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Written comments submitted to:
Vaccines and Related Biological Products Advisory Committee (VRBPAC) September 17, 2021 Meeting

Booster Doses for Pfizer-BioNtech Vaccine

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Summary

- There is inadequate evidence for safety of booster doses amidst mounting concerns for first two doses
- Significant safety concerns need to be addressed for the Covid-19 vaccines as presently used, and with the use of booster doses.
- We show intense safety signals for the Covid-19 vaccines compared with influenza vaccines with 176 times the number of deaths/person vaccinated reported in VAERS.
- To account for any stimulated reporting, compared with H1N1 vaccines where stimulated reporting was suspected, this ratio is still high at 35.
- Although classical disproportionality analysis is inadequate and superseded by methods that normalize for actual doses administered or people vaccinated, we nonetheless detected strong age-dependent signals for deaths, serios events coagulopathy and myocardial infarction.
- We identified three separate pools of vaccine associated deaths, totaling 45,000-147,000 deaths.
  - Non C19 deaths under reported in VAERS 20,400-62,500
  - C19 deaths occulting in vaccinated 25,000-85,000
  - An unknown number of deaths in non-vaccinated contributed by transmission from vaccinated.
  - These figures should be placed in the context of the upper estimate of 140,000 lives saved due to the vaccines (to May 2021)(1)
  - The benefits of vaccination should be considered in light of resistant strains, waning immunity(2) and development of natural immunity(3).
  - Unresolved safety questions for pregnant mothers must be resolved.
- Products must be regulated as gene therapy products, with appropriate long term follow up for autoimmune diseases, cancers etc.
- Significant short and Long term health issues require the ***Recognition of short and long term vaccine -related effects as a major public health issue.*** To concretize recognition of, and to spur action to avert and confront this potential public health crisis, we propose the term:

Post Covid Vaccine Syndrome – pCoVS

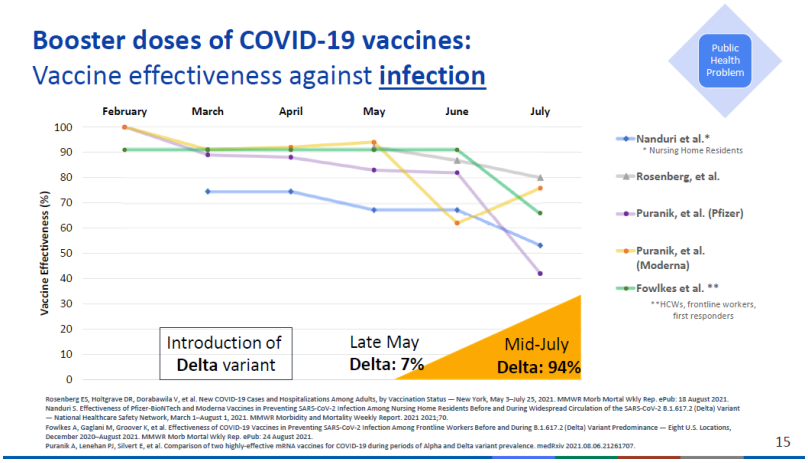
A syndrome occurring after injection of antigen-inducing, gene therapy vaccines to SARS-Cov-2 virus. The syndrome is currently understood to manifest variously as cardiac, vascular, hematological, musculoskeletal, intestinal, respiratory or neurologic symptoms of unknown long-term significance, in addition to effects on gestation. Manifestations of the syndrome may be mediated by the spike protein antigen induced by the delivered nucleic acids, the nucleic acids themselves, or vaccine adjuvants. As more data become available, subsets and longer-term consequences of pCoVS may become apparent, requiring revision of this definition. Sub-categories may be designated by suffix for example:

- We propose the establishment of an ICD10 code for pCoVS, and an mechanism to fund research into pCoVS.

Contents

1. Introduction: Waning or Reduced Effectiveness of Covid-19 Vaccines

Globally[1] (9/13/21) around 5.5 billion doses of Covid-19 vaccines have been administered, mostly pursuant to Emergency Use Authorization (USA) or equivalent status. At a recent (8/30/21) meeting of CDC's Advisory Committee on Immunization Practices (ACIP), evidence was presented by CDC staff(4) regarding reduced effectiveness of the Covid-19 vaccines, in some scenarios as low as 42% for the Pfizer-BioNTech Covid-19 vaccine.(5)



Slide 15 from (4)

Whether this decline is due to waning immunity over time, or reduced effectiveness against the relatively new delta variant, is not fully understood. Whatever the case, the decline has prompted the *"the Pfizer-BioNTech supplemental Biologics*

[1] covid19.who.int/

License Application for COMIRNATY for administration of a third dose, or "booster" dose, of the COVID-19 vaccine, in individuals 16 years of age and older" which is the subject of the discussion at this meeting.[2]

The purpose of this document is to document concerns that we believe should be considered by VRBPAC in its deliberations. Our concerns fall into five categories:

- **Regulatory:** Which legally distinct product is being discussed and under what regulatory authorization type and product classification?
- **Transparency and public trust:** The issuance of a BLA without a public meeting or comment, apparent withholding of evidence prior to CDC's ACIP recent vote to recommend the Pfizer vaccine, and announcement of ancillary safety studies suggest a lack of transparency that erodes trust in public health officials. Such erosion, we suggest, is a major driver in vaccine hesitancy.
- **Safety:** Since there are mounting and unresolved safety concerns for the two-dose regime, and a paucity of data on the booster dose, how can FDA assure the public of the safety of additional doses?
- **Efficacy:** Concerns for bias and sources of confounding
- **Policy towards repurposed drugs** must be re-examined due to a change in risk-benefit analysis.

