COVID-19 vaccine booster and new variant doses. Confusion and lack of a plan evident to ACIP

Written comments submitted re: CDC ACIP Meeting April 20th 2022
CDC-2022-0051

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(Drs. Seligmann and Pantazatos were primarily responsible for the study of: “All population booster COVID19 vaccine injections are associated with all-cause mortality in all ages: European and US data” (see section 4)

April 20 2022

Capsule
As CDC’s ACIP met to discuss the use of booster and new variant doses, we show that key vaccine efficacy and safefy data were again withheld from that could have better guided their discussion. We discuss continuing and unanswered safety concerns, particularly with regard to the gene therapy nature of the Covid-19 vaccines. In the face of public “vaccine fatigue”, the lack of a plan that can rapidly respond to new variant surges, is evident.

We reintroduce the subject of repurposed rugs and summarize our findings from re-analyses of pivotal studies in this regard. Lastly, we provide data concerning associations of vaccine and booster use with all cause mortality from both European (Euromomo.eu) and US (CDC) sources

Contents

1. Overview

Due to the ambiguity for the deadline to submit written comments between the Federal Register as being April 27th [1] or the date provided on the regulations.gov portal, we are adapting comments submitted recently to FDA's VRBPAC. (1)

On April 20 2022, CDC convened a meeting of ACIP (Advisory Committee on Immunization Practices). The meeting took place in the context of FDA"s EUA on March 29 2022 of a 2nd booster dose after 4 months of modRNA quasi-vaccines in persons ≥ 50 years and certain immunocompromised persons older than 12 (Pfizer) or 18 (Moderna) years. CDC also issued an EUI regarding a second booster dose of either modRNA quasi-vaccine 4 months after two doses of the Janssen product.[2]

The ACIP meeting also follows both chronologically and thematically, a meeting of FDA's VRBPAC on April 6th 2022 whose goal was to *"discuss considerations for use of COVID-19 vaccine booster doses and the process for COVID-19 vaccine strain selection to address current and emerging variants."*[3]

In addition to an FDA update, the committee heard the following presentations (links to slide presentations):

- Introduction Dr. M Daley
  Updates on vaccine effectiveness of COVID-19 booster dose Dr. R Link-Gelles
- Updates on safety of COVID-19 booster dose Dr. N Klein, Dr. T Shimabukuro
- VaST assessment Dr. K Talbot
- Updates to the EtR Framework: COVID-19 vaccine booster doses in adults ≥50 years of age and immunocompromised individuals Dr. S Oliver
- CDC guidance for second COVID-19 booster dose Dr. E Hall
- Framework for future COVID-19 doses and next steps Dr. S Oliver

These presentations were intended to provide background information to allow ACIP to answer the following non-voting questions (Slide 18, Dr. Sarah Oliver[4]):

1. What does ACIP think should be the primary **goal** for future doses of COVID-19 vaccines?
2. What other **data** would be important for ACIP to review?
3. What are other **considerations** for future doses of COVID-19 vaccines?

To summarize the discussion under these headings:

1.1. What does ACIP think should be the primary goal for future doses of COVID-19 vaccines?

[1] https://www.federalregister.gov/documents/2022/04/14/2022-08050/advisory-committee-on-immunization-practices-acip
[2] It is unclear how CDC can issue an EUI for an EUA product, from earlier presentations, and EUI can only be issued for a BLA product.
[3] https://www.fda.gov/advisory-committees/vaccines-and-related-biological-products-advisory-committee/2022-meeting-materials-vaccines-and-related-biological-products-advisory-committee
[4] https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-04-20/07-COVID-Oliver-508.pdf

The committee struggled with this question the most, tending towards the prioritization of reduction of severe outcomes (after boosting), and not necessarily to prevent Covid-19 illness itself. This was mainly driven by the practical reality of waning vaccine immunity to infection, despite modest and sustained protection against severe outcomes.

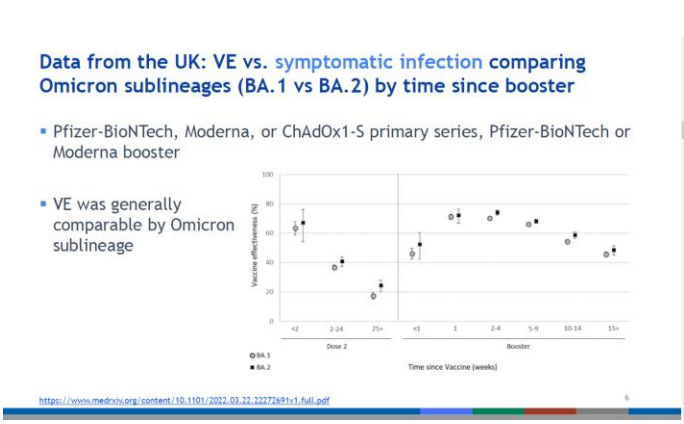
This was not the first time this question has been raised. ACIP members had started to question the goals of vaccination at least as early as the January 5th ACIP meeting. Realizing the limitations of the vaccine program, ACIP members discussed briefly the use of non-vaccine approaches to Covid-19, including monoclonal antibodies and antiviral drugs.

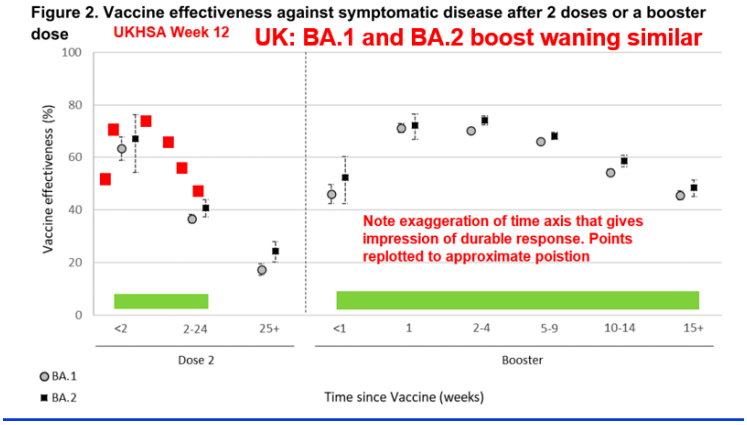
Key to guiding ACIP's deliberations is the provision of complete and timely data, especially regarding vaccine efficacy. We have previously noted that this is not always the case,(2) and suggest that withholding of data showing potential negative VE in some circumstances, likely cloused the committee's deliberations.

Waning and negative efficacy for the Covid quasi-vaccines falls below FDA's guidance(3,4) of 50% or and/or the lower CI of 30%, before 4 months. (Source (5-9))

Study	Country	Time	VE	LowCI	Other	Boost
Accorsi	USA, CDC	1 month	25%		10% @ 3m	
Hansen	Denmark Serum Inst	30d	16%	-25%	-77% @ 91d	55% (30.4) @30d
Buchan	Canada Pub Health Ontario	7-50d	~5%	-25%	-40% @ 120d	40% @7d
UKHSA	UK, week 13	10-14w	30%		18% @ 15w	40% @15-19w

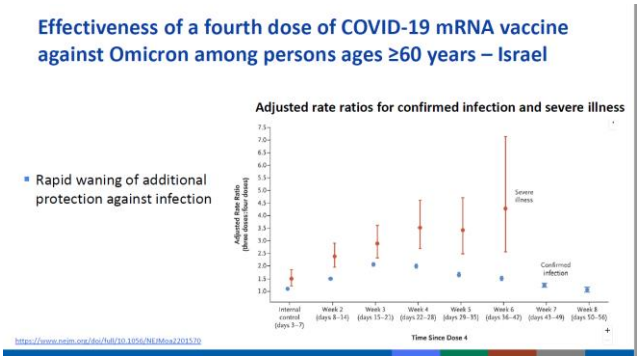
One of the principal slides presented (Dr. Link-Gelles) was the one on the left, taken from UK data and showing that that the primary series and booster VE wane similarly, both for the BA.1 and BA.2 variants.(8) Note however on the right, how, in the original source, the x axis has been exaggerated to falsely suggest the durability of the booster response.

