FDA Briefing Document
Vaccines and Related Biological Products Advisory Committee Meeting
April 6, 2022

Considerations for COVID-19 Vaccine Booster Doses and Process for COVID-19 Vaccine Strain Selection to Address Current and Emerging Variants

1. Meeting Objective

The ongoing COVID-19 pandemic continues to present an extraordinary challenge to global health, complicated by rapidly evolving epidemiology. While the development, authorization and deployment of safe and effective COVID-19 vaccines has been a critical component of the global response to the pandemic, uncertainties about the future course of the pandemic and a still incomplete understanding of SARS-CoV-2 immunology leave open scientific and policy questions regarding the optimal use and further development of COVID-19 vaccines. These questions include: what is the optimal strain composition for COVID-19 vaccines to address current and emerging SARS-CoV-2 variants; when and how frequently to consider strain composition changes; how to implement a formal process for COVID-19 vaccine strain selection; and what is the optimal timing for use of COVID-19 vaccine booster doses among the general population and among specific sub-populations. The purpose of today's VRBPAC meeting is to discuss a framework to address some of the challenges posed by these outstanding questions.

2. Background

2.1 SARS-CoV-2 Pandemic

The SARS-CoV-2 pandemic continues to present a challenge to global health and, as of March 25, 2022, has caused approximately 474.7 million cases of COVID-19, including 6.1 million deaths worldwide. In the United States (U.S.), more than 79.6 million cases and 972,000 deaths have been reported to the Centers for Disease Control and Prevention (CDC). In addition to case fatalities, COVID-19 has been responsible for significant short-term and long-term morbidity. Furthermore, the pandemic has caused significant challenges and disruptions in worldwide healthcare systems, economies, and many other aspects of human activity (e.g., travel, employment, and education).

Since the start of the pandemic caused by the original Wuhan strain of SARS-CoV-2, surges in SARS-CoV-2 activity and resultant COVID-19 cases, hospitalizations, and deaths have been associated with a combination of factors including but not limited to: emergence of variants with greater transmissibility; greater virulence, and/or antigenic mutations, enabling at least partial escape from immunity conferred by prior vaccination or infection; relaxation of public health measures aimed at preventing transmission; and seasonal variation typical of respiratory viruses. The most recent surge, both globally and in the U.S., was associated with rapid spread of the highly

transmissible Omicron (B.1.1.529) variant, which became the predominant variant circulating in the U.S. in December, 2021. While COVID-19 cases, hospitalizations, and deaths in the U.S. are now declining since the peak of the Omicron surge (CDC Data Tracker), an even more transmissible Omicron sublineage (BA.2) has been associated with recent increases in COVID-19 case rates in Europe and has been accounting for an increasing proportion of cases in the U.S. (CDC Variant Proportions).

2.2 COVID-19 Vaccines

Two COVID-19 vaccines (both based on an mRNA platform encoding the SARS-CoV-2 Spike (S) protein from the Wuhan strain with D614G mutation) have been approved by FDA for use as a 2-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2. Comirnaty (manufactured by Pfizer Inc. for BioNTech Manufacturing GmbH) is approved for use in individuals 16 years of age and older, and Spikevax (manufactured for Moderna US, Inc.) is approved for use in individuals 18 years of age and older. These two vaccines have also received emergency use authorization (EUA) for additional uses related to active immunization to prevent COVID-19 caused by SARS-CoV-2. The Pfizer-BioNTech COVID-19 Vaccine is authorized for use as a 2-dose primary series in individuals 5 years of age and older, as a third primary series dose in individuals 5 years of age and older with certain types of immunocompromise, as a first booster dose for use in individuals 12-17 years of age after completion of the primary series, as a first booster dose for use in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination), and as a second booster dose for use at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in individuals 50 years of age and older and individuals 12-49 years of age with certain types of immunocompromise. The Moderna COVID-19 Vaccine is authorized for use as a 2-dose primary series in individuals 18 years of age and older, as a third primary series dose in individuals 18 years of age and older with certain types of immunocompromise, as a first booster dose for use in individuals 18 years of age and older after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination), and as a second booster dose for use at least four months after a first booster dose of any authorized or approved COVID-19 vaccine in

individuals 50 years of age and older and individuals 18-49 years of age with certain types of immunocompromise.