Please note that this document extends our previous comments discussed in written submissions (6,7) for the recent ACIP meeting of CDC (8/30/21) as well as in an Op-Ed article of a respected clinical trials web site.(8)

2. Regulatory Concerns

2.1. Which legally distinct product is under consideration and under which authorization type?

According to the FDA's announcement of this meeting, the topic under discussion is *"the Pfizer-BioNTech supplemental Biologics License Application for COMIRNATY."* (footnote 2)

Prior to August 23rd, an EUA (Emergency Use Authorization) was in place for a product known as the "Pfizer-BioNTech COVID-19 Vaccine" as referred to in a revised EUA letter of May 10.(9)

On August 23rd 2021, in a letter to Pfizer, Inc., FDA disclosed the existence of two legally distinct [footnote 8 in (10)] vaccine products:

- Pfizer-BioNTech COVID-19 Vaccine: this product was to remain under EUA.
- COMIRNATY (COVID-19 Vaccine, mRNA) – a BLA was issued on August 23rd for this product(11) to BioNTech Manufacturing GmbH.

According to that letter, these two products can be used "interchangeably" but have "certain differences that do not impact safety or effectiveness"

According to FDA, since the COMIRNATY product, as a practical matter is not available, the EUA for the Pfizer-BioNTech product would remain in place. However, as popularly understood, for example in this Reuter's news headline[3] the *"Pfizer-BioNTech COVID-19 vaccine gains full U.S. regulatory approval."*

Accordingly, the announced topic for this meeting

"the Pfizer-BioNTech supplemental Biologics License Application for COMIRNATY."

is at best unclear. The only company of record with a product called COMIRNATY with a BLA to which a supplement could be added is BioNTech Manufacturing GmbH. Pfizer-BioNTech has a legally distinct product referred to in official documents (10) as *"Pfizer-BioNTech COVID-19 Vaccine."*

Will the agency clarify:

- For which legally distinct product is an approval of a booster dose being considered?
- If FDA intends to supplement BLA approval for booster doses for a product (COMIRNATY) that is not available, but not authorize their emergency use under an EUA, how can this be of any help whatsoever?

[2] www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-september-17-2021-meeting-announcement#event-materials

[3] www.reuters.com/business/healthcare-pharmaceuticals/us-fda-grants-full-approval-pfizer-biontech-covid-19-vaccine-2021-08-23/

- If two legally distinct products exist, why is it only possible in VAERS (9/13/21) to report events for the Pfizer-BioNTech product and not for the BioNTech (ie COMIRNATY) product?
- What are the "certain differences that do not impact safety or effectiveness" between the EYa and BLA products?(10)
- What are the legal ramifications of having two legally distinct products in terms of:
    - Operation of different regulatory standards to conduct safety monitoring, reporting of advesrse events, or adherence to other regulatory requirements?
    - Liability of manufacturers or health providers for injuries resulting from the use of vaccines?
    - Ability of patients to bring actions under various statues for vaccine-related injuries?
    - Ability of patients to obtain compensation under the National Vaccine Injury Compensation (or similar) Program?[4]
    - Other ramifications?

2.2. Vaccines or Gene Therapy Products? Regulatory and Safety Consequences

2.2.1. Regulatory Classification

Although these Covid-19 agents fall under FDA's definition of vaccines and vaccine-associated products,[5]

> *"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.[6]

> (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.(12)

Moderna, Inc., the maker of another mRNA Covid-19 vaccine, acknowledged in their 2Q2020 SEC filing(13)[7] thus *"Currently, mRNA is considered a gene therapy product by the FDA."* These vaccines might be more appropriately be described as "Gene Therapy Vaccines" (GTV).

Consistent with the FDA June 2020 guidance(14) on the development of vaccines for Covid-19, Pfizer,[8] Moderna[9] and Johnson & Johnson,[10] declared their intent in their requests for EUA status to follow study subjects for up to 36 months. Parenthetically, an additional concern has arisen in the unblinding of at least some of the clinical trials, thus preventing full assessment of safety as previously declared.(15)

Even this 36-month 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

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[4] www.hrsa.gov/vaccine-compensation/index.html

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

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

[7] 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.

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

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

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

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."(12) 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 (12) was made in FDA's guidance on development of Covid-19 vaccines(14), nor in the EUA briefing documents provided by Pfizer, Moderna and Johnson & Johnson.

Will FDA provide an explanation as to why the provisions relating to Gene Therapy products have not been incorporated into the risk-benefit analysis of these vaccines, or the types and durations of studies it has required of these products?

Will FDA explain why the classification of these products as Gene Therapy Products, evinced by Moderna's disclosure in August 2020, has been all but ignored in terms of the types and durations of studies it has required of these products?

2.2.2. Will long term studies and cancer be performed?

THE BLA for COMIRNATY acknowledges LONG term myocardial issues with a 5 year follow up in a required post-marketing study consistent with the lower range for LTFU for Gene Therapy Products.

As contemplated in the FDA Gene Therapy Guidance document?(12), there appear to be no plans for FDA or CDC to collect other long-term data (or require studies) on autoimmune disease, cancer and other disorders This is particularly concerning as the package insert(16) 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,(11) or Summary Basis for Regulatory Approval(17) is there a POST MARKETING REQUIREMENT to conduct carcinogenicity, genotoxicity or male fertility.

A number of Covid vaccine surveillance systems operate under the aegis of FDA[11] and/or CDC.[12] CDC lists six follow-up studies below.

