Vaccines and Related Biological Products Advisory Committee Meeting
January 26, 2023
FDA Briefing Document
Future Vaccination Regimens Addressing COVID-19

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Capsule

This document contains my annotations to FDA's briefing document release prior to the January 26th 2023 VRBPAC meeting on the subject of future strain composition for Covid-19 vaccines, simplification of the different formulations and dose schedules, and plans for future COVID-19 vaccine composition recommendations.

FDA's justification for the use of current Wuhan/BA.5 bivalent vaccines as primary doses, comes from weak data. Most studies were performed before or during the era of the BA.5 strain, which is almost extinct. A number of studies cited by FDA point out the reduced antibody response to the now predominant BQ and XBB variants. Several important studies are missing from the discussion that highlight how futile the use of the current bivalent variant is likely to be. VRBPAC member Dr. Paul Offit has stated *"chasing these Omicron variants with a bivalent vaccine is a losing game"* (cited in Time Magazine).

This the current bivalent Covid-19 vaccines are obsolete.

The document is also at odds with the comments made by FDA's Dr. Peter Marks in JAMA (1):
"Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally."

FDA policy remains focused on the spike protein, known to be toxic. No discussion of alternate targets is provided and no acknowledgement that the bivalent vaccines may give rise to at least four heterotrimers, at least two of which represent novel pharmacology and likely toxicology.

FDA makes no note of the continued absence of an immune correlate of protection,. And continues to rely on neutralizing antibody studies. FDA appears to intend to not require extensive safety and efficacy testing for new variant vaccine versions.

There is no discussion of safety, or safety signals, as we have provided in various submissions to FDA (2-7) or CDC.(5,7-13). There is no discussion of the concerning safety signals evident in the recent FOIA disclosure of PRR signals from CDC.

These vaccines remain experimental. There is no discussion of the consequences of repeated dosing of these genetic vaccines, nor is there discussion related to the long-term consequences of these genetic vaccines and the failure of FDA to publicly involve the sections within FDA responsible for gene therapies. Long overdue studies on cancer, genotoxicity, sub-clinical myocarditis are not discussed.

It is unclear whether FDA intends to authorize only a two dose primary series for the Pfizer 6 month to 4 years vaccine, despite the paucity of data for the original strain version necessitating a three dos series.

There are a number of welcome acknowledgements from FDA related to: the reduction of dosing errors by reducing the confusing array of different formulations, doses and schedules; the acknowledgement of natural immunity in place of vaccination; the limitations in the reliability of some of the data used.

Comparisons with policies regarding influenza vaccination should be made carefully, to avoid the impression that the Covid-19 genetic vaccines are similar in mechanism of action to classical vaccines such as those used for influenza.

There is no indication on how this discussion affects future plans for the Novavax and J&J vaccines.

Acknowledgements: I am grateful to a number of colleagues with whom I have collaborated and whose work is cited herein and referenced as “we.”

Table of Contents (Original page number)

ORIGINAL DOCUMENT	COMMENTS
PAGE 3 **1. Executive summary** The ongoing COVID-19 pandemic continues to present an extraordinary challenge to global health, complicated by rapidly evolving epidemiology. The complexities associated with the differences in composition and regimens of the currently authorized and approved COVID-19 vaccines in the United States (U.S.), the still incomplete understanding of SARS-CoV-2 immunology, and the absence of an established framework to inform periodic vaccine composition updates, leave open scientific and policy questions regarding recommendations for simplifying the immunization schedule and updating the current COVID-19 vaccines for future vaccination campaigns. The January 26th Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting will consider questions around simplifying the composition and immunization schedules of the authorized and approved COVID-19 vaccines, the process for determining the need for recommending a periodic update to COVID-19 vaccines, and the timing for implementation of such an update. The VRBPAC met on April 6 and June 28, 2022, to discuss the framework for updated vaccine composition and the strain composition for the fall 2022 COVID-19 vaccine, respectively. Based on emerging clinical data, there was a preference for a bivalent vaccine booster that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as the future circulating strains were unknown at that point. Based on the totality of the evidence, on June 30, 2022, FDA notified COVID-19 vaccine manufacturers of its recommendation to develop a bivalent vaccine (original and Omicron BA.4/BA.5) as a booster dose to improve protection during the fall 2022 booster vaccination campaign. There are currently four authorized or approved monovalent COVID-19 vaccines in the U.S.: Spikevax (COVID-19 Vaccine, mRNA) referred to as Moderna COVID-19 Vaccine under Emergency Use Authorization (EUA), manufactured by ModernaTX; Comirnaty (COVID-19 Vaccine, mRNA), referred to as Pfizer-BioNTech COVID-19 Vaccine under the EUA manufactured by Pfizer Inc. and BioNTech; the Janssen COVID-19 Vaccine, which is a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain manufactured by Janssen Biotech, Inc.; and the Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant manufactured by Novavax, Inc. Both Spikevax and Comirnaty contain a nucleoside-modified messenger RNA (mRNA) encoding the Spike (S) protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Only the two mRNA vaccines	**In the absence of seasonality, attempts to update vaccines in a flu-like manner are futile.** **There is currently a confusing array of doses by primary vs. boosting series, monovalent vs. bivalent** **The data was at best weak and based on original/BA.1 bivalent data.** **Only limited animal data were shown. VRBPAC did not vote to authorize the bivalent BA.4/5, merely to recommend that manufacturers go ahead and make them,** **The campaign based was on unvalidated modeling.** **Based on comments made by Moderna at the Sept 1 2022 ACIP meeting, the term "bivalent" is misleading as novel**

were ultimately updated to have a bivalent composition (original and Omicron BA.4/BA.5) and authorized as a booster: Pfizer-BioNTech COVID-19 Vaccine, Bivalent; and Moderna COVID-19 Vaccine, Bivalent. Pfizer-BioNTech COVID-19 Vaccine, Bivalent was also authorized as a third dose in the 3-dose primary series in individuals 6 months to 4 years of age.

The SARS-CoV-2 Omicron (B.1.1.529 lineage) variant of concern (VOC) emerged in late 2021 and rapidly became the dominant circulating SARS-CoV-2 virus throughout the world, replacing earlier strains of SARS-CoV-2 (e.g., Wuhan) and the previously designated VOCs (e.g., Alpha, Beta, Gamma, and Delta). Omicron has continued to evolve into sub lineages with additional amino acid mutations in the spike glycoprotein and the receptor binding domain (RBD), the predominant target of neutralizing antibodies elicited by infection and vaccination. The distribution of Omicron sub lineages varies at different points in time in different regions of the world.

heterotrimers are formed in vivo, leading to the possibility of at least four types of spike protein.
The 3-dose Pfizer regime was only regime because the two dose regime had failed (with the 3-dose data not being much better) See our comment at June 23 2022 ACIP (14)

As of 1/21/23 according to CDC Nowcast, the proportions are:

XBB.1.5	**49.1%**
BQ.1.1	**26.9%**
XBB	**3.3%**
BA.5	**2.0%**
BA.4	**0%**
Wuhan	**Not listed**

https://covid.cdc.gov/covid-data-tracker/#variant-proportions

PAGE 4

More recently, even as Omicron sublineage BQ.1.1 became the dominant virus strain in the U.S., infections with the XBB and XBB.1.5 sublineages also began to increase, rising from about 7% to >30% of characterized viruses during December 2022. The XBB sublineage viruses are derived from a recombination of Omicron BA.2.10.1 and BA.2.75 sublineages, with a breakpoint in the S1 region of the spike gene and contains parts of spike protein from each virus parent. The large number of mutations in the Omicron variant sublineages, and the continuing evolution of the virus, remains a concern for potential evasion of vaccine-induced immunity.

The proportions of BA.4/5 and Wuhan, render the bivalents obsolete especially given the significant escape of XBB1.5 and BQ.1.1

Multiple studies describe neutralizing antibody responses to the currently available authorized bivalent mRNA vaccines administered as boosters. Interpreting the data from these studies is complicated because of the limited sample size, the variability in the assays used and the status of assay qualification, the populations tested, and the intervals between vaccination and serum collection. In summary, however, both of the bivalent mRNA vaccines have been demonstrated to produce improved neutralizing antibody responses to the BA.5, BQ.1.1, and XBB variants as compared to the original vaccines (encoding S protein from the original strain of SARS-CoV-2) while maintaining excellent neutralizing capability against the original strain.

This is quite an admission from FDA attesting to the low reliability of these studies. Most importantly is the fact that while these assays continue to be used, there remains no validated immune correlate of protection. See especially question by Dr Ofer Levy at June 28 VRBPAC and response from FDA's Dr. Marks.
[LINK]

Recently, clinical effectiveness data have been reported from several sources. Although there are limitations specific to each of these effectiveness assessments, these data provide preliminary real-world evidence that support the use of the bivalent mRNA boosters. Although the beneficial effect associated with a reduction in hospitalization and death in these studies is most apparent in older individuals, younger individuals appear to also benefit with a reduction in symptomatic disease and health care utilization. Though perhaps not identical, this pattern of response

[LINK] The main limitation is that these studies only examine effectiveness in the era of BA.5 which is now almost extinct.

The vaccines are not authorized for this indication, they are indicated for "active immunization to prevent

is analogous to that observed with annual influenza vaccination, a well-accepted intervention in individuals 6 months of age and older.	**coronavirus disease 2019 (COVID-19) caused by […] SARS-CoV-2"**
Although the use of the bivalent mRNA boosters is supported by the available evidence, their deployment has been associated with significant implementation complexities. Given these complexities, and the available data, a move to a single vaccine composition for primary and booster vaccinations should be considered. This simplification of vaccine composition should reduce complexity, decrease vaccine administration errors due to the complexity of the number of different vial presentations, and potentially increase vaccine compliance by allowing clearer communication.	**This appears to be an attempt to make the Covid-19 vaccines a "normal" part of life, just like flu vaccine.** **Use for what? Wuhan and BA.5 are irrelevant.** **This is a welcome admission on the part of FDA. This problem, along with labelling errors was flagged in several ACIP meetings in the summer of 2022, eliciting the comment from one member to the effect of the manufacturers needing to get their act together.**
Given the evolution of SARS-CoV-2 variants and associated changes in the epidemiology, susceptibility to reinfection, and waning of vaccine-induced immunity, barring development of a significantly improved vaccine, periodic future updates to the S protein sequence(s) contained or encoded in COVID-19 vaccines and revaccination will likely be needed to induce and maintain vaccine effectiveness (VE), respectively. Therefore, an approach to both simplifying the immunization schedule, and periodically updating the composition of COVID-19 vaccines as needed, requires consideration.	**This conflicts with FDA's Dr. Peter Marks in JAMA Dec 2022: (1)** ***"Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally."***
Review of the totality of the available evidence on prior exposure to and vaccination against SARS-CoV-2 suggests that, moving forward, most individuals may only need to receive one dose of an approved or authorized COVID-19 vaccine to restore protective immunity for a period of time. Two doses of an approved or authorized COVID-19 vaccine may be needed to induce the expected protective immunity for those who have a low likelihood of prior exposure (the very young) or those who may not generate a protective immune response (older and immunocompromised individuals).	**See also Dr. Paul Offit in NEJM Jan 11 2023 (15)** ***"chasing these Omicron variants with a bivalent vaccine is a losing game"*** **(cited in Time Magazine).** **time.com/6246525/bivalent-booster-not-very-effective-paul-offit/**
PAGE 5 Similar to the approach with influenza, the global nature of SARS-CoV-2 strain evolution warrants a global response when evaluating and recommending vaccine strain composition changes. Ideally, any change in vaccine composition, when appropriate, would be implemented broadly and would be coordinated by the World Health Organization (WHO) with national regulatory authorities. However, unlike influenza, a well-established, highly coordinated infrastructure and governance of global semi-annual vaccine composition evaluation and recommendations do not currently exist for SARS-CoV-2. Furthermore, at this time the current diversity of vaccine manufacturers and complexities in global supply of COVID-19 vaccines would make a globally coordinated, simultaneous vaccine composition evaluation and recommendation quite challenging.	**Once again, trying to normalize use of the C19 vaccines by comparison with flu.** **FDA stated above: *"The distribution of Omicron sub lineages varies at different points in time in different regions of the world."* Thus coordination of strain composition may produce ineffective compromises.** **So are FDA reversing the earlier statement?**