In addition to the two authorized and approved mRNA COVID-19 vaccines, the Janssen COVID-19 Vaccine (based on a replication-deficient adenovirus type 26 vector platform encoding the SARS-CoV-2 S protein from the Wuhan strain with D614G mutation) is available under EUA for use in individuals 18 years of age and older as a single dose primary vaccination and as a first booster dose after completion of primary vaccination with any authorized or approved COVID-19 vaccine (with the same interval as authorized for a booster dose with the vaccine used for primary vaccination).

Other COVID-19 vaccines based on various platforms have been authorized or approved for use in other countries but are not authorized or approved for use in the U.S.. These include vaccines based on various adenovirus vector platforms, one adjuvanted protein subunit vaccine, and one inactivated whole virus vaccine (WHO Vaccine Tracker). Additional COVID-19 vaccine candidates based on various platforms are under development but not yet authorized or approved for use anywhere.

2.3 COVID-19 Vaccine Effectiveness

While the current authorized or approved COVID-19 vaccines in the U.S. are based on the original Wuhan strain, recently and currently circulating SARS-CoV-2 variants harbor mutations in the S protein that confer at least partial antigenic escape from vaccine-elicited immunity. Nonetheless, currently available vaccines have retained some level of effectiveness against all epidemiologically important SARS-CoV-2 variants that have emerged to date, with higher level effectiveness preserved against more serious outcomes (hospitalization and death) than against mild symptomatic disease (Tseng, et al, 2022; Andrews, et al, 2022; Taylor, et al, 2022; Korves, et al, 2022; Stowe, et al, 2022; Ferdinands, et al, 2022; Chemaitelly, et al, 2022; Tenforde, et al, 2022; Arbel, et al, 2022; Bar-On, et al, 2022; Gazit, et al, 2022).

Results from observational studies that have investigated the effectiveness of the primary vaccination series of authorized or approved vaccines have shown decreased effectiveness against

certain variants (notably Omicron, associated with lower neutralizing antibody titers vs. Wuhan strain) and waning effectiveness over time (Tseng, et al, 2022; Andrews, et al, 2022; Taylor, et al, 2022). Although first booster doses have restored waning vaccine effectiveness (VE), including against severe disease and hospitalization associated with Omicron (Tseng, et al, 2022; Andrews, et al, 2022; Taylor, et al, 2022; Korves, et al, 2022), observational studies have also indicated waning effectiveness of the first booster dose over time, mainly against mild disease, with some studies also suggesting waning effectiveness against hospitalization (Tseng, et al, 2022; Stowe, et al, 2022; Ferdinands, et al, 2022; Chemaitelly, et al, 2022) and lower effectiveness among the immunocompromised (Tenforde, et al, 2022). The Israeli experience with second booster dose of the Pfizer-BioNTech COVID-19 Vaccine in adults 60 years of age and older indicates that a second booster dose improves VE overall, including through a reduction in mortality (Arbel, et al, 2022; Bar-On, et al, 2022; Gazit, et al, 2022), although effectiveness against mild disease decreased during a 10-week follow-up period.

3. Considerations for Strain Composition of COVID-19 Vaccines

3.1 General Considerations

Currently authorized and approved COVID-19 vaccines are designed to elicit a protective immune response to the S protein from the SARS-CoV-2 virus that circulated early in the pandemic. Virus evolution, however, was apparent within months after the beginning of the pandemic (e.g., D614G) and has continued as the virus continues to adapt to the human host. Some of these genetic variants, classified as variants of interest (VOI) and variants of concern (VOC) (e.g., Delta and Omicron), have become dominant and have globally replaced prior strains of circulating SARS-CoV-2 (CDC Variant Proportions). New variants are often more infectious, transmissible, and antigenically distinct from earlier virus strains due to accumulated mutations in the S protein that also render them less susceptible to neutralization by antibodies elicited by current COVID-19 vaccines or prior infection by earlier strains of virus. Although a complete understanding of how emerging SARS-CoV-2 variants impact the effectiveness of current COVID-19 vaccines is lacking, the accumulating data suggest that the composition of vaccines may need to be updated at some point to ensure the high level of efficacy demonstrated in the early vaccine clinical trials. An orderly, logical, and transparent process should be delineated for making recommendations for possible changes in COVID-19 vaccine composition and will require the cooperation and collaboration of

