ACIP October 19-20-2022. BA4/5 bivalent quasi-vaccines in yet younger children: Further erosion of scientific and ethical standards

ACIP October 19 2022 - Written Remarks: Dr. David Wiseman
Docket No. **CDC-2022-0111**
David Wiseman PhD, MRPharmS (Synechion@aol.com)

Tracking:
Capsule: Following FDA's September EUA of the BA4/5 boosters based on scant human BA1 data and limited murine BA4/5 data and using an "extrapolative" approach, FDA extended the EUA to children 5 years (Pfizer) and 6 years (Moderna) old, with no VRBPAC meeting. CDC endorsed this action, without convening an ACIP meeting. No efficacy data were presented to support this decision intensifying the significant questions of FDA's ever relaxed standards and reduced transparency. 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 September presentation, the BA4/5 bivalent product may generate four types of spike protein, including two novel spike protein heterotrimers which raises significant safety issues and the misnaming of a "bivalent" vaccine to what might be better described as a "quadrivalent" vaccine. FDA's authorization is based partly on the premise that the manufacturing process for the bivalent versions is the same as for the monovalent versions. It is evident that significant QA issues are generated that can affect safety and efficacy.

ACIP voted to include the Covid-19 vaccines in the Vaccines for Children program, and the Adult and Children's Immunization schedules. ACIP members attempted to provide assurances that the addition of Covid-19 vaccines to the VFC and Immunization Schedules did not constitute a mandate. However, there is every danger that local authorities will be emboldened by these additions to impose work or school mandates.

CDC presented data on the use of the vaccines in pregnancy aimed to reinforce CDC recommendations that circumvent manufacturers' off-label claims outside of FDA approved instructions stating that data are insufficient to inform vaccine risks in pregnancy. If the data are robust, let FDA modify the label. We highlight CDC studies where the conditions may have been created for the coercion of pregnant women in pregnancy studies without their knowledge or consent.

With no discussion of emerging variants and immune escape significant questions are raised as to the soundness of FDA and CDC's strategy, and the erosion of scientific and ethical standards.

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

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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 2, comment 10)

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.

No meeting of FDA's VRBPAC had been convened. The decision follows two FDA VRBPAC meetings to discuss preparedness for potential waves of Covid-19 based on new variant strains, on April 6th [7] and June 28th 2022,[8] We have

[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
[7] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-April-6-2022-meeting-announcement
[8] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement

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.[9] Additionally, I provided extensive comments for an article in Trial Site News[10] on the June 28th VRBPAC meeting.

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. We posted comments to the docket for the September 1 2022 ACIP meeting.(6)

On October 12 2022,(7) FDA extended the authorization for the bivalent boosters down to 5 years for the Pfizer product,(1) and 6 years for Moderna.(8). No VRBPAC meeting was convened and details as to whether any data were considered beyond that for the September 1st decision are scant. On the same day, CDC endorsed FDA's decision(9), unusually with convening an ACIP meeting to discuss this matter.

An ACIP meeting was however convened for October 19 and 20. Meeting materials are posted on the ACIP web page[11] consisting of the following presentations:

- Introduction Dr. M Daley
- COVID-19 in pregnant people and infants ages 0-5 months; COVID-19 vaccine safety in pregnancy; Effectiveness of maternal COVID-19 vaccination in pregnant Dr. S Ellington; Dr. C Olsen and Dr. E Kharbanda; Dr. K Fleming-Dutra
- COVID-19 vaccines in children Dr. S Oliver
- Vaccines for children Dr. J Santoli

Two votes were cast. The first of these was to include the Covid-19 vaccines in the Vaccine for Children program. The second was to discuss revisions to the adult and children immunization schedule, which included the addition f Covid-19 vaccines. These presentations are here:

- Combined Immunization Schedule
- Introduction Dr. S Cineas
  2023 child and adolescent schedule revisions; 2023 adult schedule revisions
- Dr. P Wodi; Dr. N Murthy

I refer to previous submissions made either to FDA (4,10-14) or CDC.(5,13-19) on the subject of th Covid-19 quasi-vaccines.

2. ORAL COMMENTS VERBATIM

David Wiseman – Oral Comments: ACIP October 19 2022
Docket No. **CDC-2022-0111**

Thank you. CDC's (9) and FDA's extension (7) of the bivalent booster EUAs to younger children without VRBPAC or ACIP votes exudes regulatory steamrolling that avoids questions about:

- extrapolations from data described by FDA[12] as preliminary, imprecise, and potentially unstable,
- the use of "not be scientifically established" immunobridging data, per FDA
- relevance of extinct Wuhan and BA1 strains
- and BA4/5 data based on as few as 8 mice.
- Whether new variant vaccines can be relied on based on mouse data to offer significant protection against a rapidly mutating virus, in a way that the benefits of using them outweigh the risks (see section 5). These concerns have been raised by a number of VRBPAC members.

CDC asserts that FDA says these *"vaccines are safe and effective"*[13] No. the EUA standard (20) is "may be effective" which FDA have lowered further.

FDA have introduced a 2 month boost interval, likely due to evidence of negative efficacy by 3 months. Does this signal immunologic harm? ACIP's efforts to revise this interval were rebuffed despite other examples of CDC modifying FDA decisions.

[9] youtu.be/BFdzNUus_CE?t=19314
[10] www.trialsitenews.com/a/all-day-hearing-by-fdas-vrbpac-omicron-specific-boosters-recommended-by-19-2-vote-despite-growing-concern-d99f00e5
[11] https://www.cdc.gov/vaccines/acip/meetings/slides-2022-10-19-20.html

[12] https://youtu.be/Ixm4UmldTGQ?t=14397
[13] https://www.cdc.gov/vaccines/covid-19/planning/children/6-things-to-know.html

mRNA vaccines are not flu vaccines which are not gene therapies that turn your body into a factory for a toxic spike protein. Questions asked by VRBPAC's Dr. Portnoy[14] and ACIP's Dr. Sanchez about the locus and duration of spike production and crossing the placenta have been repeatedly evaded.

FDA's guidance on variant vaccines applies to monovalents made by a prototype process. Bivalent production raises significant QA, safety and efficacy implications.

At the last ACIP meeting Moderna revealed that the two mRNAs in their bivalent product generates heterotrimers. Is their vaccine tetravalent with two homotrimers and two novel heterotrimers with unstudied pharmacology and toxicology?

Today's pregnancy discussion spotlights CDC's recommendations[15] that circumvent manufacturers' off-label claims outside of FDA approved instructions stating that data are insufficient to inform vaccine risks in pregnancy.[16] [17] [18] [19] If the data are robust, let FDA modify the label.

More concerning are two VSD studies. 1346[20] and 1345, including some of today's presenters[21] which stated pertinently:

> *Now that […] pregnancy is not a contraindication, there is an urgent need to monitor the safety of these vaccines […] during […] pregnancy.*

You cannot recommend a product saying it is safe without informing patients of the urgent need to study its safety and seek to *"waive the requirement"* for informed consent.
Alarmingly, since the conditions appear to have been created where not only pregnant women participated in a study without their knowledge, they may have been coerced to do so by Federal and other mandates.

Along with CDC's ignoring safety signal studies by NIH, scientific standards have been eroded beyond recognition, ethical standards appear compromised. A more robust discussion of the safety and efficacy of these products must occur, including before they are added to the VFC program. ACIP members, please demand answers. Thank you for your work.

