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October 20 2021
Booster Doses for Moderna and Janssen Vaccines[1]

Written comments submitted to:
Advisory Committee on Immunization Practices (ACIP), October 14-15, 2021 Meeting
Booster Doses for Moderna and Janssen Vaccines[2]

Written comments submitted to Vaccines and Related Biological Products Advisory Committee (VRBPAC), October 26, 2021, as follow up to meeting of Meeting of October14-15.

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[1] Meeting announcement: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-14-15-2021-meeting-announcement
[2] Meeting announcement: https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-october-14-15-2021-meeting-announcement

1. Introduction: Booster Doses for Moderna and Janssen (J&J) Covid-19 Vaccines

The purpose of this document is to contribute comments and questions for the discussion of safety of the Covid-19 vaccines.

These comments are intended for consideration by ACIP and CDC in their discussion regarding booster doses for the Moderna and Janssen vaccines. They are also intended for consideration by VRBPAC as a follow-up and update to the comments we submitted(1,2) to the meeting of October14/15.

We also refer ACIP and VRBPAC to our comments submitted to earlier meetings of VRBPAC(3) and CDC's ACIP.(4,5)

2. SUMMARY - Importance of ACIP and VRBPAC Committee Members

We have watched the deliberations of both committees for several months and feel that the panel members have honestly and diligently tried to grapple with difficult issues with a mountain of data and under pandemic conditions.

However, the committees are only as good as the information that is presented to them. FDA's Dr. Krause criticized Pfizer for not providing certain data to FDA, at the September 17 meeting. We have suggested that data were withheld from ACIP members regarding waning immunity at the Aug 30 meeting.(6)

Although the decisions of both committees are not binding on FDA or CDC, both agencies have broadened the scope of the recommendations made by the committees. This is evident in today's announcement by FDA (10/20/21[3]) that broadens the scope of booster usage, even for the Pfizer vaccine, despite the committee's deliberations.

The legal distinctions between the Pfizer-Biontech (EUA) and the COMIRNATY (BLA)(7) do not appear to have been explained to the committees, and are becoming ever more blurred not only in the general media but also in official documents (eg CDC - (8))

Significant ethical questions remain, particularly regarding the use of these vaccines in pregnancy (see our comments previously submitted (3) and in the context of mandates.

Presentations to the committees outside the context of a vote but open to discussion or a non-voting discussion question have resulted in significant pronouncements by FDA or CDC with regard to Heterologous Boosters or use of vaccines in pregnancy(9).

The committees appear unaware that these vaccines are classified by FDA as Gene Therapy products and the consequences for this.

Most concerning is that ACIP and VRBPAC are being asked to evaluate safety and efficacy data which FDA has admitted it has not verified.
The public is trusting you to follow the science in a way that transcends any political considerations and in a way that considers the broader consequences of these deliberations such as vaccine mandates based on extrapolations from extrapolations of data that has not been properly reviewed.

This will be all the more important as you consider vaccinations in children.

3. What is the a need for booster doses?

Given the significant safety concerns regarding the Covid-19 vaccines, the issue of whether there is a true need for booster doses is not trivial. In a paper published in the Lancet(10) and in a presentation made at the recent Sep 17 meeting of VRBPAC, senior FDA staff (Krause, Gruber) with responsibility

[3] https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-takes-additional-actions-use-booster-dose-covid-19-vaccines

for vaccines, and leading evidence-based medicine experts, challenged the need for booster doses based on:

- Persistent high vaccine efficacy against both symptomatic and severe disease due to the delta variant.
- Statistical artifacts from observational studies incorrectly indicating waning immunity
- *"reductions in neutralising antibody titre do not necessarily predict reductions in vaccine efficacy over time"*

Indeed, the FDA briefing document for the Moderna portion of this meeting (p13)[4] states:

"Some real world effectiveness studies have suggested declining efficacy of Moderna COVID-19 Vaccine over time against symptomatic infection or against the Delta variant, while others have not. However, overall, data indicate that currently US-licensed or authorized COVID-19 vaccines still afford protection against severe COVID-19 disease and death in the United States."

4. <u>What is the immune correlate of protection?</u>

Decisions concerning booster doses are largely based on antibody titers in three respects:

- A decay in antibody titers is interpretated as evidence of waning immunity
- Restoration/ elevation of antibody titers by a booster dose to levels similar to those seen after the primary series is taken as evidence of restoration of immunity (immunobridging)
- Elevation of antibody titers after heterologous boosting is interpreted as evidence of efficacy of a heterologous booster dose.

Several studies presented at FDA meetings, including the "NIH Max and Match"(11) – heterologous boosting study and a study conducted on behalf of Janssen (12) have also examined other components of immune function including T cell responses. In cases, authors emphasize that "immune correlates for protection" are not known."[5]

Moderna in their briefing document to the October 14 VRBPAC meeting state (p17) *"…a definitive immune correlate of protection has not been established"*

At the VRBPAC meeting of October 14, FDA's Dr. Fink stated,[6]

"Boy 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 [inaudible] is fully predictive of protection –In the meantime we are tasked with evaluating data and taking action to address public health needs. And so 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. And we use that immune marker to bridge back to a dosing regimen in a population in which efficacy has been demonstrated."