vaccine manufacturers, vaccine regulators, and global public health laboratories. As described below, certain aspects of the process used for the annual updating of seasonal influenza vaccines may provide insights for how to consider updating the composition of COVID-19 vaccines.

Currently authorized and approved COVID-19 vaccines are monovalent formulations based on the S protein from a SARS-CoV-2 virus that circulated early in the pandemic. While modification of a monovalent COVID-19 vaccine to be more closely aligned to a specific variant may improve vaccine effectiveness against that variant, it is not known whether such modification might come at a cost of reduced breadth of coverage and potentially decreased effectiveness against variants that might emerge in the future. Depending on the evolution of the virus and the epidemiology of circulating variants, a multivalent vaccine based on S antigens from more than one SARS-CoV-2 variant may offer benefit over a monovalent vaccine. However, any decision about the benefit offered by a multivalent vaccine and the strains to be included in a multivalent vaccine would have to be data driven and include FDA authorization or approval of the vaccine prior to its deployment. Manufacturing issues related to the production and control of a multivalent vaccine would need to be addressed before authorization or approval.

3.2 Capability of Modeling to Predict Future Variants

Since a pandemic was declared on March 11, 2020, there has been an evolution of SARS-CoV-2 over time from the initial Wuhan strain into multiple different variants that have caused various waves of disease, most notably, among others: Alpha, Delta, and Omicron, including subvariants. Notably, as the Omicron variant demonstrated, evolution of SARS-CoV-2 is not necessarily linear. It appears that the virus can develop new mutations relatively rapidly, particularly in the setting of an immunocompromised host (Choi, et al, 2020). Some of these variants may be more transmissible, such as Omicron, whereas others may be more pathogenic, such as Delta. These features, combined with the large number of hosts infected, creates a situation in which it is quite difficult to accurately predict how the virus will evolve over time. Predictive modeling has been performed by various groups to try to assess the most likely driving mutational changes that may next occur (Maher, et al, 2022). However, such models are limited by the nature of the assumptions and the data input.

3.3 Need for Coordinated Strain Selection Process

The global nature of the crisis argues for a global response in terms of vaccines and vaccine composition. Ideally, when appropriate, any change in vaccine composition would be implemented broadly and coordinated by the World Health Organization (WHO) with national regulatory authorities. Further, most vaccine manufacturers supply vaccine to many parts of the world and producing different vaccine formulations of sufficient quantity to maintain an adequate supply would be difficult, if not impossible. Nevertheless, SARS-CoV-2 continues to evolve and spread in an unpredictable manner and there have already been examples of regional dominance of a variant virus that has not led to world-wide spread (e.g., Beta VOC). Careful consideration will need to be given before any change in vaccine composition is recommended and any such decision will need to be data driven and based on need, but it remains impossible to predict which virus variant will gain dominance in any particular region of the world and how long that variant will remain dominant. There is likely a practical limit as to how often vaccine composition changes can be implemented either regionally or globally, regardless of the vaccine platform.

3.4 Manufacturing Considerations

An authorized or approved COVID-19 vaccine (prototype vaccine) might be modified to cover new or additional SARS-CoV-2 variants (modified vaccine). The time to produce tens of millions to hundreds of millions of doses of a modified vaccine, whether monovalent, bivalent, or multivalent, must be accounted for in developing any plan for the deployment of modified vaccines, including not only decisions about strain composition but also the time to develop the necessary reagents, the time to manufacture the vaccine, and the time to formulate and fill the final vaccine product. This time may differ for different types of vaccines. Additionally, the experience of the manufacturer and the facility and its capacity can affect the time to manufacture the new vaccine.