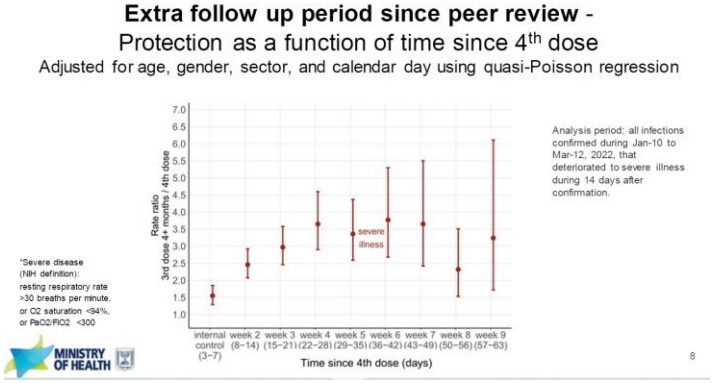




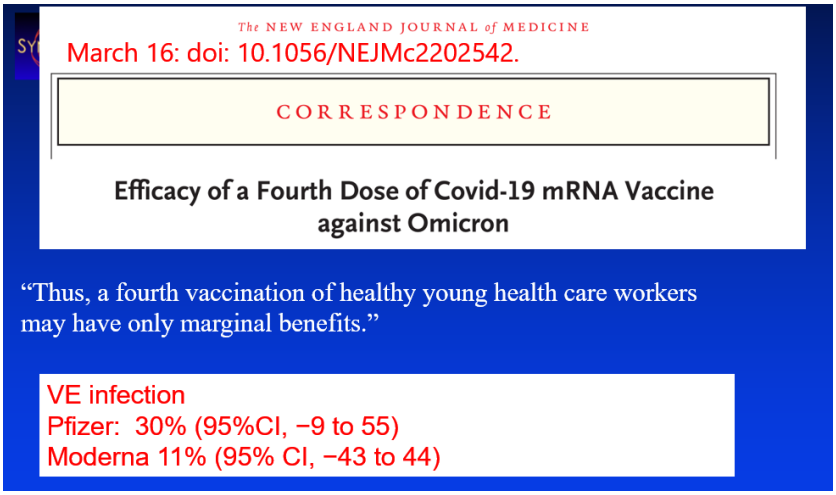
Another presentation (Dr. Oliver) showed Israeli data recently published (10) and presented by the Israeli Ministry of Health at the April 6th VRBPAC meeting[5] showing 4th dose data for infection to week 8 and severe illness to week 6 (left). What was NOT shown to the committee was the slide on the right, presented as an updated by the Israeli MoH at the April 6th VRBPAC meeting and showing evidence of waning protection against severe illness with three more weeks of data.

[5] https://www.fda.gov/media/157492/download\





Another Israeli 4th dose study using only a 4 month interval(11) reported a paltry vaccine efficacy against infection of only 30% (95% confidence interval (–9% to +55%) (Pfizer) and 11% (–43% to +44%) (Moderna). Note that these figures fall well below the FDA target efficacy of 50% with a lower confidence interval of 30%.(3,4) In this case, the confidence intervals indicate that negative efficacy is possible.



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Consistent with these data are other Israeli data for a 4th dose showing waning from 52.9% at one month to 2.6% at 4 months.(12) with limited initial (Omicron) efficacy of the 3rd Pfizer booster of 53.4%, waning to 16.5% and 3.6% in three or four months respectively. This is well before FDA's current boost interval of 5 months.(12) The marginal effectiveness of a 3rd dose vs. 2nd dose-only vaccinees was 29.1% at 3 months and 18.3% at 4 months.(12)

1.2. What other data would be important for ACIP to review?

ACIP heard presentations from Drs. Klein, Shimabukuro and Talbot on the safety of the quasi-vaccines.

- Updates on safety of COVID-19 booster dose Dr. N Klein, Dr. T Shimabukuro
- VaST assessment Dr. K Talbot

In an additional slide not provided in the uploaded slide deck, rates of myocarditis after the modRNA quasi-vaccines were given by Dr. Shimabukuro:

Reporting rates of myocarditis (per 1 million doses administered) among males after dose 2 mRNA COVID-19 vaccination, by risk interval, VAERS

	Pfizer-BioNTech	Moderna
age group	Days 0–7	Days 0–7
12 to 15	46.5	N/A
16 to 17	73.1	N/A
18 to 24	36.6	41.3
25 to 29	12.3	18.5
30 to 39	6.0	8.2
40 to 49	2.8	3.4
50 to 64	<1.0	<1.0
65+	<1.0	<1.0

Reporting rates of myocarditis (per 1 million doses administered) among males after 1st mRNA COVID-19 booster COVID-19 mRNA vaccination, by risk interval, VAERS

	Pfizer-BioNTech	Moderna
age group	Days 0–7	Days 0–7
12 to 15	17.2	N/A
16 to 17	23.2	N/A
18 to 24	5.4	12.1
25 to 29	4.8	4.0
30 to 39	1.5	1.5
40 to 49	0.0	<1.0
50 to 64	<1.0	0.0
65+	<1.0	<1.0

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For the primary series, the rates are similar to those previously described by CDC at the October 26th 2021 VRBPAC meeting and the ACIP meeting of January 5th. They are however lower than the rates published by CDC staff in JAMA (13)

Comparison of q-vaccine induced myocarditis rates reported by CDC and FDA
Rates per million doses shown for dose 1 or dose 2

										PFIZ
	Male									
Source	FDA		Oster		Oster		CDC		CDC	
Reported	10/26/21		10/26/21		01/25/22		01/05/22		02/04/22	
Where	VRBPAC		VRBPAC		JAMA		ACIP		ACIP	
data date	Sept 2021		10/06/21		08/31/21		12/19/21		01/13/22	
interval			days 0-6		7d		7d		d0-7	
total reports			797 P+M, d1+2		147 M+F	928 M+F				
Age	Scen1-5	Scen6	d1	d2	d1	d2	d1	d2	d1	d2
5-11							0	4.3		
12-15	179	89	4.2	39.9	7.06	70.73	4.8	45.7		
16-17	200		5.7	69.1	7.26	105.86	6.1	70.2		
18-24			2.3	36.8	3.82	52.43				
25-29			1.3	10.8	1.74	17.28				
30-39			0.5	5.2	0.54	7.1				
40-49			0.3	2	0.55	3.5				
50-64			0.2	0.3	0.42	0.68				
>65			0.2	0.1	0.19	0.32				

FDA, including in a recent paper,(14) have specifically acknowledged the underreporting by VAERS, on which these CDC numbers are primarily based. FDA, prefer the Optum database. We have detailed this issue previously.(2)

The rates provided here for myocarditis of 17.2 and 23.2/million for the booster dose in 12-15 and 16-17 year old males, are higher than the 11.4/million rate described by CDC for 12-17 year old males(15). It was acknowledged by CDC that their rates may be lower due to a treatment selection bias for people who already had myocarditis after the primary series.

Not presented were active surveillance data from the Israeli Ministry of Health that had been presented at the April 6th VRBPAC meeting[6] (highlight added): These show for 12-15 and 16-19 year old males, one myocarditis case in approximately 11,000 third doses, that is about 91 cases/ million.

[6] https://www.fda.gov/media/157492/download\

Myocarditis & perimyocarditis cases and number of vaccinees (Pfizer) by age group and sex

Active surveillance. All cases reported in Israel Dec. 2020 - Mar. 29th, 2022[1]

Gender	Age Group	1st dose (0-21 days after the vaccine)			2nd dose (0-30 days after the vaccine)			3rd dose (0-30 days after the vaccine)			4th dose (0-30 days after the vaccine)		
		Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees	Number of vaccine doses	Number of cases of myocarditis reported	Risk for myocarditis for all vaccinees. One case in X vaccinees
Female	5-11	158,185	0		113,218	0	0	23	0		0	0	
	12-15	212,762	0		177,909	1	177,909	50,449	0		0	0	
	16-19	257,503	0		231,241	2	115,621	145,530	2	72,765	421	0	
	20-24	269,472	1	269,472	248,780	5	49,756	183,186	0		1,603	0	
	25-29	252,008	0		234,265	2	117,133	167,328	0		2,510	0	
	30+	2,147,109	2	1,073,555	2,058,476	8	257,310	1,726,149	4	431,537	382,639	*2	191,320
Male	5-11	169,127	0		121,915	0	0	36	0		0	0	
	12-15	222,096	1	222,096	186,317	11	16,938	55,379	5	11,076	0	0	
	16-19	264,132	3	88,044	234,090	34	6,885	145,600	13	11,200	539	0	
	20-24	282,772	6	47,129	260,290	27	9,640	185,795	7	26,542	1,980	0	
	25-29	263,681	3	87,894	245,906	21	11,710	175,219	2	87,610	2,823	0	
	30+	2,006,779	6	334,463	1,929,859	28	68,924	1,622,533	17	95,443	359,066	0	
Total		**6,347,441**	**22**		**5,929,048**	**139**		**4,457,204**	**50**		**751,581**	**2**	

[1] Not including cases that have been ruled out by special committee

* Case 1 - Susp. Myocarditis – no hospitalization, to be confirmed by MRI in community. Case 2 – Active COVID-19 at admission

Two cases (Females) one of susp myocarditis reported 4 days following 4th dose, one case 28 days following 4th dose (active COVID-19 at admission)

Note: Sex unknown for 53,927 vaccine recipients, Age unknown for 329 vaccine recipients