FDA anticipates conducting an assessment of SARS-CoV-2 strains at least annually and to engage VRBPAC in about early June of each year regarding strain selection for the fall season. Subsequently, a decision on the recommended vaccine composition would be made in time for any updated vaccine to be in production in time to be deployed for use no later than September of each calendar year. Of note, circulation of a more pathogenic vaccine-escape variant of SARS-CoV-2 would likely prompt, on an as needed and emergent basis, an ad-hoc strain selection meeting of VRBPAC.	**"Fall season" No seasonality has been established. This was discussed at the April 6th and June 28th 2022 VRBPAC meetings.** **Even with minimal testing, new variant vaccines cannot keep pace with mutation rates. Reiterating Paul Offit (15): *"chasing these Omicron variants with a bivalent vaccine is a losing game"*** **1) Makes no sense given BA.5 is almost extinct, Wuhan is extinct and XBB.1.5 and BQ1.1. have significant escape.** **2) Does this attempt to gloss over the failure of Pfizer's 2 doses in young children? Will this also reduce the confusion added by CDC's instructions to increase the primary dose interval?** **3) See above**
The VRBPAC will be asked to discuss: 1) use of the same vaccine strain composition for primary series and booster doses, 2) simplification of the COVID-19 immunization schedules, and 3) routine periodic strain selection procedures.	**Why is this still regarded as "ongoing"?**
2. 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 bivalent COVID-19 vaccines have been a critical component of the global response to the evolving pandemic, uncertainties about the future course of the pandemic persists. The complexities associated with the differences in composition and regimens of the currently authorized and approved COVID-19 vaccines in the U.S., the still incomplete understanding of SARS-CoV-2 immunology, and the absence of an established framework to inform periodic vaccine composition updates, leave open scientific and policy questions regarding simplifying the immunization schedule and updating the current COVID-19 vaccines for future vaccination campaigns.	**The bivalent boosters have been an abject failure. Only 15.3% of those eligible have taken the updated booster. (CDC 1/23/23)** ***"the erosion of trust in governments and public-health institutions […] COVID-19 vaccines has exacerbated rather than dampened."(16)***
The January 26th VRBPAC meeting will consider questions around simplifying the composition and immunization schedules of the authorized and approved COVID-19 vaccines, the process for determining the need for recommending a periodic update to COVID-19 vaccines, and the timing for implementation of such an update. Specifically, we hope for VRBPAC members to consider the following issues during the meeting: • Transitioning to a single vaccine composition for primary series and booster vaccination;	**From the voting question this looks like the current BA.5/Wuhan bivalent** **Novavax already said at the 6/28/22 VRBPAC that their vaccine behaves very differently. What has changed?** **On 6/25/22 BA.4 and BA.5 accounted for ~52% of US variants. By 9/1/22 they had**

• Harmonizing the strain composition of all COVID-19 vaccines (mRNA, protein-based); • Simplifying the immunization schedule for future vaccination campaigns to administer a two-dose series in certain young children, and in older adults and persons with compromised immunity, and only one dose in all other individuals; • Establishing a process for vaccine strain selection recommendations, similar in many ways to that used for seasonal influenza vaccines, based on prevailing and predicted variants that would take place by June to allow for vaccine production by September.	**just dropped from their peak of ~90% declining by the end of the year to ~7%. So there is an extremely narrow window of opportunity.**
PAGE 6 • Convening a strain selection meeting at any time in between routine periodic strain selections to address a more pathogenic escape variant.	
3. Background **3.1 Previous VRBPAC discussions and vaccine composition recommendations**	**See our written and oral comments to VRBPAC April 6 2022 (6) and ACIP (April 20 2022) (13)**
On April 6, 2022, the 172nd meeting of VRBPAC convened in open session to discuss considerations for future COVID-19 vaccine booster doses and the process for COVID-19 vaccine strain selection to address current and emerging variants. The committee heard presentations on: the epidemiology of SARS-CoV-2 strains (H Scobie, Centers for Disease Control and Prevention (CDC)); COVID-19 VE (R Link-Gelles, CDC); the Israeli experience with a 2nd booster dose of Pfizer-BioNTech COVID-19 Vaccine in adults (S Alroy-Preis, Ministry of Health, Jerusalem and R Milo, the Weizmann Institute, Rehovot, Israel); future SARS-CoV-2 variants prediction (J Beigel, National Institutes of Health and T Bedford, Fred Hutchinson Cancer Research Center); modeling of future U.S. COVID-19 outbreaks (C Murray, University of Washington); the World Health Organization (WHO) perspective on variants for COVID-19 vaccine composition (K Subbarao, WHO Collaborating Center for Reference and Research on Influenza, Melbourne, Australia); and manufacturing timeline considerations (R Johnson, Biomedical Advanced Research and Development Authority). Following the FDA presentation of a proposed framework for addressing future COVID-19 vaccine strain composition, the committee was then asked to discuss the considerations to inform strain composition decisions to ensure that available COVID-19 vaccines continue to meet public health needs; how often the adequacy of strain composition for available vaccines should be assessed; the conditions that would indicate a need for updated COVID-19 vaccine strain composition; the data that would be needed to support a decision on a strain composition update; and the considerations that should guide the timing and populations for use of additional COVID-19 vaccine booster doses. There was general agreement among committee members that given the complexities of changing COVID-19	**The was some antipathy to the manufacturers who were not asked to**

vaccine strain composition, decisions on vaccine strain composition should be undertaken as a coordinated process led by FDA, with input from VRBPAC, and with consideration of any global recommendations that WHO might provide.
The committee noted that any strain change decision should be data-driven, and that there should be evidence that the current vaccine strain composition is not adequately effective against severe disease caused by circulating variants coupled with compelling evidence that a proposed modified vaccine composition will provide improved VE. There was relatively uniform agreement that a single vaccine composition to be used by all manufacturers was desirable. Committee members expressed that, ideally, a vaccine based on a modified strain composition could be used for both primary vaccination and booster.

present to VRBPAC. However, Moderna filled one of the public comment slots.

It was not made clear to the VRBPAC members that the FDA guidelines on new strain composition has just been revised a short time earlier. This revision provided for attenuated pre-clinical and clinical requirements for new variant vaccine authorization.

The April 6th meeting was not intended to make a specific recommendation for COVID-19 vaccine strain composition and the committee did not suggest specific strain recommendations. Rather, the committee acknowledged that continued monitoring of VE, virus variant epidemiology, and clinical immunogenicity evaluation of modified vaccines would be critical for decisions of the strain composition of COVID-19 vaccines.

See our oral comments for 6/28/22 VRBPAC
https://youtu.be/BFdzNUus_CE?t=19314
and article in Trial Site News:
www.trialsitenews.com/a/all-day-hearing-by-fdas-vrbpac-omicron-specific-boosters-recommended-by-19-2-vote-despite-growing-concern-d99f00e5

On June 28, 2022, the 175th meeting of VRBPAC convened in open session to discuss whether and how the SARS-CoV-2 strain composition of COVID-19 vaccines should be modified. The committee heard presentations on the current epidemiology of the COVID-19 pandemic and

PAGE 7

SARS-CoV-2 variants in the U.S. and COVID-19 VE (CDC) and future COVID-19 pandemic epidemiology modeling (J Lessler, University of North Carolina). In addition, available clinical data on modified COVID-19 vaccines were presented by COVID-19 vaccine manufacturers (Pfizer Inc., ModernaTX, and Novavax Inc. referred to as Pfizer, Moderna, and Novavax respectively elsewhere in this document) and considerations for vaccine strain composition from the WHO Technical Advisory Group on COVID-19 Vaccine Composition were also presented (K Subbarao, WHO). FDA perspective on considerations for strain composition for modifications of COVID-19 vaccines was also provided. After these presentations and committee discussions, the VRBPAC voted 19-2 in favor of the inclusion of a SARS-CoV-2 Omicron component for COVID-19 booster vaccines in the U.S. Although there was no vote on a more specific strain composition, there was general preference among committee members for a bivalent vaccine with an original strain component and an Omicron variant component and a preference for vaccine coverage of Omicron sublineages BA.4 and BA.5. Several members stressed the need to continue to accumulate data on this complex issue.

This modeling was not validated. Dr. Lessler responded to a question from VRBPAC member Dr. Ofer Levy: ***"What we are not doing, at the hub level where we aggregate, we are not weighing the models based on the performance in past rounds"***

Pfizer and Moderna presented limited clinical data on BA.1 vaccines. Drs. Offit and Bernstein voted against the recommendation based on lack of convincing data to establish a need. VRBPAC did not vote to approve the bivalent vaccines.

Others expressed concerns as to safety: Hildreth: "*This is a new product and as new product should be handled as a new product" "These new vaccine derivatives or sequences are new substances and [I just wonder whether*

	they need to be more carefully tested for safety. Maybe some molecular mimicry could cause auto antibodies, there are a lot of things that are possible I just think we need to be more careful using these new vaccines without more testing." **Meisner: "We need more study or research into what the association with vaccines and myocarditis is."**
Following the June 28, 2022, VRBPAC meeting, FDA and other global regulatory authorities met to discuss preliminary data on adapted vaccines addressing emerging variants and to discuss alignment on the criteria for strain selection and regulatory approaches to address new waves of COVID-19 (see ICMRA website for additional details). Based on emerging clinical data, there was a preference for a bivalent vaccine that incorporated a component based on the original strain and an Omicron variant component to provide greater breadth of immunity against SARS-CoV-2 variants including Omicron, as the future circulating strains were unknown at that point.	**https://icmra.info/drupal/covid-19**
On June 30, 2022, FDA notified COVID-19 vaccine manufacturers of a recommendation to develop a bivalent vaccine (original and Omicron BA.4/BA.5) as a booster dose to improve protection during a potential fall 2022 booster vaccination campaign. FDA requested that sponsors expeditiously begin clinical trials to generate safety and immunogenicity data evaluating a bivalent vaccine in relevant populations. FDA recognized that data sufficient to confirm superiority of the bivalent vaccine in trial participants who had received it would not likely be available in time to support authorization prior to a potential fall 2022 booster vaccination campaign. Consequently, to address the urgent public health need for COVID-19 vaccine booster doses more closely matched to circulating variants, FDA considered it appropriate to issue an EUA of a bivalent vaccine based primarily on relevant safety and effectiveness data from participants who received an earlier bivalent vaccine, in addition to supportive pre-clinical animal data for the recommended bivalent vaccine and data from use of already-authorized or approved original vaccines.	**The public need was no less urgent in the summer of 2022 with about 300-400 deaths per day. Given, according the FDA logic, the likelihood of some effect of outdated vaccines, the BA.1 variant vaccines studied by Pfizer and Moderna could have been immediately or quickly deployed, according to Pfizer and Moderna.** **The bivalent authorizations marked further erosion in FDA's standards, to adopting what Dr. Fink called and extrapolative approach that included only limited data on the bivalent vaccines in mice. The admission by Moderna of the formation of heterotrimers was startling.** **See our comments at the Sept 1 2022 (17) and October 19 (18) ACIP meetings.**

3.2 FDA authorized and approved COVID-19 vaccines
3.2.1 Moderna COVID-19 Vaccines

Spikevax (COVID-19 Vaccine, mRNA), manufactured by Moderna, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. Spikevax contains nucleoside-modified messenger RNA (mRNA) that encodes for the full-length spike (S) protein of the original SARS-CoV-2 strain encapsulated in lipid particles. Under EUA, the vaccine is called the Moderna COVID-19 Vaccine and is authorized for use as a two-dose primary series for individuals 6 months of age and older and a third primary series dose for individuals 6 months of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Moderna COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) referred to as Moderna COVID-19 Vaccine, Bivalent elsewhere in this document, is authorized

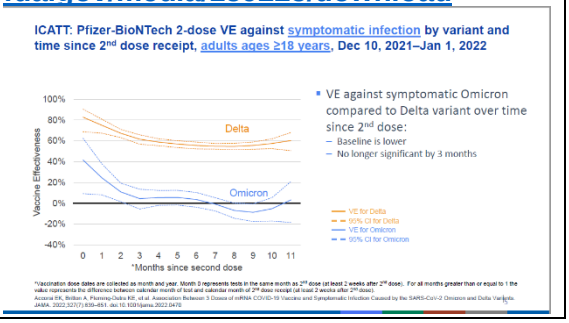
Note indication says nothing about hospitalization or severe outcomes. See earlier note.