3.5 Data to Support Authorization and Deployment of Modified COVID-19 Vaccines

FDA considers experience to date with COVID-19 vaccines insufficient to support authorization or approval of a modified vaccine based on manufacturing information alone. Therefore, in addition to data to support manufacturing consistency, authorization or approval of the modified vaccine would require clinical data to support its safety and effectiveness, which could be derived

from immunogenicity and safety studies. These data would not only need to support the effectiveness of the modified vaccine against clinically relevant SARS-CoV-2 variants but also would also need to provide a clear basis for deploying the modified vaccine in lieu of the prototype vaccine. Considerations for manufacturing, as well as nonclinical, and clinical data to support EUA of modified COVID-19 vaccines are described in detail in the FDA Guidance for Industry, Emergency Use Authorization for Vaccines to Prevent COVID-19 (See Appendix 2: Evaluation of Vaccines to Address Emerging SARS-CoV-2 Variants). It is possible that with additional experience manufacturing and evaluating modified vaccines, future changes to COVID-19 vaccine strain composition could eventually be implemented without the need for clinical data, similar to the annual strain selection process for seasonal influenza vaccines (see Section 4 below).

4. Seasonal Influenza Vaccine Strain Selection Process

As noted above, there is a well-defined process for the annual updating of seasonal influenza vaccines. While influenza and coronaviruses are different viruses and will undoubtedly evolve and behave differently in the human population, the process for updating influenza vaccine composition may provide some useful guidelines and considerations for possible updating of COVID-19 vaccine composition. The following is a brief review of the current influenza strain selection process.

4.1 Role of WHO in influenza vaccine strain recommendation

Global influenza virus surveillance has been conducted through the WHO's Global Influenza Surveillance and Response System (GISRS) since 1952. Twice a year, WHO organizes an invitation-only consultation with experts to analyze virus surveillance data generated by GISRS and to make recommendations for the composition of influenza virus vaccines.

Participants include representatives from 1) WHO Collaborating Centers (CC) for influenza, 2) WHO Essential Regulatory Laboratories (ERL), 3) WHO H5 Reference Laboratories, 4) National Influenza Centers (NIC), 5) WHO Collaborating Center for Modeling, Evolution, and Control of Emerging Infectious Diseases, and 6) OIE/FAO network (animal influenza experts).

The data analyzed include: 1) genetic characteristics of circulating seasonal influenza viruses, 2) epidemiology of circulating viruses, and 3) antigenic characteristics of circulating viruses. Genetic characterization and epidemiology are supported by a large database of virus sequences generated by WHO CCs and NIC (e.g., CDC sequences all virus isolates that are submitted to the Agency). Extensive antigenic characterization is achieved using animal sera data from virus infected ferrets with a combination of hemagglutination inhibition (extensive) and neutralization assays (more limited) to distinguish circulating strains from each other and from strains in the most recent vaccine. Additional antigenic characterization data are obtained using the same types of assays (HI and neutralization), to test human sera from recent vaccinees against a selected subset of circulating viruses. In considering the composition of influenza vaccines for the next influenza season, the committee focuses on a core group of questions that must be addressed each year:

- Are new (drifted or shifted) influenza viruses present?
- Are these new viruses spreading in people?
- Do current vaccines provide protection against the new viruses?
- Can new vaccines be manufactured in time to affect disease caused by new viruses?

Following review and analysis of the available data, the consultation makes recommendations on the composition of influenza vaccine to be manufactured and deployed approximately 5-6 months (Northern hemisphere) or 3-4 months (Southern hemisphere) later. Recommendations are published and accompanied by the usual note: "National or regional authorities approve the composition and formulation of vaccines used in each country."

4.2 Role of FDA and VRBPAC in influenza vaccine strain recommendation

Approximately one week after each WHO consultation on strain composition of influenza vaccines, FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) to make recommendations for the composition of influenza vaccine to be manufactured and deployed in the U.S. The vaccine strain decision of the FDA, taken with VRBPAC input, serves to standardize the composition of all influenza vaccines in the U.S. each season (Weir and Gruber, 2016).