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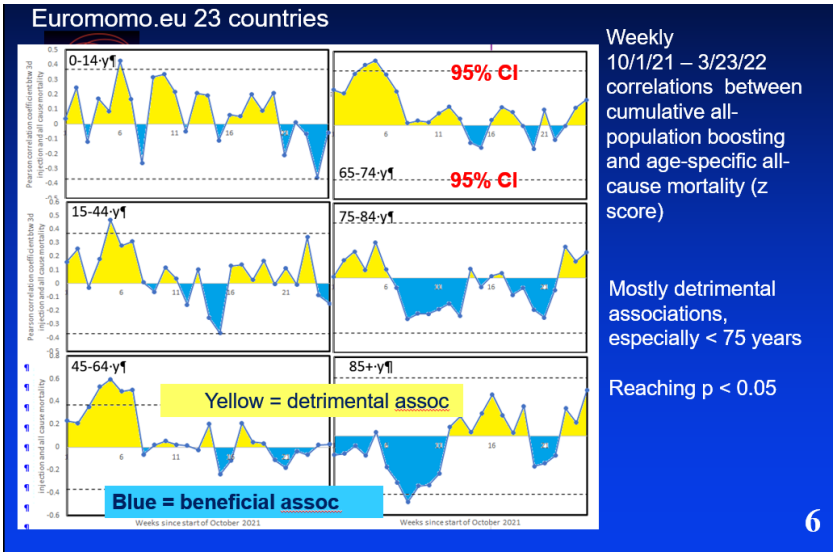
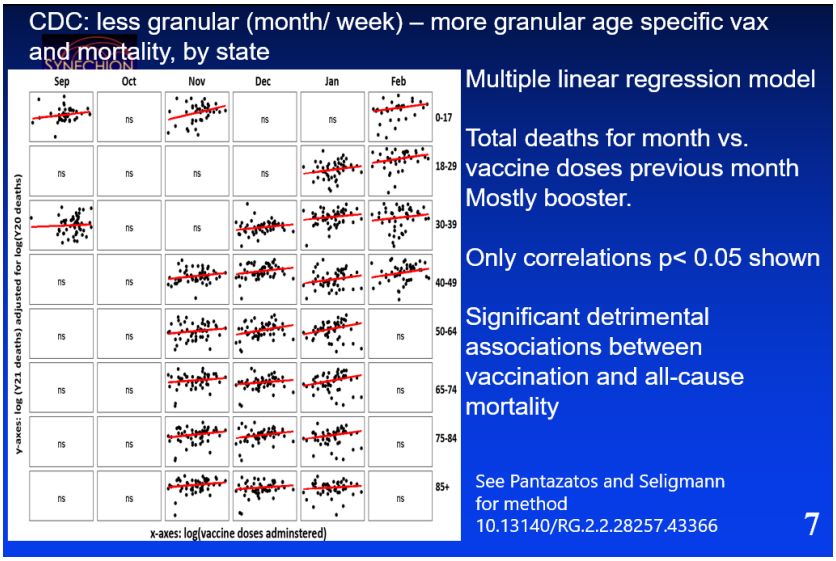
Surely this changes significantly, any perception of the safety of the third dose.

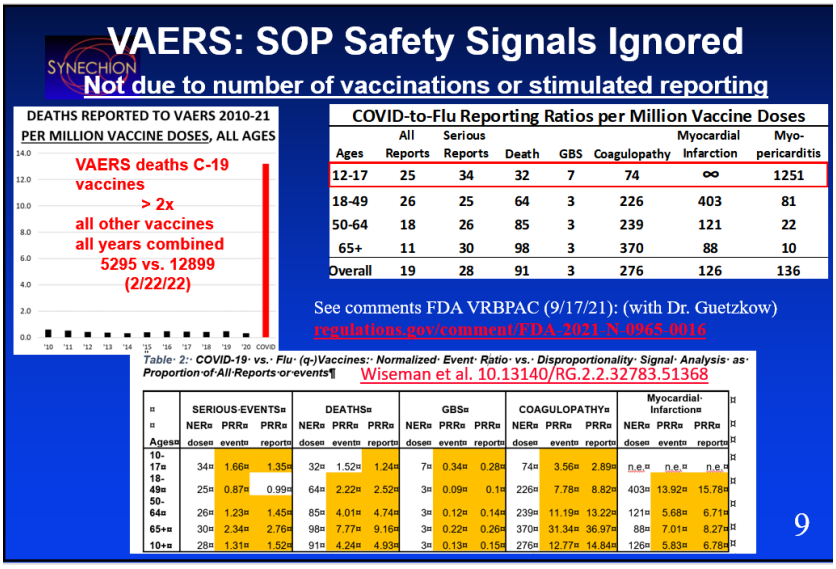
Also not considered were wider questions of safety. Examining European mortality data (see section 4), we observe limited periods of benefit in the over 60s, in terms of the association between boosting rates and all-cause deaths; amidst other periods where there is a detrimental association. We see more detrimental associations in those younger than 60.



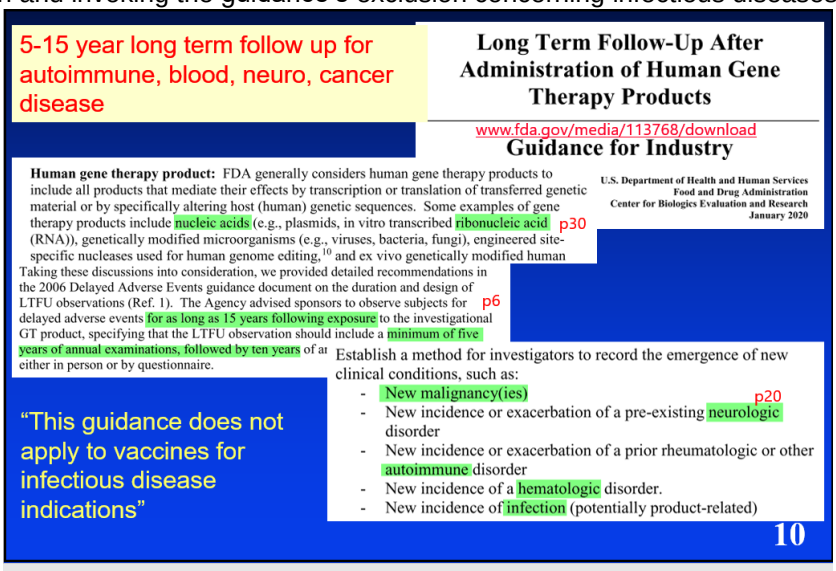
We have found similar detrimental associations in CDC data both for all-cause mortality and non-Covid deaths.



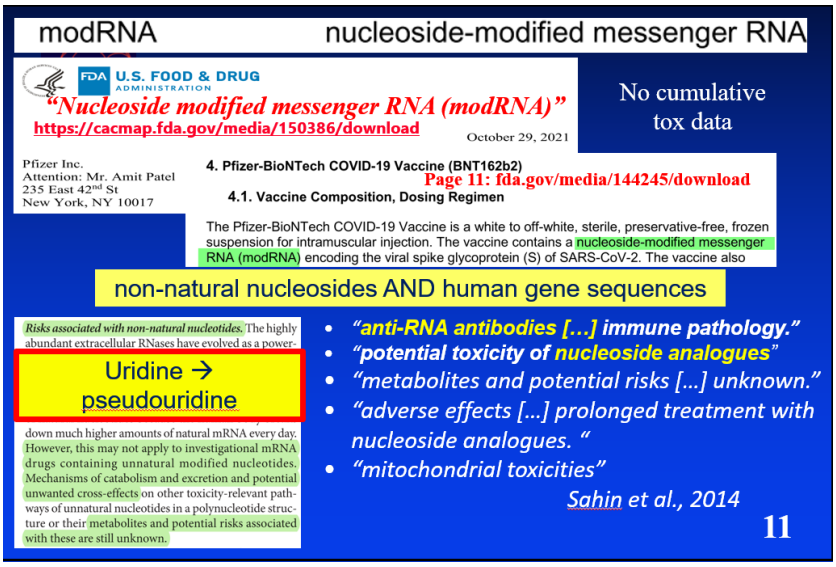
As we have previously reported, safety signals with event ratios over flu rates in the hundreds, continue to be ignored.



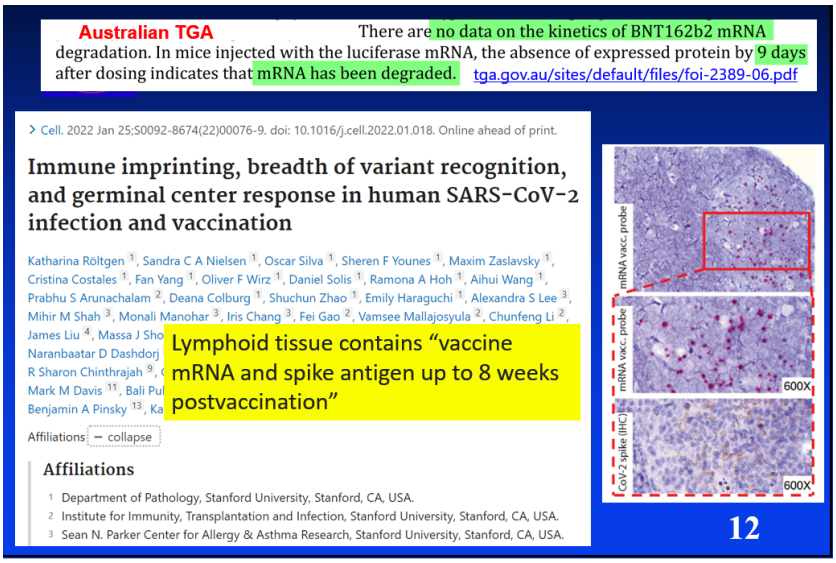
With today's discussion of booster and new variant dosing, how are long term toxicological concerns allayed by ignoring the gene therapy definition and invoking the guidance's exclusion concerning infectious diseases?



