Docket No. CDC-2021-0089

Follow -up written comments submitted to:
MEETING OF THE ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP)
Centers for Disease Control and Prevention Atlanta, Georgia 30329 August 30, 2021

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SUMMARY
The dedication of the participants in this ACIP meeting to eradicate the Covid-19 pandemic was evident and is unquestioned. However, the lack of discussion on safety signals, such as those we have discussed, the confusing wording of their recommendations, the non-awareness of flaws in key studies informing risk-benefit analyses do not inspire public confidence. We welcome the opportunity to work with public officials to help inspire public confidence and to beat the Covid-19 pandemic.

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1. Introduction

This document contains follow-up comments submitted subsequent to the above meeting. Please note our comments submitted prior to the meeting under the same docket.(1)

We certainly appreciate the enormous amount of work on the part of the speakers and their teams that went into the presentations. Respectfully, we suggest that erroneous conclusions have been drawn based on:

- Non-awareness of flaws in studies that have informed some of the presentations.
- Well-meaning attempts to reduce the impact of the pandemic that are likely to backfire, serving only to reduce trust in public health officials.

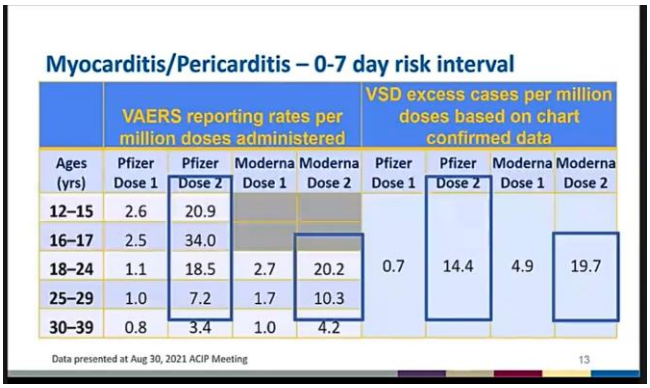
2. Resolved Issues

We are pleased to note that a number of our concerns, either in our posted comment(1) or otherwise related to the pandemic, were allayed by comments made by presenters or in the discussions that ensued.

2.1. Is there over-reporting in VAERS?

We noted in our earlier comment the confusion given specific reporting requirements pursuant to the EUA. The CDC web site states[1] that under an EUA, health providers are required to report certain categories of events following vaccination including serious events, deaths and life-threatening events, regardless of if the report think the AE caused the event or not. We further noted, that if reports of death for example, were being made strictly according to these criteria, we would expect conservatively to find 150,000 deaths reported in VAERS for the Covid-19 vaccines.

Clearly this is not the case, and a number of the presentations referenced data from VAERS without expressing concern that there had been any sort of over- or stimulated reporting. Indeed, the point was made by Dr. Lee's presentation, that for myocarditis/ pericarditis at least, the VAERS and VSD agreed closely.



Myocarditis/Pericarditis – 0-7 day risk interval

	VAERS reporting rates per million doses administered				VSD excess cases per million doses based on chart confirmed data			
Ages (yrs)	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2	Pfizer Dose 1	Pfizer Dose 2	Moderna Dose 1	Moderna Dose 2
12–15	2.6	20.9						
16–17	2.5	34.0						
18–24	1.1	18.5	2.7	20.2	0.7	14.4	4.9	19.7
25–29	1.0	7.2	1.7	10.3				
30–39	0.8	3.4	1.0	4.2				

Data presented at Aug 30, 2021 ACIP Meeting 13

One of the discussants (Dr. Su?) opined that VAERS had captured a substantial portion of these types of reports.

2.2. Disregard of Disproportionality Signal Analysis (DSA)

We discussed in our posted comment the shortcomings of the Disproportionality Signal Analysis methodology described in the VAERS SOP for Covid-19 vaccines.(2) Although we were able to show signals that met the Evans (3) criteria for a number of events or event types, these signals were muted compared with signals we calculated using methodology previously published by CDC.(4) For example, we found intense safety signals for the Covid-19 vaccines compared with influenza vaccines with 176 times the number of deaths/person (97.5 times the number of deaths/dose) vaccinated reported in VAERS.
We are pleased to note that in several presentations similar types of normalized event ratios were used to analysis safety signals for the Covid-19 vaccines.

2.3. Use of observational and pre-printed studies to inform decisions

The use of observational or non-peer reviewed (preprinted) studies by proponents of re-purposed drugs has been heavily criticized by public health officials as well as the media, who have insisted on evidence from large RCTs that have undergone peer review. It was with some wonder that observational and non-peer reviewed studies were included in one of the key analyses provided to support ACIP's recommendation. In one analysis (slide 19) from the presentation[2] entitled: *"Grading of Recommendations, Assessment, Development, and Evaluation (GRADE): Pfizer-BioNTech COVID-19 Vaccine,"* 17 observational studies, including 7 non-peer-reviewed, were employed.