3. EXPANDED COMMENTS

CDC's (9) and FDA's extension (7) of the bivalent booster EUAs to younger children without VRBPAC or ACIP votes exudes regulatory steamrolling that avoids questions about:

- extrapolations (see 8) from data some of which is described by FDA[22] as preliminary, imprecise, and potentially unstable, Other data relied upon by FDA were limited in size, duration and age group.
- the use of "not be scientifically established" immunobridging data, per FDA (see section 9)
- the lack of data in humans with BA4/5 versions and the relevance of extinct Wuhan and BA1 strains
- and BA4/5 data based on as few as 8 mice.
- Concerns expressed by VRBPAC members (see section 4).
- Companies can avoid answering various questions about their product as has occurred in Europe.[23]

CDC asserts that FDA says these *"vaccines are safe and effective"*[24] No. the EUA standard (20) is "may be effective" which FDA have lowered further.

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[14] https://www.youtube.com/watch?v=Ixm4UmldTGQ&t=11575s
[15] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html
[16] https://www.fda.gov/media/157233/download
[17] https://www.fda.gov/media/161318/download
[18] https://www.fda.gov/media/153715/download
[19] https://www.fda.gov/media/161327/download
[20] *PROTOCOL: COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety Data Link* (April 28, 2021), available at www.cdc.gov/vaccinesafety/pdf/VSD-COVID-Vaccine-SAB-SB-Protocol-508.pdf.
[21] *PROTOCOL: COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants* (June 29, 2021), available at www.cdc.gov/vaccinesafety/pdf/COVID19-acute-maternal-outcomes-508.pdf.
[22] https://youtu.be/Ixm4UmldTGQ?t=14397
[23] See this report of a Dutch MEP challenging Pfizer about the lack of data showng that the vacines reduce transmission. https://theconservativetreehouse.com/blog/2022/10/11/dutch-member-of-european-parliament-questions-pfizer-about-covid-vaccine-the-answer-destroys-foundation-for-covid-passport/
See also this report of Pfizer EO Dr. Bourla refusing to appear to answer questions https://data-matter.tvwfc.co.uk/videochannel/covid-19_news/v-7103_12102022/

[24] https://www.cdc.gov/vaccines/covid-19/planning/children/6-things-to-know.html

FDA have introduced a 2-month boost interval, likely due to evidence of negative efficacy by 3 months. Does this signal immunologic harm? (see section 6) ACIP's efforts to revise this interval were rebuffed despite other examples of CDC modifying FDA decisions.

We have previously commented on the gene therapy nature of these vaccines.[25]

mRNA vaccines are not flu vaccines which are not gene therapies that turn your body into a factory for a toxic spike protein. Questions asked by VRBPAC's Dr. Portnoy[26] and ACIP's Dr. Sanchez about the locus and duration of spike production (section 13) and crossing the placenta (see section 14) have been repeatedly evaded or, in the case of the Pfizer product, unimportant. . A related question involves differences in the ug doses used in the Pfizer and Moderna products. This is critical to understanding the mechanism of action, the efficiency of transfection and translation. Dr. Daley's (ACIP) attempt to understand this were met with silence at the June 23 ACIP meeting (section 12)

Regarding the persistence of spike protein produced from Moderna's vaccine, at the June 23 meeting, Moderna said that it lasted less than a week. This is contradicted by published studies (21,22) (some involving Pfizer), with others showing spike protein still present in small amounts at 4m in exosomes.(23) There is in vitro production of Moderna spike up to 14 days. (24) The Stanford study in Cell showed persistence of vaccine message and antigen persists for at least 60 days.(22)

FDA's guidance on variant vaccines applies to monovalents made by a prototype process. Bivalent production raises significant QA, safety and efficacy implications. FDA already relaxed preclinical and clinical testing guidelines for new variant vaccines in March 2022.(25) 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 versions must be made by the same manufacturer and process as the original, authorized "prototype" version. (see section 7). Although comparisons are made to the way flu vaccines are developed each year, it is evident that the manufacturing and other issues are far mor complex than described for flu vaccine production.[27]

At the last ACIP meeting Moderna revealed that the two mRNAs in their bivalent product generates heterotrimers. Is their vaccine tetravalent with two homotrimers and two novel heterotrimers with unstudied pharmacology and toxicology?

Today's pregnancy discussion spotlights CDC's recommendations[28] that circumvent manufacturers' off-label claims outside of FDA approved instructions (see 11.1) stating that data are insufficient to inform vaccine risks in pregnancy.[29] [30] [31] [32] If the data are robust, let FDA modify the label. The position of the UK's MHRA is discussed in section 11.2 .

More concerning are two VSD studies. 1346[33] and 1345, including some of today's presenters[34] which stated pertinently:

> *Now that […] pregnancy is not a contraindication, there is an **urgent need** to monitor the safety of these vaccines […] during […] pregnancy.*

You cannot recommend a product saying it is safe without informing patients of the urgent need to study its safety and seek to *"waive the requirement"* for informed consent.

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[25] Wiseman D, Seligmann, H, Pantazatos SP. Covid-19 gene therapy vaccines: Why no review by FDA's Office of Tissues and Advanced Therapies (OTAT) and Cell Therapy Gene Therapy Advisory Committee (CTGTAC) Written comments submitted re: FDA- CTGTAC Meeting June 10th 2022 FDA-2022-N-0470
https://www.regulations.gov/comment/FDA-2022-N-0470-0179
https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment_1.pdf
https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment_2.pdf
Oral comments: https://youtu.be/Eo2BXnGienc?t=11547

[26] https://www.youtube.com/watch?v=Ixm4UmldTGQ&t=11575s

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

[28] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html

[29] https://www.fda.gov/media/157233/download

[30] https://www.fda.gov/media/161318/download

[31] https://www.fda.gov/media/153715/download

[32] https://www.fda.gov/media/161327/download

[33] *PROTOCOL: COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety Data Link* (April 28, 2021), available at www.cdc.gov/vaccinesafety/pdf/VSD-COVID-Vaccine-SAB-SB-Protocol-508.pdf.

[34] *PROTOCOL: COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants* (June 29, 2021), available at www.cdc.gov/vaccinesafety/pdf/COVID19-acute-maternal-outcomes-508.pdf.

Alarmingly, since the conditions appear to have been created where not only pregnant women participated in a study without their knowledge, they may have been coerced to do so by Federal and other mandates. (see 11.3 for further detail).

CDC have continued to ignore safety signal and claimed in an FOAI response that they had not conducted PRR analyses, as specified by the VAERS SOP.(26) A paper has been published recently(27) which has in fact conducted exactly this sort of analysis. This work was supported by NIH NIAID grants. This work references another paper(28) whose authors include an NIH scientist. FDA has also published work on signal analysis.(29)

Dr. Daley's question as to CDC or NIH's long-term plans to study the pathogenesis of AEs, have gone unanswered, despite NIH's Dr. Beigal undertaking provide a written answer.

https://www.youtube.com/watch?v=iZTuP806RTU&t=6880s
1:54:40 >> Thank you. >> Thank you. Dr. Daley. >> Yeah. So, I have a question about sort of our long-term plans for risk mitigation and risk reduction, and I'm not sure who best to direct this to. Perhaps Dr. Beigel or if he's unavailable Dr. Shimabukuro. But sort of what are the plans to study the biology or the pathophysiology of this [referring to AEs], and I ask that in the hope that we better understand it and then we're better able to reduce it in the future.