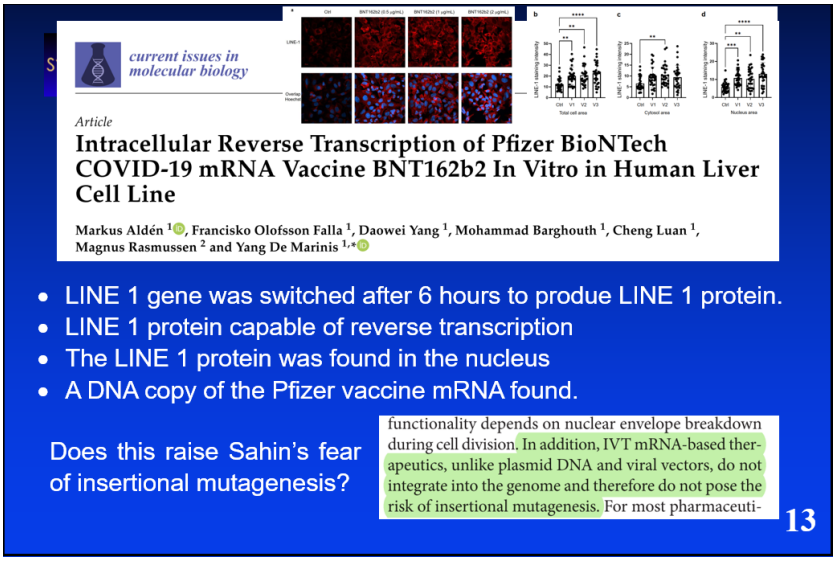
The Pfizer and Moderna quasi vaccines contain “nucleoside-modified mRNA” or modRNA, containing the non-natural nucleoside of pseudouridine (small amounts may occur naturally). The toxicity of this non-natural nucleoside, especially with prolonged treatment has been raised by BioNTech’s founder, Dr. Sahin.(16)



The pharmacokinetics of the modRNA, or of the spike protein it produces, has not been described publicly by FDA or Pfizer. Given the persistence of both modRNA and vaccine-Spike protein for at least 8 weeks(17), this should be cause for some concern.

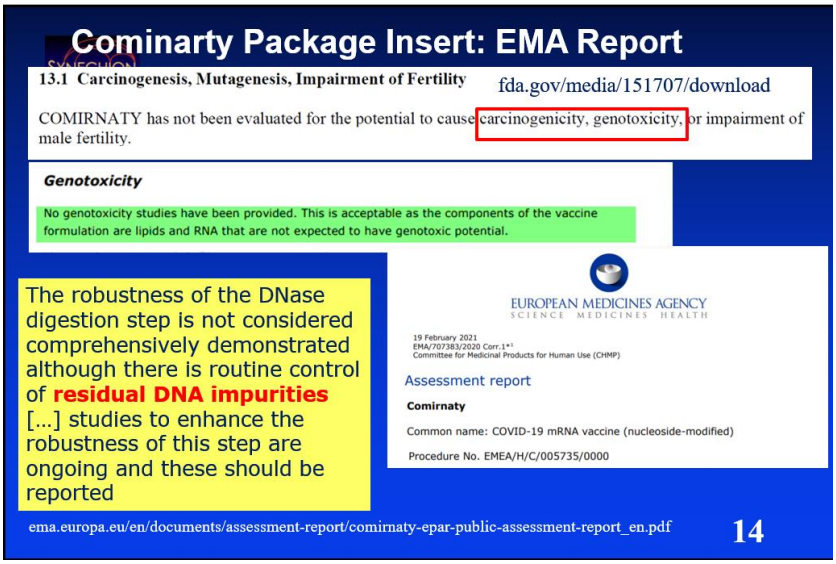


Furthermore, this recent study(18) found evidence of reverse transcription of vaccine mRNA to DNA, invoking Dr. Sahin’s fear(16) of insertional mutagenesis for DNA-based vaccines.



According to the COMIRNATY package insert,(19) no carcinogenicity or genotoxicity studies have been performed.

An EMA report(20) discusses the possible presence of DNA impurities in the Pfizer quasi-vaccine remaining from the manufacturing process. With repeated booster dosing or dosing of variant specific Covid vaccines, what is the risk of insertional mutagenesis?

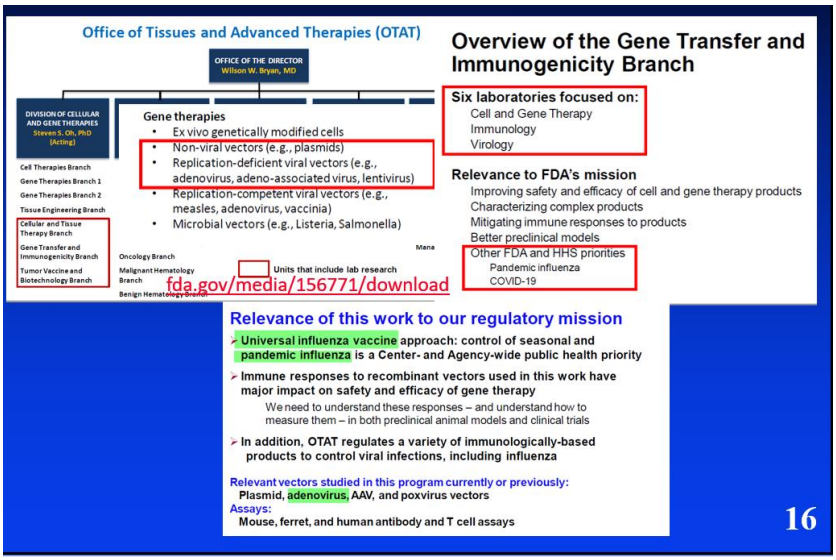


Both Moderna and BioNTech expected to see their products regulated as gene therapies. Moderna, Inc., acknowledged in their 2Q 2020 SEC filing(21)[7] thus *"Currently, mRNA is considered a gene therapy product by the FDA."* Further, the founder of BioNTech in a 2014 paper(16) stated ***"****One would expect the classification of an mRNA drug to be a biologic, a gene therapy or a somatic cell therapy.****"***

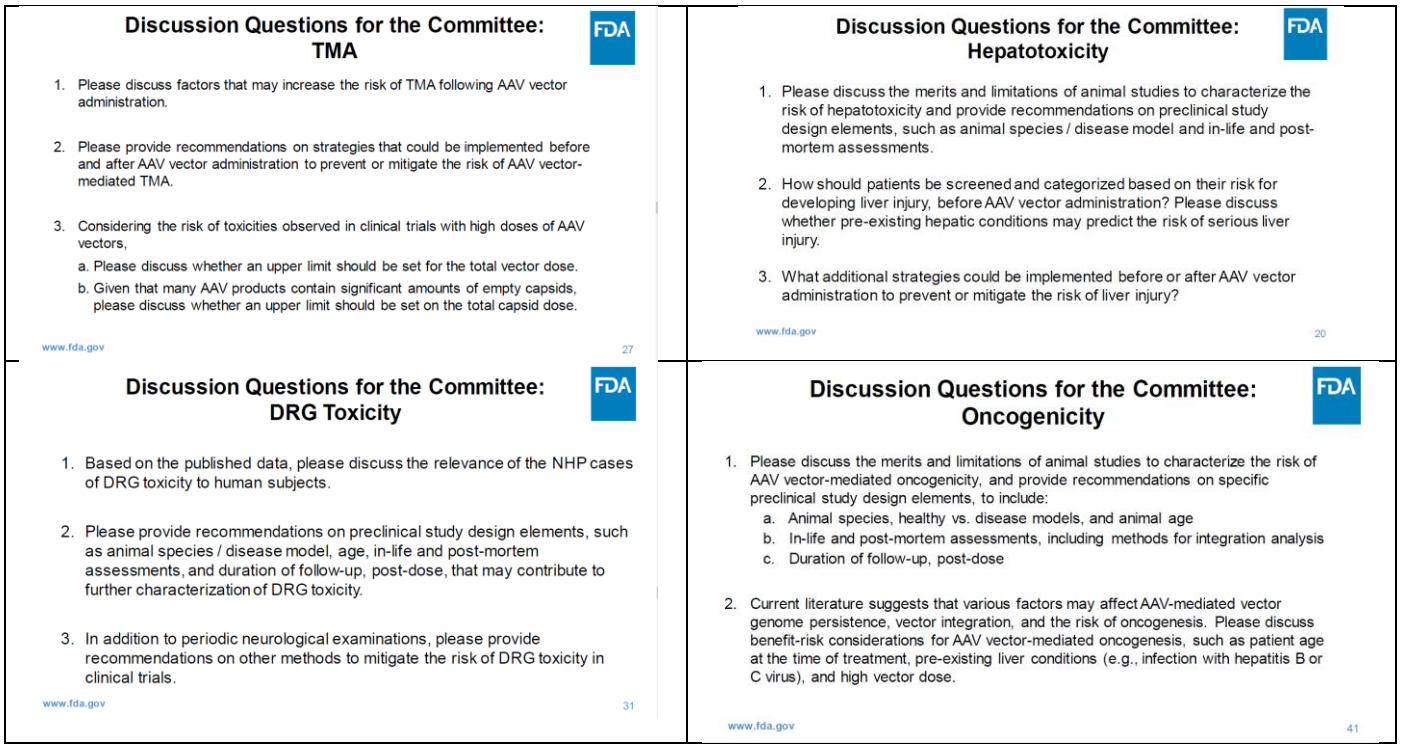
Although not widely known within FDA's Office of Tissues and Advanced Therapies (OTAT) (see Cellular, Tissue, and Gene Therapies Advisory Committee March 10, 2022 Meeting Presentation- Overview of OTAT[8]) is FDA's Gene Transfer Branch (GTIB). This has six labs researching, inter alia, Covid as well universal flu vaccine. This is an excellent fit with one subject of today's meeting, namely multivalent Covid vaccines.