Presentations at the VRBPAC influenza strain selection meeting include a summary of global influenza virus surveillance and characterization from the recent WHO consultation. In addition, the CDC presents data from virus surveillance in the U.S. and any available data on effectiveness of the most recent influenza vaccines, and the Department of Defense presents their own surveillance data and vaccine effectiveness data from military outposts around the world (a population with high influenza vaccine coverage). Finally, FDA and influenza vaccine manufacturers present on some of the practical aspects of updating influenza vaccines, e.g., availability of key reagents and any issues that manufacturers have with working with new vaccine strains and the effect on production timelines.

Following review and analysis of the presented data, the VRBPAC votes on the strains to be included in influenza vaccines for the U.S. Although the discussion and voting starts with the WHO recommended strains as the default placeholder, the Committee is not bound by those recommendations and may suggest an alternative strain composition for the U.S. Differences between the WHO-recommended strain composition and that approved by individual national regulatory authorities does occasionally happen, although this possibility is extremely unlikely for the U.S. Following the VRBPAC recommendations and FDA decision on strain composition, manufacturers submit a supplement to their license that includes seed information and updated labeling. Once the strain change supplement is approved manufacturing begins, and formulated vaccine bulks are submitted to the Center for Biologics Evaluation and Research for release.

5. Considerations for Adaptation of a Seasonal Influenza Vaccine Strain Selection Approach to COVID-19 Vaccines

The strain selection process for determining the composition of seasonal influenza vaccines may provide a general outline for the approach needed for updating the composition of COVID-19 vaccines to address current and emerging SARS-CoV-2 variants. Nevertheless, unique issues for COVID-19 vaccines will need to be addressed in formulating a rational selection process that is applicable to decisions on the composition of COVID-19 vaccines.

5.1 Key Factors Underlying the Seasonal Influenza Vaccine Strain Selection Process that may be Different for COVID-19 Vaccines

The influenza strain selection process has been remarkably successful in maintaining the effectiveness and availability of seasonal influenza vaccines in spite of the constant antigenic drift of the influenza virus hemagglutinin and neuraminidase glycoproteins that form the basis of most current vaccines and the long manufacturing timelines involved in updating the vaccine. Several factors are key to a successful update of the influenza vaccine composition, and some of these may be different for a COVID-19 vaccine composition update and will need to be taken into consideration before such a recommendation is made. First, in the absence of a major antigenic shift such as the 2019 H1N1 pandemic, a predictable winter seasonality for influenza in both Northern and Southern hemispheres allows time for vaccine composition recommendations to be implemented by vaccine manufacturers. At this time, a predictable pattern for a SARS-CoV-2 surge of infection has yet to emerge; for example, Delta and Omicron virus surges in the U.S. were separated by only about 5 months (August 2021 to January 2022). Second, most licensed influenza vaccines are of similar platforms, and the challenges to updating influenza vaccines in a timely manner are similar for all influenza vaccine manufacturers. It is not clear whether the various platforms used for authorized and approved COVID-19 vaccines can accommodate an updated composition in similar timeframes. Third, animal sera data and *in vitro* assays reliably distinguish antigenically different influenza viruses, and in general, antigenic differences among influenza viruses predict differences in immunogenicity and corresponding clinical responses to vaccines. Even for influenza viruses, genetic data are not as predictive as antigenic data for distinguishing differences in immunogenicity and clinical responses to vaccines. However, because of the predictive power of in vitro antigenic data and the extensive manufacturing experience of manufacturers, new clinical data are not required for an updated influenza vaccine. As noted above, the accumulated experience to date with COVID-19 vaccines is insufficient to support authorization or approval of a modified vaccine based on manufacturing information alone, and clinical immunogenicity and safety data would still be needed.