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[1] www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/reportingaes.html
[2] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf

The authors appear to have used appropriate methods to assess bias in these sorts of studies. The presenter concurred with a remark by one of the discussants that there was close agreement between the observational studies and the RCT. We welcome the example that CDC has set to allow for these sorts of analyses to inform other decisions relating to the pandemic and public health.

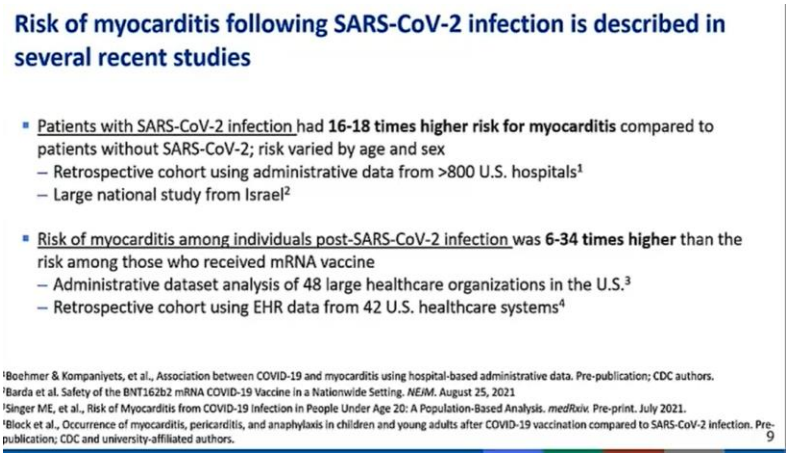
2.4. Discussion of Vaccine Efficacy and Safety

Contributing significantly to the analysis by several presenters of safety and efficacy, as well as the risk-benefit analysis for the Pfizer vaccine are two studies:

- Pfizer's own study (~40,000) described (presentation by Dr. Perez[3]) and recently preprinted.(5)
- The large Israeli Clalit efficacy (~1.2 million) (6) and related safety (~1.7 million) studies.(7)

During the discussion of ACIP's recommendation concerning the Pfizer vaccine, it was recognized that the vote was being taken based on data generated from these studies only up to March 2021. Further, the presenters may not be aware of significant sources of bias in the two Israeli studies. Both studies exclude certain high-risk categories of subjects. A data re-analysis of the efficacy study (8) found that that the entire apparent reduction in Covid-19 deaths, attributed to a two-dose vaccine, might instead be entirely due to selection bias occurring due to data censoring when either one of matched pair of subjects was removed from the analysis due to death, or, in the case of control subjects, become vaccinated. Although the original authors recognized this issue and showed in a sensitivity analysis a reduction in crude efficacy from about 72% to 49%, accounting for censoring that could have occurred over the entire study period could have attenuated the efficacy estimates significantly. Other biases were detected. Due to similar kinds of matching employed in the related safety study (7), a similar censoring bias appears to exist.

Our earlier comment included details of an intense safety signal regarding death. None of the presentations remarked on the 4 vs 1 deaths due to cardiac arrest reported in the 6-month Pfizer study.(5) None of the presentations discussed the large number of deaths being reported to VAERS associated with the vaccines. Neither did the Israeli safety study.(7) Rather, the discussion focused on myocarditis and pericarditis. One presentation[4] cited data, for example by Barda et al., (7), reporting a risk ratio of 3.24 for myocarditis associated with vaccination, compared with a risk ratio of 18.28 associated with SARS-CoV-2 infection. No adjustment was made for a conservatively estimated 8% risk of a SARS-Cov-2 infection.



Prior to ACIPS vote on recommending the Pfizer vaccine, there was no consideration of the effects of the delta variant and also waning immunity described in a later presentation.[5] The issue of waning immunity is

[3] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/02-COVID-perez-508.pdf
[4] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/06-COVID-Rosenblum-508.pdf
[5] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/09-COVID-Oliver-508.pdf

exemplified by two recent CDC papers which describe a loss of VE from 74.7% to 53.1% in nursing home residents(9) and 91% to 66% in front line workers.(10)

Lastly, we note there was no discussion about events reported elsewhere. In the United Kingdom, the Yellow Card system(11) for the period 4th January 2021 to 7th July 2021 shows 1,470 deaths and 1,059,307 adverse events (317,025 individual reports) associated with Covid-19 vaccines. European data are available through the EudraVigilance System,[6] from which we estimate the number of deaths associated with the Pfizer, Moderna, J&J and Astra-Zeneca vaccines, combined to be between approximately 3537 and 18926 (2021, to 7/17/21).[7] The WHO provides the Vigiaccess[8] database from which 8,703 deaths and 1,537,994 ADR records were registered as at 26th July 2021.[9]

