BA4/5 bivalent quasi-vaccines: Further relaxation of FDA standards, manufacturing changes and novel spike protein heterotrimers.

ACIP September 1 2022 - Written Remarks: Dr. David Wiseman
Docket No. **CDC-2022-0103**

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Tracking:
Capsule: Significant questions are generated as to FDA's ever relaxed standards in authorizing the new bivalent BA4/5 quasi-vaccine boosters. These include lack of clinical data, and reliance on unvalidated surge modelling, Contrary to FDAs guidelines, there are likely significant manufacturing process changes, In addition, at least from Moderna's presentation, the BA4/5 bivalent product may generate four types of spike protein, including two novel spike protein heterotrimers.

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

1. Background

On August 31st 2022 FDA announced[1] that they had issued EUAs for "bivalent" Covid-19 versions of the Pfizer(1) [2] and Moderna(2) modRNA[3] quasi-vaccines.[4] Since the spike proteins of the BA.4 and BA.5 variants are identical,(3) these vaccines are said to be "bivalent" because they contain modRNA encoding for the spike proteins of the Wuhan and BA4/5 variants. As will be discussed, the term bivalent may be a misnomer (section **Error! Reference source not found.**).

The new EUAs were issued for the Pfizer and Moderna products "for the prevention of COVID-19" (1) (2) and for *"use a single booster dose at least two months following primary or booster vaccination"* with *"any FDA authorized or approved monovalent COVID-19 vaccine."*

The Pfizer product was authorized in individuals 12 years of age and older; the Moderna product was authorized for individuals 18 years of age and older.

The FDA also announced that they were withdrawing their EUA authorization of the previously authorized monovalent vaccines when used as boosters (Pfizer and COMIRNATY, Moderna and Spikevax) for the age ranges where the new bivalent boosters have now received an EUA. The monovalent Pfizer booster dose EUA for 5–11-year-olds, remains in place.

Although not available in the USA, full BLA approvals exist for the original monovalent versions of the Pfizer (i.e. COMIRNATY[5]) and Moderna (i.e. SPIKEVAX[6]) EUA products when used as a primary series. As described above the EUAs for the use of COMIRNATY (> 18 years) and SPIKEVAX (>12 years) as boosters were withdrawn, but not replaced with bivalent versions.

[1] Press Release, FDA August 31, 2022 www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-moderna-pfizer-biontech-bivalent-covid-19-vaccines-use. See also press conference www.youtube.com/watch?v=QNFES1RLf1M

[2] The term "Pfizer" is used for brevity to refer to the "Pfizer-BioNTech Covid-19 Vaccine."

[3] The term "Nucleoside modified messenger RNA" (modRNA) is used throughout the regulatory documents to describe the Moderna and Pfizer products. For example, see Pfizer's EUA letter www.fda.gov/media/150386/download and Moderna-SPIKEVAX Summary Basis for Regulatory Action which uses the term ""Nucleoside modified messenger RNA" www.fda.gov/media/155931/download

[4] To facilitate transparency and informed consent, we distinguish the classical vaccines from this novel class meeting FDA's definition of gene therapy products by the term "quasi-vaccine" (q-vaccine).

[5] www.fda.gov/vaccines-blood-biologics/comirnaty

[6] www.fda.gov/vaccines-blood-biologics/spikevax

No meeting of FDA's VRBPAC had been convened, and no meeting appears to be planned.[7] The decision follows two FDA VRBPAC meetings to discuss preparedness for potential waves of Covid-19 based on new variant strains, on April 6th [8] and June 28th 2022,[9] We have provided oral and written comments previously to the April 6th VRBPAC meeting (4) and the associated ACIP meeting on April 20th (5), and oral comments to the June 28th VRBPAC meeting.[10] Additionally, I provided extensive comments for an article in Trial Site News[11] on the June 28th VRBPAC meeting.

FDA held a press conference on August 31, 2022 with Commissioner Dr. Robert Califf and Director of FDA's Center for Biologics Evaluation and Research Director, Dr. Peter Marks.[12]

Following FDA's decision, CDC convened a meeting of ACIP on September 1 2022, to discuss whether and how CDC should recommend the new variant booster doses. Meeting materials are posted on the ACIP web page[13] consisting of the following presentations:

- Introduction Dr. M Daley
- Update on SARS-CoV-2 Variants and the Epidemiology of COVID-19 Dr. H Scobie
- Immunology of SARS-CoV-2 variants Dr. N Thornburg
- Updates to COVID-19 vaccine effectiveness in the United States Dr. R Link-Gelles
- COVID-19 vaccine safety updates Dr. T Shimabukuro
- Moderna COVID-19 Bivalent vaccine (Original and Omicron BA.4/BA.5) Dr. J Miller
- Pfizer/BioNTech COVID-19 Omicron-modified Bivalent vaccine candidate Dr. K Swanson
- Evidence to recommendation Framework: Bivalent COVID-19 vaccine booster doses Dr. S Oliver
- Clinical Considerations update Dr. E Hall

ACIP voted on whether CDC should issue recommendations regarding the bivalent products. There were separate voting questions for the Moderna and Pfizer products, to reflect the different age ranges specified in the EUAs with alternate text for the Pfizer product shown in [brackets].