Scientific standards have been eroded beyond recognition; ethical standards appear compromised. A more robust discussion of the safety and efficacy of these products must occur, including before they are added to the VFC and Immunization Schedule. Despite assurances from ACIP members that the addition of Covid-19 vaccines to the VFC and Immunization Schedule did not constitute a mandate, there is every danger that local authorities will be emboldened by these additions to impose work or school mandates.

4. Concerns expressed by VRBPAC members

VRBPAC's vote on to recommend the development of BA4/5 bivalent vaccines on June 28, 2022, did not extend to recommend the products of that development. Moderna and Pfizer were not giving a blank check to BA4/5 vaccines without first seeing data that was expected to be generated. Several VRBPAC members expressed concerns for safety and the need for appropriate testing certainly beyond mice.[35]
Dr. Paul Offit, a member of VRBPAC was quoted as saying:
""I'm uncomfortable that we would move forward-that we would give millions or tens of millions of doses to people-based on mouse data,""
"data from mice is not enough to demonstrate that is the case. The vaccine companies and the FDA need to present human data to the public that shows a dramatic increase in neutralizing antibodies from the omicron BA.4 and BA.5 shots in people compared with the original vaccine. […] "You can't ask millions of people to get this booster dose without showing some human data that you have a dramatic increase in neutralizing antibodies to the BA.4/BA.5 strains as compared to boosting with the ancestral type."

VRBPAC's Dr. James Hildreth stated at the June 28 VRBPAC meeting:[36]
"Thank you, Dr. Monto, and thank you, Dr. Weir, for the information you provided us. I just have three thoughts to share. One is I mentioned this last time that these new vaccine derivatives are sequences -- are new substances, and I just wonder whether or not they need to be more carefully tested for safety. Maybe some electro [molecular] mimicry could cause antibodies. I mean, there are a lot of things that are possible. I just think that we have to be more careful about using these new vaccines without more thorough testing."

VRBPAC's Dr. Meisner expressed concerned about monitoring for myocarditis n the new variants.[37]

5. Can we produce new-variant vaccines quickly enough?

5.1. Emergence of new variants

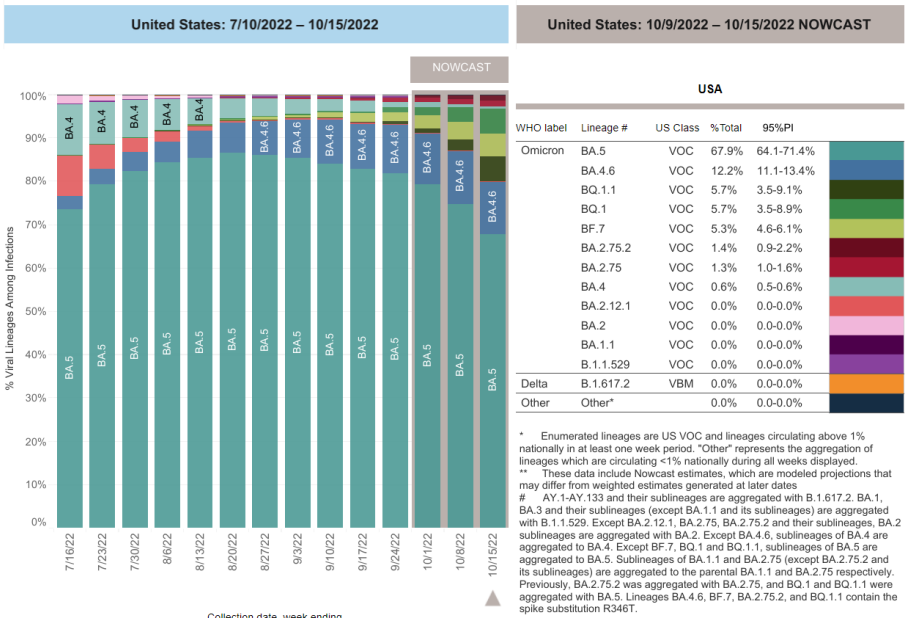
The original versions of the Pfizer, Moderna and Janssen Covid-19 quasi vaccines were designed to produce the spike protein to the ancestral Wuhan SARS-CoV-2 strain. These vaccines versions are essentially obsolete as the virus has evolved significantly since its recognition almost three years ago.

35 What's behind the FDA's controversial strategy for evaluating new COVID boosters. August 18 2022 www.npr.org/sections/health-shots/2022/08/18/1117778748/whats-behind-the-fdas-controversial-strategy-for-evaluating-new-covid-boosters

36 https://www.youtube.com/watch?v=BFdzNUus_CE&t=24375s, *p292 of transcript*

37 https://youtu.be/BFdzNUus_CE?t=28356 see p344 of transcript

The chart below is CDC's Nowcast[38] as of 10/15/22 showing CDC's estimates of recent proportions of circulating variants. By June 2022, the original Wuhan, along with the Alpha and Delta variants had become extinct. The original subvariant of Omicron B.1.1.529 which started its ascendency around December 2021 had all but disappeared along with the BA1.1. Omicron sub-variant. At that time the BA.2 and BA 2.12.1 variants accounted for over 90% of the variants in circulation.



By August 2022, those BA 2 variants had largely disappeared, with the BA.5 variant appearing close to a peak of just under 90%, which is now lower than 80% including subvariants. The BA.4 variant which had peaked at 13.1% at the beginning of July 2022, has now declined to 0.6%, with a BA4.6 variant beginning to rise, now at 12.2%.

5.2. Efforts to plan for new variant waves

FDA and other public health officials have been trying to address the problem of preparing vaccines for a virus that mutates so quickly, there is insufficient time to make new variant vaccines and to conduct adequate testing. The fear expressed by FDA was that a new Covid-19 surge may occur in the fall and that we would be unprepared, vaccine-wise, to be able to protect many people.

5.2.1. Inability to use influenza planning methodology to plan for new variants

FDA held two VRBPAC meetings on this subject, on April 6th 2022 [39] with a follow up on June 28, 2022.[40] In the various presentations made at these meetings, there was consensus that although well-established procedures exist for determining in the early part of any year, which sort of vaccines might be needed for the largely predictable seasonable influenza wavs in the later part of the year, this sort of planning could not be easily applied for SARS-Cov2 coronavirus. The two main reasons for this were firstly that there was no establish seasonal pattern for SARS-Cov2, and secondly that the SARS-Cov2 virus much more rapidly (about 2.5 times) than the influenza virus. This means that even if a particular strain of SARS-Cov2 were prevalent in any given January it would likely be extinct (and probably irrelevant) by the Fall.

5.2.2. New BA.1 versions became obsolete by June

At the June 28 2022 VRBPAC meeting, Pfizer and Moderna presented data from clinical studies using Omicron BA.1 versions of their quasi vaccines that had been initiated soon after the emergence of the Omicron variant in December 2021. However, by the time of the June 28 meeting, the BA.1 variant was almost extinct, with the BA.1 quasi-vaccine versions performing marginally better against the now prevailing (and also in June 2022) BA.4/5 variant than the original vaccine versions, and attenuated benefits in those with prior infections. Based on FDA and other presentations, VRBPAC agreed that rather than deploy the BA.1 versions, manufactures be asked to produce BA.4/5 vaccine versions for a Fall delivery.