Study	Final analysis	Interim (short term)
COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants	March 2023	July 2021 Jan 2022
Mortality and Vaccination with COVID-19 Vaccines	April 2024	Oct 2021 Apr 2022
COVID-19 Vaccine safety, Spontaneous Abortion (SAB) and Stillbirth in the VSD	April 2023	Monthly surveilance
COVID-19 Vaccine-Mediated Enhanced Disease (VMED) and Vaccine Effectiveness in the VSD	Q1 2023	Q2-3 2021 Q2-3 2022
VSD Tree-Based Data Mining	Aug 2023	
VSD RCA Protocol version	Approx 2023	Ongoing

While it is appropriate to conduct these sorts of studies, it is noteworthy that the concerns expressed in the objectives for a number of these studies are not reflective of the extensive media campaign to promote vaccination and its safety. We will discuss specific details of some of these studies in the sections below. In our opinion this contravenes the principles of obtaining informed consent for medical treatment.

2.2.3. Economic cost of long term follow up of Gene Therapy products – who will pay?

Understanding the concerns that this distinction reveals has other significant long-term consequences. Given that these Gene Therapy Vaccines (GTV) have been used on what may fairly be termed an experimental basis, **every** GTV recipient

[11] www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/covid-19-vaccine-safety-surveillance

[12] www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/emergencypreparedness/index.html

may be subject to, or even entitled to long-term monitoring, as well as early intervention of delayed events. Assuming, conservatively, an annual cost of $500 per person, and based on an estimated (8/29/21) 204 million of Americans having received at least one GTV dose, this amounts to an annual cost of some $102 billion, just for the USA. This figure is comparable to the 2020 budgets or revenues of NIH ($42b), Pfizer ($42b), Johnson & Johnson ($83b) or Facebook ($86b) and eclipses estimates of between $25 billion and $35 billion for the global Covid-19 vaccine market. Considering the approximately 4.5 billion GTV recipients around the world, this annual global cost, before any treatment or indirect costs, will approach trillions of dollars. Who will absorb this cost? Government? Medicare? Medicaid? The manufacturers of the Gene Therapy Vaccines? Private insurers? Patients?

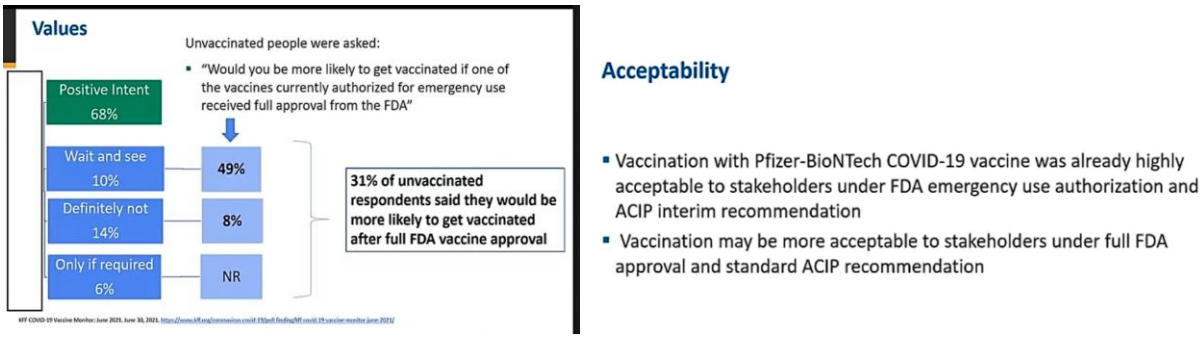
3. Transparency and Public Trust Concerns

Much is being made about vaccine hesitancy, particularly that attributed to "*misinformation*." Allow us to suggest that the problem is not unjustified mistrust in the vaccines. It is justified mistrust of public health officials fueled by contraventions of the best traditions of American democracy such as:

- FDA's issuance of a BLA without a public meeting or comment.
- The apparent withholding of evidence of waning immunity prior to CDC's ACIP recent vote to recommend the Pfizer vaccine.(8)
- The lack of transparency within NIH regarding the formulation of their treatment guidelines.
- The effective admission by CDC that the primary driver to issue a full FDA approval for any one of the Covid-19 vaccines, along with a CDC.ACIP recommendation was vaccine hesitancy,(18) rather than the accumulation of sufficient evidence for safety and efficacy. CDC referenced a survey which asked unvaccinated people:

  *"Would you be more likely to get vaccinated **if one** of the vaccines currently authorized for emergency use received full approval from the FDA"* (emphasis added). *Of these, "31% of unvaccinated respondents said they would be more likely to get vaccinated after full FDA vaccine approval," meaning - OF ANY OF THE VACCINES.*

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



Another source of mistrust is the inconsistent use of standards of evidence. 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 a presentation[13] analyzing vaccine efficacy, 17 observational studies, including 7 non-peer-reviewed, were employed. 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.

There is also mistrust due to the demonization and censorship of the many medical professionals and scientists who have raised concerns about these vaccines and have advocated for the use of repurposed drugs. These workers are from across the political spectrum who are not only proponents of classical type vaccines, but also proponents of gene therapy products

[13] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/07-COVID-Gargano-508.pdf

that employ DNA or mRNA technologies to treat cancer and other heretofore incurable diseases. As with all new technologies, safety is paramount, and we assert that until proven otherwise, the risk-benefit balance demands a re-assessment of the justification for the continued use of these Gene Therapy Vaccines (GTVs), especially as booster doses are now being considered.

In addition to concerns related to the gene therapy nature of these products there are concerns about the toxicology of the spike protein antigen, the adjuvants themselves as well as downstream consequences at the gene or mRNA level. Importantly, inexpensive, safe and effective prevention and treatment based on repurposed drugs are readily available. (19)

The contentions that our motivations are rooted elsewhere or that allegedly politically motivated advocacy for use of repurposed drugs in Covid-19 has spewed misinformation fueling vaccine hesitancy is a perversion of the truth as such advocacy is subject to heavy censorship within social media, the peer reviewed scientific literature and in professional contexts. At a time when unity against Covid-19 is sorely needed, this demonization serves to increase divisiveness and political polarization. This demonization erodes patients' fundamental rights to choose whether or not to undergo any sort of medical treatment, and erodes physicians' freedom to practice medicine, by prescribing treatments they believe to be in the best interests of their patients.