Making a bivalent vaccine introduces significantly new process steps that, without proper validation could affect safety and efficacy. FDA's revised guidelines only speak of reduced testing requirements for new-strain monovalent vaccines.(19) At the Sept 1 2022 ACIP meeting, Moderna revealed that the two different mRNA molecules are loaded into the same LNP. This creates a significant departure from the "same process"

PAGE 8

for use as a single booster dose (1) in individuals 6 years of age and older, to be administered at least 2 months after either completion of primary vaccination with an authorized or approved COVID-19 vaccine or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 vaccine, and(2) in individuals 6 months through 5 years of age administered at least 2 months after completion of primary vaccination with the ModernaCOVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series doses is specified for the age group in which the vaccine is being administered: 25 µg in 0.25 mL for 6 months through 5 years of age, 50 µg in 0.5 mL for 6 through 11 years of age, and 100 µg in 0.5 mL for 12 years of age and older. The total mRNA content for the authorized booster dose of Moderna COVID-19 Vaccine, Bivalent is specified for the age group in which the vaccine is being administered:10 µg in 0.2 mL for6months through5 years of age,25 µg in 0.25 mL for 6 through 11 years of age, and 50 µg in 0.5 mL for12 years of age and older. Safety and effectiveness data supporting approval of Spikevax and authorization of the Moderna COVID-19 Vaccine and Moderna COVID-19 Vaccine, Bivalent are detailed in the decision memoranda available on the FDA website.

The 2-month interval had not been studied or discussed at a VRBPAC meeting. ACIP members in the 9/1/22 meeting attempted to modify the vote language to address this concern, but were rebuffed by CDC staff, despite CDC modifying other FDA decisions with their power to issue EUIs (Emergency Use Instruction), eg by widening the primary series dose interval to up to 8 weeks. FDA in a press conference had tried to downplay this decision that was driven by CDC's data showing the vaccines to be ineffective by about 3 months, and having negative efficacy by 6-7 months. See Link-Gelles June 14 2022
fda.gov/media/159225/download



3.2.2Pfizer-BioNTech COVID-19 Vaccines Comirnaty (COVID-19 Vaccine, mRNA), manufactured by Pfizer and BioNTech, is approved for use as a two-dose primary series for active immunization to prevent COVID-19 caused bySARS-CoV-2 in individuals 12 years of age and older. Comirnaty contains a nucleoside-modified mRNA encoding the S protein of the original SARS-CoV-2 strain that is formulated in lipid particles. Under EUA, the vaccine is called the Pfizer-BioNTech COVID-19 Vaccine and is authorized for use as the first 2 doses of a 3-dose primary series (Pfizer-BioNTech COVID-19Vaccine, Bivalent is authorized as the third dose, see below) for individuals 6 months through 4 years of age, a two-dose primary series for individuals 5 years of age and older, and a third primary series dose for individuals 5 years of age and older with certain types of immunocompromise. A bivalent formulation of the vaccine manufactured using the same process, Pfizer-BioNTech COVID-19 Vaccine, Bivalent (Original and Omicron BA.4/BA.5) referred to as Pfizer-BioNTechCOVID-19 Vaccine, Bivalent elsewhere in this document, is authorized for use as (1) a third dose of the three-dose primary series following two doses of the monovalent Pfizer-BioNTechCOVID-19 Vaccine in children 6 months through 4 years of age, and (2) a single booster dose in individuals 5 years of age and older, to be administered at least2 months after either completion of primary vaccination with an authorized or approved COVID-19 vaccine or receipt of the most recent booster dose with an authorized or approved monovalent COVID-19 Vaccine. The total mRNA content for each of the authorized and/or approved primary series and booster doses is specified for the age group in which the vaccine is being administered: 3 µg in 0.2 mL (primary series only) for 6 months through 4 years of age, 10 µg in 0.2 mL for 5 through 11 years of age, and 30 µg in 0.3 mLfor 12 years of age and older. Safety and effectiveness data supporting approval of Comirnaty and authorization of the Pfizer-BioNTech COVID-19 Vaccine and Pfizer-BioNTech COVID-19 Vaccine, Bivalent are detailed in the decision memoranda available on the FDA website. **3.2.3Janssen COVID-19 Vaccine** The Janssen COVID-19 Vaccine, a non-replicating adenovirus type 26-vectored vaccine encoding the S protein of SARS-CoV-2 original strain, is authorized for active immunization to prevent COVID-19 in individuals 18 years of age and older for whom other FDA-authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, or who elect to receive the Janssen COVID-19 Vaccine because they would otherwise not	**See earlier note** **This is based on stunningly poor clincal data. See our comment (14) to June 23 2022 ACIP meeting.** **See earlier comment regarding Moderna heterotrimers and loading of two mRNAs in same LNP. The exact mode of LNP loading has not been disclosed for the Pfizer bivalent, however even if LNPS are loaded separately, it is possible for them to coalesce on storage, or for two different LNPs to transfect the same cell, thereby producing the same result of allowing heterotrimer formation.** **At a meeting between the react19 vaccine injury group and FDA on December 14 2022, FDA acknowledged that heterotrimer formation is possible with the bivalent vaccines, but claimed that just because heterotrimers may behave display differently antigen properties from homotrimers, their toxicological properties would likely be the same. No data supporting this contention has been provided.** **J&J are not listed on the agenda for the Jan 26 VRBPAC meeting.** **FDA issued a contraindication for the Janssen product in December 2021 for TTP. Note our comments to ACIP regarding FDA's inaction for other thromboembolic signals present for the Pfizer and Moderna products. (11)**

receive a COVID-19 vaccine. The vaccine is authorized for use in these individuals as a single primary vaccination

PAGE 9
dose and as a single homologous or heterologous booster dose (the dosing interval for a homologous booster is at least 2 months after the single primary vaccination dose, and the dosing interval for a heterologous booster is the same as that authorized for a booster dose of the vaccine used for primary vaccination). The safety and effectiveness data supporting authorization for the Janssen COVID-19 Vaccine and limitations on its use are detailed in the decision memoranda available on the FDA website.

3.2.4 Novavax COVID-19 Vaccine, Adjuvanted
The Novavax COVID-19 Vaccine, Adjuvanted, which contains recombinant S protein of the SARS-CoV-2 original strain and Matrix-M adjuvant, is authorized for use as a two-dose primary series for active immunization to prevent COVID-19 in individuals 12 years of age and older and a first booster dose for individuals 18 years of age and older for whom an FDA-authorized mRNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate or who elect to receive the Novavax COVID-19 Vaccine, Adjuvanted because they would otherwise not receive a booster dose of a COVID-19 vaccine. The authorized dosing interval for a booster isatleast6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine. Safety and effectiveness data supporting authorization for the Novavax COVID-19 Vaccine, Adjuvanted are detailed in the decision memoranda available on the FDA website.

Novavax have suggested that due to the presence of preserved epitopes, their vaccine product is less prone to variant escape than the modRNA products.

Despite the Novavax product using more traditional technology, significant concerns remain about the rates of myocarditis. See our comments (20) to the July 19 2022 ACIP meeting.

The vaccine is produced in the armyworm whose cells have been transfected with baculovirus that has been modified to carry the code for spike protein. The vaccine uses a novel adjuvant extracted from the soap tree,

4.Considerations for strain composition of COVID-19 vaccines

4.1Epidemiology and antigenic characterization of current SARS-CoV-2 variants of concern

The SARS-CoV-2 Omicron (B.1.1.529 lineage) VOC emerged in late 2021 and rapidly became the dominant circulating SARS-CoV-2 virus throughout the world, replacing earlier strains ofSARS-CoV-2 (e.g., Wuhan) and the previously designated VOCs (e.g., Alpha, Beta, Gamma, and Delta). Compared to earlier strains of virus, Omicron is more transmissible, contains considerably more amino acid mutations (including in the spike protein that is the basis for currently authorized/approved vaccines), and is less pathogenic in animal models (consistent with available clinical data in humans). Omicron has continued to evolve into sublineages with additional amino acid mutations in the spike

glycoprotein and the RBD, the predominant target of neutralizing antibodies elicited by infection and vaccination. The distribution of Omicron sublineages varies at different points in time in different regions of the world.

In the U.S., the Omicron BA.1 sublineage became the dominant virus variant by late December2021 but was quickly replaced by the BA.2 sublineage by April 2022. Although BA.1 and BA.2 share many of the same amino acid mutations relative to ancestral strains of SARS-CoV-2, BA.2 has an additional six amino acid changes in the S protein, two in the N-terminal domain (NTD) (T19I and V213G) and four in the RBD (S371F, T376A, D405N, and R408S). There is also a nine-nucleotide deletion in the NTD of BA.2 that results in deletions of amino acids 24-26 and the mutation A27S. Subsequent Omicron sublineages have evolved from BA.2. BA.2.12.1, with two additional amino acid changes at L452Q (in the RBD) and S704L (not in the RBD), relative to BA.2, became the dominant strain in the U.S. by May 2022. By July 2022, BA.2.12.1 was replaced by two other Omicron sublineages, BA.4 and BA.5, which appeared a few months earlier in South Africa. BA.4 and BA.5 share the same spike amino acid sequence, which differs from that of BA.2 with RBD changes at L452R and F486V, the absence of the BA.2 Q493R mutation, and containing the deletions at H69 and V70 present in Omicron BA.1. Omicron BA.4/BA.5 remained dominant in the U.S. through October 2022 until two new Omicron

So how is it possible to implement a global solution?

PAGE 10

sublineages, BQ.1 and XBB, spread to the U.S. and began to account for an increasing number of SARS-CoV-2 infections.

By early December 2022, SARS-CoV-2 BQ.1 and BQ1.1 accounted for more than 50% of U.S. infections. BQ.1 appears to have evolved from BA.5 and has additional spike mutations at K444T, N460K, and R346T (BQ.1.1). Even with this small number of amino acid changes relative to BA.5, neutralization titers appear to be further reduced in sera from previously infected or vaccinated individuals compared to BA.5 neutralization titers. Even as BQ.1.1 became the dominant virus strain in the U.S., infections with the XBB and XBB.1.5 sublineages also began to increase, rising from about 7% to >30% of characterized viruses during December 2022. The XBB sublineage viruses derived from a recombination of Omicron BA.2.10.1 and BA.2.75 viruses, with a breakpoint in the S1 region of the spike gene and contains parts of spike protein from each virus parent. A recombination event requires co-circulation of viruses and co-infection in the same individuals, and the resulting recombinant virus must have elements of improved fitness to be successful. Nevertheless, genetic recombination in coronaviruses is not uncommon, and in fact, may be an important driver of virus evolution. To the amino terminal side of spike before the breakpoint, XBB has all the mutations of the BA.2.10.1 parent, and to the carboxy side of the breakpoint, all the mutations of the BA.2.75 parent virus. As well as the mutations

Obsoleting the bivalent Wuhan/ BA4/5

Emergence of BQ variants is further rendering the bivalent vaccines obsolete.

common to all BA.2 virus descendants, XBB includes spike mutations from BA.2.10.1 at V83A, Y144-, H146Q, Q183E, V213E, G339H, R346T, L386I, V445P, and G446S, and spike mutations from BA.2.75 at N460K, F486S, and F490S. XBB.1 has an additional S amino acid mutation at G252V; XBB.1.5 has an additional S486P change relative to XBB.1.

The large number of mutations in the Omicron variant sublineages and the continuing evolution of the virus raise concern for potential evasion of vaccine-induced immunity. The need for continual surveillance of virus variants and monitoring of vaccine-induced cross-protection remains critical.

4.2 Update on COVID-19 vaccine immunogenicity and effectiveness

Although clinical studies gathering safety, immunogenicity, and effectiveness data using the authorized bivalent mRNA booster vaccines (Moderna COVID-19 Vaccine, Bivalent and Pfizer-BioNTech COVID-19 Vaccine, Bivalent) are ongoing, the available data to assess immunogenicity and effectiveness of these bivalent mRNA boosters against recently and currently circulating Omicron subvariants include: preliminary immunogenicity data reported by vaccine manufacturers; immunogenicity data reported in the literature; and observational effectiveness data reported by the CDC and Israel.

See earlier comments on immune correlate of protection.