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

[39] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-april-6-2022-meeting-announcement

[40] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-june-28-2022-meeting-announcement#event-materials

Given that there have been approximately 300-500 Covid-19 deaths per day since mid-June,[41] even a small improvement in vaccine efficacy by deploying the BA.1 variants, may have saved some lives. Rather than doing this, VRBPAC considered the BA.1 versions obsolete and recommended that Pfizer and Moderna be asked to produce BA.4/5 versions for a Fall delivery.

5.2.3. Will BA4/5 versions provide adequate protection?

FDA's strategy was to ask the manufacturers to produce a variant vaccine based on what is considered to the most evolutionarily advanced variant in the hope that if new variants emerge, they will have some cross reactivity with the BA4/5 versions.

A recent report(30) noted the potential for the BA4.6 variant to escape immunity produced by the original Wuhan vaccine version.

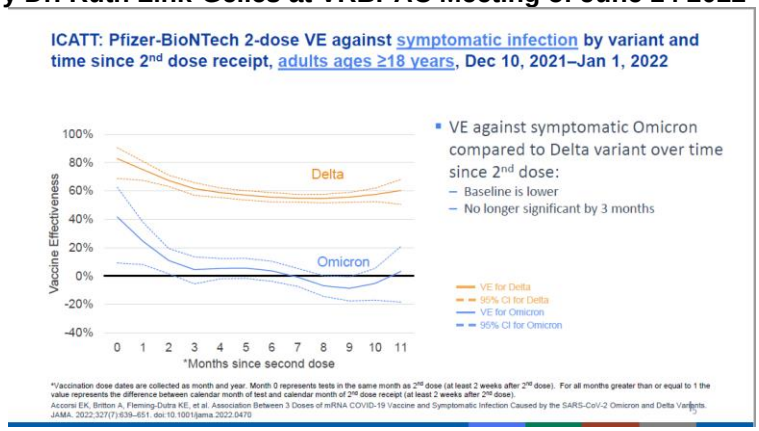
This begs the question as to whether new variant vccines can be produced quickly enough to keep up with viral mutations.

6. Waning and negative efficacy

There is no safety or other data justification for reducing the boosting dose interval from 5 to 2 months as FDA have done. This concern was expressed by ACIP members at the September 1st meeting , 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 the primary sis dose interval up to 8 weeks.

FDA's decision may be related to data presented 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[42]



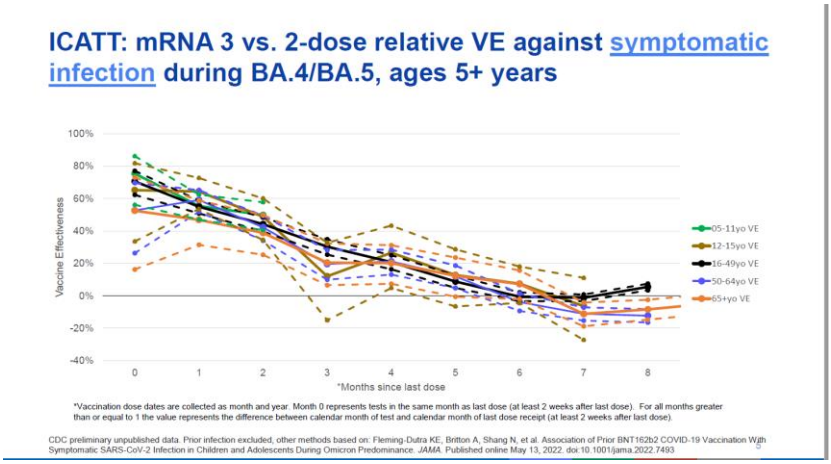
According to these data (also published (31)), vaccine effectiveness against the earlier delta strain (prevalent from about mid- to late 2021) started at around 80%, and waned to about 60% after about 5 months. Vaccine effectiveness against the Omicron strain, however, started at around only 40%. This means that AT NO TIME does the Vaccine Effectiveness meet FDA's standard of 50% (with a lower CI of 95%) (25) 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 becomes negative. The fact that this happens may indicate some sort of compromise to the immune system.

[41] https://covid.cdc.gov/covid-data-tracker/#trends_dailydeaths_select_00

[42] *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,[43] 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(25) 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.



6.1. Early indications, pre-Omicron

Even before the emergence of the Omicron variant there were indications that the immune response to the quasi-vaccines could wane over time and/or that their effectiveness in real world settings were not consistent with data from clinical trials. This included indications of negative efficacy, a situation where there is greater risk of Covid-19 disease after vaccination that without vaccination.

A paper using the Danish health records indicates negative efficacy in some high-risk groups in the early part of the quasi-vaccine roll-out.(32) We reported to CDC(33) and FDA(11) our analyses of Israeli data from the early Pfizer quasi-vaccine roll-out showing an early up-tick in cases following vaccination as well as an excess mortality associated with vaccination of between 121/413 per million vaccinees. We also analyzed data presented by the Israeli Ministry of Health to the VRBPAC Meeting on September 17 2021 and notified CDC of our findings that following initiation of the booster campaign in Israel in July 2021 (delta wave), cases and serious cases rose sooner for "old" vaccinees (those vaccinated more than six months earlier) than for those without vaccination.(13)

As we reported to the ACIP meeting of December 16 2021, (18) our analysis of European data found that all- cause deaths appear to correlate with percentage vaccination in a definite pattern. After an initial detrimental phase of about 4 weeks, there followed a beneficial phase of about 20 weeks. This was then followed by a detrimental phase. These observations were extended with booster dose data from CDC as well as the European Union, where we found that all population booster COVID19 vaccine injections are associated with increases in all-cause mortality in all ages, punctuated by limited periods of benefit.(34,35)

There were also indications of waning efficacy during the Delta period. I documented (15) that for the ACIP meeting of August 30 2021 convened to discuss the BLA for the COMIRNATY product, CDC withheld at least six studies, including those by CDC and Pfizer scientists, describing rapidly waning vaccine effectiveness against symptomatic disease, or effectiveness against the delta strain, from the 90-95% range to, in one case, as low as 42%.

6.2. Omicron Era reduced Primary and Booster Effectiveness: other studies

The finding of negative efficacy has been confirmed by studies around the world such as Denmark, (36) Canada, (37) and Qatar. (38) The Danish study found negative VE of -76.5% by day 90 after primary series, well before the new 5 month boosting interval authorized by FDA. Even more concerning is almost immediate negativity effectiveness reported by the Public Health authority of Ontario, (37) Here the negative effectiveness -40% can be boosted to about +40%, but with no information as to its sustainability. The encouraging news is that persons who received their primary series >240 days, may start to recover their ability to counteract Omicron.

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

7. FDA relaxes testing requirements for new-variant vaccines

Although the vaccines now under development are bivalent (i.e. they are directed against both the original Wuhan strain, and a BA4/5 version) the revised guidance (25) (Appendix 2) appears only to apply to monovalent vaccines.

Anticipating the logistic problems of identifying which variants to produce vaccines against, manufacturing and preliminary testing of new-variant vaccines, FDA revised its Covid-19 EUA guidelines in March 2022. This revision relaxes the preclinical and clinical testing requirements for new variant vaccines applied to the original versions, excerpted here:

> **2. Nonclinical**
>
> A list of the nonclinical studies conducted to support vaccine effectiveness and safety (e.g., characterization of markers associated with enhanced disease, biodistribution, shedding, and attenuation) obtained with the prototype COVID-19 vaccine made by the same manufacturer and process should be provided.
>
> In general, for a modified COVID-19 vaccine directed against a SARS-CoV-2 variant and made by the same manufacturer and process, conducting additional repeat dose toxicity studies or DART studies may not be warranted. Data from the vaccine platform or from the prototype vaccine will be considered in making this decision.