[4] https://www.fda.gov/media/152991/download

[5] Dr. Barouch, https://youtu.be/c-H40GrvWz4?t=3863

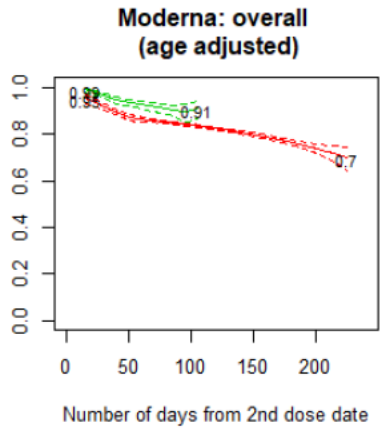
[6] https://youtu.be/BhlshZ7Lkr0?t=20304

Finally, Dr. Janet Woodcock, at the press conference of 10/20/21 following FDA's announcement regarding Moderna and Janssen booster doses[7] stated that the connection between antiibody responses and how well someone is protected.is unknown.

5. What evidence supports the authorization or recommendation of booster doses?

5.1. Moderna

Notwithstanding the above remarks, CDC estimates (Link-Gelles, ACIP, Sept 22) that the VE of the Moderna vaccine has waned to about 70%.



In Moderna's briefing document to this meeting (p15) the need for a booster dose is unclear. *"Observational studies demonstrate high effectiveness of mRNA-1273 against most VoCs; however, decreased effectiveness of mRNA-1273 against the Delta variant has been shown, particularly in individuals ≥ 65 years old "*

5.1.1. Immunobridging study

As with the Pfizer vaccine, Moderna appears to have agreed with FDA that, as with classical vaccines, an immune-bridging study involving 171 subjects (50ug boost to 100ug primary) would be sufficient to justify authorization of booster doses. The study would need to show an increase in antibody titers within certain non-inferiority margins of post second dose titers. Further, the results from such a study could be broadly extrapolated to populations not included in the study.

Moderna have done such a study that appears to meet these targets. However, as with the Pfizer study, the numbers of subjects are very small to provide sufficient safety information. The study is not an RCT and not efficacy can be determined. The study is of short duration and provides no information on cellular immunity or immune memory.

5.1.2. Limitations in the Israeli experience that challenge the notion of booster effoacy.

It appeared obvious from the discussion of VRBPAC on September 17, that immunobridging data in isolation were too limited to justify the recommendation for boosters. The committee spent considerable time in reviewing the results of an Israeli study(13) presented at the meeting by senior Israeli MOH scientists. This study summarized the experience of the use of a booster dose of the Pfizer vaccine in Israel.

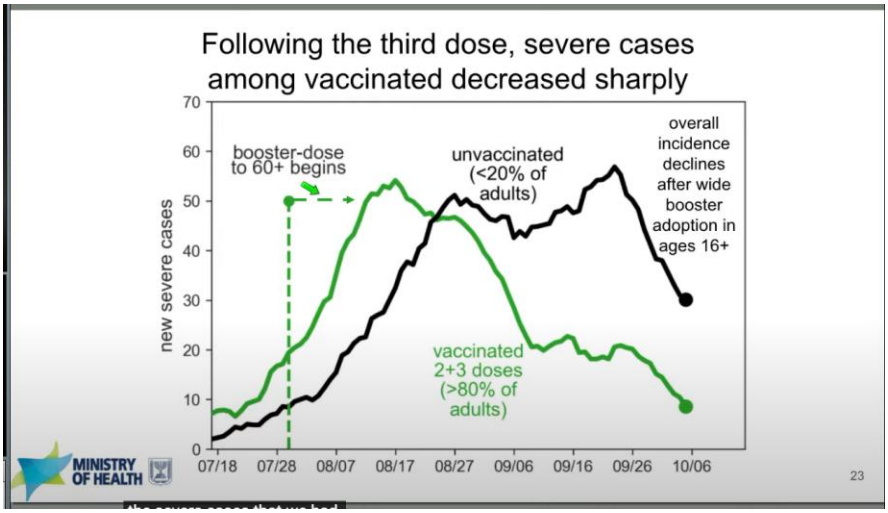
[7] https://www.youtube.com/watch?v=rou7tf4vaUU

The October 14 meeting of VRBPAC included a presentation made by Israel's MOH to update the September 17 presentation under the item *"Data Relevant to the Need for Boosters."* It was stated that those data, despite pertaining to the Pfizer vaccine, were considered sufficiently pertinent to the Moderna vaccine, with an implication that they also had some bearing also on the Janssen vaccine.

Given the centrality of this particular study in the discussion of booster dosing, we bring to the attention of ACIP, VRBPAC, FDA and CDC a number of unresolved limitations that call into question this premise.

Severe C19 cases among the vaccinated precede those of the unvaccinated
The following slide was presented by the Israeli MOH:

Figure 1: Covid-19 severe cases following booster rollout in Israel



This appears to show that following the initiation of booster dosing, severe cases among the vaccinated (and boosted) rise ahead of those in the unvaccinated. To determine whether this apparent horizontal shift could be abrogated by plotting the number of cases as a percentage of the particular population, we downloaded data from the Israeli MOH Corona Dashboard.[8] As defined there as well as in a MOH announcement (8/29/21),[9] we have the following categories of individuals.