Governments, public health agencies and the medical community must address the safety consequences of these vaccines and at the same time make fundamental corrections to heretofore employed approaches to Covid-19 and the suppression of legitimate scientific debate.

Can FDA and this committee provide an assurance that it will do everything in its power to defuse the current toxic atmosphere that is stifling scientific discussion?

4. Ongoing and Unresolved Safety Concerns for Covid-19 vaccines

The discussion on booster doses in the August 30 meeting of CDC's ACIP recognized the challenges in producing reliable data that could support the use of booster doses. It was unclear that there was any significant body of data available to address either safety of efficacy of booster doses. Limited data on efficacy have now emerged. One recent study(20) suggested that waning or reduced immunity can be restored with a booster dose, but this is only partial, and is at best, according to the study, temporary.

Before considering the safety of a third vaccine dose, it is entirely appropriate to discuss the ongoing concerns regarding the first two doses.

4.1. Safety signal analysis of events from VAERS

4.1.1. 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.(21) 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" (22)* 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 note that presentations made at CDC's ACIP meeting on August 30 largely relied on event incidence rates expressed as the number of events per 100,000 (or million) doses.

4.1.2. Use of normalized event ratios for signal detection

We adopted the approach published (23) 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).

We were particularly interested in the H1N1 data, as the paper published by CDC scientists (23) had stated that there had been active efforts to encourage people to use the VAERS system for H1N1 (see p7251 *"These findings, however, should be interpreted in light of the publicity around the 2009-H1N1 vaccine and efforts to increase reporting to VAERS"*).

Examining the data in VAERS (7/30/21) obtained using the WONDER portal, the per population- or per dose- normalized event ratios are very high, particularly for reports of death (177, 98 respectively) (Table 1).

Estimates of PPR are clearly highly muted, challenging their value and appropriateness. Nonetheless, the signal (5.2) for deaths was significant according to the Evans criteria.(24) 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.

***Table 1:* Normalized Event Ratio (NER) or Proportional Reporting Ratio (PRR) for Covid-19 Vaccines Compared with Seasonal Flue or H1N1 Vaccines**

	NER or PPR				
	C19 vs Flu			C19 vs H1N1	
Event Category	NER people[a]	NER Doses[b]	PRR[c]	NER People[d]	PRR[e]
Death	176.7	97.5	5.2*	35.1	0.4
Life Threatening	58.9	32.5	1.7	13.2	1.1
Permanent Disability	29.6	16.3	0.9	19.5	0.7
Congenital Anomaly / Birth Defect *	47.0	26.0	1.4	0.0	0.0
Hospitalized	53.8	29.7	1.6	13.5	1.1
Existing Hospitalization Prolonged	44.3	24.5	1.3	1.3	11.3
Emergency Room * (note)	42.1	32.3	1.7	18.2	0.8
Office Visit * (note)	22.4	17.2	0.9	13.1	1.1
None of the above	37.8	20.9	1.1	15.7	0.9
Serious	51.4	28.3	1.5	14.8	0.97
Not serious	33.1	18.3	1.0	14.9	0.96

We used estimates from CDC for the number of doses delivered/ people vaccinated.[14] We used USAFACTS[15] for age-related population figures for various years, and CDC figures on numbers of people vaccinated [16]for seasonal flu or H1N1 vaccines. Original figures obtained from VAERS 7/30/21 using "USA Territories, unknown"" as the location filter.

[a] Normalized Event Ratio (NER) of number of events in each event category (denominator number of unique events) adjusted for number of people given at least one dose of C19 (all dates) or Flu vaccine for 2016/7, 17/18 or 18/19 seasons

[b] NER of number of events in each event category adjusted for number of doses given of C19 (all dates) or Flu vaccine for 2016/7, 17/18 or 18/19 seasons

[c] PRR, C19, vs. flu (using unique events as denominator)

[d] Ratio of number of events in each event category adjusted for number of people given at least one dose of C19 (all dates) or H1N1 vaccine for 2009/10 season

[14] cdc.gov/coronavirus/2019-ncov/covid-data/covidview/index.html
[15] usafacts.org/data/topics/people-society/population-and-demographics/population-data/population/
[16] cdc.gov/flu/prevent/vaccine-supply-historical.htm

[e] PRR C19 vaccines vs. H1N1.

* p <0.00001. (chi squared test). Although other values for example for life-threatening or serious conditions do meet the Evans(24) criteria because they do not exceed 2, the chi-squared test nonetheless yields p<0.00001.

We refined our analysis (Table 2) using VAERS data as of August 6 2021. We considered only reports from the 50 States plus Washington DC, excluding US territories and "unknown" locations to ensure that only AE's reported from the US were used when calculating rates based on vaccination coverage in the US. For the flu vaccines, data from the 2015/16, 2016/17, 2017/18, 2018/19 and 2019/20 were considered. The 2020/21 season was excluded to avoid confounding effects with Covid-19. For the Covid-19 vaccines, reports with an indication of SARS-CoV-2 infection or COVID-19 were not included in counts for COVID-19 vaccines. Because data availability in VAERS is ephemeral, we needed to repeat parts of our earlier analysis on what was the currently available dataset. In addition to deaths and serious events, we examined three categories of events noted to be of interest in the VAERS' Standard Operating Procedures for COVID-19:(21) Guillan-Barré Syndrome (GBS), coagulopathy, and acute myocardial infarction.