> *"A single dose of bivalent Moderna* [Pfizer-BioNTech] *COVID-19 vaccine is recommended for individuals ages 18* [12] *years and older at least 2 months after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA.*
> *ACIP repeals its previous recommendations for administration of monovalent Moderna [Pfizer-BioNTech] COVID-19 vaccine boosters for persons ages 18* [12] *years and older"*

Each vote passed by a margin of 13 votes in favor to 1 vote against.

I refer to previous submissions made either to FDA (4,6-10) or CDC.(5,9-15) on the subject of th Covid-19 quasi-vaccines.

2. COMMENTS

Yesterday's ACIP proceedings provided an insight into the basis for FDA's decision to issue EUAs for the Pfizer and Moderna bivalent quasi vaccines.
The decision was driven by:

1. Waning and negative efficacy of the existing "original" versions of the quasi-vaccines against the Omicron strain.

[7] www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/2022-meeting-materials-vaccines-and-related-biological-products-advisory-committee
[8] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-April-6-2022-meeting-announcement
[9] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement
[10] youtu.be/BFdzNUus_CE?t=19314
[11] www.trialsitenews.com/a/all-day-hearing-by-fdas-vrbpac-omicron-specific-boosters-recommended-by-19-2-vote-despite-growing-concern-d99f00e5
[12] www.youtube.com/watch?v=QNFES1RLf1M
[13] www.cdc.gov/vaccines/acip/meetings/slides-2022-09-01-02.html

2. A virus that evolves so rapidly, that vaccines targeting new variants become obsolete before identification, manufacturing, testing and regulatory review can be completed.
3. Prediction, of Fall surge of Covid-19 in the fall, based on unvalidated modeling.

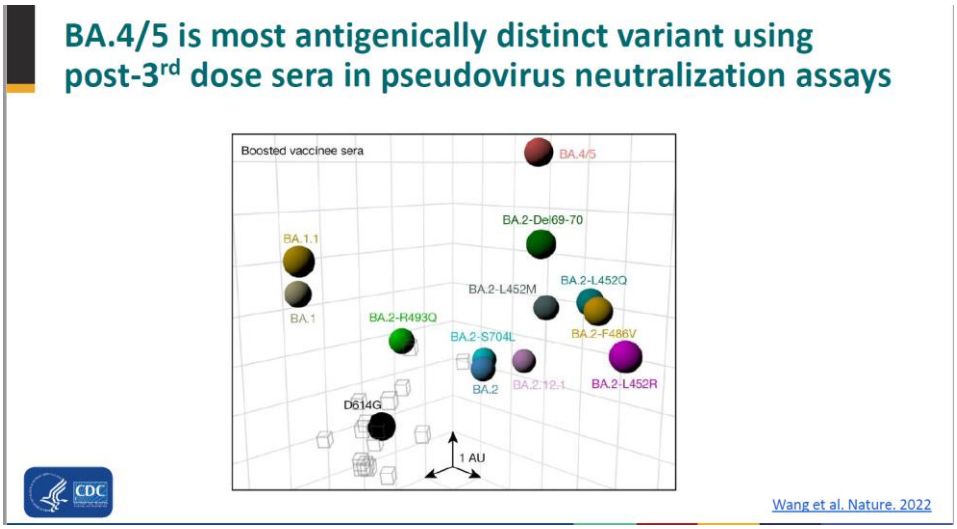
FDA already relaxed preclinical and clinical testing guidelines for new variant vaccines in March 2022.(16)
FDA allowed for consideration of new variant versions based on human immunobridging studies, limited safety studies, limited animal studies and clinical and post-marketing safety and efficacy data from the manufacture's prototype vaccine. The new version must be made by the same manufacturer and process as the original, authorized "prototype" version.

This decision signals that FDA have relaxed these standards still further.

The standard for full approval of a medical product is "safe and effective."
The standard for an EUA product (17) is "may be effective" and "based on the totality of the scientific evidence available, that the known and potential benefits outweigh the known and potential risks"
Along with the stunningly poor data supporting children's quasi-vaccines (18) the scarcity of data supporting this recent decision lowers the standard further to "whimsically effective."