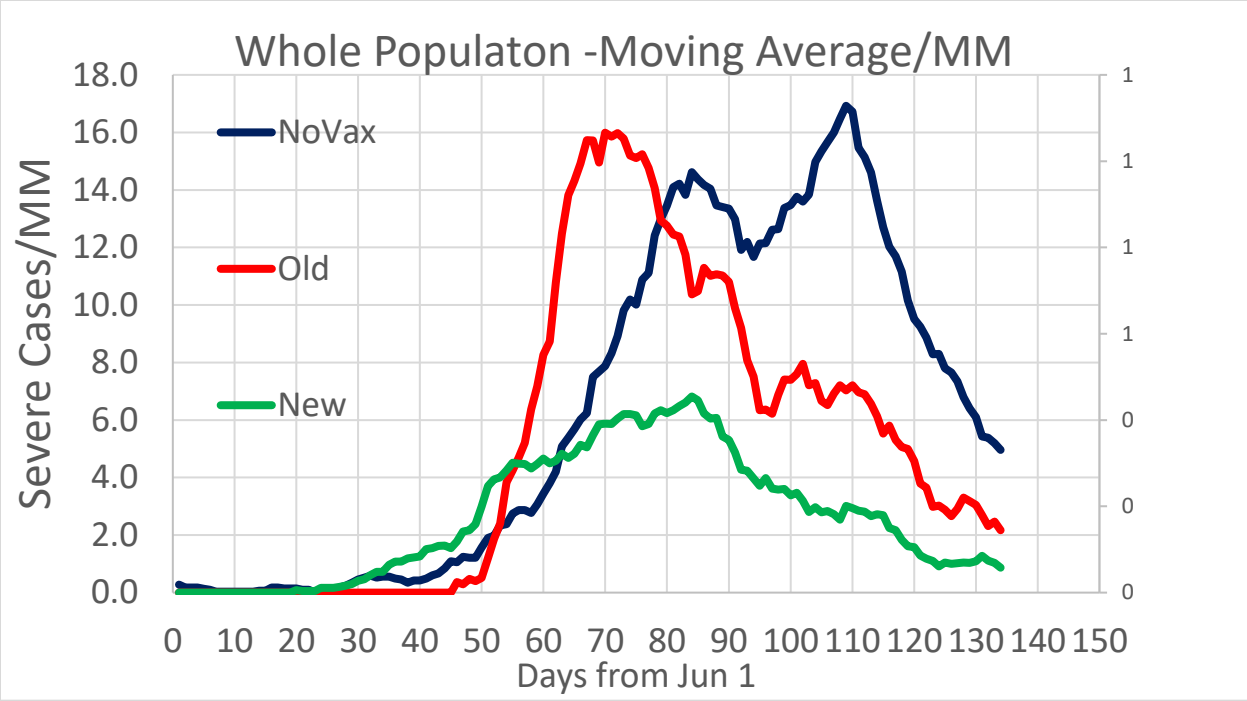
- Non-vaccinated – no vaccine at all
- Old vaccinated – second dose more than six months ago
- Newly vaccinated, a second or third dose more than 7 days ago, but not more than half a year.

From the downloaded data, we replicated the above graph, noting that the green curve is the sum of severe cases (7 day forward moving average) for both the newly and "old" vaccinated. The data for single dose recipients, or subjects within one week of vaccination are not available. The number of cases have been normalized/per million subjects in the respective subgroups.

Figure 2: Covid-19 severe cases following booster rollout in Israel, normalized to subgroup

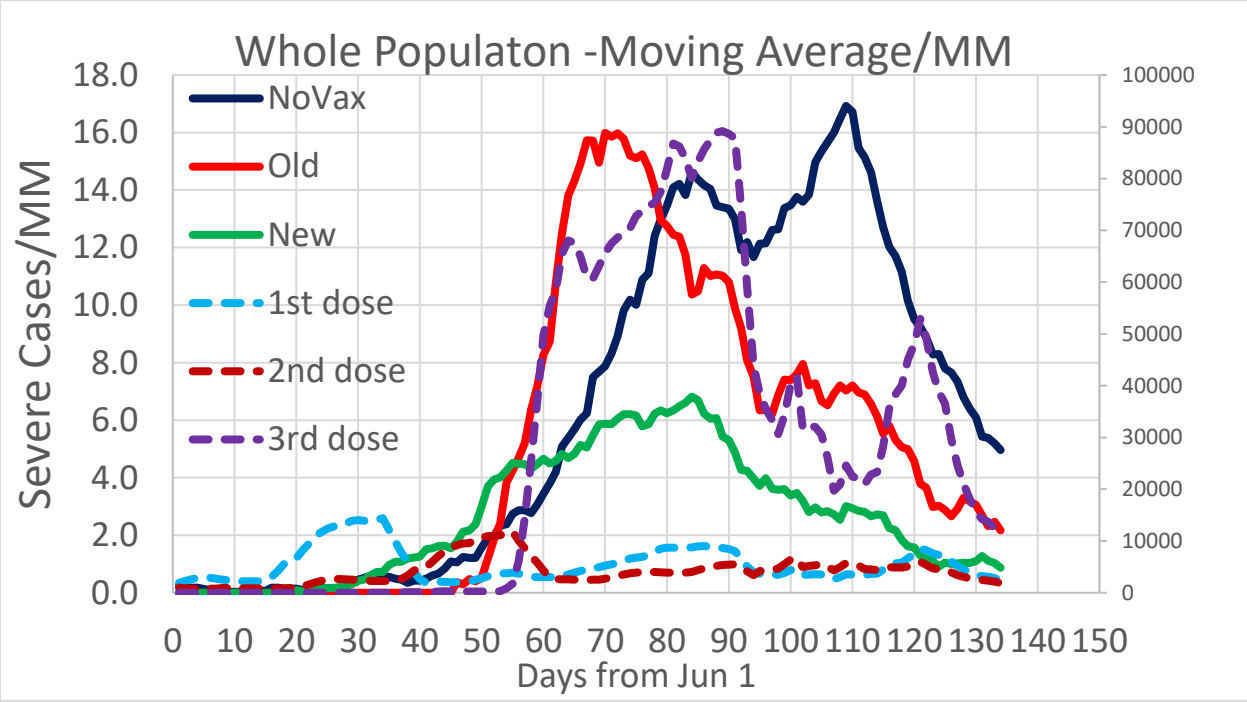
[8] https://datadashboard.health.gov.il/COVID-19/general

[9] https://www.gov.il/en/departments/news/29082021-01



This is the same graph, but includes the number of 1st, 2nd and third doses administered (right axis).