[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/156771/download



FDA has also a Cellular, Tissue, and Gene Therapies Advisory Committee. The summary minutes[9] for the CTGTAC meeting held September 2-3rd 2021 include a series of questions posed by FDA to the committee soliciting their opinion on various matters related to the evaluation of adverse events in gene-therapy products with closely related adeno-associated virus vector technology. These questions were focused on oncogenesis (cancer production), liver injury, clotting issues (thrombotic microangiopathy) and neurotoxicity. These questions are also directly relevant to the Covid-19 vaccines and yet have not been discussed within the VRBPAC committee.



There is remarkable overlap between the neurological, hematological and hepatic concerns expressed by FDA and the spectrum of adverse events reports for the Covid-19 vaccines. Indeed, a recent paper from CDC recognized a post-vax multisystem inflammatory syndrome that includes blood liver and neurological events.(22) Others have referred to MIS-V.(23)

[9] https://www.fda.gov/media/154397/download

Reported cases of multisystem inflammatory syndrome in children aged 12–20 years in the USA who received a COVID-19 vaccine, December, 2020, through August, 2021: a surveillance investigation

Anna R Yousaf, Margaret M Cortese, Allan W Taylor, Karen R Broder, Matthew E Oster, Joshua M Wong, Alice Y Guh, David W McCormick, Satoshi Kamidani, Elizabeth P Schlaudecker, Kathryn M Edwards, C Buddy Creech, Mary A Staat, Ermias D Belay, Paige Marquez, John R Su, Mark B Salzman, Deborah Thompson, Angela P Campbell, and the MIS-C Investigation Authorship Group*

Summary

Background Multisystem inflammatory syndrome in children (MIS-C) is a hyperinflammatory condition associated

Lancet Child Adolesc Health 2022

Case report

Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V)

Arvind Nune ,[1] Karthikeyan P Iyengar ,[2] Christopher Goddard,[3] Ashar E Ahmed[1]

BMJ Case Rep: firs

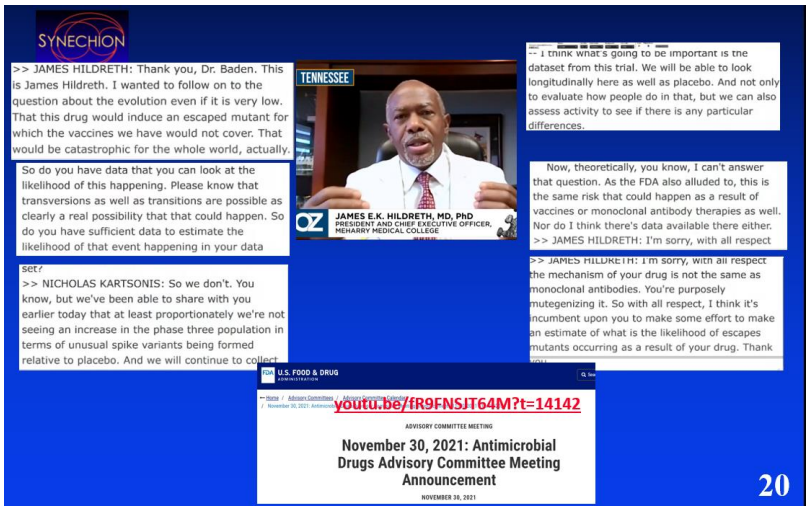
Panel: **US Centers for Disease Control and Prevention case definition for multisystem inflammatory syndrome in children**

Must meet all the following clinical and laboratory criteria:

- Age younger than 21 years with subjective or objective (>38·0 °C) fever for 24 h or longer
- Clinically severe illness requiring hospitalisation
- Multisystem (two or more) organ system involvement
  - Cardiac: includes elevated troponin, elevated B-type natriuretic peptide or N-terminal pro hormone BNP, arrythmia, coronary artery aneurysm, cardiac dysfunction, or shock
  - Renal: includes acute kidney injury or renal failure
  - Respiratory: includes pneumonia, acute respiratory distress syndrome, or pleural effusion
  - Haematological: includes elevated D-dimer, thrombophilia, or thrombocytopenia
  - Gastrointestinal: includes elevated bilirubin, elevated liver enzymes, or diarrhoea
  - Dermatological: includes rash or mucocutaneous lesions
  - Neurological: includes cerebrovascular accident, aseptic meningitis encephalopathy, or headache

It is fair, therefore to ask, if FDA is hiding its gene therapy concerns in plain sight? Have OTAT and the CTGTAC have been consulted and what are their views on these vaccines, particularly with regard to gene therapy questions? Why has this not been disclosed publicly? What kind of Covid-19 research is being conducted in FDA's own labs?

There must be detailed public discussion on the risks associated with these gene therapy products. To our knowledge, the only time a substantive discussion was held on the toxicology of any Covid-19 related product, was in FDA's AMBAC advisory meeting to discuss an EUA for molnupiravir. (see interview and review of this subject.[10])



On questioning, FDA's own toxicology experts were quizzed and expressed concerned about the toxicology and mutagenic potential of molnupiravir. A number of probing questions were asked by committee member Dr. James Hildreth who also serves on VRBPAC. This is the sort of public discussion that is needed to instill public confidence in the vaccine program, as extensively discussed in today's ACIP meeting.

1.3. What are other considerations for future doses of COVID-19 vaccines?

1.3.1. Is frequent boosting sustainable?

CDC and the committee recognized the phenomenon of "vaccine fatigue" and that asked the public to vaccinate/boost every 4 months or so is impractical and unsustainable. Since the toxicity of two doses has not been fully explored, even less is

[10] https://trialsitenews.com/dr-david-wiseman-on-molnupiravir-and-fda-advisory-committee/

known about the toxicity of three doses. The wisdom and sustainability of frequent boosting has been questioned by Dr. Marco Cavaleri[11] (Head of Biological Health Threats and Vaccines Strategy, EMA) and by ACIP member Dr. Sarah Long,[12] who described the use of Pfizer boosting in 12–15-year-olds for Omicron as the "last whack a mole" and neither sustainable nor smart. Concerns in mainstream editorials have been expressed about a fourth dose(24) in particular and boosters in general.

Attempting to use boosters may be the immunological equivalent of heroin addiction, with ever less benefit for ever greater risk of harm.

1.3.2. What is the plan?

The committee remained confused as to what exactly was being planned, and by whom, for potential surges in Covid-19, with as yet unknown variants. Despite the extensive discussion at the April 6th VRBPAC meeting, FDA were unable to inform ACIP as to the sorts of timelines needed to react to new variants in time for a possible winter 2022-3 surge.

There was no discussion of efforts to improve the health of vulnerable populations by taregtting nutrition and comorbidities such as obesity, hypertension of diabetes.

The committee agreed that a simple set if guidelines as to boosting, or annual updates, would be preferable, bt not always practical. The still non-availability of an immune correlate of protection remains a priority.

1.3.3. Time to revisit repurposed drugs?

Give the granting of an EUA for molnupiravir under very controversial circumstances, and in the face of low or negative vaccine efficacy and mounting toxicological concerns, this is an appropriate time to revisit the subject of repurposed drugs. We will only discuss our own work in this regard.

Our own dataset reanalysis of one of the central hydroxychloroquine (HCQ) studies(25) that was used to justify the removal of the EUA for HCQ in June 2020, we found serious flaws in the dat and after requesting and obtaining key data concerning shipping times, we found a 42% (p< 0.,05) reduction in Covid-19 when drug was given within three days of exposure. We suspect that a related study(26) involving early treatment with HCQ had similar flaws, but we have been unable to obtain the additional data. NIH have not amended their guidelines based on information we have provided them.(27)

Our re-analysis of a study involving early treatment with ivermectin(28) also found significant flaws, which when adjusted for, yielded a 56% reduction in residual Covid-19.(29) The TOGETHER platform trial from Brazil involving ivermectin has been recently published.(30) The dose used appears to have been too small, used for too short a duration and may have

[11] www.youtube.com/watch?v=0Gz8MTPV5qs&t=238s Dr. Marco Cavaleri. European Medicines Agency Press Briefing Jan 18, 2022 ema.europa.eu/en/events/ema-regular-press-briefing-covid-19-12#event-summary-section
[12] https://youtu.be/8yIPhOJuX98?t=5208 ACIP member - Dr. Sarah Long, Prof Pediatrics, Drexel University. https://youtu.be/8yIPhOJuX98?t=5208

been administered too late in a number of subjects. Non-statistically significant reductions in hospitalization (17%) and death (12%) were noted, and the PI in an NIH Grand Rounds[13] as well as well as in emails has suggested that:

> *"there was a 17% reduction in hospitalizations that would be significant if more patients were added. I really don't view our study as negative and, […] you will hear me retract previous statements where I had been previously negative. "*

There appear to be discrepancies in how placebo subjects rare handled compared with other arms of the TOGETHER platform study, as well as possible randomization issue. Significantly, 317 subjects were missing from a key time stratification analysis. Our calculations show s 49% reduction in primary outcome (RR 0.507, CI 0.29-0.88, p=0.019) in this subgroup (a similar problem appears to exist in another TOGETHER study involving fluvoxamine(31)). This awaits further investigation, since the data are as yet unavailable for review, despite the data sharing statement. We have noted other issues with the HCQ arm of the TOGETHER study.(32)

2. What are these vaccines?

2.1. Gene therapy quasi-vaccines.

"Quasi-vaccine" more appropriately describes these novel vaccine-**like** drugs. The Covid-19 vaccines from Pfizer, Janssen and Moderna are not classical type vaccines. A **Classical Vaccine** such as polio, measles etc. could be a:

- killed version of disease-causing virus
- live virus that is a less-disease causing version of the target virus (live attenuated)
- non-replicating extracts of virus

The **mRNA Vaccines (Pfizer, Moderna) as well as the Janssen (DNA) vaccine,** contain genetic instructions which are read by a person's own cells to produce spike protein – those protrusions on the coronavirus familiar to most.