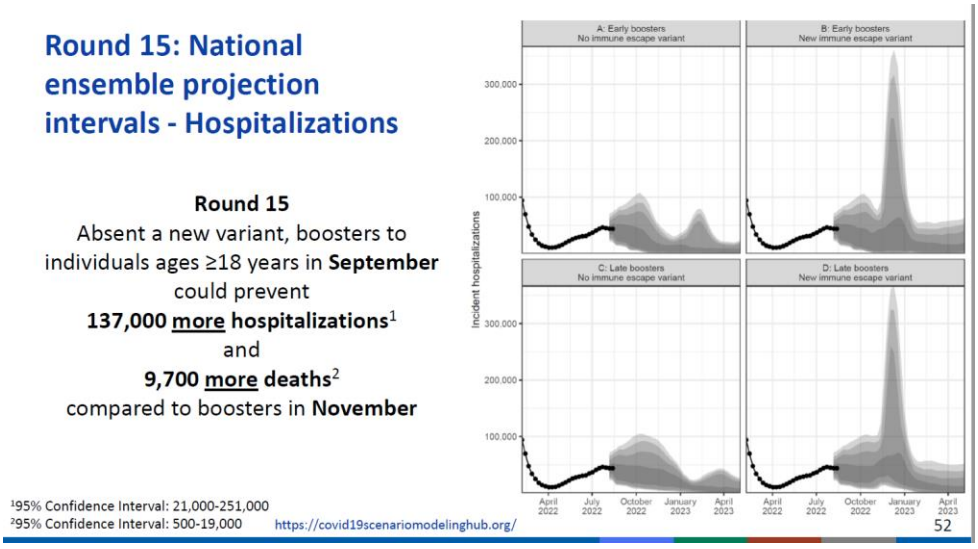
The data provided are likely sufficient, under non-pandemic conditions, to justify initiation of well-regulated clinical trials. However, the authorization of these new variant products will form the basis for mandates and further social division. It is important therefore to place the basis for this decision in proper context and to allow patients fully informed consent in making their decision as to the use of these investigational products without coercion.

1. No clinical data were provided regarding the safety or efficacy of BA4/5 bivalent quasi-vaccines
   In addition to their data on their prototype quasi-vaccines, FDA based their decision on Pfizer's and Moderna's data involving limited immunogenicity and safety studies in humans with various bivalent BA.1+Wuhan and/or monovalent BA.1 versions.
   These studies involved about 300-400 subjects per group and dose intervals of 4-6 months, follow up less than 2 months. The Pfizer study involved adults over 55 years.
   Both companies provided data in mice for BA4/5 bivalent versions.
   These studies are limited in size and duration and do not address use in children as young as 12 years.
2. FDA's revision of its guidelines (16) did provide for the use of immunobridging as the basis for any decision, without further clinical efficacy data. Even had BA4.5 data been presented (which it was not), these data would still have been weak because FDA freely admits that there is no Immune Correlate of Protection (ICOP).
3. By the June 28 2022 VRBPAC meeting the Pfizer and Moderna BA.1 versions were considered obsolete to the point that their deployment was not implemented. Why are data with the BA.1 variant now considered relevant? This is borne out by the antigenic cartography presented by Dr. Thornburg at the ACIP meeting.



On the other hand, if they are considered relevant some activity of the BA.1 versions against BA4/5 based on immunogenicity, why were the BA.1 versions NO deployed in June when the opportunity to prevent the approximately 400 deaths per day that have occurred since then (ie about 24,000 people)?

4. The strategy to hurriedly develop these quasi-vaccine with ever relaxed standards of safety and efficacy is based on predictive modeling of a possible surge[14] that predicted between 95,000 and 211,000 new Covid-19 deaths between March 2022 and 2023 with a Fall surge. It is important to note that the predictive ability and validation of these models is unproven. When questioned on this point by VRBPAC Member Dr. Ofer Levy[15] Dr. Lessler noted [16] that *"What we're not doing is we're not -- at the hub level where we aggregate, we're not weighting the models based on their performance in past rounds."*
   An extension of that model was presented to ACIP to justify advancing the availability of the BA4/5 vaccines to September prior to full testing in November when 9700 deaths were modeled to be saved. This is fewer than the up to 24000 deaths that could have been prevented by deploying the BA.1 versions in June.