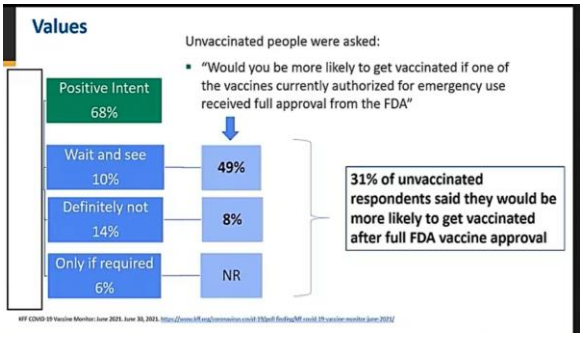
2.5. ACIP recommendation regarding the Pfizer-BioNTech Vaccine

ACIP voted unanimously to approve this recommendation:

> ***The Pfizer-BioNTech Covid-19 vaccine is recommended for people 16 years of age and older under FDA's Biologics License Application (BLA) approval***

Extensive discussion preceded the vote based on a presentation: *"Evidence to Recommendations Framework: Pfizer-BioNTech COVID-19 vaccine".*[10] One concern of that discussion was the issue of vaccine hesitancy. According to one survey: *"31% of unvaccinated respondents said they would be more likely to get vaccinated after full FDA vaccine approval."*

The presentation suggested that: *"Vaccination may be more acceptable to stakeholders under full FDA approval and standard ACIP recommendation."*



Acceptability

- Vaccination with Pfizer-BioNTech COVID-19 vaccine was already highly acceptable to stakeholders under FDA emergency use authorization and ACIP interim recommendation
- Vaccination may be more acceptable to stakeholders under full FDA approval and standard ACIP recommendation

Accordingly, it was felt that a recommendation from ACIP, such as the one approved, along with full FDA approval (i.e. BLA) for at least one of the vaccines, would be a significant step in reducing vaccine hesitancy.

Presumably, this rationale prevailed at FDA when they puzzlingly issued the BLA for a vaccine (COMIRNATY) on August 23 that was not yet available in the USA.

ACIPs recommendation is even more puzzling. Its wording takes no account of the legal reality of there being two legally distinct vaccines as described in FDA's letter to Pfizer of August 23 [footnote 8 in (12)].

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[6] www.adrreports.eu/en/search_subst.html

[7] The estimate is provided here in the form of a range due to the disclaimer on the database web site "*This website does not provide the total number of cases reported with a fatal outcome."* Because the same fatality may be counted for different reaction types, the number of fatalities appearing in the database may exceed the number of individual patient deaths. The database includes reports from outside of the European Union.

[8] http://vigiaccess.org/

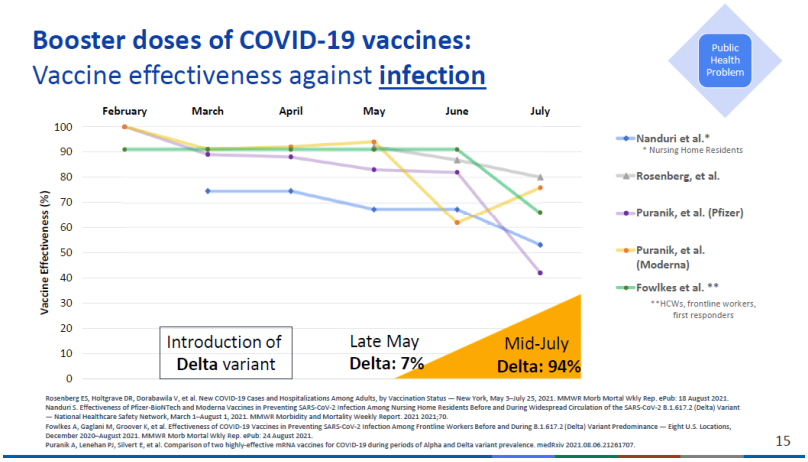
[9] Dr. Tess Lawrie https://ebmcsquared.s3.eu-west-2.amazonaws.com/Yellow+Card+Report_June+21.mp4. See video at 46 minutes. (update, personal communication)

[10] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/08-COVID-Dooling-508.pdf

The wording of the recommendation is misleading to the point of being meaningless because on the one hand it speaks about the "***Pfizer-BioNTech Covid-19 vaccine"*** (still under EUA) and on the other hand it speaks of BLA approval (COMIRNATY COVID-19 Vaccine, mRNA).

2.6. Booster dose

It was only after the vote was taken to approve the ACIP recommendation, that a discussion regarding booster doses took place, in particularly the not-previously discussed issue of waning immunity.



The discussants recognized the challenges in producing reliable data that could support the use of booster doses and a plan was outlined to be able to obtain data that could support an ACIP recommendation for booster doses following a planned approval by FDA around September. It is unclear what data currently exist or would even be available by that time.

The use of the term "booster" was questioned and suggested to have less positive connotations than positioning the "third dose" as merely one in a series of a planned course of immunizations, similar to that sed for other kinds of vaccines. This has clearly not been the case with the Covid-19 vaccines.

3. References

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