Table 2 shows strong signals for serious events, death, coagulopathy and myocardial infarction. The signals are more evident using the Normalized Event Ratio (by dose) than with the PRR. No major differences were evident if the PRR was calculated by number of unique events or by number of unique reports (i.e. symptoms). The values for Normalized Event Ratios (by dose) for death and serious events were similar to those from our earlier analysis (Table 1).

For death and coagulopathy, the signals appear to increase with age. The reverse is true for myocardial infarction. For serious events an age-dependency is not evident. For Guillan-Barré syndrome, the signals appear weak and not detected at all using the DSA/ PRR method.

We conclude from this portion of our work that:

- There are strong safety signals evident for death, serious events, coagulopathy and myocardial infarction associated with the Covid-19 vaccines compared with the flu vaccines.
- Signals are age dependent for death and coagulopathy (increase with age) and myocardial infarction (decreases with age).
- Even after accounting for possible stimulated reporting, by comparison with H1N1 vaccines, strong safety signals are still evident.
- Using Normalized Event Ratios, consistent with CDC published methodology (23) appears a far more sensitive method of identifying signals than DSA/PRR methods.
- Further investigation is warranted to determine causality.
- Caution is warranted as booster doses are being considered.

Table 2: COVID-19 vs. Flu Vaccines: Normalized Event Ratio vs. Disproportionality Signal Analysis as Proportion of All Reports or events

	SERIOUS EVENTS			DEATHS			GBS			COAGULOPATHY			Myocardial Infarction		
Ages	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report	NER dose	PRR event	PRR report
10-17	34	1.66	1.35	32	1.52	1.24	7	0.34	0.28	74	3.56	2.89	n.e.	n.e.	n.e.
18-49	25	0.87	0.99	64	2.22	2.52	3	0.09	0.1	226	7.78	8.82	403	13.92	15.78
50-64	26	1.23	1.45	85	4.01	4.74	3	0.12	0.14	239	11.19	13.22	121	5.68	6.71
65+	30	2.34	2.76	98	7.77	9.16	3	0.22	0.26	370	31.34	36.97	88	7.01	8.27
10+	28	1.31	1.52	91	4.24	4.93	3	0.13	0.15	276	12.77	14.84	126	5.83	6.78

Note: The PRR is the ratio of the proportion of a particular event or event type out of all reports (or events) for COVID-19 to the proportion of all reports (or events) for the combined 2015-2019 flu seasons. Orange shading indicates a statistically significant difference between the proportion of COVID-19 proportion of COVID-19 and flu reports for that age group and event type (chi squared test. Flu reporting rates represent the total reports to VAERS across the 2015/16-2019/20 flu seasons for each age group. Covid-19 reporting rates include all reports to VAERS for COVID-19 vaccines for each age group as of Aug. 6, 2021. The Normalized Event Ratio shown is calculated according to the number of doses given.

The "coagulopathy" category includes a set of 26 preferred terms (PT) for thromboembolic events (although the category does not include coagulopathy PT). The full list of PT's for GBS, coagulopathy and acute myocardial infarctions can be found in Table 4.6 of the VAERS SOP document.(21)

A signal does not prove that the vaccines were the cause of these events. The intense signal for death awaits a transparent explanation[17] that includes a comprehensive report of the types and numbers of investigations performed, including autopsies. Although CDC has provided guidance for the conduct of autopsies of Covid-19 cases, there is no prospective protocol for the conduct of autopsies to determine whether or not the death is vaccine-related. This would include a detailed description of the types of histopathological methods to distinguish vaccine-induced spike protein from spike protein derived from a Covid-19 infection. Where is this analysis? Where is there a protocol? Similarly, the strong signal of heart attacks in younger than in older people (403 vs. 88, Table 1) must be investigated.

Lastly, it is worth discussing the signal for myocarditis, acknowledged to be an issue as a warning in the COMIRNATY package insert attests:(16)

> *"Postmarketing data demonstrate increased risks of myocarditis and pericarditis, particularly within 7 days following the second dose."*

In
Table **3**, we show PRR signals that meet the Evans(24) criteria that are of a similar magnitude (or smaller, except for GBS) to those shown in Table 2, justifying their further investigation.

***Table 3:* COVID-19 vs. Flu Vaccines: PRR for myopericarditis**

Ages	Myopericarditis
12-17	66.8
18-49	5.6
50-64	7.4
65+	4.0
All	7.9

Flu seasons from 2015/16 – 2019/20 were used. Covid vaccine reports were through Aug 6 2021. Reports for codes that includes Covid of SARS-Cov-2 were excluded.

Rapid Cycle Analysis (RCA) of the VSD system was unable to detect a safety signal for myocarditis[18] until data were age stratified. Although in theory RCA should be able to detect signals in near real-time as medical records are being generated, the method appears even less sensitive than those prescribed for VAERS(21) with limitations described above. A paper was published in JAMA (25) on September 3rd describing the findings from the Rapid Cycle Analysis of the VSD system. It concluded that:

> *"incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination."*

We suggest that publication of this paper without the context of the acknowledged myocarditis signals from VAERS, within the conclusion, is highly misleading.

4.2. Estimate of under-reporting in VAERS using CDC published methods

CDC has acknowledged the many limitations inherent in the VAERS system, including that the system is prone to under-reporting for a variety of reasons. There is additional confusion given specific reporting requirements pursuant to the EUA. The CDC web site states[19] that under an EUA, health providers are required to report certain categories of events following

[17] As far as we can tell, the only statement regarding these deaths appears on CDC's web site (9/2/21) *"**Reports of death after COVID-19 vaccination are rare**. More than 369 million doses of COVID-19 vaccines were administered in the United States from December 14, 2020, through August 30, 2021. During this time, VAERS received 7,218 reports of death (0.0020%) among people who received a COVID-19 vaccine. FDA requires healthcare providers to report any death after COVID-19 vaccination to VAERS, even if it's unclear whether the vaccine was the cause. **Reports of adverse events to VAERS following vaccination, including deaths, do not necessarily mean that a vaccine caused a health problem.** A review of available clinical information, including death certificates, autopsy, and medical records, has not established a causal link to COVID-19 vaccines."* (their emphasis)
www.cdc.gov/coronavirus/2019-ncov/vaccines/safety/adverse-events.html

[18] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/04-COVID-Klein-508.pdf

[19] www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/reportingaes.html

vaccination including serious events, deaths and life-threatening events, regardless of if the report think the AE caused the event or not.