While the process for updating the composition of influenza vaccines is routine, the effectiveness estimates for even well-matched influenza vaccines are only approximately 60% for the overall population. When seasonal influenza vaccines are poorly matched with circulating strains of influenza virus, vaccine effectiveness is substantially reduced, particularly in more susceptible populations such as the elderly. The most common reasons for a poorly matched influenza vaccine

have relevance for COVID-19 vaccine composition recommendations. For example, in some years, antigenically distinct influenza viruses emerge after recommendations have been made, and these viruses either co-circulate or dominate over recommended vaccine viruses. The emerging influenza virus may have been undetected at the time of vaccine composition recommendation, or it may have been one of many co-circulating virus variants at that time. The pattern of SARS-CoV-2 variant evolution and dominance is just as uncertain as that for influenza. Mismatches between influenza vaccines and circulating influenza strains are sometimes due to manufacturing issues that cannot be resolved in timely manner and that preclude production of a well-matched vaccine. For example, an optimally matched influenza candidate vaccine strain may not be available in time for manufacturers to employ in the production process, and sometimes there are unavoidable antigenic changes to the vaccine that are platform specific (e.g., egg adaptation of vaccine viruses). While these manufacturing issues are influenza specific, they emphasize the importance of considering manufacturing concerns when any change in COVID-19 vaccine composition is considered.

5.2 Role of WHO in COVID-19 Vaccine Strain Recommendation

WHO has established the Technical Advisory Group on COVID-19 Vaccine Composition (TAG-CO-VAC) to review and assess the public health implications of emerging SARS-CoV-2 VOC on the performance of COVID-19 vaccines and to provide recommendations to WHO on COVID-19 vaccine composition. The TAG-CO-VAC has highlighted the need for the development of vaccines that provide protection against infection and prevent transmission and identified key issues that will be important in any decision on COVID-19 vaccine composition. Many of these issues identified by the TAG-CO-VAC are similar to those noted above, but the WHO advisory group also notes the different levels of population immunity among countries due to different patterns of virus variant circulation and different states of vaccine uptake. The TAG-CO-VAC intends to issue more specific advice to WHO on adjustments needed to COVID-19 vaccine strain composition as additional data on vaccine performance and virus epidemiology becomes available. It is not yet clear how often such assessments of vaccine composition will be undertaken, and it is possible that individual countries may have different considerations for changing the composition of COVID-19 vaccines than WHO. The TAG-CO-VAC notes that they recognize "the independent

role and procedures of relevant regulatory authorities in establishing the necessary requirements for evaluation under the currently established regulatory pathways."

5.3 Role of FDA and VRBPAC in COVID-19 Vaccine Strain Recommendation

A decision and input from the FDA would be important to standardize the strain composition of all COVID-19 vaccines in the U.S., and the FDA would likely seek the advice of the VRBPAC in making recommendations to change the strain composition of authorized COVID-19 vaccines. The current influenza strain change process could serve as a general framework for the process of updating the composition of authorized COVID-19 vaccines in the U.S. Similar to the influenza strain selection process, following a recommendation from the WHO to update the composition of COVID-19 vaccines, the data that supported the WHO decision, along with epidemiological data pertinent for the U.S. and relevant immunogenicity and effectiveness results from manufacturers studies would likely be presented to the VRBPAC for discussion and a possible recommendation for authorized COVID-19 vaccines in the U.S. Under the current circumstances of the COVID-19 EUA declaration, and until additional experience accumulates with COVID-19 vaccine strain composition changes, FDA decisions on such changes would likely result in modified vaccines being made available (at least initially) under EUA, with licensure to potentially follow later.

At this time, it is not clear if or when the epidemiology of SARS-CoV-2 will fall into a pattern that will make a global recommendation for an updated COVID-19 vaccine composition obvious or needed. Neither is it clear that in the near future most areas of the world will be at the same level of vaccination status or have available the same types and quantities of vaccines. With these two uncertainties taken together, the FDA and VRBPAC may need to consider at some point a change in COVID-19 strain composition for U.S. vaccines without a prior WHO strain recommendation when 1) sufficient virus genetic data and epidemiology data are available to suggest the need for a better matched vaccine, 2) substantial evidence exists to determine that a new variant vaccine will provide a significantly better outcome than current vaccines, and 3) manufacturers have the ability and capacity to produce new variant vaccines in sufficient quantities for use in the U.S.