The new version must be made by the same manufacturer and process as the original, authorized "prototype" version.
For non-clinical studies - conducting additional repeat dose toxicity studies or DART (Development and Reproductive Toxicology) studies may not be warranted. Data from the vaccine platform or from the prototype vaccine will be considered in making this decision. Data from studies in a relevant animal model *"are encouraged as they contribute to the totality of the evidence supporting the authorization of a modified COVID-19 vaccine."*
In terms of clinical data supporting the effectiveness of the modified vaccine, FDA's revised guidance states that it will base its determination on:

"The efficacy of primary vaccination with the manufacturer's authorized or approved prototype COVID-19 vaccine made by the same process and for which a clinical disease endpoint efficacy study has been conducted that met FDA pre-specified success criteria, AND
Comparison of immune responses (assessed by neutralizing antibody) induced by the modified vaccine and the prototype vaccine."

> **3. Clinical data**
>
> **a. Clinical data to support effectiveness of a modified vaccine**
>
> The effectiveness of a modified COVID-19 vaccine against a particular SARS-CoV-2 variant of concern (VOC) can be evaluated based on:
>
> - The efficacy of primary vaccination with the manufacturer's authorized or approved prototype COVID-19 vaccine made by the same process and for which a clinical disease endpoint efficacy study has been conducted that met FDA pre-specified success criteria, AND
> - Comparison of immune responses (assessed by neutralizing antibody) induced by the modified vaccine and the prototype vaccine.

Safety studies of only limited size and follow up period may be required.

> *"Safety assessments, including solicited local and systemic adverse events assessed daily for at least 7 days after each study vaccination as well as serious and other unsolicited adverse events assessed during the immunogenicity evaluation period, may be sufficient to support EUA of the modified COVID-19 vaccine. However, evaluation of the modified COVID-19 vaccine in a larger safety database than initially planned for immunogenicity studies may be warranted if safety signals arise, and studies should also plan for longer-term assessments of serious and other medically attended adverse events."*

The introduction of a second mRNA strand into the bivalent vaccines adds a new step into the manufacturing process wherein missing efficiencies are undetermined. Transfection and translation efficiencies must be defined. His is all the more important if two mRNA are loaded into the same LNP (see 10).

The changes in the manufacturing process are on a scale of complexity much greater than for gg-based flu vaccines.[44]

FDA (Dr. Doron Fink) has stated that the process used for the bivalents is the same as for the prototype monovalent vaccines, as seen here at the September 1st ACIP meeting.

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

https://youtu.be/JpkatvpuKBM?t=8854
2:28 >> Yeah, Dr. Fink, please go ahead. >>
[FINK] Thank you. I did want to weigh in on this discussion on behalf of FDA, and I do appreciate the amount of discomfort that I'm hearing from committee members who are being asked to take this leap with the COVID vaccines that you haven't been asked to make previously with the COVID vaccines but yet, as Dr. Wharton just reminded us, we do want to on a regular basis annually with influenza vaccines, but as Dr. Long mentioned, with her wonderful construction analogy, these are vaccines that we understand very well in terms of the original monovalent vaccine, and we are talking about bivalent vaccines that are manufactured using the ***very same process and which contain the same total amount of RNA and are otherwise the same except for the fact that they now contain two mRNA sequences*** *instead of one. And so, FDA felt very comfortable with the approach of extrapolating the safety and effectiveness or rather the known and potential benefits and risks which underly our emergency use authorization. Based on the clinical trial experience with the bivalent vaccine containing the BA.1, sub-lineage component, which is also an omicron sub-lineage component we felt similar enough to BA.4/5 to allow us to make that extrapolation. We recognize that we've taken a different path 2:29:42 than the regulatory authorities have in Europe and in Canada, but we made our decision based on several factors including feedback and advice that we got from our vaccines and related biological products advisory committee meeting in June as well as data that we had toward the beginning of the summer including some out of South Africa indicating that neutralizing antibody responses against BA.4/5 natural infection appeared to be more cross reactive than responses against BA.1 infection. And so for the purposes of improving protection heading into the fall and winter, the best we could against the strain that we knew or sorry the variant and sub-lineage that we knew would be predominant, we went with the choice of a BA.4/5 component, and we felt confident in that. I also just want just want to address briefly the concern about extrapolating across age groups. Again, we have a tremendous amount of experience with the monovalent original vaccines in the age groups in which they're authorized. There are some differences across various age groups in terms of reactogenicity profile or immune response, but by and large the experience and trends are very similar across age groups and even more so what we're seeing as we move from primary series doses to booster doses trends in the exact same direction no matter which age group we're talking about. And so, for that reason we felt very comfortable taking data from a specific age group whether it was adults 18 years of age and older or adults 55 years of age and older and extrapolating that experience with a bivalent product to authorize another bivalent product, again, manufactured using the exact same process to authorize use of that product in all age groups. And I think we will be intending to take that approach for consideration of authorizing the bivalent vaccines in younger pediatric age groups once we have a product and manufacturing information that would allow us to do so. Thank you.*

8. FDA's Extrapolation Approach

FDA's press release of August 31, 2022 stated that it based its decision on:

- *"the totality of available evidence, including extensive safety and effectiveness data for each of the monovalent mRNA COVID-19 vaccines*
- *safety and immunogenicity data obtained from a clinical study of a bivalent COVID-19 vaccine that contained mRNA from omicron variant BA.1 lineage that is similar to each of the vaccines being authorized*
- *and nonclinical data obtained using a bivalent COVID-19 vaccine that contained mRNA of the original strain and mRNA in common between the BA.4 and BA.5 lineages of the omicron variant."*

FDA's Dr. Fink characterized this authorization of the Pfizer (1) and Moderna(2) bivalent products as an extrapolation approach as seen in this transcript from the September 1 ACIP meeting:
https://www.youtube.com/watch?v=_SgTNFlQlqg&t=1085s
FDA authorized these bivalent vaccines with the goal 18:12 of improving protection afforded by vaccine booster doses by having the vaccine strain composition more closely matched to the currently circulating SARS-CoV-2 strain, the vast majority of which in the U.S. are now BA.5 and additionally by retaining the original strain component for which we have so much experience with these vaccines being ***safe and effective****. FDA in its authoritarian [authorization] considered a totality of evidence that consisted primarily of an* ***extrapolation*** *approach based on data from clinical trials with similar bivalent vaccine formulations consisting of original and omicron BA.1 sub-lineage components as well as extensive experience with the use of the original monovalent vaccines of both primary series and booster doses. All of these data represent data collected with human experience. Additionally, FDA considered supportive data from some animal studies that provided additional reassurance about our* ***extrapolation*** *approach.*

9. Immune Correlate of Protection (ICOP) has still not been established

Even in those instances when some clinical efficacy data were available, the use of immunobridging has been the subject of repeated discussion among the VRBPAC vaccine experts, and FDA have repeatedly admitted that there is no established "Immune Correlate of Protection" (ICOP). In the October 14 2021 VRBPAC meeting, convened to discuss booster doses

for the Moderna quasi-vaccine, and in response to a question on from VRBPAC member Dr. Ofer Levy, Dr. Doron Fink, head of FDA's Vaccine section, stated:[45] (bold added)