Figure 3: Covid-19 severe cases following booster rollout in Israel, normalized to subgroup, included doses administered



Although booster dosing began in early July, there was a small uptick in primary series recipients starting in late June. After normalizing for the doses given and splitting apart new primary series and booster

recipients, the increase in cases among newly or boosted (green curve) vaccinees precedes the other two groups by about 10 days over about a 20-30 day period. Further, after a small initial phase, the increase in cases among "old" vaccinees precedes non-vaccinees by 15-20 days.

There are certainly limitations to this observation that ideally would be resolved by obtaining individual level patient data, as well as stratifying for age and the age-dependent roll-out.

Nonetheless, these findings demand further investigation as to the utility of booster doses, and the possibility that boosted subjects, may transmit disease to others, included "old" vaccinees."

Note this this analysis complements our earlier analysis on overall cases and deaths follwomg booster rollout, and compares the trajectory of the Summer 2021 wave with that of 2020 (**Figure 4**, **Figure 5**).

The Israeli dataset ideally needs detailed review

Remarks made by senior FDA official Dr. Krause at the September 17th meeting criticized Pfizer for not providing for FDA detailed review the full dataset for a study (14) cited by Pfizer in support of their application for a booster dose. Evinced by its discussion at the September 17 meeting, and its inclusion (in updated form) at the Oct 14 VRBPAC meeting, understanding the Bar-On study is essential to understanding the efficacy of booster doses in the Covid-19 pandemic.

Consonant with the remarks of Dr. Krause we suggest that the full dataset be made available to FDA for review. Although the Bar-On paper as published, indicated the availability of data, we were unable to obtain those data.

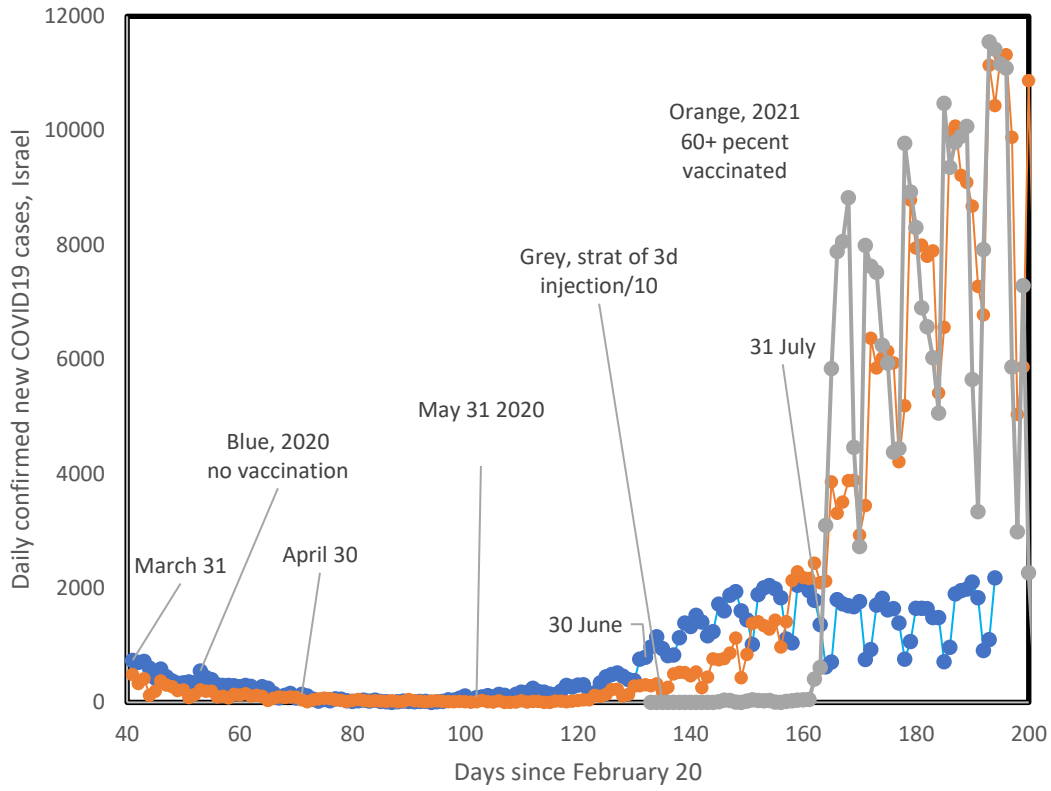
Other significant statistical limitations on the Bar-On study[10]