Although these Covid-19 agents fall under FDA's definition of vaccines and vaccine-associated products,[14]

> *"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."*

these vaccines also meet FDA's definition of gene therapy products.[15]

> (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.(33) Both this and an earlier guidance (34) for the "Preclinical Assessment of Investigational Cellular and Gene Therapy Products" states:

"This guidance does not apply to therapeutic vaccines for infectious disease indications that are typically reviewed in CBER/Office of Vaccines Research and Review (OVRR)"

Moderna, Inc., the maker of a mRNA Covid-19 vaccine, acknowledged in their 2Q 2020 SEC filing(21)[16] thus *"Currently, mRNA is considered a gene therapy product by the FDA."* Further, the founder of BioNTech in a 2014 paper(16) stated ***"**One would expect the classification of an mRNA drug to be a biologic, a gene therapy or a somatic cell therapy.**"***

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[13] https://rethinkingclinicaltrials.org/news/grand-rounds-march-18-early-treatment-of-covid-19-the-together-adaptive-platform-trial-edward-mills-phd-frcp-craig-rayner-pharmd/

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

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

[16] 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

Since these agents are Gene Therapy products, long term surveillance is warranted for delayed malignant, neurologic, autoimmune, hematologic, other disorders or effects on the genome or gene expression. This is reflected in FDA's guidance document *"Long Term Follow-up After Administration of Human Gene Therapy (GT) products."*(33) 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 the 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 (33) was made in FDA's guidance on development of Covid-19 vaccines(3), nor in the EUA briefing documents provided by Pfizer, Moderna and Johnson & Johnson.

Two of the current Covid-19 vaccines use the mRNA technology. The third vaccine type, made by Janssen (Johnson & Johnson) uses a DNA payload to deliver the genetic instructions that eventually lead to the production of spike protein. The payload is delivered not by Lipid Nanoparticles, as is the case for the Moderna and Pfizer vaccines, but instead a "zombie-ized" and most harmless virus called Adenovirus (Ad26). This platform has been used to evaluate other vaccines such as for Ebola and Zika. That this technology is clearly a gene therapy technology to deliver "transgenes" is widely understood, for example in recent reviews for Adenovirus-based vaccines (35) or the genetic mRNA vaccines.(36)

Given the controversy over the Covid-19 gene therapy quasi-vaccines, continuing to refer to these products as "vaccines" and to attempt to impose mandates for children, may well undermine public confidence in conventional vaccines. As has been reported, there is already an adverse impact on MMR immunization rates in the UK.(37)

Failing to describe properly the gene therapy nature of these quasi-vaccines, deprives parents and children of informed consent.

2.2. Have gene therapy quasi-vaccines had a long history of study?

There is a popular notion that the mRNA gene therapies had been extensively studied prior to the Covid-19 pandemic. Indeed CDC states:[17] *"This type of vaccine is new, but research and development on it has been underway for decades."* This statement is misleading. While it is true that, depending on how one defines the "beginning, these approaches have been studied since the late 1980s, it is only very recently that these therapies have been administered to human subjects.

The lack of experience with the mRNA technology is attested to by Dr. Albert Bourla in a recent interview by the Washington Post.[18] (highlight added, formatted as Q&A from youtube transcript feature, typos preserved. Basic punctuation and clarifications added)

> *Q i want to get a little into the weeds here and the mr mRNA technology when you and you and your your colleagues were trying to decide which route to go down the traditional vaccine route or the mRNA route. you you write that um it was quote* ***most counter-intuitive to go the mRNA route*** *and yet you went that route. explain why*
>
> *A it was* ***counterintuitive*** *because pfizer was mastering or let's say we had very good experience and expertise with the multiple technologies that could give a vaccine. antenna viruses [adenovirus]that some of the other vaccines are we we were very good in doing that. protein vaccines we were very good in doing that, and plus many other technologies. the mRNA was the technology but* ***we had less experience only two years working on this and actually mRNA was a technology that never delivered a single product until that day not vaccine not any other medicine*** *so so* ***it was very counterintuitive****. and i was surprised when they suggested to me that this is the way to go and i questioned it and i asked them to justify how can you say something like that but they came and they were very very convinced that this is the right way to go they felt that the two years that of war [work] on mRNA since 2018 together with bionde [BioNtech] to develop a flu vaccine made them believe that the technology is mature and we are at the cusp of uh delivering a product. so they convinced me i followed my instinct that they know what they are saying they're very good and we made this very difficult decision at that time.*

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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.

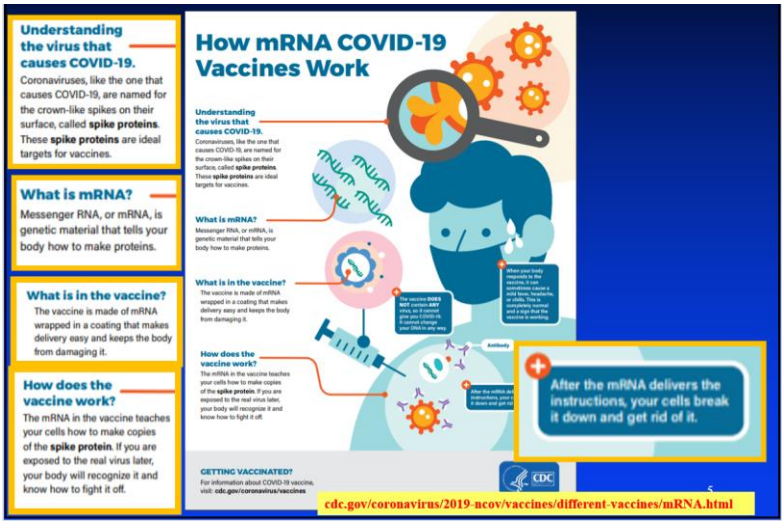
[17] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/facts.html

[18] https://www.washingtonpost.com/video/washington-post-live/wplive/albert-bourla-on-why-mrna-technology-was-counterintuitive-in-producing-an-effective-vaccine/2022/03/10/c397ca8c-afaa-4254-b860-b2cca54b0ecf_video.html
https://www.youtube.com/watch?v=t9_YRw7jBF4

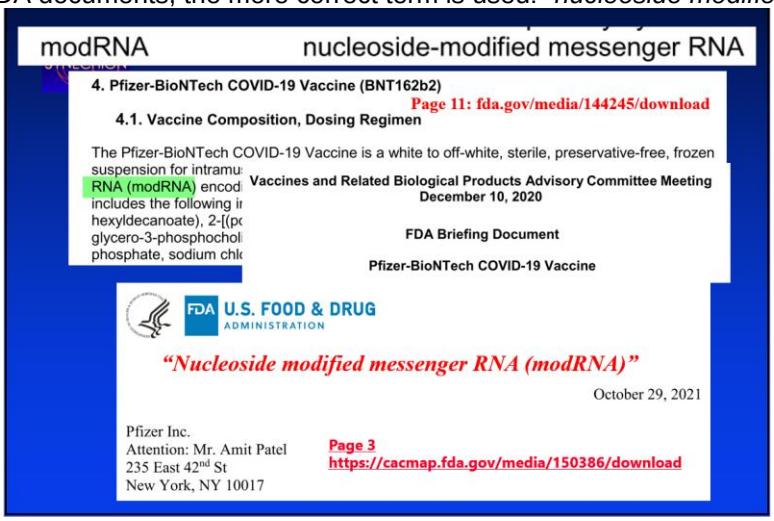
The phrase ***"mRNA was a technology that never delivered a single product until that day not vaccine not any other medicine" speaks for itself.***

2.3. Nucleoside modified mRNA and human gene sequences

The Pfizer and Moderna quasi-vaccines are referred to as "mRNA vaccines." Below is a blown-up version of a CDC explanation of "how mRNA Covid-19 vaccines work."

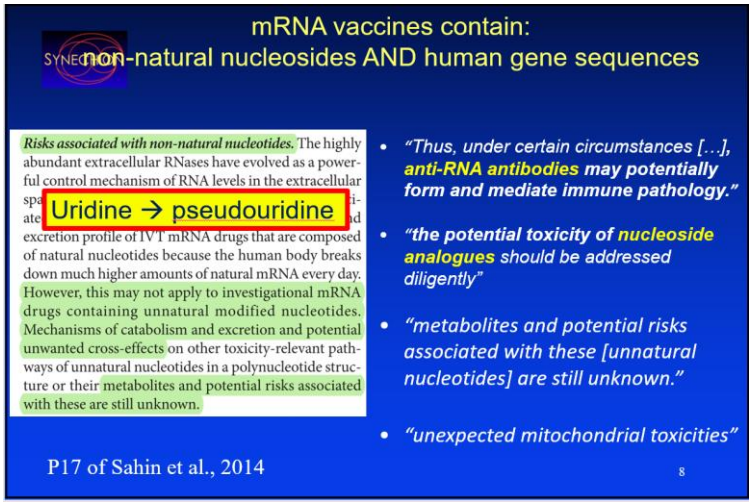


The use of the term "mRNA" is inaccurate. It implies that the type of mRNA is similar to that found in the human body. In fact, in the more technical FDA documents, the more correct term is used: *"nucleoside modified mRNA. or* ***modRNA."***[19]



As is discussed by Dr. Sahin,(16) the founder and president of BioNTech, the modRNA contains *"non-natural nucleosides"* for which, there may be a number of toxicological concerns. (small amounts of pseudouridine do exist in nature).