With about 2/3 of the US population vaccinated, we would expect about 5000 per deaths to occur every day from non-Covid-19 causes. Using a conservative 30-day follow up, we would expect to see 150,000 deaths reported in VAERS. As of 8/29/21, 6128 deaths (USA, territories and unknown) have been reported in connection with Covid-19 vaccines (4805 deaths 50 States and Washington DC). The system does not appear to be functioning as designed.

In CDC's recent ACIP meeting 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 in one presentation,[20] 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				

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

CDC scientists published (26) a method to estimate the degree of under-reporting in VAERS, by comparing the rates of AEs published in clinical trials, with rates normalized for population found in VAERS.

We used the 3 deaths classified as adverse events in Table S3 of the 6 month follow up study for the Pfizer vaccine (27). Conservatively, we did not use the 15 deaths in Table S4 there. Note the discrepancy between total deaths in the Thomas paper (18 vs 19 deaths in vaccine vs. placebo) and in the Summary Basis for Regulatory Action(17) where the total number of deaths reported are 21 and 17 for the vaccine and placebo groups respectively

Using these conservative data, we estimated the numbers of deaths tentatively associated with the Pfizer vaccine may be 4.9-15 times higher than reported. Applied to all vaccines, using the figure of 4805 deaths (50 states. DC) but subtracting deaths where Covid-19 or SARS is mentioned (639) this may represent a true report rate of between 20,400-62,500 deaths. The number of life-threatening events may be 24-64 times higher than reported. Noe that this estimate does not infer causality.

4.3. Estimate of number of deaths possibly associated with Covid-19 vaccines

We have so far estimated 20,400-62,500 deaths unrelated to Covid-19, that we might have expected to find in VAERS (50 States+DC). These non-Covid-related deaths may be related to the toxicity of the spike protein towards heart cells and effects on coagulation. We now estimate deaths related to Covid-19 subsequent to vaccination.

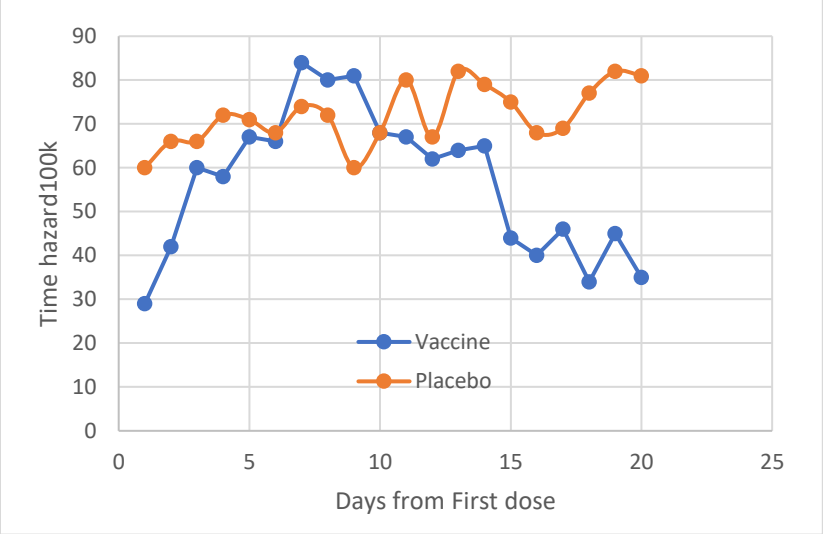
4.3.1. Post-vaccination deaths estimated from Israeli Ministry of Health and Clalit data.

Increased numbers of Covid-19 related deaths associated with vaccination

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 (28), one of us (HS) observed an early (<7 days) uptick in Covid-19 cases following vaccination.

Figure 1: Covid-19 cases following vaccination in Dagan et al.

[20] www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-08-30/05-COVID-Lee-508.pdf



A letter to NEJM (March 11) was rejected but described in an article in France Soir – May 5.[21] There, the incidences of Covid-19 tripled from day 1 to 7 among the vaccinated,[22] 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."*

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. The recent finding from a large Israeli cohort of an increased (40%) risk of Herpes zoster infection(29) 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.(3)

4.3.2. Deaths in the unvaccinated population resulting from transmission by the vaccinated

There is a third pool of deaths and Covid-19 cases that must be considered in assessing the risk and benefits of the Covid-19 vaccines. Contrary to initial hopes, vaccines may not reduce transmission.(30), thus Covid-19 may have been unwittingly transmitted by vaccinees to the non-vaccinated.(31,32) including by fecal aerosol(33) in subjects sharing bathrooms.

4.4. Unresolved pregnancy and reproductive-related related safety issues

4.4.1. Pregnancy

The COMIRNATY package insert(16) provides little guidance for pregnant mothers:

> *"Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy."*

Instead, the prescribing info says: *"There is a pregnancy exposure registry for COMIRNATY. Encourage individuals exposed to COMIRNATY around the time of conception or during pregnancy to register by visiting https://mothertobaby.org/ongoingstudy/covid19-vaccines/."*

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

As stated in their approval letter,(11) what FDA have done to determine what sorts of risks are posed during pregnancy is to obtain the commitment from BioNTech to conduct a post-marketing pregnancy/neonatal study with a four-year term.