- This is not a RCT. As Dr. Krause and colleagues assert in their paper on the use of booster doses: *"Given the data gaps, any wide deployment of boosters should be accompanied by a plan to gather reliable data about how well they are working and how safe they are. Their effectiveness and safety could, in some populations, be assessed most reliably during deployment via extremely large-scale randomization, preferably of individuals rather than of groups"*
- **Censoring bias from dropped matches**. As with two other related studies (15,16), this study permitted matched control subjects to become vaccinated. A data re-analysis(17) of one of these studies(16) found that that the entire apparent reduction in Covid-19 deaths, attributed to a two-dose vaccine, might instead be substantively 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. In the Dagan study(16), the authors did attempt to account for this censoring, but did so only partially.
- **Exclusion of events in the first 11 days after boosting**. This may lead to survivorship bias. Exactly how this was done is not clear and the dataset needs to be provided for verification.
- **Inclusion and testing bias** is possibly evident from Figure S5 showing about 25% of subjects developing severe illness within 3 days of PCR testing.
- **Another bias,** is suggested by Figure 2 which shows a small but unexpected benefit in days 1-11 after boosting. Although the authors suggest that this bias is transient and diminishes (see Figure 1) , if given the rising trend as the study period progressed, various testing bases could have persisted (to different degrees) both among the boosted and on-boosted.
- **Testing bias** during the study period is again evinced by an analysis of data (Oz et al.) appearing on the Israeli Ministry of Health Covid dashboard. Examining data for the number of Covid-19 cases of people entering the country during the booster study period who must undergo PCR testing, the degree of testing bias may be estimated. Adjusting for this bias in the Bar-On study necessitates the revision of the approximately 11-fold benefit of boosting to about a 2.75 fold benefit. It must be noted that shortly after dissemination of the analysis by Oz et al., the source data on the official dashboard had been revised. This requires further explanation and analysis.

[10] We thank a number of colleagues for their insights on this particular study that have contributed to this discussion, including Prof E Shahar, Prof R. Levi and S. Gevish.

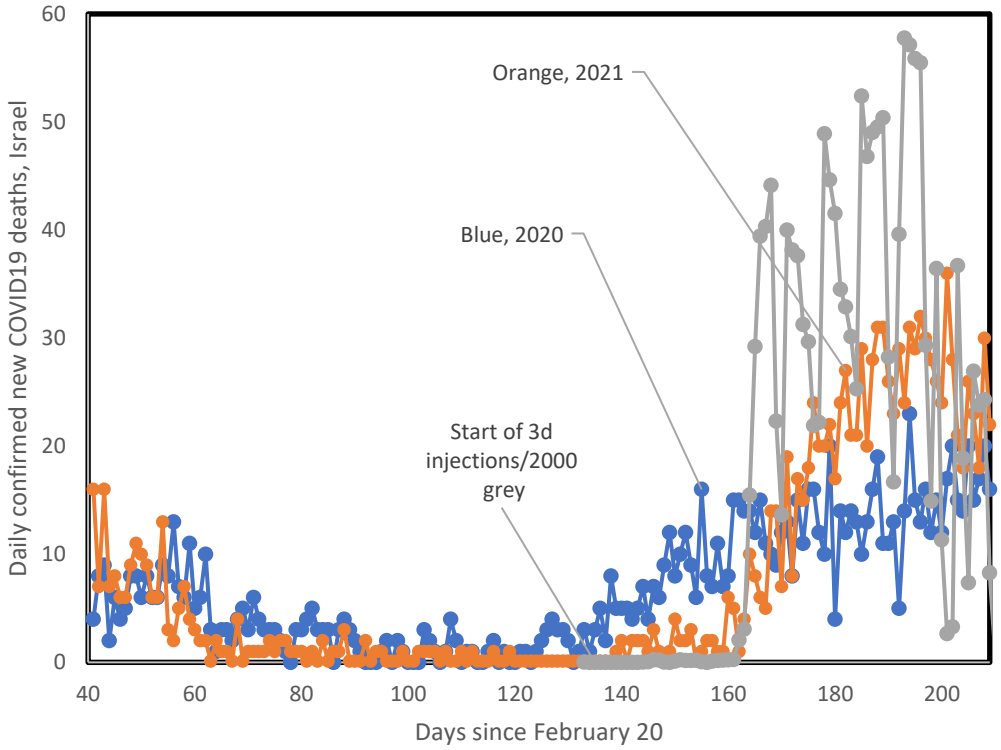
- **Cases and deaths increase in Israel after booster rollout, compared with 2020.** Our own extraction of data from the Israeli MOH dashboard, below, shows that Covid-19 cases and deaths increase (and decrease) with the number of booster dose injections. For comparison the numbers of cases and deaths for the same period in 2020 are shown.

Figure 4: Covid-19 cases following booster rollout in Israel



Israeli daily confirmed COVID19 cases, from the Israel Health Ministry dashboard קורונה - לוח בקרה (health.gov.il) as a function of days since February 20 (2020, blue; 2021, orange) and numbers of daily booster injections divided by 10 to fit the scale of COVID19 cases (grey)