[19] www.fda.gov/media/150386/download



These modRNA quasi vaccines, as described on page 4 of the same paper contain human gene sequences (and not just the viral spike protein sequence) in the UTRs (untranslated regions).

5′- and 3′-UTRs. Another strategy to optimize the translation and stability of IVT mRNA in cells is to incorporate 5′- and 3′-UTRs containing regulatory sequence elements that have been identified to modulate the translation and stability of endogenous mRNA.

For example, many IVT mRNAs contain the 3′-UTRs of α- and β-globin mRNAs that harbour several sequence elements that increase the stability and translation of mRNA[30,45]. The stabilizing effect of human β-globin 3′-UTR sequences is further augmented by using two human β-globin 3′-UTRs arranged in a head-to-tail orientation[29]. In addition, various regions of cellular and viral 5′- and 3′-UTRs enhance the stability and translational efficiency of mRNA. The 3′-UTR of the eukaryotic

The toxicological consequences of these sequences are unknown, but the onus is on Pfizer-BioNTech to show that they are safe.

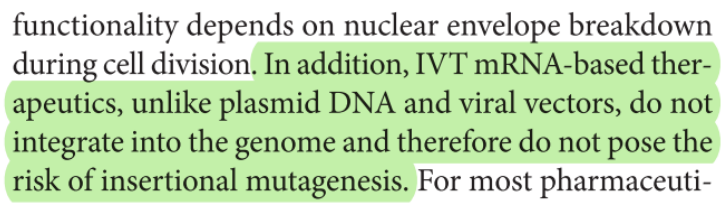
2.4. Production of DNA from vaccine modRNA: possibility of insertional mutagenesis.

At the heart of the Pfizer quasi-vaccine is a sequence of modified messenger RNA (mRNA). To briefly understand the job of mRNA, consider a factory that produces widgets, along with many other items. The factory stores the blueprints (genes, as DNA) for all of its products in its central blueprint archives (nucleus). When it wants to make a batch of widgets it must make (transcribe) a working copy of the original widget blueprints, keeping the originals safe in the archives. The working copy is released from the archive and sent to a particular workshop in the factory, where the instructions are used to assemble the actual widget by translating the instructions into tangible product.

This is the normal process of how our bodies make proteins, a vital class of molecules (factory products) in our body, each uniquely performing one of a myriad of tasks. DNA in our genes (stored in the nucleus) constitute the blueprints for the proteins. A working copy of DNA is made (transcribed) into mRNA which is sent to the factory floor where the instructions are used to assemble the final protein product (translation).

In the Pfizer (and Moderna) mRNA-based vaccine, we fool the machinery of the body to produce the spike protein by sending to the factory floor a form of mRNA that looks as if it had been copied from the body's own blueprints (DNA). What we would not want to happen is for this flow of information to go in the reverse direction, and for externally administered instructions to result in the temporary or permanent alteration of the instructions in the original blue prints. For such an edit to happen, mRNA would first need to be "reverse transcribed" into DNA, before that reverse transcribed DNA is incorporated into the blueprints (genes) in a process called **insertional mutagenesis**.

This has been known to occur in nature, including from the SARS-CoV-2 virus under some conditions.(38) According to Dr. Sahin, the founder of BioNTech (Pfizer's partner company) there is the possibility of insertional mutagenesis with the DNA-based vaccines, which would include the Johnson & Johnson and AstraZeneca products.


functionality depends on nuclear envelope breakdown during cell division. In addition, IVT mRNA-based therapeutics, unlike plasmid DNA and viral vectors, do not integrate into the genome and therefore do not pose the risk of insertional mutagenesis. For most pharmaceuti-

From Sahin et al. (16) (Founder BioNTech).

Insertional mutagenesis, according to Dr. Sahin, should not be a problem with the mRNA vaccines. However, a recent paper has shown in a standard liver cell culture system, vaccine mRNA can be reverse-transcribed into DNA, creating the conditions for the concern raised by BioNTech's Dr. Sahin that insertional mutagenesis may occur. Specifically this paper(18) showed that, regarding the Pfizer vaccine

- The vaccine mRNA entered the liver cells grown in culture
- A gene called LINE 1 was switched on in the liver cells after 6 hours, resulting in the production of the LINE 1 protein. The LINE 1 protein is known to be capable of reverse transcription, namely the production of DNA from mRNA.
- The LINE 1 protein was found in the nucleus of the cells (where the genes are stored).
- A DNA copy of the Pfizer vaccine mRNA was found.

This alone is sufficiently concerning to reconsider the use of vaccines until further studies can be carried out. The concern is amplified by Pfizer data, released by FDA under an FOIA request,[20] showing, in animal studies, accumulation of the Lipid Nanoparticles (the "fat bubbles" used to deliver the mRNA) in the ovaries, bone marrow, adrenal glands, and to a smaller extent, the testes. (see section **Error! Reference source not found.**).

3. Adverse Event Signals from VAERS

We refer again to previous submissions which raise numerous issues (39-49) including those related to intense safety signals for death, MI, coagulopathy and thrombotic events. Other issues are highlighted here.

Does negative efficacy and increase in all-cause mortality signal immune compromise?

Negative VE may have been evident as early as June 2021 in a report from Denmark.(50) Taken with reports of negative VE against Omicron described here (6,7) as well as the doubling of reports of herpes zoster in the Moderna trial,(51) the effect of the q-vaccines on medium to long term immune function must be fully characterized.

The labels for Spikevax(52) and Comirnaty(19) conflict with CDC statements conflict regarding the immunocompromised, who *"may have a diminished immune response*."

Pregnancy

There has now been enough time to collect data but the Spikevax and Comirnaty labels says that data *"are insufficient to inform risks in pregnancy"*(52), something similar for lactation. Yet CDC still[21] recommends vaccination in pregnancy and lactation. If a manufacturer were to suggest this in any other context, this might well constitute off-label promotion.

We previously reported(44) Normalized Event Ratios, in comparison to similar events types for flu vaccines, normalized by dose. These produce intense safety signals which have not been acted upon.

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

[20] https://phmpt.org/wp-content/uploads/2022/03/125742_S1_M2_26_pharmkin-tabulated-summary.pdf
[21] https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html

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

Using 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 rates 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.

4. All population booster COVID19 vaccine injections are associated with all-cause mortality in all ages: European and US data

Hervé Seligmann, Spiro P. Pantazatos, David Wiseman PhD, MRPharmS

Summary

We set out to determine what associations exist, if any, between Covid booster dose adoption and all-cause mortality. One set of analyses examined correlations between all-cause mortality data from EUROMOMO.EU for six age classes and percentages of booster-injected individuals for the last 14 weeks of 2021 and the first 11 weeks of 2022. A second set of independent analyses of US CDC data tested whether monthly vaccination doses between September, 2021 through February, 2022 predicted age-stratified all-cause and non-COVID mortality in subsequent months.

Our results do not indicate any benefits of booster doses as no significant negative (beneficial) associations between boosters and mortality were observed for ages below 75, and limited benefits for ages above 75. For US data, boosters are associated with an increase in all-cause and non-COVID mortality in all ages. We found statistically significant associations in the younger age groups, suggesting indirect effects of boosters on those without the booster as was observed for the primary series. Findings are consistent across both the European and American datasets. Comparison of estimated regression slopes with our previous analysis of the primary series suggest that the booster are associated with a higher mortality risk.

Introduction

Our previous analyses(53) of weekly all-cause mortalities from 23 countries obtained from EUROMOMO.EU show overall associations between weekly increases in percentages of the general population injected with at least 1 dose and subsequent weekly all-cause mortalities, at all lag times from 0-42 weeks. Data were stratified for 6 age classes for which weekly all-cause mortalities are available (ages 0-14, 15-44, 45-64, 65-74, 75-84 and 85+). Three periods could be generally discerned for all ages above 14.

In the first (approximately weeks 0-6 after injection) and third (approximately weeks 20-36) periods, general population vaccination rates associate with increased all-cause mortality. In the second period (approximately weeks 6-20), the opposite association was noted.

The first period corresponds to the assumed delay (3-4 weeks dose interval, plus 1-2 weeks post second dose) for vaccination to produce a protective effect. The second period during which a presumed protective effect is observed (weeks 6-20) corresponds to the period vaccine-induced antibodies are detected in the blood of vaccinees(54) as well as other estimates of waning vaccine effectiveness.(5-8) The latter disappear from their blood after week 20 post 1st injection.

The third period corresponds to a period when vaccine efficacy is known to have waned substantially. However, we would expect no association in either direction between vaccination and all-cause mortality for that period. The observed increased mortality associated with vaccination during that period may have been due to collinearity with the booster campaigns which began ~6 months after the initial vaccination campaigns in each country.