> *"DR. DORAN FINK: I wish I could tell you what FDA thinks is the correlate of protection. That would make all of our lives so much easier, wouldn't it? But at this point, FDA's position is that we don't have enough information to understand what specific threshold of any immune response is fully predictive of protection. In the meantime, we're tasked with evaluating data and taking action to address public health needs. To do that, we are relying upon established regulatory science and precedent, in which we use an immunobridging approach based on an immune marker which, although it may not be scientifically established to predict protection at a given threshold, we have reasonable enough confidence in the clinical relevance. We use that immune marker to bridge back to a dosing regimen in the population in which efficacy has been demonstrated. "*

Dr. Levy continued to press the point:

> *"Has the FDA made an estimate of this number and is not free to talk about it? Is that the situation?"*
> *DR. DORAN FINK: No. We are continuing to await traditional data that are both from vaccine manufacturers as well as U.S. government partners and elsewhere."*

Similar questions, with similar answers continued to be raised at various FDA or CDC meetings, but at the June 28th VRBPAC meeting to discuss the new variant quasi-vaccines, Dr. Levy tackled FDA Biologics Head. Dr. Peter Marks: [46]

> *"DR. OFER LEVY: I wanted to make a statement again about correlates of protection. I would like to hear from FDA what their overall approach will be in the coming year around improving our understanding of correlates of protection. We spend a good amount of time reviewing antibody data. We have no doubt that antibodies are important, and yet for all the antibody data we have, we don't have a level of antibody that anybody is comfortable stating is a correlate of protection. So yes, the antibodies are important, but so are the T cells. We heard from Dr. Weir, yes, T cell assays are trickier. They're more diverse, but it's not going to happen without federal leadership to have a standardization of a T cell assay and encourage or in fact require the sponsors to gather that information. So what is the effort to standardize the preclinical assays? This is an effort that's critical not just now but for future cycles of vaccine revision. If we aren't able to define a correlate of protection, we're fighting with one arm tied behind our backs. And for the preclinical data on mice, are assays standardized? Do we (Audio skip)? And then there can be species specificity, so what about preclinical human in vitro models? So I'd be eager to hear from FDA about these topics.*
>
> […] DR. PETER MARKS: The issue of this is -- I mean, Dr. Levy brings up an incredibly important point that T cell mediated immunity is very important here. It is just -- it was difficult to study initially. It's not for a lack of understanding of the importance here. We have been having conversations with our colleagues at NIH and throughout government about how we might move forward here. It's something that we don't have an answer to yet, but it is something, Dr. Levy, we are pursuing and continuing to pursue for how we move forward because obviously as we develop vaccines in the future it will become ever more important because we won't be able to have a large naïve population to vaccinate with newer vaccines. And we will need to understand the T cell response better, so I take your point. It's just we haven't solved the problem yet."

10. Heterotrimer Spike Protein

The transcript from the September 1 2022 ACIP meeting records Moderna's statement about heterotrimer formation.

https://youtu.be/i34wDDfhRpg?t=2176

[LEE] >> Did you want to describe the slide, Dr. Miller? [MILLER] >> Sure. I can do that. I mean, in all cases, the antibody titers 36:20 with the beta bivalent-containing vaccine are numerically higher than what we see with a 1273 vaccine. And the distance between the two actually increases at the six-month time point. And we believe that there is a biologic basis for this. That's actually why we advocated fairly strongly for the bivalent composition. And it's because, when the mRNA in a bivalent formulation is delivered to the cell, both mRNAs so the mRNA for the original strain spike sequence and for the -- whatever the bivalent-containing sequences are delivered to the cell, which means that the ribosomes are translating in the same cell strands of both the original and the variant of concerns. These amino acid chains still naturally assemble into trimers. But we've been working with the University of Washington and been able to demonstrate in a publication that we're in the process of submitting that heterotrimers are actually formed. So what that means is, unlike with the original 1273 where the original three spike sequence is the only one available, we have sequences from both the original strain and the variant of concerns. This actually leads to more open confirmation and exposure of additional antigens. And we

[45] VRBPAC October 14 2021 transcript p216 line 21
www.fda.gov/media/154883/download
youtu.be/BhlshZ7Lkr0?t=20304
[46] VRBPAC June 28 2022 Transcript, P310 line 8
www.fda.gov/media/160778/download
youtu.be/BFdzNUus_CE?t=25665

believe that it's exposure to those additional antigens that leading to the improved antibody persistence, not only against the variant of concern but against the original strain and other variants as well.

The paper referenced by Moderna appears to be that by Scheaffer et al.(39), however that paper does not mention heterotrimer formation:

The preclinical material used in this study were: (1) monovalent mRNA-1273 vaccine that contains a single mRNA encoding the SARS-CoV-2 S2P antigen; (2) monovalent mRNA-1273.529 vaccine that contains a single mRNA encoding the SARS-CoV-2 S2P antigen for BA.1; (3) monovalent mRNA-1273.045 vaccine that contains a single mRNA encoding the SARS-CoV-2 S2P antigen of the BA.4/BA.5 subvariants of Omicron; (4) research-grade bivalent mRNA-1273.214 vaccine, which is a 1:1 bench side mix of separately formulated mRNA-1273 and mRNA-1273.529 vaccines; and (5) research grade bivalent mRNA-1273.222 vaccine, which is a 1:1 bench side mix of separately formulated mRNA-1273 and mRNA-1273.045 vaccines; (6) clinically representative bivalent mRNA-1273.214 vaccine, which is a 1:1 mix in the vial of separately formulated mRNA-1273 and mRNA-1273.529; and (7) clinically representative bivalent mRNA-1273.222 vaccine, which is a 1:1 mix in the vial of separately formulated mRNA-1273 and mRNA-1273.045

See also the comments of Moderna's Dr. Edwards in section 14.

11. Pregnancy and Lactation

11.1. Label statements

Pfizer's preclinical studies show accumulation of the lipid nanoparticles in the ovaries,(40) suggesting that caution is warranted regarding matters relating to menstrual and reproductive health. Additional caution is warranted due to the gene therapy nature of the quasi-vaccines and the interaction of the spike protein with the BRCA protein. (41) Although retracted (for rather dubious reasons), this paper has received support from another paper showing nuclear translocation of spike mRNA and protein.(42)

The FDA approved instructions (representing what the companies are legally allowed to say about their products) still state that available data for the Pfizer, Moderna, and Janssen products "*administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.*" [47]

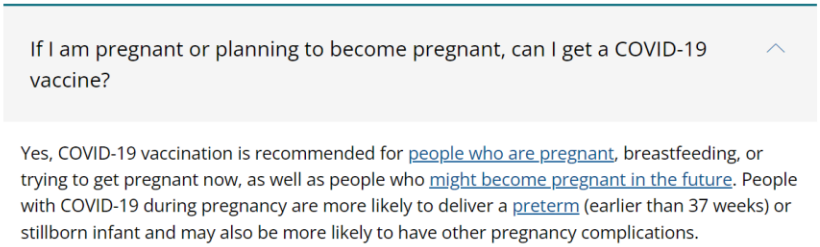
As for lactation, the COMIRNATY label states *"It is not known whether COMIRNATY is excreted in human milk. Data are not available to assess the effects of COMIRNATY on the breastfed infant or on milk production/excretion."*[48]