Figure 5: Covid-19 deaths following booster rollout in Israel

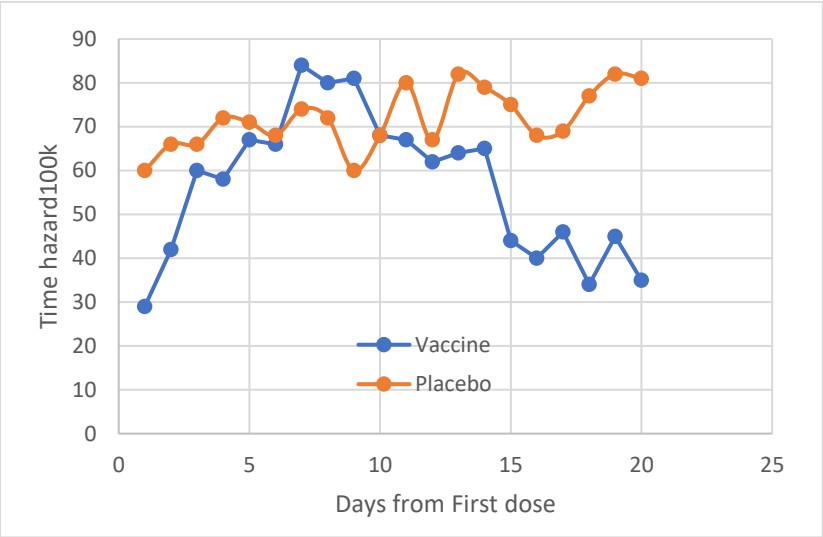


Israeli daily COVID19 deaths, from the Israel Health Ministry dashboard קורונה - לוח בקרה (health.gov.il) as a function of days since February 20 (2020, blue; 2021, orange) and numbers of daily booster injections divided by 2000 to fit the scale of COVID19 deaths (grey)

- **Increased cases and deaths after booster rollout are not unexpected.** Again, drawing parallels between booster doses and first doses, in an analysis of the data from the initial use (first 44 days) in 596,000 subjects of the Pfizer vaccine in Israel reported by Dagan et al. in NEJM (16), one of us (HS) observed an early (<7 days) uptick in Covid-19 cases following vaccination. A letter to NEJM (March 11) was rejected but described in an article in France Soir – May 5.[11] There, the incidences of Covid-19 tripled from day 1 to 7 among the vaccinated,[12] and decreased to their initial rate 20 days after 1st injection, remaining at that level until day 28.The letter continues: "*This suggests a weakened immunity of the vaccinees which causes other, unreported, short-term (non-COVID-19) adverse effects, including some deaths. This analysis should have influenced decisions about who to vaccinate and when. Long-term risks can be expected with age and sex factors.*"

[11] francesoir.fr/societe-sante/le-new-england-journal-medecine-refuse-une-lettre-davertissement-du-dr-seligman-sur
[12] The imbalance between the two groups on initiation poses a separate problem as to the matching of the two groups.

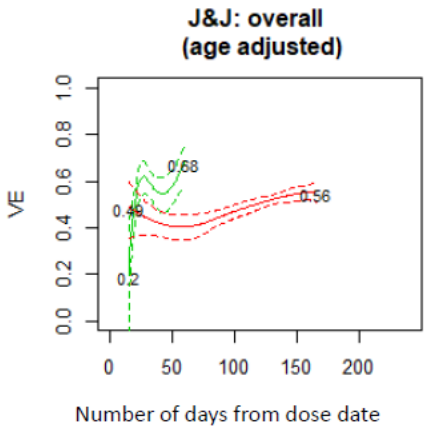
- ***Figure 6: Covid-19 cases following vaccination in Dagan et al.***



- **Covid-related post-vaccination deaths in Israel equate to 25-000 to 85,000 US deaths**. Combining data in Dagan et al., with statistics from the Israeli Ministry of Health, an increase in the number of deaths in vaccinated subjects could be found following vaccination. These Israeli data are particularly informative because by the cut-off date, 54% of adult Israelis had been vaccinated, mitigating to some degree biases due to early vaccination of those most at risk. Further, by combining these data sources, we can see what is happening **among vaccinated patients**. There are a number of limitations as to causality and potential time biases, but this analysis suggests that there may be 121-413 excess deaths/million associated with vaccination, in those vaccinated (>= 1 dose), equating to about 25,000-85,000 deaths in the USA. Again, we cannot ascribe cause, merely association.
- **These effects may be due to immunosuppression.** The recent finding from a large Israeli cohort of an increased (40%) risk of Herpes zoster infection(15) may indicate immunosuppression related to vaccination in some subjects. In one study naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected.(18) Further evidence of immunosuppression comes from the phase I/II study of the Pfizer vaccine*: "Transient decreases in lymphocyte counts (grades 1–3) were observed within a few days after vaccination, and returned to baseline within 6–8 days in all participants."*(19)

5.2. Janssen

The question was raised at the CDC ACIP meeting of Sept 23 by Dr Talbot as to the utility of the J&J vaccine given that its maximal VE of about 50-70% is in the same range at the Pfizer and Moderna vaccines after waning.



(from Link-Gelles CDC Sept 23)

The question repeatedly recurred with no good answer of whether the 2nd dose is to be considered as "booster" or "2nd injection" is to revise a dosing decision made at the outset. The overall message from J&J was that their vaccine produces durable immunity, but always with room for improvement. This was challenged at one point in the Oct 15 meeting by FDA's Dr. Marks, who said that in some populations, this may not be true.

J&J provided data for their study3009 (mentioned in their Feb 2021 EUA documents) involving 31,300 subjects equally divided among treated controls with a 2 dose / 2 month regime (their one-dose study involved some 44,325 subjects). With about 7000 subjects per arm, the VE in the US increased from about 70% to 95% and ex-US from 53 to 75% using a second dose given after about 2 months.

J&J also provided an immunobridging type study with about 200 subjects across several arms.