4.2.1 Immunogenicity data from vaccine manufacturers

Moderna COVID-19 Vaccines

In a preprint article, Moderna published preliminary data from a Phase 2/3 study comparing immune responses to the Moderna COVID-19 Vaccine, monovalent (original) mRNA-1273 vaccine (n=376) and the Moderna COVID-19 Vaccine, Bivalent (Omicron BA.4/BA.5 and Original) mRNA-1273.222 vaccine (n= 511) when administered as a second booster dose (non-contemporaneous comparisons with median interval between first and second booster doses of 134 days and 289 days, respectively) (Chalkias et al. 2022). Neutralizing antibody GMTs at 50% inhibitory dilution (ID_{50}) were assessed using validated SARS-CoV-2 spike-pseudotyped lentivirus neutralization assays against pseudoviruses containing the SARS-CoV-2 full-length spike proteins of original SARS-CoV-2 (D614G) or Omicron subvariants BA.4/BA.5, BQ.1.1 and XBB.1.

mRNA-1273.222 - Wuhan/BA.5 bivalent
mRNA-1273.214 - Wuhan/BA.1 bivalent

PAGE 11

• In participants with no prior SARS-CoV-2-infection, Omicron BA.4/BA.5 and ancestral SARS-CoV-2 D614G neutralizing antibody geometric mean titers (GMTs [95% confidence interval]) after mRNA-1273.222 (2324.6 [1921.2, 2812.7] and 7322.4 [6386.2, 8395.7], respectively) were significantly higher than after mRNA-1273 (488.5 [427.4, 558.4] and 5651.4 [5055.7, 6317.3] respectively), at day 29 post-boost. Between the monovalent and bivalent booster groups, the geometric mean ratio (GMR) for Omicron BA.4/BA.5 neutralizing antibody titers was 6.29 (95% CI: 5.27, 7.51) and the seroresponse rate (SRR) difference (using a pre-boost baseline) was 53.9% (95% CI: 46.7, 61.2), which met

Small number of subjects, short f/u
Now these data are irrelevant

No prior

GMT vs.	BA5	D614G
Orig monov	488	5651
BA5 biv	2324	7322

Note that the 488 number is considered sufficiently reduced response to warrant bivalent. Compare this with the

the pre-specified superiority and non-inferiority criteria, respectively.

• Additional exploratory analyses of neutralizing antibody responses to the Omicron BQ.1.1 and XBB.1 sublineages were reported for 60 mRNA-1273.222 recipients and 60 mRNA-1273.214 (Omicron BA.1-containing bivalent booster) recipients. In recipients without prior SARS-CoV-2 infection (n= 40), the observed GMTs (95% CI) after mRNA-1273.222 were 621.9 (422.2, 916.2) and 222.3 (147.4, 335.2) against BQ1.1 and XBB.1, respectively, at day 29 post-boost, compared to 161.1 (104.1, 249.3) and 50.6 (32.4, 79.2) after mRNA-1273.214, respectively. The corresponding geometric mean fold rises [GMFRs (95% CI)] after mRNA-1273.222 were 19.6 (11.7, 32.8) and 12.3 (7.4, 20.5) against BQ1.1 and XBB.1, respectively, at day 29 post-boost relative to pre-boost, compared to 4.1 (3.0, 5.5) and 3.6 (2.5, 5.1) after mRNA-1273.214, respectively. In recipients with prior SARS-CoV-2 infection (n= 20), the observed GMTs (95% CI) after mRNA-1273.222 were 1093.5 (536.8, 2227.9) and 381.4 (198.1, 734.4) against BQ1.1 and XBB.1, respectively, at day 29 post-boost, compared to 475.5 (304.7, 742.0) and 214.2 (116.9, 392.4) after mRNA-1273.214, respectively. The corresponding GMFRs (95% CI) after mRNA-1273.222 were 8.8 (5.5, 15.5) and 6.9 (4.0, 11.7) against BQ1.1 and XBB.1, respectively, at day 29 post-boost relative to pre-boost, compared to 3.2 (2.3, 4.5) and 2.9 (2.1,3.9) after mRNA-1273.214, respectively.

622 number below for the BA5 bivlanet vs BQ1.1 and 223 number for XBB

No prior infection

GMT vs.	BQ1.1	XBB
BA1 biv	161	51
BA5 biv	622	223
GMFR		
BA1 biv	4.1	3.8
BA5 biv	19.6	12.3

With prior infection the 1094 for the BA5biv is somewhat better, but still falls short for the 381 number vs XBB.

With prior C19

GMT vs.	BQ1.1	XBB
BA1 biv	475	214
BA5 biv	1094	381
GMFR		
BA1 biv	3.2	2.9
BA5 biv	8.8	6.9

How is this evidence that the BA5 bivalent is of any benefit?

Moderna bivalent vaccine as a primary series

On January 14, 2023, Moderna submitted preliminary data (datasets not submitted for independent analyses) from an ongoing, open-label Phase 3 study (Study P306 Part 1), in which 142 COVID-19 vaccine-naïve participants 6 months through 5 years of age received a 2-dose primary series of a bivalent (original and Omicron BA.1) COVID-19 vaccine (mRNA-1273.214). The immune responses after primary series vaccination with mRNA-1273.214 were compared to those of participants 6 months through 5 years of age who received the same dose level of a 2-dose primary series of the original monovalent Moderna COVID-19 Vaccine (mRNA-1273) in Study P204, the study used to support the initial authorization of the Moderna COVID-19 Vaccine primary series in this age group. The immune responses at 28 days after Dose 2 in the two groups were assessed by geometric mean concentrations (GMCs) of neutralizing antibodies against Omicron BA.1 and original SARS-CoV-2 (D614G).

This is going to be the justification for using bivalents for the primary series.
"preliminary"
Once again FDA fails to verify data: ***"datasets not submitted for independent analyses"***
We have documented this for the Pfizer 5-11 dose, Janssen 2nd dose, and other instances.

142 = small number. Vaccine naïve? What about C19 naïve?
This is BA.1 - why are BA5 data not available?
Other age groups?

The primary immunogenicity analysis population consisted of participants with or without evidence of prior SARS-CoV-2 infection at baseline and included 71 mRNA-1273.214 recipients from Study P306 and 632 mRNA-1273 recipients from Study

Further reason for downgrading quality of data
71 is a subset of the 142 number above.

P204. The two studies were conducted non-contemporaneously. Study P306 Part 1 enrollment started in June 2022, whereas Study P204 enrolled participants between October and November 2021. This likely contributed to the greater proportion of mRNA-1273.214 participants with evidence of prior SARS-CoV-2 infection (63.4%) compared to mRNA-1273 participants (6.6%), leading to overall higher baseline (pre-vaccination) neutralizing antibody GMCs in the mRNA-1273.214 group compared to the mRNA-1273 group. At 28 days post-Dose 2, the co-primary endpoint of GMC

Another reason why the study results are confounded

The endpoint has now switched. Why?

With prior C19
GMC Ration is ratio of Ab conc for BA1 biv/ orig monovalent

GMCRvs.	BA1	D614G
BA1 biv	25.4	0.8

This success criteria means that the bivalent only needed to be marginally better than the original monovalent.

The criteria for the second criterion were only barely met.

PAGE 12

ratio (mRNA-1273.214/mRNA-1273) of neutralizing antibodies against Omicron BA.1 was 25.4 (95% CI: 20.1, 32.1), which met the pre-specified success criterion for superiority of a lower bound (LB) of the 95% CI >1. The second co-primary endpoint of GMC ratio of neutralizing antibodies against the ancestral strain (D614G) was 0.8 (95% CI: 0.7, 1.0), which met the pre-specified success criterion for non-inferiority of a LB of the 95% CI >0.667.

Differences in seroresponse rates (SRR) between the mRNA-1273.214 and mRNA-1273 groups were assessed as secondary endpoints, without pre-specified hypothesis testing. The conventional seroresponse definition of a change from baseline neutralizing antibody concentrations from less than the lower level of quantification (LLOQ) to ≥4x LLOQ, or at least 4-fold rise if baseline was greater than the LLOQ was used. The difference in SRR (mRNA-1273.214 – mRNA-1273) against Omicron BA. 1 among all participants regardless of baseline status was -6.7% (95% CI: -17.4, 4.0). Difference in SRR against D614G among all participants regardless of baseline SARS-CoV-2 status was -8.0% (95% CI -14.0, -2.0).

This attempts to show equivalency, again for the BA1 bivalent, but with great limitations.

Given the limitations in interpretation of the primary and secondary immunogenicity analyses due to the imbalance in baseline SARS-CoV-2 status between the two study groups, the immunogenicity endpoints were also assessed in the subset of participants without evidence of prior SARS-CoV-2 infection at baseline. This subset included 26 participants in the mRNA-1273.214 group and 590 participants in the mRNA-1273 group. At 28 days after Dose 2, among these baseline SARS-CoV-2 negative participants, the GMC ratio of neutralizing antibodies against Omicron BA.1 was 15.8 (95% CI: 11.3, 22.0), which would have met the pre-specified criterion for superiority. However, the GMC ratio against D614G was 0.4 (95% CI: 0.3, 0.5), which would not have met the criterion for non-inferiority. Among these baseline SARS-CoV-2 negative participants, difference in SRR against Omicron BA.1 was 0.1% (95% CI: -12.7, 13.0) and difference in SRR against D614G was -10.0% (95% CI -19.3, -0.7).

26 = an even smaller subset

A secondary endpoint criterion was not met. This is for the BA1 bivalent vs. the Wuhan original, so it is less important. It did nonetheless fail this.

Within 7 days after any dose, solicited adverse reactions (ARs) were reported by 57.0% and 63.1% of mRNA-1273.214 recipients after Dose 1 and Dose 2, respectively. Most solicited ARs were mild to moderate in severity. Fever >38°C was reported by 8.9% and 13.5% of participants after Dose 1 and Dose 2,

respectively. After Dose 1, fever was reported by a higher proportion of participants who were baseline SARS-CoV-2 positive (11.5%) compared to those who were baseline negative (2.4%). Grade 3 fever (age 6 to ≤ 36 months: 39.6 - 40°C; age 37 months to <6 years: 39 - 40°C) was rare and reported by 1.1% and 1.4% of participants after Dose 1 and Dose 2, respectively. Within 28 days after any dose, unsolicited adverse events were reported by 30.7% of mRNA-1273.214 recipients, and generally represented illnesses and events typical of infancy/childhood. All were mild to moderate in intensity, except for one serious adverse event of asthma in a 5-year-old participant with onset 13 days after Dose 1, which was assessed as unrelated to study vaccine by the investigator.

Unclear if this is from the n=142, or n=71 subset. 1/71 or 1/142 ciuld still be a high rate. The sample size is too small to assess safety.

While study P306 Part 1 met the primary immunogenicity endpoints of superiority and non-inferiority of neutralizing antibody GMCs against Omicron BA. 1 and D614G, respectively, after a primary series of mRNA-1273.214 compared to mRNA-1273, the disparate baseline SARS-CoV-2 status among study participants in the two studies limit the interpretation of these results. If the analysis of the co-primary endpoints was restricted to participants who are baseline SARS-CoV-2 negative, then the study would have met the co-primary endpoint for Omicron BA.1 but would have failed on the co-primary endpoint for D614G. The interpretation of results from the baseline negative population only was limited by the small sample size of the P306 group (n=26).

In normal circumstances these sorts of limitations could be grounds for non-approval.

No efficacy data

PAGE 13

Pfizer-BioNTech COVID-19 Vaccines

In a preprint article, Pfizer described preliminary data comparing immune responses to the Pfizer BioNTech COVID-19 Vaccine, monovalent (original) BNT162b2 vaccine (n=40) in one study and Pfizer BioNTech COVID-19 Vaccine, Bivalent (Omicron BA.4/BA.5 and Original) BNT162b2 vaccine (n=38) in another study when administered as a second booster dose to individuals >55 years of age, at a median of 6.3- and 11.3-months post-dose 3, respectively (Zou et al. 2022). Neutralizing antibody responses were measured by 50% fluorescent focus reduction neutralization titers ($FFRNT_{50}$) using the complete spike gene from Omicron BA.4/BA.5, BA.4.6, BA.2.75.2, BQ.1.1, or XBB.1 engineered into the backbone of mNeonGreen (mNG) reporter USA-WA1/2020 SARS-CoV-2 (a strain isolated in January 2020).