[14] www.fda.gov/media/159497/download

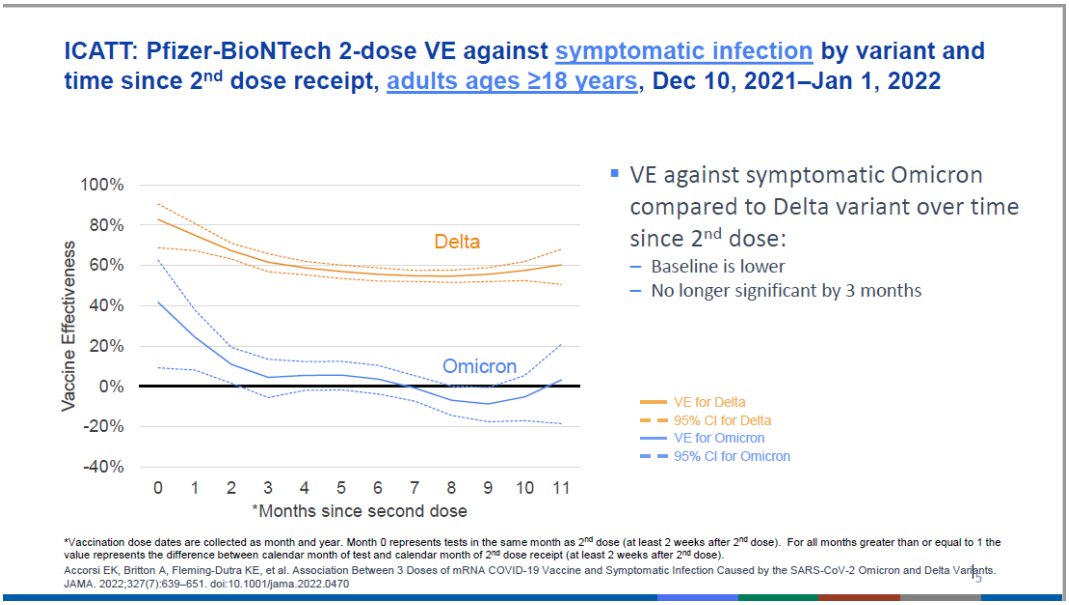
[15] Staff Physician & Principal Investigator Director, Precision Vaccines Program Division of Infectious Diseases Boston Children's Hospital Professor, Harvard Medical School Associate Member Broad Institute Massachusetts Institute of Technology Cambridge, MA 02140

[16] p98-100 of VRBPAC June 28 2022 Meeting Transcript https://www.fda.gov/media/160778/download

5. VRBPAC's vote to recommend the development of BA4/5 bivalent vaccines on June 28, 2022, did not extend to recommend the products of that development. They were not giving a blank check to BA4/5 vaccines without first seeing data that was expected to be generated. Several VRBPAC member expressed concerns for safety and the need for appropriate testing (Dr.s Hildreth, Offit, Meissner).
6. There is safety or other data justification for reducing the boosting dose interval from 5 to 2 months. This concern was expressed by ACIP members, who felt this was a safety concern. CDC staff informed ACIP members that it was not possible for legal reasons to extend this dose interval in CDC's recommendations. This is despite the fact that CDC have done exactly that by lengthening te primary sis dose interval up to 8 weeks.

FDA's decision may be related to data presnted by CDC on VE of the original vaccine versions. Not only does vaccine effectiveness wane over time since vaccination, but the initial efficacy was much reduced from the 90% or so described against the original Wuhan variant, to around 40%.as can be seen from the slide presented by CDC's Dr. Link-Gelles at the VRBPAC meeting of June 14 2022.

Slide 5 presented by Dr. Ruth Link-Gelles at VRBPAC Meeting of June 14 2022[17]