What is disturbing about these data is that on many of the slides from FDA's review of these data, including on thjose related to safety, efficacy and immunogenicity are stated either:

"Janssen analysis not verified by FDA"
"Numbers not verified by FDA"
"Analyses Not Verified by FDA"

This deficiency was challenged by VRBPAC member Dr. Chatterjee.[13] FDA's Drs. Fink and Marks justified this based on the intense public interest on boosters and the urgent need for a meeting where a small immunogenicity study of 200 or so subjects was expected requiring only a short review. Instead, a study with some 30,000 subjects was submitted whose detailed review by FDA would have taken several weeks. The answer is difficult to reconcile with the ongoing discussions alluded to FDA and the fact that this 2 dose study was described in Janssen's EUA briefing document of February 26, 2021.[14]

6. Are these Gene Therapy Products

Significant questions remain concerning the Gene Therapy nature of these vaccines and the regulatory and long-term safety consequences of that. Are these Gene Therapy Products
We are still waiting clarification as to why FDA is not enforcing its own guidelines regarding Gene Therapy Products. Although these Covid-19 agents fall under FDA's definition of vaccines and vaccine-associated products.[15]

[13] https://youtu.be/c-H40GrvWz4?t=11801
[14] https://www.fda.gov/media/146217/download
[15] www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research

> *"products, regardless of their composition or method of manufacture, intended to induce or enhance a specific immune response to prevent or treat a disease or condition, or to enhance the activity of other therapeutic interventions."*

they differ significantly from the classical vaccine consisting of an inactivated or attenuated pathogen in two major respects. Firstly, rather than an immune response being elicited by injected antigen, it is elicited by antigen (the SARS-Cov2 spike protein), whose within-subject biosynthesis is induced by mRNA or DNA deployed by the vaccine.

Secondly, these vaccines also meet FDA's definition of gene therapy products.[16]

> (emphasis added) *"Human gene therapy/gene transfer is* ***the administration of nucleic acids****, viruses, or genetically engineered microorganisms that mediate their effect by transcription and/or translation of the transferred genetic material, and/or by integrating into the host genome. Cells may be modified in these ways ex vivo for subsequent administration to the recipient, or* ***altered in vivo by gene therapy products administered directly to the recipient****."* A similar expanded definition is given in FDA's Guidance on Long Term Follow-Up After Administration of Human Gene Therapy Products.(20)

Moderna, Inc., acknowledged in their 2Q 2020 SEC filing(21)[17] thus *"Currently, mRNA is considered a gene therapy product by the FDA."*

Consistent with the FDA June 2020 guidance(22) on the development of vaccines for Covid-19, Pfizer,[18] Moderna[19] and Johnson & Johnson,[20] declared their intent in their requests for EUA status to follow study subjects for up to 36 months. Of particular concern is the unblinding of at least some of the clinical trials, thus preventing full assessment of safety issues.(23)

Even this follow up period is inadequate for two reasons. Firstly, although the sorts of events anticipated by FDA and CDC are of relatively early onset, the duration or prognosis for a number of them is unknown. Secondly, since these agents are also Gene Therapy products, much longer surveillance is warranted for delayed malignant, neurologic, autoimmune, hematologic, other disorders or effects on the genome or gene expression, as advised in FDA in its guidance document "Long Term Follow-up After Administration of Human Gene Therapy (GT) products."(20) The length of monitoring advised by FDA may be (emphasis added) "***as long as 15 years*** *following exposure to the investigational GT product, specifying that the LTFU observation should include a minimum of five years of annual examinations, followed by ten years of annual queries of study subjects, either in person or by questionnaire."*

Accordingly, the designation of these vaccines as Gene Therapy products is not merely a semantic nicety; rather it has regulatory consequences in terms of long term follow up manufacturers should be required to conduct. No reference to these FDA guidance documents on long term follow up for gene therapy products (20) was made in FDA's guidance on development of Covid-19 vaccines(22), nor in the EUA briefing documents provided by Pfizer, Moderna and Johnson & Johnson.

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[16] *www.fda.gov/combination-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research*

[17] Moderna's 2Q2020 SEC filing is dated August 6 2020, and states that the phase 1 study began March 16, 2020, with the phase 2 study being fully enrolled by July 8, 2020. Enrollment for the phase 3 study began July 27, 2020, as also reflected in for clinicaltrials.gov. Each phase would have been cleared by FDA. The start date given in clinicaltrials.gov for Pfizer's trial was April 29 2020 and for J&J Sept 7 2020.

[18] https://www.fda.gov/media/144245/download

[19] https://www.fda.gov/media/144434/download

[20] https://www.fda.gov/media/146219/download

An explanation is therefore required as to why the provisions relating to Gene Therapy products have not been incorporated into the risk-benefit analysis of these vaccines.

Will FDA and CDC collect other long-term data on autoimmune disease, cancer and other disorders as contemplated in the FDA Gene Therapy Guidance document?(20) The package insert(24) states that *"COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility*." Neither in the in the BLA Approval letter,(25) or Summary Basis for Regulatory Approval(26) is there a POST MARKETING REQUIREMENT to conduct carcinogenicity, genotoxicity or male fertility.

7. Safety Signals

We have previously discussed the pharmacovigilance methods for safety signal detection, replicated here as Appendix (Section 8). Briefly we discussed the limitations of Disproportionality Signal Analysis (DSA) and the use of Proportional Reporting Ratio (PRR) as described in the VAERS SOP.(27)

We adopted the approach published (28) by scientists from FDA and CDC to normalize the number of events reported in VAERS for the number of people receiving a particular vaccine or doses administered. This figure can be divided by a similar ratio from a reference vaccine to obtain a normalized event ratio (NER).