• In participants with no prior SARS-CoV-2-infection, Omicron BA.4/BA.5 and original (USA-WA1/2020) $FFRNT_{50}$ values (95% CI) were higher at day 29 post-boost after bivalent BNT162b2 (n=18) (517.8 [260.5, 1029.5] and 2237.2 [1238.2, 4042.2], respectively) compared to after monovalent BNT162b2 (n=20) (88.8 [55.3,142.6] and 1325.1 [924.2,1900.1], respectively). In participants (irrespective of prior infection) who received the bivalent B162b2 vaccine (n=37), the GMFRs (95% CI) at 1 month post-dose 4 relative to pre-booster dose for the original strain

Have these data been verified by FDA?

Small numbers, Ab response. No efficacy data
N=38
Non concurrent studies?
Comparibility?
>55 years, Booster only, No efficacy

With no prior C19

FFRNT vs.	BA5	Wuhan
mono	88	1325
BA5 biv	517	2237

Prior + no prior infectin

GMFR vs.	BA5	Wuhan
mono	2.9	3
BA5 biv	13	5.8

(USA-WA1/2020) and Omicron BA.4/BA.5 were 5.8 (4.0, 8.5) and 13.0 (8.0, 21.1), respectively, compared to 3.0 (2.1, 4.3) and 2.9 (2.1, 3.9), respectively, after monovalent BNT162b2 (n=40). While the GMFRs for both ancestral strain and Omicron BA.4/BA.5 in participants with and without prior infection were comparable after monovalent vaccination, the GMFRs for both were higher after bivalent vaccination in those participants without prior infection compared to those with prior infection.

• Analyses of neutralizing antibody responses to the Omicron BA.4.6, BA.2.75.2, BQ.1.1, and XBB.1 sublineages were also conducted. In recipients who received the monovalent BNT162b2 booster, the GMFRs for these subvariants at 1 month post-dose 4 relative to pre-booster dose ranged from 1.3-2.5 for those with (n= 20) and without (n=20) prior infection. Following booster vaccination with bivalent BNT162b2, $FFRNT_{50}$ values and corresponding GMFRs 1 month post-dose 4 were higher than those following monovalent vaccine. In participants without prior SARS-CoV-2 infection who received bivalent vaccine (n=19), the observed $FFRNT_{50}$ (95% CI) were 143.4 (78.7, 261.3) and 54.5 (31.0, 95.9) against BQ1.1 and XBB.1, respectively, with corresponding GMFRs (95% CI) of 12.6 (7.1, 22.5) and 4.7 (2.8, 7.9), respectively. In bivalent vaccine recipients with prior SARS-CoV-2 infection (n=19), the observed $FFRNT_{50}$ (95% CI) were 444.4 (259.4, 761.3) and 130.9 (80.0, 214.3) against BQ1.1 and XBB.1, respectively, with corresponding GMFRs (95% CI) of 6.0 (3.2, 11.2) and 4.9 (2.8, 8.5), respectively. Similar increases in $FFRNT_{50}$ were seen for the BA.4.6 and BA.2.75.2 subvariants following bivalent vaccination.

no prior infection

GMFR vs.	BQ1.1	XBB.1
mono	1.5	1.3
BA5 biv	12.6	4.7

prior infectin

GMFR vs.	BQ1.1	XBB.1
BA5 biv	6.0	4.9

NO DATA for Use in Primary series

4.2.2 Immunogenicity data from the literature

Multiple studies describe neutralizing antibody responses to the currently available authorized bivalent mRNA booster vaccines. Interpreting the data from these studies is complicated because of the limited sample size, lack of effectiveness data, variability in the assays used and the status of assay qualification, the populations tested, and the intervals between vaccination and serum collection.

Data are extremely limited

IgG4 levels should be measured? Tolerance?(21)

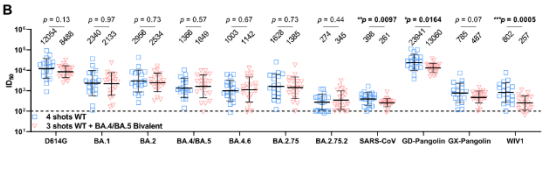
Details of the immune responses from these studies are described as follows:

• In Wang et al 2022, neutralizing antibody responses (pseudovirus neutralization assay) against D614G strain and against Omicron sublineages BA.1, BA.2, BA.4/BA.5, BA.4.6, BA.2.75, and BA.2.75.2 were measured in sera from participants who received: three doses

Booster doses only
Small samples
No BQ or XBB lineages

PAGE 14

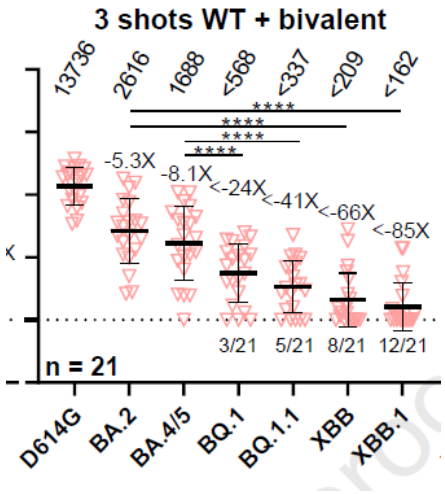
vaccine targeting BA.4/BA.5 (bivalent-booster group [n=21]), either three or four doses of monovalent mRNA vaccines (three-dose [n=14] and four-dose [n=19] monovalent groups), or three or four doses of monovalent mRNA vaccine followed by a history of BA.4/BA.5 breakthrough infection (convalescent group [n=20]). The mean interval between vaccination or infection and serum collection was 39.2 days in the three-dose group, 24.0



days in the four-dose group, 26.4 days in the bivalent-booster group, and 31.8 days in the convalescent group. In all groups, the geometric mean ID_{50} was highest for D614G, and ID_{50} values for all Omicron subvariants was highest in the convalescent group. There were no statistically significant differences between GMTs against Omicron subvariants between the four-dose monovalent and the bivalent-booster groups; GMTs for BA.4/BA.5 were 1,366 and 1,649 in each group, respectively. of either of the original monovalent mRNA vaccines followed by one dose of a bivalent vaccine targeting BA.4/BA.5 (bivalent-booster group[n=21]), either three or four doses of monovalent mRNA vaccines (three-dose [n=14] and four-dose [n=19] monovalent groups),or three or four doses of monovalent mRNA vaccine followed by a history of BA.4/BA.5 breakthrough infection (convalescent group [n=20]). The mean interval between vaccination or infection and serum collection was 39.2 days in the three-dose group, 24.0days in the four-dose group, 26.4 days in the bivalent-booster group, and 31.8 days in the convalescent group. In all groups, the geometric mean $ID_{50}$was highest for D614G, and ID_{50}values for all Omicron subvariants was highest in the convalescent group. There were no statistically significant differences between GMTs against Omicron subvariants between the four-dose monovalent and the bivalent-booster groups; GMTs for BA.4/BA.5 were 1,366 and 1,649 in each group, respectively.	**From the paper:** ***"When given as a fourth dose, a bivalent mRNA vaccine targeting Omicron BA.4/BA.5 and an ancestral SARS-CoV-2 strain did not induce superior neutralizing antibody responses in humans, at the time period tested, compared to the original monovalent vaccine formulation."*** ***"There was no significant difference in neutralization of any SARS-CoV-2 variant tested between individuals who received a fourth monovalent vaccine and those who received a fourth dose of a bivalent vaccine. 1 dose of a bivalent vaccine."***
In Collier et al 2022, neutralizing antibody titers (pseudovirus neutralization assay) against BA.4/BA.5 at approximately 3-4 weeks (range 16-64 days) post-vaccination were measured in sera from participants (n=15) who received a booster dose of monovalent mRNA vaccine and participants (n=18) who received a booster dose of bivalent mRNA vaccine (number of previous COVID-19 doses was between 2-4 and included varying combinations of mRNA and Ad26-vectored COVID-19 vaccines). Median BA.5 neutralizing antibody titers increased from 184 to 2,829 (15-fold) after a monovalent mRNA booster dose and from 211 to 3,693(17-fold) after a bivalent mRNA booster dose. The median BA.5 neutralizing antibody titer was similar after monovalent and bivalent mRNA boosting, with a trend favoring the bivalent booster by a factor of 1.3. Median USA-WA1/2020 neutralizing antibody titers increased from 5,731 to 21,507 (~4-fold) after a monovalent mRNA booster dose and from 3,633 to 40,575 (11-fold) after a bivalent mRNA booster dose. Spike-specific $CD8^+$T cell responses increased ~2-fold following both the monovalent and bivalent mRNA boosters and spike-specific $CD4^+$T cell responses increased 2-fold following the monovalent mRNA booster and 1.4-fold following the bivalent mRNA booster.	**Adults** **Booster only** **Very small sample size** **Little difference between monovalent and bivalent booster** **BA.5 target only** **No BQ or XBB** **No safety or clincal efficacy**
In Davis-Gardner et al 2022, neutralizing antibody titers (live-virus focus neutralization test [$FRNT_{50}$]) against original (WA1/2020) virus and Omicron subvariants BA.1, BA.5,BA.2.75.2, BQ.1.1, and XBB were measured in sera obtained 1-8 weeks post-vaccination from participants who received either one (n=12) or two (n=11) monovalent mRNA	**Which boosters – Pfizer or Moderna?** **Short follow up. No study of waning**

boosters and participants (n=12) who received a bivalent mRNA booster. All participants in the single monovalent booster group were naïve to SARS-CoV-2 exposure. In the one monovalent booster cohort, the $FRNT_{50}$ GMTs were 857 against WA1/2020, 60 against BA.1, 50 against BA.5,23 against BA.2.75.2, 19 against BQ.1.1, and below the limit of detection against XBB. In the two monovalent booster cohort, the $FRNT_{50}$GMTs were 2,352 against WA1/2020, 408 against BA.1, 250 against BA.5, 98 against BA.2.75.2, 73 against BQ.1.1, and 37 against XBB. In these monovalent booster cohorts, neutralization titers against BA.1 and BA.5 were 5 to 9 times as low as that against WA1/2020 and neutralization titers against BA.2.75.2, BQ.1.1, and XBB were 23 to 63 times slow as that against WA1/2020. In the bivalent booster cohort, $FRNT_{50}$GMTs against all Omicron subvariants were higher as compared with the monovalent booster cohorts: 2,481 against WA1/2020, 618 against BA.1,576 against BA.5, 201 against BA.2.75.2, 112 against BQ.1.1, and 96 against XBB. Neutralization titers against BA.1 and BA.5 were 4 times as low as that against WA1/2020 and neutralization titers against BA.2.75.2, BQ.1.1, and XBB were 12 to 26 times as low as that against WA1/2020. In Kurhade et al. 2022, neutralizing antibody titers ($FRNT_{50}$) against original (WA1/2020) virus and Omicron subvariants BA.5, BA.2.75.2, BQ.1.1, and XBB were measured in sera collected 23-94 days after dose 4 in SARS-CoV-2 naïve participants who received 4 doses	**Small sample** **From paper:** ***"Limitations of this study include the small cohort size, differences in age among the cohorts, the unknown effect of previous exposure to SARS-CoV-2, and comparison of the vaccines at a single time point.*** **Ie 3-6x lower than BA5.** **Small, mixed cohort. Low quality**
PAGE 15 of monovalent mRNA vaccine (n=25); 4-32 days after bivalent mRNA booster in SARS-CoV-2 naïve participants who previously received 2-4 doses of monovalent mRNA vaccine (n=29); and 14-32 days after bivalent mRNA booster in SARS-CoV-2-infected participants who previously received 2-4 doses of monovalent mRNA vaccine (n=23). Neutralization titers (FRNT50) against BA.4/BA.5 in the sera from the monovalent boosted group, the bivalent boosted group, and the infected/bivalent boosted group were 95, 298, and 1,558, respectively. Similar neutralization titer trends were seen in the assays for BQ.1.1 and XBB subvariants in this study and in a follow-up study from the same group (Zou et al. 2022).	**SEE WHAT THE ACTUAL PAPER SAYS!** ***"The results showed that a BA.5 bivalent booster elicited a high neutralizing titer against BA.4/5 measured at 14–32 days after boost; however, the BA.5 bivalent booster did not produce robust neutralization against the newly emerged BA.2.75.2, BQ.1.1 or XBB.1. Previous infection substantially enhanced the magnitude and breadth of BA.5 bivalent booster-elicited neutralization. Our data support a vaccine update strategy that future boosters should match newly emerged circulating SARS-CoV-2 variants."*** **THIS STUDY IS MISSING:** **Wang et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants (22)** ***"…neutralization of BQ.1, BQ.1.1, XBB, and XBB.1 by sera from vaccinees and infected persons was markedly impaired, including sera from individuals boosted with a WA1/BA.5 bivalent mRNA vaccine. Titers against***