> *Study C4591022, entitled "Pfizer-BioNTech COVID-19 Vaccine Exposure during Pregnancy: A Non-Interventional Post-Approval Safety Study of Pregnancy and Infant Outcomes in the Organization of Teratology Information Specialists (OTIS)/MotherToBaby Pregnancy Registry."*

Note the word commitment. As FDA explains[23]

> "Postmarketing *commitments* (PMCs) are studies or clinical trials that a sponsor has agreed to conduct, but that are *not required* by a statute or regulation."

This is not a requirement (as for some of the other post marketing studies on myocarditis for example). Compare not only this level of regulation, but also the length and scope of the study in question with an unrelated Janssen (J&J) biologic product for which a 7-year[24] study is required and which includes examining effects on child and early development. A recently approved (2021) Astra-Zeneca biologic product[25] requires a NINE-year study on pregnancy and maternal and fetal/neonatal outcomes.

What is disturbing about this situation is that it is in stark contrast to the language in a CDC study protocol entitled: "COVID-19 Vaccine Safety Evaluation in Pregnant Women and their Infants"[26] and dated June 29 2021:

"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."

The protocol, nonetheless states 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 appears in a related CDC protocol entitled "COVID-19 Vaccine Safety, Spontaneous abortion (SAB) and Stillbirth in the Vaccine Safety" [27] 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."

Are pregnant women being advised about this sort of language and that they are in effect unknowingly participating in a clinical study?

Preliminary findings of a CDC study(34) published in June involving 35,691 pregnant v-safe surveillance system participants and 3958 participants of enrolled in the v-safe pregnancy registry (only 827 of whom had a completed pregnancy), *"did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines."* The study acknowledged that *"more longitudinal follow-up, including follow-up of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.".* This study was updated(35) and declared a cumulative early pregnancy loss rate of 14%. This rate is significantly higher than the published rate for equivalent gestation (more than 6 weeks with dating confirmation of pregnancy) seen(36) of 9% and more recently of 5%.(37) In the same study over 80% of participants were not surveyed and the fetal loss rate of 14% was reported to be potentially higher due to missing data, perhaps reaching 18%. No data has been provided for pregnancies beyond 20 weeks in the later publication and requests for data sharing have been declined by the CDC despite being a publicly funded registry comprising voluntary unpaid participants.

It is also noteworthy that the only study of efficacy of the mRNA vaccine in pregnant women was recently published (38)and failed to show any significant differences in overall hospitalization rates (marginal), severe disease or death in a comparison

[23] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/postmarket-requirements-and-commitments
[24] www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/761061Orig1s000ltr.pdf
[25] www.accessdata.fda.gov/drugsatfda_docs/appletter/2021/761123Orig1s000ltr.pdf
[26] www.cdc.gov/vaccinesafety/pdf/COVID19-acute-maternal-outcomes-508.pdf
[27] www.cdc.gov/vaccinesafety/pdf/VSD-COVID-Vaccine-SAB-SB-Protocol-508.pdf

between vaccinated and unvaccinated pregnant women. In the same study no deaths were noted in about 20,000 participants equally distributed between groups. At a published rate of covid death in the pregnant age population of 1 per 100,00028 in fact would require a study of 1.6m people to detect a 50% reduction in mortality. This has not been shown and therefore no claims as to the efficacy of an original strain -specific mRNA vaccine specific against delta SARS-Cov-2 in pregnancy can be reliably made. Given the potential for the unknown teratogenicity involved in this novel therapy it is not possible to make any accurate claims of a positive risk-benefit profile in pregnancy despite overwhelming claims of such by the international OBGYN community.

As with two other related studies (28,29), this study permitted matched control subjects to become vaccinated. A data re-analysis(39) of one of these studies(28) 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. A similar bias is likely to operate in this pregnancy study.

4.4.2. Menstrual disorders

On the very same day (August 30) CDC staff were providing evidence to ACIP on the safety of the Pfizer vaccine, NIH made the startling announcement[29] that it was funding studies *"to explore potential links between COVID-19 vaccination and menstrual changes*." They elaborated: *"Some women have reported experiencing irregular or missing menstrual periods, bleeding that is heavier than usual, and other menstrual changes after receiving COVID-19 vaccines."*

Querying VAERS (9/3/21) for various menstrual disorders[30] we found that for reports associated with the Covid-19 vaccines there were 7037 separate menstrual disorder related symptoms described in 4783 unique reports. By comparison with all other vaccines, for ALL years COMBINED we found 897 symptoms in 798 unique events. Most of these are accounted for by the HPV vaccines (698 symptoms in 623 events) with seasonal flu vaccines contributing only 47 symptoms within 45 unique events. Another analysis of VAERS reports also detected menstrual disorders.(40) A similar pattern of symptoms relating to menstrual irregularity was seen in the MHRA yellow card reporting scheme in the UK suggesting that this is not just unique to VAERS reporting.[31]

One explanation for these irregularities is the biodistribution of the LNP based formula which has been shown to be preferentially distributed to, and accumulate in, the ovaries in female animal studies. The full biodistribution data for the LNP component of the Pfizer vaccine from animal studies is now in the public domain following freedom of information requests (41). The biodistribution studies show clearly that although the LNP vector is partially cleared from the injection site at 48 hours it accumulates over 100-fold in the ovaries during the same time period (p45).

No suitable fertility studies were subsequently performed prior to approval of the therapy to ascertain whether this could have an impact in humans and the information regarding accumulation of the product was not made public. Only one animal study addressing the fertility question was assessed prior to the issuance of the EUA which was study 20256434 (p55-56). This included only 22 rats and in each treatment group and within which one female in each group was euthanized due to total litter death. No long term studies of the pups was made as all pups were euthanized. An increased pre-implantation loss rate in rats was noted but no further studies performed.