Label statements concerning pregnancy and lactation for both monovalent and bivalent vaccines can be found for Moderna[49] [50] and Pfizer[51] [52]

In other words, FDA have made no determination whatsoever as to ANY level of safety and effectiveness for these products in pregnancy and lactation. However, CDC continues to recommend these products in both cases [53] If a manufacturer were to suggest this in any other context, this would constitute off-label promotion. Specifically, the CDC site states for pregnancy:

> *Evidence continues to build showing that COVID-19 vaccination before and during pregnancy is safe, effective, and beneficial to both mother and baby. The benefits of receiving a COVID-19 vaccine outweigh any potential risks of vaccination during pregnancy.*

[47] *SPIKEVAX Package Insert*, FDA, at 10, available at www.fda.gov/media/155675/download; *COMIRNATY Package Insert*, FDA, at 16, available at www.fda.gov/media/154834/download.
[48] *COMIRNATY Package Insert*, FDA, available at https://www.fda.gov/media/154834/download.
[49] https://www.fda.gov/media/157233/download
[50] https://www.fda.gov/media/161318/download
[51] https://www.fda.gov/media/153715/download
[52] https://www.fda.gov/media/161327/download
[53] *COVID-19 Vaccines While Pregnant or Breastfeeding*, CDC (last updated July 14, 2022), available at www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html.



https://www.cdc.gov/coronavirus/2019-ncov/vaccines/faq.html

And, for breastfeeding:

> *CDC recommends that people who are breastfeeding get vaccinated and stay up to date with their COVID-19 vaccines, including getting a COVID-19 booster shot when it's time to get one.*
> *Clinical trials for the COVID-19 vaccines currently used in the United States did not include people who were breastfeeding. Therefore, there are limited data available on the:*
> - safety of COVID-19 vaccines in people who are breastfeeding;
> - effects of vaccination on the breastfed baby; and
> - effects on milk production or excretion.

These statements are made despite having almost 2.5 years to conduct proper, definitive studies to demonstrate that the vaccines are safe during pregnancy.

11.2. MHRA Position on Pregancy and Lactation

The UK's MHRA (Medicines and Healthcare products Regulatory Agency) issued their "Public Assessment Report for COVID-19 Vaccine Pfizer/BioNTech." (43) Reflecting the lack of data discussed above, MHRA's toxicity conclusions are as follows (emphasis added):

> The absence of reproductive toxicity data is a reflection of the speed of development to first identify and select COVID-19 mRNA Vaccine BNT162b2 for clinical testing and its rapid development to meet the ongoing urgent health need. In principle, a decision on licensing a vaccine could be taken in these circumstances without data from reproductive toxicity studies animals, but there are studies ongoing and these will be provided when available. In the context of supply under Regulation 174, it is considered that sufficient reassurance of safe use of the vaccine in pregnant women cannot be provided at the present time: *however, use in women of childbearing potential could be supported provided healthcare professionals are advised to rule out known or suspected pregnancy prior to vaccination. Women who are breastfeeding should also not be vaccinated.* These judgements reflect the absence of data at the present time and do not reflect a specific finding of concern. Adequate advice with regard to women of childbearing potential, pregnant women and breastfeeding women has been provided in both the Information for UK Healthcare Professionals and the Information for UK recipients.

The statements ruling out pregnancy before vaccination, as well as the conclusion not to vaccinate if breastfeeding, concern millions of America women.

The MHRA statement is particularly disturbing in the context of CDC's actions following the EUA for the Covid-19 quasi-vaccines, as we documented in our comments to the VRBPAC meeting of September 17, 2021. (10)

11.3. CDC pregnancy studies without consent: conditions created where patients were may have been coerced

CDC study protocol VSD 1345, whose team includes CDC presenters today at the October 12 ACIP meeting and entitled: "COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants"[54] and dated June 29 2021 stated:

> *Now that COVID-19 vaccines are in use in the U.S., and pregnancy is not a contraindication, there is an urgent need to monitor the safety of these vaccines when administered during or around the time of pregnancy.*

[54] *PROTOCOL: COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants* (June 29, 2021), available at www.cdc.gov/vaccinesafety/pdf/COVID19-acute-maternal-outcomes-508.pdf.

The protocol, nonetheless, stated that the American College of Obstetrics and Gynecology "broadly supports that COVID-19 vaccines be available for use in pregnant women and that pregnant women not be denied vaccination." Similar language appeared in a related CDC protocol VSD 1346 entitled "COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety" [55] and dated April 28 2021:

> *Nevertheless, there is an urgent need for data to inform pregnant women and their providers deciding whether to receive a COVID-19 vaccine during pregnancy or following an inadvertent exposure."*

This "urgent need" for study was never communicated when CDC made their recommendations to pregnant women, many of whom may only have agreed to be vaccinated because of mandates.

Further in both these studies, a request was made to *"waive the requirement to obtain informed consent, parental permission."* In other words, pregnant women were participating in a study, without their knowledge or consent in order to gather data because of an urgent need to collect safety data about which they knew nothing.

12. **Transcript of Dr. Daley attempting to get an explanation of the ug dose difference between Pfizer and Moderna**
https://www.youtube.com/watch?v=iZTuP806RTU&t=6911s

[DALEY}
1:55:10 And then, there's a second question that's related to that which is if, again, Dr. Beigel or others on the call could help me understand the exact dose difference between these two different vaccine platforms, because when we hear of 25, 50, or 100 micrograms for Moderna or 3, 10 or 30 micrograms for Pfizer, is that an apples to apples measurement, or does that include other things that come along with the mRNA so that it's not an exact comparison of dose amount?

1:55:46
Thank you. >> Yeah. So, this is John Beigel. So, I will get you a written response. I'm not aware of any studies specifically evaluating the pathophysiology, as you suggested, but let us delve into that and get you a written response to make sure I do a comprehensive review of all the possible paths for that. And then I don't think, I'm trying to think who is best situated for your second question. I'm not sure it's within my purview. [SHIMABUKURO} >> Dr. Daley, could you repeat your second question. [DALEY] >> Well, so there are cited micrograms differences between Moderna and Pfizer, and I'm just trying to understand if those are measuring the exact same thing or if they're measuring something different and we can't really say this dose is 10 times higher than that dose when we're comparing across platforms. And Dr. Beigel, I apologize for putting you on the spot, but I appreciate your answer. Thank you. [SHIMABUKURO] >> Dr. Daley, I have to defer to the folks in the immunization program on that question.
[LEE] >> Why don't we give them a moment to respond. As we're doing that, Dr. Poehling, maybe you can ask your question, then we'll ask the folks in the room if they can also identify a response to Dr. Daley. [go to 2:03:51 for answers]

https://www.youtube.com/watch?v=iZTuP806RTU&t=7434s
[LEE] Actually, I forgot to go back to Dr. Daley's question.
2:03:57 I don't know if anyone wants to comment on that. And then I'd like for us to move on to the next presentation. That can get pulled up in the meantime. 2:04:20 [SILENCE] It might just be me, but I can't hear anybody.
>> Grace, we hear you. There's nothing coming from the room. >> Okay. Did we lose the room?
2:04:35
>> I don't think we lost the room. Is Dr. Das able to speak? >> Yes. No.
2:04:41
I'm on. Yep. >> [inaudible] Dr. Das. Dr. Oliver, [LEE] sorry. I just wanted to clarify, and I might have missed the answer, but just to respond to Dr. Daley's question about the microgram dosing, is there anybody who can respond to that?
2:04:54
[OLIVER]>> Oh, apologies, sorry. Yeah, I mean we're, again, defer to the manufacturers and would love it if actually Moderna wanted to comment as well. But we can say that, you know, fundamentally, a Pfizer vaccine at 30 micrograms compared to a Moderna vaccine at 100 micrograms, those are -- there's different components. There's the spike protein. There's the lipid nanoparticles, and it's certainly not that they're a one to one comparison in that we do not expect that the Moderna vaccine at 100 micrograms would be, you know, three times as high as Pfizer at 30. They have both, you know, been shown to elicit similar levels of antibodies and efficacy. There are some differences between the two, but we certainly do not expect that there would be, you know, a dose response that 30 micrograms of one vaccine would be directly comparable to 100 micrograms of the other and that we would expect, you know, three or more times the response.

