variants.

Figure 1: Experimental design to determine the capacity of antibodies to neutralize Omicron (B.1.1.529) variant of SARS-CoV-2 in subjects vaccinated with two doses (Group A) or three doses (Group B) of Pfizer/BioNTech Vaccine

Group A:



Group B:



Disclosures

SR declares no conflicts of interest.

MS declares no conflicts of interest.

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