BQ and XBB subvariants were lower by 13- to 81-fold and 66- to 155-fold, respectively, far beyond what had been observed to date. […] Together, our findings indicate that BQ and XBB subvariants present serious threats to current COVID-19 vaccines…"



Also missing: Miller et al. (23)

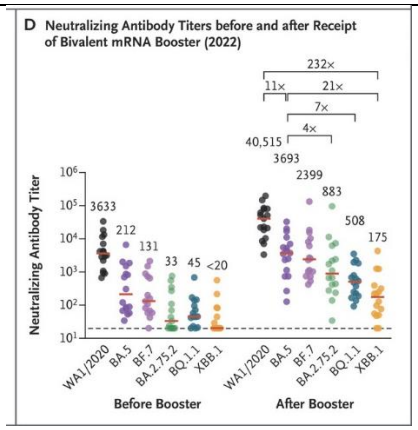
"BQ.1.1 and XBB.1 variants escaped neutralizing antibodies substantially more effectively than the BA.5 variant by factors of 7 and 17, respectively, after monovalent mRNA boosting and by factors of 7 and 21, respectively, after bivalent mRNA boosting. The neutralizing antibody titers to BQ.1.1 and XBB.1 were dramatically lower than titers to the WA1/2020 strain by factors of 53 and 127, respectively, in the monovalent booster cohort and by factors of 80 and 232, respectively, in the bivalent booster cohort. These findings suggest that the BQ.1.1 and XBB.1 variants may reduce the efficacy of current mRNA vaccines"

4.2.3 Observational effectiveness data

Three recent publications describe observational data on the effectiveness of bivalent mRNA booster vaccines in the U.S.in preventing: (1) symptomatic SARS-CoV-2 infection during circulation of BA.4/BA.5 and their sublineages (Link-Gelles et al. 2022); 2) COVID-19-associated emergency department or urgent care encounters and hospitalizations among immunocompetent adults (Tenforde et al. 2022);and 3) COVID-19-associated hospitalization among immunocompetent adults aged ≥65 years (Surie et al.2022). Although there are limitations specific to each of these effectiveness assessments, and though not definitive, these data provide preliminary real-world evidence that support the use of the bivalent mRNA boosters.

An observational study of the effectiveness of bivalent mRNA booster vaccines in preventing symptomatic SARS-CoV-2 infection was conducted using data from the Increasing Community Access to Testing (ICATT) national SARS-CoV-2 testing program collected between September and November 2022 (during circulation of BA.4/BA.5 and as other Omicron subvariants emerged). The relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥2 monovalent vaccine doses among persons for whom 2 to 3 months and ≥8 months had elapsed since last monovalent dose was 30% (95% CI: 22, 37%) and 56% (95% CI:53,58%) among persons 18-49 years of age, 31% (95% CI: 24, 38%) and 48% (95% CI:45, 51%) among persons 50-64 years of age, and 28% (95% CI: 19, 35%) and 43% (95% CI:39, 46%) among persons ≥65 years of age, with relative benefits increasing with time since receipt of the most recent monovalent vaccine dose. Absolute VE (95% CI) for a single bivalent mRNA COVID-19 booster dose after ≥2 monovalent vaccine doses against symptomatic SARS-CoV-2 infection was 43% (39, 46%) among persons 18-49 years of age, 28% (22, 33%) among persons 50-64 years of age, and 22% (15, 29%) among persons ≥65 years of age (Link-Gelles et al. 2022).

An observational study (test-negative, case control study design) of the effectiveness of a bivalent mRNA booster dose (after 2, 3, or 4 monovalent mRNA doses) compared with 1) no previous vaccination and 2) previous receipt of 2, 3, or 4 monovalent-only mRNA vaccine doses, among immunocompetent adults aged ≥18 years with an emergency department/ urgent care encounter or hospitalization for a COVID-19-like illness, was conducted using data from the VISION network (9 states) between September and November 2022 (Tenforde et al. 2022).These data were collected during a period when the BA.5 subvariant was circulating and as other Omicron subvariants emerged.



All studies are in the BA5 era, they do not consider waning or activity againsts BQ and XBB.

These estimates fall below FDA guidelines for VE> 50% and lower CI >30% (24)

"Multivariable logistic regression models were controlled for age, gender, race, ethnicity, SVI of the testing location, underlying conditions (presence versus absence), state of residence of person tested, pharmacy chain conducting the test, local incidence (cases per 100,000 by site zip code during the 7 days preceding test date), and date of testing."

There is quite a large discrepancy between the adjusted values of 22-43% and an UNADJUSTED VE = 12%

VE of a bivalent mRNA booster dose (after 2, 3, or 4 monovalent mRNA doses) administered ≥7 days earlier against COVID-19-associated emergency department / urgent care encounters was 56% (95% CI: 19-41%) compared with no vaccination (absolute VE). The rVE (95% CI) of the bivalent mRNA booster dose compared to monovalent vaccination only by the time from the last dose in the monovalent vaccine only group was as follows:

PAGE 16

31% (19, 41%) for 2-4 months, 42% (32, 50%) for 5-7 months, 53% (46, 60%) for 8-10 months, and 50% (43,57%) for ≥11 months.

•VE of a bivalent mRNA booster dose (after 2, 3, or 4 monovalent mRNA doses) against COVID-19 associated hospitalizations was 57% (95% CI:41-69%) compared with no vaccination (absolute VE). The rVE (95% CI) of the bivalent mRNA booster dose compared to monovalent vaccination only by the time from the last dose in the monovalent vaccine only group was as follows: 38% (13, 56%) for 5-7 months, 42% (19, 58%) for 8-10 months, and 45% (25,60%) for ≥11 months. There was insufficient sample size for an estimation of the rVE of a bivalent booster dose compared with receipt of ≥2 monovalent-only mRNA vaccine doses with last dose 2-4 months before illness onset.

An observational study (test-negative, case control study design) of the effectiveness of a bivalent mRNA booster received after ≥2 doses of monovalent mRNA vaccine against COVID-19-associated hospitalization among immunocompetent adults ≥65 years of age was conducted using data from the VISION network (18 states) between September and November 2022 (Surie et al. 2022). These data were collected during a period when the BA.5 subvariant was circulating and other Omicron subvariants emerged. VE of a bivalent mRNA booster dose (after≥2 monovalent doses) received ≥7 days before illness onset (median=29 days) against COVID-19-associated hospitalization was84% (95% CI: 64, 93%) compared with no vaccination. The rVE of a bivalent mRNA booster dose was73% (95%CI:52,85%) compared to ≥2 monovalent-only mRNA vaccine doses≥2 months before illness onset. In analyses by the time since last Monovalent mRNA vaccination, the rVE of a bivalent mRNA booster dose was 78% (95% CI:57, 89%) and 83% (95% CI: 63, 92%) for patients with the most recent monovalent mRNA dose 6-11 months and ≥12 months before illness onset, respectively. There was insufficient sample size for an estimation of the relative VE of a bivalent mRNA booster dose compared with receiptof≥2 monovalent-only mRNA vaccine doses with last dose 2-5 months before illness onset.

As with the other studies this uses a test-negative case-control design: ***"comparing the odds of having received versus having not received a bivalent booster dose among case-patients (those who received a positive SARS-CoV-2 test result) and control patients (those who received a negative SARS-CoV-2 test result)."***

Reduction of "associated emergency department / urgent care encounters" etc. is not a stated indication under BLA or EUA. The indication needs to be changed following conduct of RCTs etc.

Main limitations in study paper:

1. **Previous infection not accounted for**
2. **Residual confounding possible, (behavioral differences, use of C19 drugs)**
3. **Did not compare product-specific bivalent booster VE estimates.**
4. **Patients might not be representative of the entire population.(eg adults who received bivalent booster doses shortly after authorization).**

Again observational not RCT data.

See earlier remark about the label indication not including severe outcomes.
This study had a total of 381 Covid and 417 test negative patients – very small.
Limitations described in study:

5. **Sample size insufficient to estimate VE by number of monovalent vaccine doses received before the bivalent booster dose or compared with patients whose most recent monovalent vaccine dose was**

Additionally, a preprint in the *Lancet* described data from a retrospective cohort study in Israel designed to assess effectiveness of the Pfizer-BioNTech Bivalent COVID-19 Vaccine (originalSARS-CoV-2 strain and Omicron BA.4/BA.5 components) in preventing severe COVID-19 outcomes (hospitalization and death) in individuals ≥65 years of age during September-December 2022 (Arbel et al. 2023). Hospitalizations and death due to COVID-19 among participants who received a booster with the Pfizer-BioNTech Bivalent COVID-19 vaccine were compared with those who did not. The adjusted hazard ratio for hospitalization due to COVID-19 following receipt of a Pfizer-BioNTech Bivalent COVID-19 vaccine booster dose was 0.19 (95% CI: 0.08-0.43) and was 0.14 (95% CI, 0.02-1.04) for death due to COVID-19. The VE was 81% for COVID-19-related hospitalizations and 86% for COVID-19-relateddeaths.

4.2.4 Summary of available data

In summary, the preponderance of immunogenicity data from the vaccine manufacturers and independent researchers indicates improved neutralizing antibody responses to currently and recently circulating Omicron subvariants following bivalent mRNA booster vaccination when compared to monovalent mRNA booster vaccination. Additionally, observational data suggest that bivalent mRNA booster vaccination provides additional protection against symptomatic infection, emergency department/urgent care visits, and hospitalization.

received 2–5 months before illness onset.

6. **Analysis could not compare the VE of a bivalent booster dose with a monovalent booster dose administered during the same period.**
7. **Analysis period includes both BA.5- and BQ.1/BQ.1.1–predominance.**
8. **Could not evaluate impact of previous infection on VE.**
9. **Possible selection bias, residual confounding eg risk behaviors or preventive treatments.**

As with other studies involving medical records, there are errors in determining which events are WITH or FOR Covid.

Accordingly, the effect of vaccination on All-cause mortality is more useful.

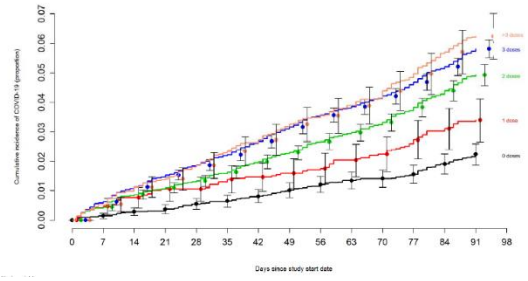
See our analysis showing correlations fom EU and CDC data between ACM and vaccine usage.(25)

This statement appears misleading.

Also missing: Safety of bivlant vaccines: Wagenhauser et al.(26)

"The rate of adverse reactions for the second booster dose was significantly higher among participants receiving the bivalent 84.6% (95% CI 70.3%-92.8%; 33/39) compared to the monovalent 51.4% (95% CI 35.9-66.6%; 19/37) vaccine (p=0.0028)"

Also missing: Shrestha et al Cleveland clinic(27)
Estimated (VE) of bivalent 30% (95% CI, 20-39%).
However study also found higher risk of C19 with more vaccine does:
"This is not the only study to find a possible association with more prior vaccine doses and higher risk of COVID-19. A large study found that those who had an Omicron variant infection after previously receiving three doses of vaccine had a higher risk of reinfection than those who had an Omicron variant infection after previously receiving two doses of vaccine [21]. Another study found that receipt of two or three doses of a mRNA vaccine following prior COVID-19 was associated with a higher risk of reinfection than receipt of a single dose [7]. We still have a lot to learn about protection from COVID-19 vaccination, and in addition to a vaccine's effectiveness it is important to examine whether multiple vaccine doses given over time may not be having the beneficial effect that is generally assumed."