[55] *PROTOCOL: COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety Data Link* (April 28, 2021), available at www.cdc.gov/vaccinesafety/pdf/VSD-COVID-Vaccine-SAB-SB-Protocol-508.pdf.

[LEE] >> Thank you, and Dr. Das, the floor is yours, and if you would like to address that along the way, that would be terrific.

13. **Transcript of Dr. Sanchez asking how long the spike protein persists for**
2:37:28
https://www.youtube.com/watch?v=iZTuP806RTU&t=9447s
Dr. Sanchez. >> Yes. Thank you. And thank you for the presentation. But getting back to Dr. Daley's question, measuring I think it is really critical that we know the exact, what is exactly being measured and then this, we really do need more information on the pathogenesis so that we can try to prevent it. And so, is there a standard measurement of messenger RNA content. I mean do you measure -- is there any standardization of that or does each company or each person's laboratory measure messenger RNA differently? And I guess what I'm trying to get at is, is there a measurement, you know, 50 micrograms, 100 micrograms, can we correlate, is it measured the same way as Pfizer's,
2:38:25 you know, 30 micrograms.
[DAS] >> So we have a validated method for mRNA measurement, and that's how we, that's how we are reporting our doses. No, I'm not aware of other vaccine's measurement methodology. We might need to ask others to comment on that, you know, perhaps the FDA has a better idea of that. [SANCHEZ] >> That's what I was wondering if the FDA also may be able to comment on that if they review the different manufacturers.
[LEE] >> I think Dr. Fink mentioned he'd be in and out today, so I actually don't know if he's available at the moment. Yeah, I don't see him coming on. He's on, but I think I can see an away sign for a moment. You know, I'd have to ask, but I do think this question is going to keep coming up, so I think it'd be really helpful if both Moderna and Pfizer could, if there's any written responses that can be provided, I think that would be incredibly helpful. [SANCHEZ] >> Thanks, Dr. Lee. >>[DAS] Yeah, and we'll take that back as well. >> Thank you. I don't see any other hands raised. I just want to confirm, any other questions for Dr. Das before I move on?
https://youtu.be/iZTuP806RTU?t=9592
>> I have another question. >> One last question, Dr. Sanchez.
2:39:58 Okay. >> I'm sorry. >> It's okay. >> And I've asked this before, and I just don't have a clear idea of how long the spike proteins that the messenger RNA in our bodies produce. How long has it been detected in patient's serum or tissues, and maybe, you know, even in animal studies, you know, how -- I know that, you know, it is said that the messenger RNA disappears quite quickly, but do you know, A, first of all, how long it may persist in blood or serum or tissues, and also, do you know what is the molecular weight of the spike protein that our bodies do produce? And I guess I'd say that with respect to transplacental transfer as well. But I mean this is a separate issue. But those are issues that have, you know, that I've brought up previously, and I'm not, and I really don't have an answer. I don't know if anything new has been developed on those. Thank you.

DAS >> Thus far, you know, we have looked at the persistent, the detectability of spike protein as well as the mRNA. You're absolutely right. The mRNA degrades quite quickly. The spike protein availability, I believe, is on the order of days, but like less than a week. But I will confirm that with our tox folks as well. And then your other question was about the molecular weight of the spike protein. So, I mean, we do have the full spike here, but I will take back to get the, you know, the molecular weight, which would be expected for the full spike.

14. Transcript of Dr. Sanchez asking if the spike protein crosses the placenta
https://youtu.be/i34wDDfhRpg?t=2697
Thank you. >> Thank you. Dr. Sanchez.
45:01
>> Thanks again. Question: Studies in pregnancy? And then the other one is really more basic and just trying to get an idea of how the vaccine is formulated. Are these two different messenger RNA strains that are encoding the, you know, the different spike protein? So it's just one strand that codes both? And does the ultimate protein cross the placenta.[MILLER] >> Okay. Again, I'm going to start. And then I'm going to actually ask some other experts to help me, particularly Dr. Edwards. But maybe first to start with respect to pregnancy. So we are conducting a safety follow-up study in pregnant women. It's a registry where the study is currently ongoing, and we'll examine approximately 800 pregnancies overall. The question around the mRNA sequences, so there are two distinct mRNA sequences. The first sequence is the original sequence that was in mRNA 1273. It encodes for the full length spike protein from the original Wuhan strain. The second sequence includes the sequence from a BA.4/5. And it's important to note that the spike protein sequence is identical from BA.4, BA.5, which is why we refer to it as a BA.4/5 sequence. Those two are individual sequences on lipid nanoparticles. Those lipid nanoparticles so more than one is able to enter the cell, and that's how both mRNA sequences are able to be translated inside the same cell. And then, in terms of transfer across the placenta, so we have conducted developmental and reproductive toxicology studies with mRNA 1273 but also with other vaccines in our pipeline, maybe in particular a CMV vaccine that's actually a hexavalent vaccine. And we do not see that the pregnancy or fetus is impacted by vaccination. But I'm going to ask Dr. Edwards to comment further
47:27

on the pregnancy piece. >> [EDWARDS] Thank you, Dr. Miller. So, on the mRNA response, just one clarification. So the two mRNAs that are included are coformulated in the same lipid nanoparticles and delivered then to the same cells. Further, we also introduced to both mRNAs the two proline mutations that stabilize the conformation of the spike protein into the prefusion conformation. And then, on the pregnancy piece, we do have evidence from animal studies that there is placental transfer of both IgG and to a limited degree IgA. And that also includes maternal transfer via breast milk. 48:13
>> Thank you. >> Sorry. >> [SANCHEZ] What was your question? >> How about the protein that's the -- you know, the protein that's generated by the messenger RNA, does that cross the placenta? >> Thank you for that. So we have done developmental and reproductive toxicity studies. And maybe we can come back at a later time point during this call to share the results from those studies. I unfortunately am not the expert on that study, and I don't believe our tox expert is available. But we can get back to you later on this call. >> [MILLER] Dr. Edwards, I apologize. I was on mute. What I was going to say, Dr. Sanchez, is I didn't understand your question initially.But I mean, in terms of the protein, this protein has been engineered to be cell surface expressed.So it's not a protein that is secreted in the same way that like a subunit protein might be injected and flowing freely. It is mRNA that is entering the cells, and then the protein itself is cell surface expressed. So it's not secreted protein. >> Thank you.

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