"Menstrual disorders" are far too often trivialized, leaving its victims and their families to suffer. A number of these disorders lead to early hysterectomies which trigger another set of complications that can include adhesions, pain, bowel obstruction, heart disease and dementia. Will these sorts of problems be examined as part of the NIH studies?

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[28] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1016465/Vaccine_surveillance_report_-_week_36.pdf

[29] www.nichd.nih.gov/newsroom/news/083021-COVID-19-vaccination-menstruation

[30] 9/3/21 – searched under "USA, Territories and Unknown" using the terms AMENORRHOEA, DYSMENORRHOEA, HEAVY MENSTRUAL BLEEDING, HYPOMENORRHOEA, MENORRHAGIA, MENSTRUATION DELAYED, MENSTRUATION IRREGULAR.

[31] www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

NIH illustrates a number of reasons for these reported menstrual changes, including *"pandemic-related stress."* But stress is not our prime suspect. Effects on the ovaries and uterus are, and we must view these reported menstrual changes in the context of unresolved questions about the safety of the vaccines on the reproductive system in general, and on pregnancy in particular.

4.5. AE events reported elsewhere

In the United Kingdom, the Yellow Card system(42) 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,[32] 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).[33] The WHO provides the Vigiaccess[34] database from which 8,703 deaths and 1,537,994 ADR records were registered as at 26th July 2021.[35]

4.6. Establishment of LTFU program: pCoVS

The growing list of short-term effects attributed to the Covid-19 vaccines, as well as unresolved long term concerns poses a major public health issue. To concretize recognition of, and to spur action to avert and confront this potential public health crisis, we propose the term:

Post Covid Vaccine Syndrome – pCoVS

A syndrome occurring after injection of antigen-inducing, gene therapy vaccines to SARS-Cov-2 virus. The syndrome is currently understood to manifest variously as cardiac, vascular, hematological, musculoskeletal, intestinal, respiratory or neurologic symptoms of unknown long-term significance, in addition to effects on gestation. Manifestations of the syndrome may be mediated by the spike protein antigen induced by the delivered nucleic acids, the nucleic acids themselves, or vaccine adjuvants. As more data become available, subsets and longer-term consequences of pCoVS may become apparent, requiring revision of this definition. Sub-categories may be designated by suffix for example:

-C Cardiac
-N Neurologoc
-H Hematologic
-V Vascular

We propose:

- Recognition by public health agencies, governments and professional societies of pCoVS.
- Assignment of ICD10 and related tracking or re-imbursement codes for pCoVS.
- Establishment of transparent systems to monitor and track for long-term and delayed pCoVS.
- Establishment of funding for research into the prevention and treatment of pCoVS.
- Regulation of the Pfizer, Moderna and Janssen vaccines (GTVs) as Gene Therapy products.
- Insistence on long term (15 years) pharmacovigilance by manufacturers of AI-GTVs for pCoVS consistent with FDA guidelines for gene therapy products.
- Legislation to prevent discrimination of patients based on vaccination[36] or actual or potential pCoVS status.
- Establishment of funding to determine what effects if any the GTVs have on the genome or gene expression, including their effects on toxicity and other disorders. Develop and implement methods to screen for, and treat the consequences of, such genetic changes.

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

[33] 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.

[34] http://vigiaccess.org/

[35] 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)

[36] According to one writer, those choosing to remain unvaccinated, rather than being demonized, should be thanked for serving as a valuable control population enabling the effects of vaccines to be more fully evaluated.

- Comprehensive funding for the development of programs to prevent Covid-19 or reduce its impact by promoting good health practices, proper use of nutritional supplements and conduct of well-executed clinical trials to examine the effects of promising repurposed rugs.

5. Efficacy and Risk-Benefit

Although a number of studies are beginning to emerge regarding vaccine efficacy, the major decisions regarding FDA approval and CDC recommendation for the Pfizer vaccine have been based on two studies:

- Pfizer's own study (~40,000) presented at CDC[37] and recently preprinted.(27), with a data cut-off of March 2021.
- The large Israeli Clalit efficacy (~1.2 million) (28) and related safety (~1.7 million) studies.(29)

There are 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 (39) 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 a 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 (29), a similar censoring bias appears to exist.

6. Repurposed Drugs

Once vaccine effectiveness falls from the 90-95% range towards and below 50% any risk-benefit analysis would change greatly, placing these vaccines in close competition with repurposed drugs with far fewer safety concerns, and effectiveness under different scenarios of 30-60% [hydroxychloroquine;(43-45) ivermectin;(46,47) fluvoxamine;(48) Zinc/Vitamin D/other Vitamins(49,50)]. Options are running out as we consider authorizing a booster dose. At the same time Pfizer have announced that the first patient in their phase 2/3 study received a dose of their proprietary PF-07321332 – a drug intended to treat *"non-hospitalized, symptomatic adult participants who have a confirmed diagnosis of SARSCoV-2 infection and are not at increased risk of progressing to severe illness, which may lead to hospitalization or death."(51)* Will we need to wait another year for the arrival of PF-07321332 when a critical evaluation of the data for HCQ and IVM, as we have done, has revealed significant flaws in key studies(45,46) that have shaped policy on these drugs. Not only have we detected key flaws, but once corrected, impressive efficacy estimates are obtained justifying further study.

Table 4 makes interesting reading.

Table 4: Comparison of Deaths and ADR Reports made in Vigiaccess.org database to 9/13/21 (courtesy Dr. Tess Lawrie)

	Deaths	ADR Reports
ivermectin	20	5650
covid-19 vaccine	10541	1995744
remdesivir	557	7262

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