6. Strategic Considerations for Optimal Use of Additional COVID-19 Vaccine Booster Doses

The COVID-19 pandemic has exacted great individual, societal, and economic costs on the entire population of the U.S., and for that matter, the world. Among the most striking, however, is the number of deaths in older people, with COVID-19 having taken the lives of about 1 in 100 individuals age 65 and above in the U.S.. Acknowledging that, children and adults across the age spectrum have also suffered significantly in terms of hospitalization and death.

The administration of additional booster doses to those previously vaccinated should optimally prevent hospitalization and death in those at greatest risk and should aim to provide protection against existing or emerging COVID-19 variant(s) that may circulate during a future period (e.g., during the respiratory virus season from Fall 2022 through Winter 2023 season, or at least a significant portion thereof). Another potential benefit that would be desirable is the prevention of symptomatic disease, which can be associated with the development of Post-Acute Sequelae of SARS-CoV-2 Infection (PASC) (Nalbandian, et al, 2021). Although a reduction in asymptomatic disease transmission would also be desirable, the current generation of COVID-19 vaccines appear to be only partially effective in this regard (CDC Vaccine Effectiveness). Any of these benefits of a potential future booster campaign in a portion of or the entire population must be tempered against the potential associated risks (adverse events) and costs. The benefit and risk considerations for an additional booster campaign will need to be accounted for across different age groups based upon the best available data at the time a decision is made to proceed. In some populations, such as younger and healthier individuals, protection against serious disease from known variants is of sufficient duration that additional protection against milder forms of disease must be balanced against the risk of uncommon serious adverse events such as myocarditis. Alternatively, the potential benefits of the generation of a broader immune response that may address emerging variants across the entire population may be determined to outweigh known and potential risks.

The optimal selection of vaccine composition is important. Unnecessarily changing the vaccine composition could have adverse operational consequences, and novel monovalent, bivalent, or multivalent vaccines may be associated with new concerns regarding safety or effectiveness. Additionally, because of the advance preparation necessary (noted in Section 3.4 above), the planning for any such booster campaign would need to account for contingency plans should a

new SARS-CoV-2 variant emerge that largely or completely escapes the protection provided by the vaccines that are intended to be deployed have already been deployed.

Recommendations for an additional vaccine booster dose will also raise the question of when the next booster dose might be needed. The answer to that question may depend on a combination of factors, including data that will emerge over the coming months on the duration of protection in individuals who have received a first and/or second booster vaccination and the evolving epidemiology of circulating SARS-CoV-2 variant(s). Additionally, practical operational considerations will need to be taken into account, such as how a booster vaccine can most efficiently be deployed to all those for whom it is intended. In this regard, there may be some benefit to concomitant COVID-19 vaccine booster administration at the time of the annual influenza vaccine campaign. However, whether such a plan would provide for the optimal timing of either of these vaccines would need to be carefully considered.

7. Topics for VRBPAC Discussion

The April 6th VRBPAC meeting will consider questions around the process for determining the strain composition of COVID-19 vaccines and considerations for optimal use of additional COVID-19 vaccine booster doses. The committee will be asked to discuss the role of the FDA and VRBPAC in deciding the composition of COVID-19 vaccines for the U.S. and to discuss the situations and conditions that would indicate that an updated vaccine composition is needed. In addition, the committee will be asked to discuss the data and information needed to make such a recommendation, whether and how such a recommendation might be applied to all authorized or approved vaccines, and how often COVID-19 vaccine composition should be reviewed. Considering that FDA currently requires clinical data (safety and immunogenicity) to support authorization of modified COVID-19 vaccines, the committee will also be asked to discuss what experience and data might allow for an transition toward an approach where strain modifications could be supported by manufacturing information alone (e.g., similar to the current process for seasonal influenza vaccines). Finally, the committee will be asked to discuss the timing and populations for use of additional COVID-19 booster doses, considering current knowledge and uncertainties about COVID-19 epidemiology and vaccine effectiveness, as well as practical aspects and goals of public health vaccination programs.