4.3 Alignment of primary series and booster vaccine compositions

When the first mRNA COVID-19 vaccines were authorized in December 2020, the duration of protection of the vaccines against symptomatic disease, hospitalization, and death were not yet known. In addition, the ability of the SARS-CoV-2 virus to rapidly evolve to evade the immune response had not yet been observed. However, by mid-summer of 2021, waning of protection

PAGE 17

against symptomatic and severe disease, particularly in older individuals, along with viral variant evolution was observed. Thus it was recognized that additional vaccines, or boosters, would be needed to supplement the initial primary vaccination series to maintain adequate protection of the population. Although some scientific uncertainty remains as to the duration of protection against symptomatic disease, hospitalization, and death across all age ranges, it appears clear from multiple clinical studies that additional boosters restore protection against COVID-19. Although the beneficial effect associated with a reduction in hospitalization and death is most apparent in older individuals, younger individuals appear to also benefit with a reduction in symptomatic disease and health care utilization (Link-Gelles et al. 2022, Tenforde et al. 2022, Surie et al. 2022).Though perhaps not identical, this pattern of response is analogous to that

observed with annual influenza vaccination, a well-accepted intervention in individuals 6 months of age and older that on an average year provides a 10%to 60% in reduction of influenza-like illness (CDC 2022, Treanor 2016, Minozziet al. 2022).	**See Paul Offit** ***"The experience of the past year has taught us that chasing these Omicron variants with a bivalent vaccine is a losing game"*** **(cited in Time Magazine, Jan 11, 2023)**
Because of the evolution of the SARS-CoV-2 variants and subvariants, a recommendation was made at the June 28, 2022 VRBPAC meeting to move to a booster composition incorporating an Omicron variant component. Bivalent vaccines, containing mRNAs encoding the S protein of the original strain and the Omicron BA.4/BA.5 subvariant, were deployed in fall of 2022, and safety, immunogenicity, and effectiveness data for these vaccines are currently available and are described above in Section 4.2. In summary, the bivalent mRNA boosters from Moderna and Pfizer-BioNTech produce immune responses not only to the Omicron BA.4/BA.5 subvariant, but also to a variety of other variants, including a robust response to the original strain. The immune response generated by the bivalent mRNA boosters against the Omicron BA.4/BA.5 subvariant as well as the more recent BQ.1.1, and XBB subvariants is better than that observed with the original monovalent vaccine. Although randomized comparative clinical trial data comparing the vaccine efficacy of an original monovalent booster versus a bivalent booster (Original plus Omicron BA.4/BA.5) are not available at this time, effectiveness of the bivalent mRNA boosters against both symptomatic disease, hospitalization, and death have been observed to be improved following a bivalent mRNA booster compared to those who did not receive a bivalent mRNA booster. While the use of the bivalent mRNA boosters is supported by the available evidence, their deployment has been associated with substantial implementation complexities.	**See Paul Offit:(15)** ***"I believe we should stop trying to prevent all symptomatic infections in healthy, young people by boosting them with vaccines containing mRNA from strains that might disappear a few months later.*** ***"trying to prevent, in otherwise healthy people, mild illness for a few months,.. until the next variant comes along to replace it. ..That doesn't make sense."*** **Influenza. It is not identical. Why mentin this?** **Full safety is not available, See also our discussion on heterotimers in the bivalent vaccine.(18)** **The responses to BQ and XBB are unimpressive** **Eg: see missing study above** **Wang et al. Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants (22)** **Even if true, the risk-benefit ratio changes** **See comments above** **It is not. BA5 is currently less than 2% according to CDC Nowcast, and XBB and BQ variants escape significantly.** **The React19 Vaccine Injury group met with FDA on December 14 2022. FDA's**

There are operational challenges with keeping track of several vaccine presentations across the age spectrum, which are administered in different volumes, some after dilution, and with intervals ranging from three weeks to several months. When the recommendation was made in June 2022 to update the composition of booster vaccines to a bivalent formulation, little data were available to support updating the composition of vaccines for use as a primary series, and thus, at the present time, vaccines used for primary series immunization are monovalent vaccines (based on original strain) rather than the bivalent vaccines authorized for booster vaccination. From a practical point of view, this doubles the number of vials required by a practitioner or pharmacy to appropriately vaccinate all vaccine recipients. Given these complexities, a move to a single vaccine composition for primary and booster vaccinations should be considered. This simplification of vaccine composition should reduce complexity, decrease vaccine administration errors (refer to the CDC's Interim Clinical Considerations for Use of COVID-19 Vaccines)due to the complexity of the number of differential presentations, and potentially increase vaccine compliance by allowing clearer communication. Recent pre-clinical data supports the improved antibody response of bivalent vaccines (compared to monovalent vaccine) against Omicron variants when used in naïve animals (Scheaffer et al. 2022, Muik et al. 2022), as does recent clinical data from studies with a bivalent vaccine when used as a primary series in young children. Of note, in a statement issued December 6, 2022, the European Medicines Agency's

Dr Marks affirmed for four types of spike proteins could be synthesized in vivo by the bivalent vaccines. These include two new in nature heterotrimers, which, according to Moderna (ACIP Meeting 9/1/22) provide broader immunological properties. This therefore represents new chemistry and therefore potentially new toxicology. This could explain the 50% greater rate of adverse events with the bivalent vaccines (26)
The production of bivalent vaccines clearly introduces new QA challenges that could affect safety and efficacy, and thus do not fall under the "same process" rules described in FDA's guideline(19) for monovalent vaccine variant changes.

This is a welcome admission on the part of FDA. This problem, along with labelling errors was flagged in several ACIP meetings in the summer of 2022, eliciting the comment from one member to the effect of the manufacturers needing to get their act together.

PAGE 18

Emergency Task Force concluded that bivalent original/Omicron BA.4/BA.5 mRNA vaccines may be used for primary vaccination.

5. Approach to future COVID-19 vaccine schedule and composition recommendations

Given the evolution of SARS-CoV-2 variants and associated changes in the epidemiology, susceptibility to reinfection, and waning of vaccine-induced immunity, periodic future updates to the S protein sequence(s) contained or encoded in COVID-19 vaccines and revaccination will likely be needed to induce and maintain VE, respectively. As noted in Section 4.3 above, multiple COVID-19 vaccine compositions and immunization schedules have been authorized or approved in the U.S., complicating vaccine administration, communication, and uptake. An approach to both simplifying the immunization schedule and periodically updating the composition of COVID-19 vaccines as needed, requires consideration.

5.1 Simplification of immunization schedule

However no convincing data has been presented on the safety and efficacy of the bivalent mRNA for primary series doses.
Which study?
No data has been presented at all for new variant versions of the Novavax and J&J vaccines.

A data-driven approach that is well founded, and similar in many ways to the process used for updating the composition of influenza vaccines, could achieve significant immunization schedule simplification by adopting:

- the same COVID-19 vaccine compositions for primary series and booster vaccination (see Section 4.3);
- a schedule that applies to all COVID-19 vaccines; and
- the same composition of S protein sequence(s) contained or encoded in all COVID-19 vaccines in use in the U.S.

"will be likely" No discussion has been made of natural immunity and the risks associated with repeat dosing of nucleoside modified mRNA. See our discussion on the lack of public involvement of the gene therpy group within FDA.(25)

FDA expects that simplification of COVID-19 vaccine composition and annual immunization schedules may contribute to more facile vaccine deployment, fewer vaccine administration errors, and less complex communication, all potentially leading to improved vaccine coverage rates and, ultimately, to enhanced public health.

One approach to immunization schedule simplification relies upon the following two key underlying assumptions:

What is this data-drive approach?

• That two or more exposures to S protein through vaccination and/or infection provide sufficient pre-existing immunity such that a single dose of COVID-19 vaccine induces or restores sufficient VE for a desired duration.

The sequences have not been published. The details of other parts of the modRNA such as the 5' cap, the poly A tail and the UTR's have not been disclosed and may be different between Pfizer and Moderna.

• That a well-founded age- and/or risked-based approach can be defined, allowing substantial simplification of the current immunization schedule to one dose for those presumed to have sufficient pre-existing immunity, and two doses for those who do not.

Although the data are not fully consistent and several knowledge gaps remain, emerging evidence suggests that a combination of SARS-CoV-2 infection and vaccination, termed hybrid immunity, confers significant protection against COVID-19 and that immunity acquired by infection should be considered in determining the immunization schedule (Pilz et al 2022).

This is a welcome acknowledgement regarding natural immunity. However, the pattern of waning has not been well-described.

5.1.1 Evidence supportive of proposed simplification approach

Multiple studies report that at least two exposures to S protein, through vaccination and/or infection, provide a degree of protective immunity. Interpreting the data from these studies is complicated because of the diversity of study designs, populations studied, and clinical endpoints used. However, all may support in part a simplified immunization schedule based upon two or more exposures to S protein through vaccination and/or infection.

The data provided give no assurance that they can be extrapolated across ages. Regarding risk, no discussion of safety has been made yet in this document, especially regarding safety signals.

At this stage in the pandemic this is somewhat puzzling.

PAGE 19

High-level summaries of some of these published studies are provided as follows:

• Powell et al. 2022 reported that previous infection with any SARS-CoV-2 variant alone provided some protection in

adolescents against symptomatic reinfection with another variant, while vaccination added to this protection. Vaccination alone provided low-to-moderate protection against symptomatic Omicron infection in adolescents with waning protection after each dose. Authors note that hybrid immunity (from previous infection irrespective of variant plus vaccination) offered the highest protection against Omicron infection. • Hansen at al. 2022 reported that previous Omicron infection in triple vaccinated individuals in Denmark provided high-level protection against BA.5, supporting the notion that vaccination can boost preexisting hybrid immunity and lead to protection against infection by variants. • Flury et al. 2022 reported that hybrid immunity and booster vaccination in health professionals were associated with reduced risk of fewer reported symptoms during SARS-CoV-2 infection during the Delta and Omicron waves in Switzerland. Booster vaccination in uninfected individuals was associated with reduction in risk of symptomatic Omicron infection while this immunity was found to wane over time. • Chin et al. 2022 reported data from effectiveness studies in two high-risk populations in a prison system. Preexisting immunity generated through infection alone or a combination of mRNA vaccination (two or three doses) and previous infection (hybrid immunity) was effective in preventing Omicron infection. Immunization with three doses of mRNA vaccine was associated with the highest protection compared to two doses, even in previously infected individuals. • Andeweg et al. 2022 reported that a combination of previous infection and primary vaccination provided better protection against Omicron infection than either one alone. Boosting offered highest protection even in previously infected individuals. Protection was found to be similar in individuals who were infected first followed by vaccination or who were vaccinated first followed by infection, indicating that order of infection or vaccination did not influence protection offered by hybrid immunity. • Bates et al. 2022 found that individuals who had breakthrough infections after vaccination and those who were vaccinated after a natural infection neutralized SARS-CoV-2 infections to a similar degree. Hybrid immunity was observed irrespective of the order of infection and vaccination and broadly neutralized SARS-CoV-2 variants to a similar degree. **5.1.2 Evidence inconsistencies and critical gaps** Carazo et al. 2023 reported that health-care workers who acquired hybrid immunity through the receipt of two doses of mRNA vaccine and a previous BA.1 infection were subsequently well protected for a prolonged period against BA.2 reinfection and a third vaccine dose did not offer improvement to the protection conferred by “pre-existing hybrid immunity.” The authors of this study noted that if the protection from pre-existing hybrid immunity also pertains to future variants, there might be limited	**What will happen for mandates? Will evidence of infection be required?** **Is this FDA’s way of backing down from mandates gracefully?** **No mention is being made of transmission.** **For all of these studies a risk-benefit analysis needs to consider only the incremental benefit, if any, of vaccination over natural immunity.** **FDA has not fully discussed here the increased risk for severe AEs with vaccination after infection, see Beatty et al.(28)**

benefit from additional vaccine doses for people with hybrid immunity, depending on timing and variant.
Carazo et al. 2022 reported that a third vaccine dose in twice-vaccinated individuals who had had a non-Omicron SARS-CoV-2 infection offered limited protection against Omicron-associated hospitalization.