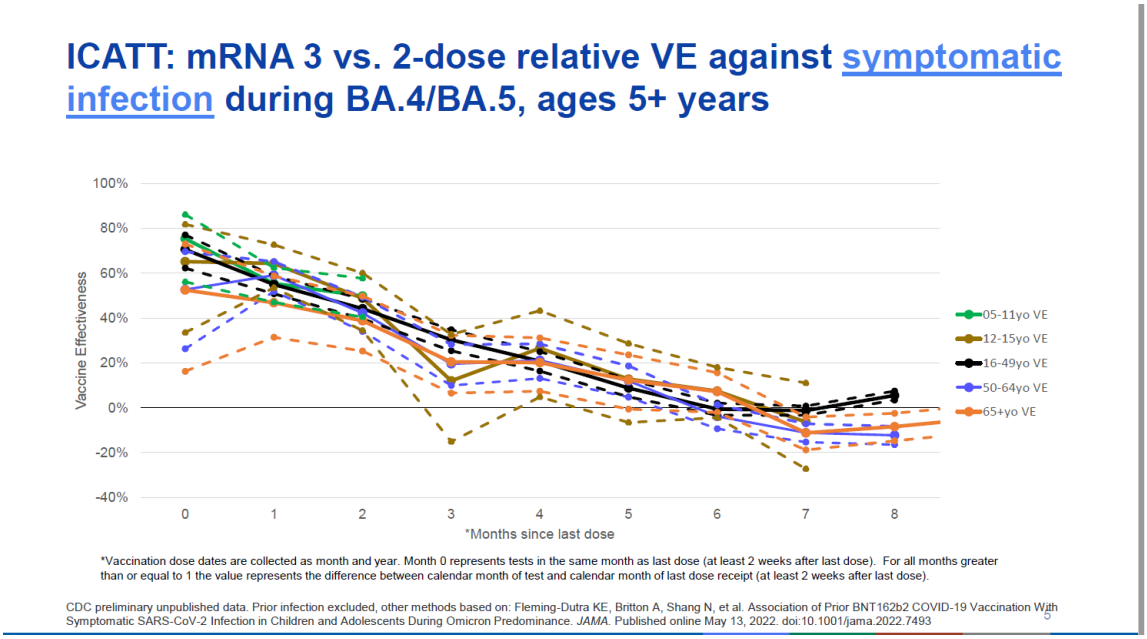
According to these data (also published (19)), vaccine effectiveness against the earlier delta strain (prevalent from about mid- to late 2021) started at around 80%, and waned to about 60% after about 5 months. Vaccine effectiveness against the Omicron strain, however, started at around only 40%. This means that AT NO TIME does the Vaccine Effectiveness meet FDA's standard of 50% (with a lower CI of 95%) (16) for issuing an EUA, or to justify the continued existence of the EUA.

There are two other startling features to this slide. Firstly, the slide notes that by 3 months, the VE (Vaccine Effectiveness) against Omicron is not only lower than FDA's 50% standard, it is "no longer significant by 3 months," and even the lowest level of vaccine effectiveness cannot be distinguished statistically from zero effectiveness. This is indicated by the fact that the lower blue dashed line (Confidence Interval) dips below the value of zero percent.

Secondly, the vaccine effectiveness dips below zero at about 7 months, that is it become negative. The fact that this happens may indicate some sort of compromise to the immune system.

[17] *COVID-19 vaccine coverage & effectiveness during Omicron for children and adolescents*, FDA VRBPAC Meeting Presentation, Jun 14, 2022, available at www.fda.gov/media/159225/download

At the September 1 2022 ACIP meeting Dr. Link-Gelles provided an update for the era of BA.4 and BA.5 Omicron, exemplified by this slide,[18] showing VE for 3 vs 2 doses of mRNA quasi-vaccines, statistically indistinguishable from zero by about 4-5 months and dipping below the lower confidence interval bound of 30% defined in FDA's guidance(16) by about 2-3 months. These observations must surely have played an important role in FDA's revision of its authorized booster dose interval from 5 months to 2 months.



[18] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-09-01/04-COVID-Link-Gelles-508.pdf

7. Yet another example of an incorrect vial label was shown, adding to the label errors described at recet ACIP meetings. With the high number of dose administration errors reported in VAERS by Dr. Shimabukuro, this is alarming.
8. The revised FDA guidelines for new variant vaccines, speak of monovalent vaccine they do not apply to bivalent vaccines.
9. Contrary to the revised guidelines requiring the same manufacturing process for a new variant vaccine, it is obvious s to anyone who has manufacturing experience, that producing a bivalent vaccine adds complexity and quality control issues to a process designed to produce a monovalent vaccine.
10. Moderna's Drs. Miller and Edwards disclosed that Moderna's bivalent vaccine involved the two mRNA sequences being incorporated into the same LNP. Aside from the manufacturing implications of this, Moderna also disclosed that these two sequences could be expressed I the same cell to produce a heterotrimer spike protein. It is therefor possible that FOUR different spike proteins could be expressed in patients – Wuhan, BA.1, Wuhan-BA.1 (2:1) and Wuhan-BA.1 (1:2). This raises significant new safety concerns.
11. Although comparisons are made to the way flu vaccines are developed each year, it is evident that the manufacturing and other issue are far mor complex than described for flu vaccine production.[19]
12. Dr. Sanchez repeated questions whether the spike protein could cross the placenta went unanswered. I have documented other examples from earlier ACIP or VRBAPC meitgs where these sorts of questions have been ignored.

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[19] https://www.cdc.gov/flu/prevent/how-fluvaccine-made.htm#egg

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