8. References

1. Tseng HF, Ackerson BK, Luo Y, et al. Accepted, Nature Medicine. Effectiveness of mRNA-1273 against SARS-CoV-2 Omicron and Delta variants. Nature Medicine, 2022. https://doi.org/10.1038/s41591-022-01753-y.

2. Andrews N, Stowe J, Kirsebom F, et al. NEJM 2022. DOI: 10.1056/NEJMoa2119451

3. Taylor CA, Whitaker M, Anglin O, et al. COVID-19–Associated Hospitalizations Among Adults During SARS-CoV-2 Delta and Omicron Variant Predominance, by Race/Ethnicity and Vaccination Status — COVID-NET, 14 States, July 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:466–473. DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7112e2.htm.

4. Korves C, Izurieta HS, Smith J, Zwain GM, Powell EI, Balajee A, Ryder K, Young-Xu Y. Relative effectiveness of booster vs. 2-dose mRNA Covid-19 vaccination in the Veterans Health Administration: Self-controlled risk interval analysis. medRxiv 2022.03.17.22272555; Preprint. DOI: https://doi.org/10.1101/2022.03.17.22272555.

5. Stowe J, Andrews N, Kirsebom F et al. Effectiveness of COVID-19 vaccines against Omicron and Delta hospitalisation: test negative case-control study. Preprint. (https://khub.net/documents/135939561/430986542/Effectiveness+of+COVID-19+vaccines+against+Omicron+and+Delta+hospitalisation+-+test+negative+case-control+study.pdf/d0e803c0-3dd2-0c1b-03b8-0a12fd211980)

6. Ferdinands JM, Rao S, Dixon BE, et al. Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022. MMWR Morb Mortal Wkly Rep 2022;71:255–263. DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7107e2.htm.

7. Chemaitelly H, Hussein H, Ayoub H, et al. Duration of mRNA vaccine protection against SARS-CoV-2 Omicron BA.1 and BA.2 subvariants in Qatar. medRxiv 2022.03.13.22272308; doi: https://doi.org/10.1101/2022.03.13.22272308. Preprint.

8. Tenforde MW, Patel MM, Gaglani M, et al. Effectiveness of a Third Dose of Pfizer-BioNTech and Moderna Vaccines in Preventing COVID-19 Hospitalization Among Immunocompetent and Immunocompromised Adults — United States, August–December

2021. MMWR Morb Mortal Wkly Rep 2022; 71:118–124. DOI: https://www.cdc.gov/mmwr/volumes/71/wr/mm7104a2.htm.

9. Arbel R, Sergienko R, Friger M, et al: BNT162b2 vaccine booster and mortality due to COVId-19. N Engl J Med 2021; 385:2413-2420.DOI: 10.1056/NEJMoa2115624.

10. Bar-On YM, Goldberg Y, Mandel M, et al. Protection by 4th dose of BNT162b2 against Omicron in Israel. medRxiv, February 1, 2022; doi: https://doi.org/10.1101/2022.02.01.22270232. Preprint.

11. Gazit S, Saciuk Y, Perez G, et al. Relative Effectiveness of Four Doses Compared to Three Dose of the BNT162b2 Vaccine in Israel. medRxiv 2022.03.24.22272835; doi: https://doi.org/10.1101/2022.03.24.22272835. Preprint.

12. Choi B, Qui X, Solomon IH, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. N Engl J Med. 2020; 383:2291-2293.

13. Maher MC, Bartha I, Weaver S, et al. Predicting the mutational drivers of future SARS-CoV-2 variants of concern. Science Transl Med. 2022, DOI: 10.1126/scitranslmed.abk3445

14. Weir JP, Gruber MF. An overview of the regulation of influenza vaccines in the United States. Influenza Other Respir Viruses. 2016; 10:354-60.

15. Nalbandian, A., Sehgal, K., Gupta, A. et al. Post-acute COVID-19 syndrome. Nat Med 2021; 27: 601–615. https://doi.org/10.1038/s41591-021-01283-z.