Comparing this method with the VAERS DSA methods, we found that estimates of PPR were highly muted, challenging their value and appropriateness. Nonetheless, the signal (5.2) for deaths was significant according to the Evans criteria.(29) To the extent that there was any sort of stimulated reporting, this was against a background of extensive campaigns promoting the safety of the C19 vaccines. Based on VAERS data as of (7/30/21), the per population- or per dose- NER were found to be very high, particularly for reports of death (177, 98 respectively).

We provide here an update to those numbers based on VAERS data as of 10/13/21.

We obtained the numbers of reports for various event types and categories using the "USA Territories/Unknown" filter and for ages 6 and above. We stratified by Covid vaccine type and compared event rats with those for seasonal flu vaccines from the 2015/16 to 2019/20 seasons. Flu and Covid-19 vaccine coverage data were obtained from CDC, and population estimates where needed from https://usafacts.org/. we calculated NER for the Covid-19 vaccines against seasonal flu vaccine. We normalized both for the number of doses administered and the number of people having at least one dose of vaccine.

Using the NER of 170 and above values for myocarditis as a reference point on which there is credible evidence to associate that event with use of Covid-19 vaccines, **Table 1** shows high NER signals for death, coagulopathy, embolic/ thrombotic events.

Table 1: ***Normalized Event Ratio (NER) for Covid-19 Vaccines Compared with Seasonal Flu Vaccines***

	JANSSEN		MODERNA		PFIZER\BIONTECH	
	By dose	By person	By dose	By person	By dose	By person
Death	297	297	170	316	119	225
Life Threatening	110	110	39	72	32	60
Permanent Disability	57	57	24	44	20	38
Congenital Anomaly/Birth Defect	112	112	58	108	51	95
Hospitalized	101	101	43	80	37	70
GBS	19	19	3	5	2	4
Coagulopathy	1427	1428	286	531	218	413
Myocardial Infarction	411	412	232	431	180	339
Myo/peri carditis	181	181	170	317	217	410
Embolic Thrombotic	610	610	151	280	113	213
Serious	92	92	41	76	34	65
Not serious	46	46	27	51	16	31

Table 2 compares the NER values for the three vaccines.

Table 2: Comparison of NER values among the three Covid-19 vaccines

	JJ:Moderna		JJ:Pfizer		Mod:Pfizer	
	By dose	By person	By dose	By person	By dose	By person
Death	1.7	0.9	2.5	1.3	1.4	1.4
Life Threatening	2.8	1.5	3.5	1.9	1.2	1.2
Permanent Disability	2.4	1.3	2.8	1.5	1.2	1.2
Congenital Anomaly / Birth Defect	1.9	1.0	2.2	1.2	1.2	1.1
Hospitalized	2.4	1.3	2.7	1.4	1.1	1.1
GBS	6.4	3.5	8.4	4.4	1.3	1.3
Coagulopathy	5.0	2.7	6.5	3.5	1.3	1.3
Myocardial Infarction	1.8	1.0	2.3	1.2	1.3	1.3
Myo/peri carditis	1.1	0.6	0.8	0.4	0.8	0.8
Embolic Thrombotic	4.0	2.2	5.4	2.9	1.3	1.3
Serious	2.2	1.2	2.7	1.4	1.2	1.2
Not serious	1.7	0.9	2.8	1.5	1.7	1.7

8. APPENDIX: Insensitivity of Disproportionality Signal Analysis (DSA) used to detect safety signals

Several methods have been proposed to detect safety signals related to medical products, specifically from databases of spontaneous adverse event reports, such as VAERS. In general, these methods do not infer causality, merely they provide a signal for further investigation. To mitigate a number of statistical and

informational challenges, methods involving Disproportionality Signal Analysis (DSA) have been devised, such as the use of the Proportional Reporting Ratio (PRR) or other Bayesian or data mining techniques. The VAERS team have indicated that these sorts of methods should be employed to detect safety signals for the Covid-19 vaccines.(27) Although DSA is a useful tool in pharmacovigilance (PhV) it has known limitations. A paper authored by scientists from Astra-Zeneca, Pfizer, as well as British and European regulators stated: *"Thus, the quantitative data in spontaneous reporting systems, while being useful in detecting new signals of drug-event associations, are not easily interpretable in terms of clinical impact" (30)* The authors further stated *"calculation of PRRs from spontaneous reporting databases should not replace nor delay the performance of formal epidemiological studies,"*

DSA uses the total number of reports reported for a particular drug as a surrogate denominator to estimate the incidence of a particular event in the population, to be compared with other drugs in the same class. Although methods exist to partially compensate for masking of a particular event by other events, as well as non-independence of events, the output from these techniques remains that of a signal which provides no estimate of **epidemiological or clinical impact.** This problem is compounded in the case of drugs where, even if the number of prescriptions written are known, detail as to actual usage, dose, length of treatment and so on may not be.

In the case of the Covid-19 vaccines, the primary reasons for employing a surrogate denominator do not pertain: individual doses are usually fixed, the number of doses given is fixed, with mostly uniform dose intervals. Lastly, the number of doses administered as well as the number of persons receiving those doses, is known from CDC tracking systems.

We adopted the approach published (28) by scientists from FDA and CDC to normalize the number of events reported in VAERS for the number of people receiving a particular vaccine or doses administered. This figure can be divided by a similar ratio from a reference vaccine to obtain a normalized event ratio (NER).

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