PAGE 20

Simplification of the immunization schedule for all COVID-19 vaccines that relies upon presumed prior S protein exposure through vaccination, infection, or a combination of both (hybrid immunity) has evidentiary gaps. The most critical are detailed age-based rates of presumed total S protein exposures and data on risk groups who would benefit from a two-dose series rather than a single dose in a vaccine campaign. Availability of these data could help establish a well-founded age- and/or risked-based approach that allows significant simplification of the current immunization schedule. In the meantime, population-based seroprevalence and COVID-19 incidence rates, along with vaccination coverage rates, point to a path forward.

5.1.3 Path forward and proposed simplification scheme

FDA anticipates reviewing a comprehensive data package at a population level (children and adults stratified by age) that could inform VRBPAC discussion and includes:

- Vaccination coverage rates, stratified by number of prior vaccine doses received and by age
- SARS-CoV-2 infection (any) rates, stratified by number of prior infections and by age
- COVID-19 rates stratified by severity (mild, moderate, and severe) and by age
- Presumed S protein exposure (vaccination, infection, or a combination thereof), stratified by number of exposures and by age
- Seroprevalence rates, stratified by age
- Modeling that combines natural infection and vaccine-induced immunity for current estimates of population-based immunity (i.e., landscape of population immunity) by age strata

Review of these data may define age groups who have acquired "sufficient preexisting immunity," through prior infection, vaccination, or combination thereof, such that administration of a single dose of an approved or authorized COVID-19 vaccine would likely induce or restore the expected protective immunity for a desired duration. In age and risk groups presumed to have "insufficient preexisting immunity," two doses of an approved or authorized COVID-19 vaccine may be needed to induce the expected protective immunity for the desired duration. The scheme below proposes a potential approach to simplifying the immunization schedule for use in future periodic COVID-19 vaccination campaigns.

Proposed potential simplified immunization schedule One Dose **Two Dose Series**

Again, a welcome acknowledgement.

The focus here is on S protein. What efforts are being made to develop vaccines based on less mutatable proteins? Is it possible?

All cause mortality must be considered

Why was this not done before?

Again a welcome acknowledgement. Why only now?

General population (age-based*) Young children *if ≥2 doses received previously* Older children, adolescents, and all but older adults	Risked-based adjustments** Young children *if ≤1 dose received previously* Older adults Persons with comprised immunity	**How will this affect mandates?**

*Presumed to have had at least two S protein exposures, resulting in sufficient preexisting immunity such that a single dose of COVID-19 vaccine induces or restores sufficient vaccine effectiveness for a desired duration.
**Presumed to have insufficient preexisting immunity based on age and other risks (e.g., children less than 2 years of age are presumed to have had no more than one prior immunizing SARS-CoV-2 infection, adults 50 years of age and older are presumed to have higher-level risk for severe COVID-19 and death, and persons with comprised immunity are presumed to require two rather than one dose of vaccine in each COVID-19 vaccine campaign).

PAGE 21 **5.2 Expectations and plans for future COVID-19 vaccine composition recommendations** Similar to the approach with influenza, the global nature of SARS-CoV-2 strain evolution warrants a global response when evaluating and recommending vaccine strain composition changes. Ideally, any change in vaccine composition, when appropriate, would be implemented broadly and would be coordinated by the World Health Organization (WHO) with national regulatory authorities. However, unlike influenza, a well-established, highly coordinated infrastructure and governance of global semi-annual vaccine composition evaluation and recommendations do not currently exist for SARS-CoV-2. Furthermore, at this time the current diversity of vaccine manufacturers and complexities in global supply of COVID-19 vaccines would make a globally coordinated, simultaneous vaccine composition evaluation and recommendation quite challenging.	**In the absence of seasonality, attempts to update vaccines in a flu-like manner are futile.**
In addition, SARS-CoV-2 continues to evolve and spread in an unpredictable manner, including examples of regional dominance of virus variants that do not lead to worldwide prevalence (e.g., XBB1.5). Currently, it remains impossible to predict which virus VOC will gain dominance in any particular region of the world and how long a VOC will remain dominant. As such, whether or when the epidemiology of SARS-CoV-2 will adopt a pattern that makes a regular cadence of globally coordinated recommendations for updating COVID-19 vaccine composition obvious or needed remains to be seen. Neither is it clear whether or when most areas of the world will have similar levels of pre-existing immunity (be it from vaccination or infection), susceptibility to clinically significant COVID-19, nor access to the same types and quantities of COVID-19 vaccines. With these	**See comments page 5** **FDA stated above: "The distribution of Omicron sub lineages varies at different points in time in different regions of the world." Thus, coordination of strain composition may produce ineffective compromises.** **A welcome acknowledgement to decouple FDA and WHO decisions.**

uncertainties taken together, the FDA and VRBPAC may need to consider a change in COVID-19 strain composition for U.S. vaccines without a prior WHO strain recommendation.

Before any update in vaccine composition for U.S. vaccines is recommended and any decision is made, careful consideration should be based on sufficient need and evidence, including sufficient: 1) data on changes in circulating SARS-CoV-2 variants and subvariants of concern, COVID-19 epidemiology, and current VE to suggest the need for a better matched vaccine composition; 2) evidence to support that an updated vaccine will provide improved protection compared to current vaccines; and 3) information about whether manufacturers have the ability and capacity to produce updated vaccines in sufficient quantities for timely use in the U.S.

This is somewhat similar to the framework presented at the April 6th 2022 VRBPAC meeting.

5.2.1 Timing and frequency

Given a variety of constraints, there is likely a practical limit as to how often vaccine composition changes can be implemented, regardless of the vaccine platform. That said, experience from influenza vaccine strain composition changes for U.S. vaccines suggests that implementation of an annual vaccine composition evaluation and recommendation would likely be practical for COVID-19 vaccines. Additionally, based upon modelling using the available evidence, in the absence of the emergence of a variant that essentially escapes protection conveyed by the existing vaccines, the administration of an updated vaccine on an annual basis also appears to be reasonable (Townsend et al. 2023). As such, an annual frequency may provide a reasonable and practical starting point to implement COVID-19 vaccine composition evaluation and recommendations in the U.S.

FDA/CDc have likely done their market research as to what sort of vaccination schedule the public will tolerate.

Any plans for updated COVID-19 vaccines must account for the time required to produce sufficient vaccine doses. Considerations include the time needed to develop necessary reagents, manufacture updated vaccine, and complete final fill, finish, and release. This time may differ for different types of vaccines. Additionally, the experience of the manufacturer and

No mention here of testing requirements

PAGE 22

the facility and its capacity can affect the time to manufacture the new updated COVID-19 vaccine.

As such, FDA anticipates conducting an assessment at least annually (review of data to commence in spring of each year). Anticipated information to engage VRBPAC in about early June would likely include evidence discussed in section 5.2.2. Subsequently, a decision on the recommended vaccine composition could be made in time for any updated vaccine to be in production in time to be deployed for use no later than September of each calendar year.

No Covid-19 seasonality. The models so far have not been predictive.

This provides for no significant testing

Of note, circulation of a more pathogenic vaccine-escape variant of SARS-CoV-2 would likely trigger, on an as needed and emergent basis, an ad-hoc strain selection meeting of VRBPAC as has been done previously for emerging influenza viruses (e.g., H1N1pdm09). **5.2.2 Proposed evidentiary basis for updated vaccine composition recommendations and decisions** The current seasonal influenza vaccine antigen selection process may serve as a general framework for evaluating the need for and, if necessary, selection of an updated SARS-CoV-2 Spike protein sequence(s) contained in or encoded by authorized or approved COVID-19 vaccines in the U.S. Considerations in determining the need for updating the composition of COVID-19 vaccines would ideally include reviewing evidence from: • Epidemiological and clinical surveillance to identify newly emerging and/or increasing COVID-19 outbreaks or epidemics, particularly the magnitude and clinical severity • Virus surveillance and genomic analyses to identify emerging new variants, lineages, and sublineages • Antigenic characterization of emerging viruses to identify antigenically distinct SARS-CoV-2 variant lineages and sublineages and generate candidate vaccines • Integration of epidemiology, genomic analysis, and antigenic characterization to conduct antigenic mapping (cartography) and fitness forecasting • Post-vaccination human serology studies to evaluate the protective immunity offered by the current vaccines against co-circulating and/or emerging variants that may be antigenically distant to identify candidate variants posing the greatest risk of immune escape • Vaccine effectiveness studies to assess the effectiveness of current vaccines (VE) against co-circulating/emerging variants and to provide future guidance on the need for updated vaccines Once an update of the COVID-19 vaccine composition for an upcoming vaccine campaign has been recommended by VRBPAC, FDA anticipates reviewing a comprehensive data package that may include manufacturing, non-clinical, and clinical data. With additional experience in current and improved methods for evaluating the effectiveness of COVID-19 vaccines and with additional experience in manufacturing, future updates to the COVID-19 vaccine composition may potentially be implemented without pre-authorization or pre-approval clinical data for vaccines for which efficacy has previously been demonstrated, similar to the annual strain selection process for seasonal influenza	**These methods need to be validated** **The absence of linkage between medical and vaccination records has impeded production of sound data sets.** **This remains highly problematic, and the issue of long-term effects of gene therapies has been ignored. We are stil waiting for comprehensive safety studies (cancer, genotox etc.) from the original roll-out.** **We still lack a validated immune correlate of protection to b e able to rely on immunobridging type studies.**

vaccines (please refer to Section 4 of FDA Briefing Document for April 6, 2022 VRBPAC).	**There is a world of difference between classical vaccines and gene therapy vaccines,.**
PAGE 23 **5.2.3 Evaluation of effectiveness** Once a recommendation to update the strain composition of COVID-19 vaccines in use in the U.S. has been implemented, FDA anticipates that VE of the updated vaccines will be monitored against the circulating and emerging variants, similar to the approach used for evaluating effectiveness of influenza vaccines. Approaches include real-world evidence and other observational studies of updated vaccines; genomic data to characterize infections in vaccinated individuals; and serological data using "fit-for-purpose" assays to assess protective immunity offered by the updated vaccines against emerging and "antigenically-distinct" viruses identified by ongoing epidemiological surveillance. Outcomes from these studies may suggest the need for better matched vaccines for the next vaccine campaign. In summary, the existence of multiple COVID-19 vaccine compositions, immunization schedules, and differences in vaccine compositions for primary series and booster doses complicate vaccine administration, uptake, and communication. A data-driven approach that is well founded, similar in many ways to the process that is used successfully for updating the composition of influenza vaccines, could lead to substantial simplification of COVID-19 vaccine composition and immunization schedule for all COVID-19 vaccines used in the U.S. At this time, FDA has identified critical evidence gaps and the comprehensive data package that may address those current gaps to support a simplification of vaccine composition and immunizations schedule.	**These are highly flawed designs, especially when test-negative designs are used.**
6. Topics for VRBPAC discussion The January 26th VRBPAC meeting will consider questions around simplifying the composition/dosing regimen of the authorized/approved COVID-19 vaccines, the process for determining the need for recommending strain updates for COVID-19 vaccines, and the timing for implementation of a potential strain-based composition change. **VRBPAC voting question** ***Simplification* of current COVID-19 vaccine use:** • *Vaccine composition*: Does the committee recommend harmonizing the vaccine strain composition of primary series and booster doses in the U.S. to a single composition, e.g., the composition for all vaccines administered currently would be a bivalent vaccine (Original plus Omicron BA.4/BA.5)? **VRBPAC discussion topics** **Future periodic vaccination campaigns:** ***Simplification* of COVID-19 vaccine use:**	

• *Immunization schedule*: Please discuss and provide input on simplifying the immunization schedule to authorize or approve a two-dose series in certain young children, and in older adults and persons with compromised immunity, and only one dose in all other individuals. ***Periodic update* to COVID-19 vaccines:** • *Vaccine composition:* Please discuss and provide input on the consideration of periodic updates to COVID-19 vaccine composition, including to the currently authorized or approved vaccines to be available for use in the U.S. in the fall of 2023.	**What does this mean? Is this an attempt to "cleanse" the poor data for the Pfizer 6 month to 4 years that necessitated three doses? See our comments at ACIP June 23 2022.(14)** **This conflicts with FDA's Dr. Peter Marks in JAMA Dec 2022: (1)** ***"Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally."*** **See also Dr. Paul Offit in NEJM Jan 11 2023 (15)** ***"chasing these Omicron variants with a bivalent vaccine is a losing game"* (cited in Time Magazine).** **time.com/6246525/bivalent-booster-not-very-effective-paul-offit/**

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