The above analysis was performed during the “pre-Omicron” period when vaccine efficacy fell to about 50-70%. For the later “Omicron” period FDA’s target efficacy is 50% with a lower confidence interval of 30% (3,4). According to studies from Denmark(6), Canada(7), USA (CDC) (5,55), and New York (56), point estimates and/or lower confidence interval bounds become negative at time lags from a few weeks to a few months post-injection. In our previous analysis (53) for children 0-14, associations between all-population weekly vaccination rates and weekly children all-cause mortalities are overall positive, during periods when no or few children were dosed. This suggests some indirect effects of adult vaccination on children mortality. The all- population vaccination percentage injected doses associated positively with mortality in ages <15 the following month.

The third injection, also called the booster shot, started July 1st in Israel, in Autumn in many other European countries, and in late September in the US. Accordingly, we set out to describe associations, if any, between weekly cumulative booster vaccinations (“cumulative analysis”) in different countries with age-stratified weekly mortalities at EUROMOMO.EU for that same week, and between weekly increases in boosters and all cause mortality the same and ulterior weeks. The cumulative analysis detects effects independent of the time since injection. We also tested whether booster injections showed evidence of positive associations with all-cause and non-COVID mortality one month post-injection in the US

CDC data while controlling for prior year state-to-state variability in mortality due to other factors. We show positive associations between booster vaccinations and all-cause and non-COVID mortalities, even for age classes not yet injected during those periods.

Methods

European dataset: Cumulative percentage analysis

For each of the 23 countries with age-stratified all-cause mortality rates at euromomo.eu, we recorded the weekly percentage of the population who received the booster injection that week, for each week since October 1 until March 24, using data from Coronavirus (COVID-19) Vaccinations - Our World in Data. For each of the 25 weeks separately, the Pearson correlation coefficient r between this percentage and all-cause mortality was calculated, for each of the six age classes for which all-cause mortality data were available. These Pearson correlation coefficients were plotted as a function of the weeks since the start of the study period, in early October 2021, in order to compare pattern across ages and evaluate overall trends.

European dataset: Lag analysis

For each of the 23 countries with age-stratified all-cause mortality rates at euromomo.eu, we recorded the percentage of the population who received the booster injection that week, for each week since October 1 until March 24, using data from Coronavirus (COVID-19) Vaccinations - Our World in Data. The Pearson correlation coefficient r was calculated between weekly booster injection rates and weekly all-cause mortality for that very week and all ulterior, not previous, weeks. This was done for all 25 weeks in the study period. Pearson correlation coefficients with equal number of weeks between injection and mortality weeks were pooled, independently of the injection week. This means that for lag 0 between injection and mortality, there are 25 r's, for lag 1 there are 24 r's, etc. for lag 24, there is only one r. The percentage of r's with a given lag and that were positive, meaning indicating adverse effects of boosters on all-cause mortality, was calculated for each lag. This percentage is then plotted as a function of lag. This analysis is done separately for each age group for which mortality rates were available, using in all cases injection rates for the whole population as no age-stratified injection data were available.

The sign test, using a binomial distribution expecting equal numbers of negative and positive r's, was used to test for significant depletion or excess percentages of positive r's, depletion indicating protective effects associated with boosters, and excess indicating adverse effects associated with boosters that increase all-cause mortality.

US -CDC dataset

The US analyses used publicly available data on vaccination, mortality and age-stratified population size in each US state. Data were obtained from either the CDC or US Census Bureau (see (1) for data source links). Our analyses focused on whether we could replicate the finding of higher mortality within the first 5 weeks of vaccination observed in the euromomo.eu data. Since US mortality data were limited to month-level resolution, we tested whether monthly vaccination rates predicted mortality during next month. Multiple linear regression was used to predict the total number of deaths among 8 age groups (0-17, 18-29, 30-39, 40-49, 50-64, 65-74, 75-84, >85 years) for 6 months (September, October, November and December of 2021 and January and February of 2022). For each month and age group, the following equation was fitted: (1)

$$log(Y21\_deaths) = \beta_0 + \beta_1 \log(\mathrm{Y20\_deaths}) + \beta_2 \log(\mathrm{Vax}) + \varepsilon$$

Where $Y21\_deaths$ and $Y20\_deaths$ are the number of total deaths for that month in year 2021 and 2020, respectively, and Vax is the number of vaccine doses administered in the previous month (or current month). See our earlier paper (1) a for more information and details about analysis and methods to rule out potential confounding factors such as COVID case rates and COVID deaths.

The sign test, using a binomial distribution expecting equal numbers of negative and positive β2s for the whole study period, was used to test for significant depletion or excess of positive β2s, depletion indicating protective effects associated with boosters, and excess indicating adverse effects associated with boosters that increase all-cause mortality.

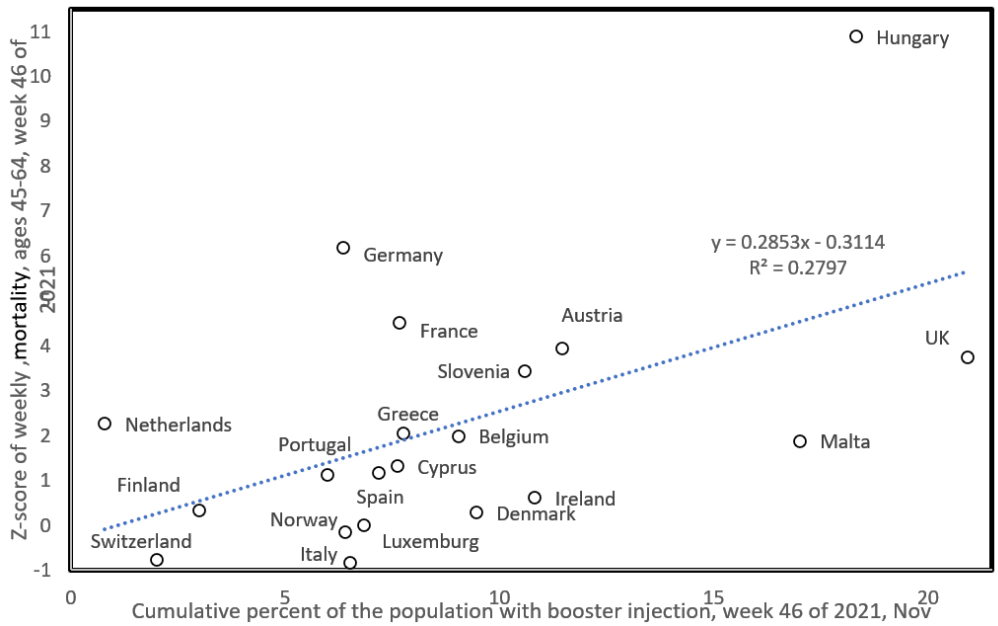
Results

European Dataset, cumulative analysis

By way of example, **Figure 1** shows the weekly z score of all-cause mortality on week 46 of 2021, for ages 45-64, as a function of the percentage of the population that already received the booster injection. The regression of **Figure 1** implies that for a cross-country increase of 7 percent of booster injected individuals in the population, all-cause mortality increases by two times the standard deviation of all-cause mortality in that age group.

Using data presented at EUROMOMO.EU for the pool of countries, two standard deviations represent about 200 additional deaths for that age class. The weekly baseline average number of deaths for that age class is 1500 weekly deaths, hence the increase is about 13 percent of the average weekly all-cause death rate.

Figure 1: Z score of all-cause mortality for week 46 of 2021, ages 45-64



Z score of all-cause mortality for week 46 of 2021, ages 45-64, as a function of the cumulative percent of individuals who got the booster injection on the same week 46 of 2021 in 20 European countries. All-cause mortality data from EUROMOMO.EU, booster vaccination percentages from Coronavirus (COVID-19) Vaccinations - Our World in Data.

The result in **Figure 1** is consistent with the prediction that booster injections are associated with increased all-cause mortality. This result is also compatible with the possibility that COVID19 vaccine injections have indirect effects on the unvaccinated.

The analysis shown in **Figure 1**, which tests for an association between all-cause mortality and the percent of individuals with booster injection at a given week, is repeated for all age classes and weeks from week 40 of 2021 until the end of 2021, and the twelve first weeks of 2022, meaning 25 weeks (**Table 2**). These are displayed graphically in Figure 2 where positive associations between cumulative booster use and all-cause mortality (i.e. detrimental effects) are shown in yellow and negative associations (i.e. beneficial effect) are shown in blue.

For the 85+ year groups there are overall beneficial associations during the first 11 weeks of the study period. For the 75–84-year group, the period of beneficial association is confined to study period weeks 6-21. Other than one datapoint in the 85+ group, none of these individual associations reached statistical significance in either direction.

For the 15-44, 45-64 and 65-74 groups, associations between all-population cumulative booster usage and age-specific all-cause mortality were almost entirely positive (i.e detrimental), a number of the associations reaching statistical significance.

For the 0-14 group the associations between all-population cumulative booster usage and age-specific all-cause mortality were also almost all positive (i.e. detrimental).

Most associations between booster injection percentages and all-cause mortalities are positive for age below 75, and these are statistically significant majorities according to sign tests for ages 0-14, 45-64 and 65-74. No statistically significant associations between booster usage and all-cause mortality of ages above 74 were found.

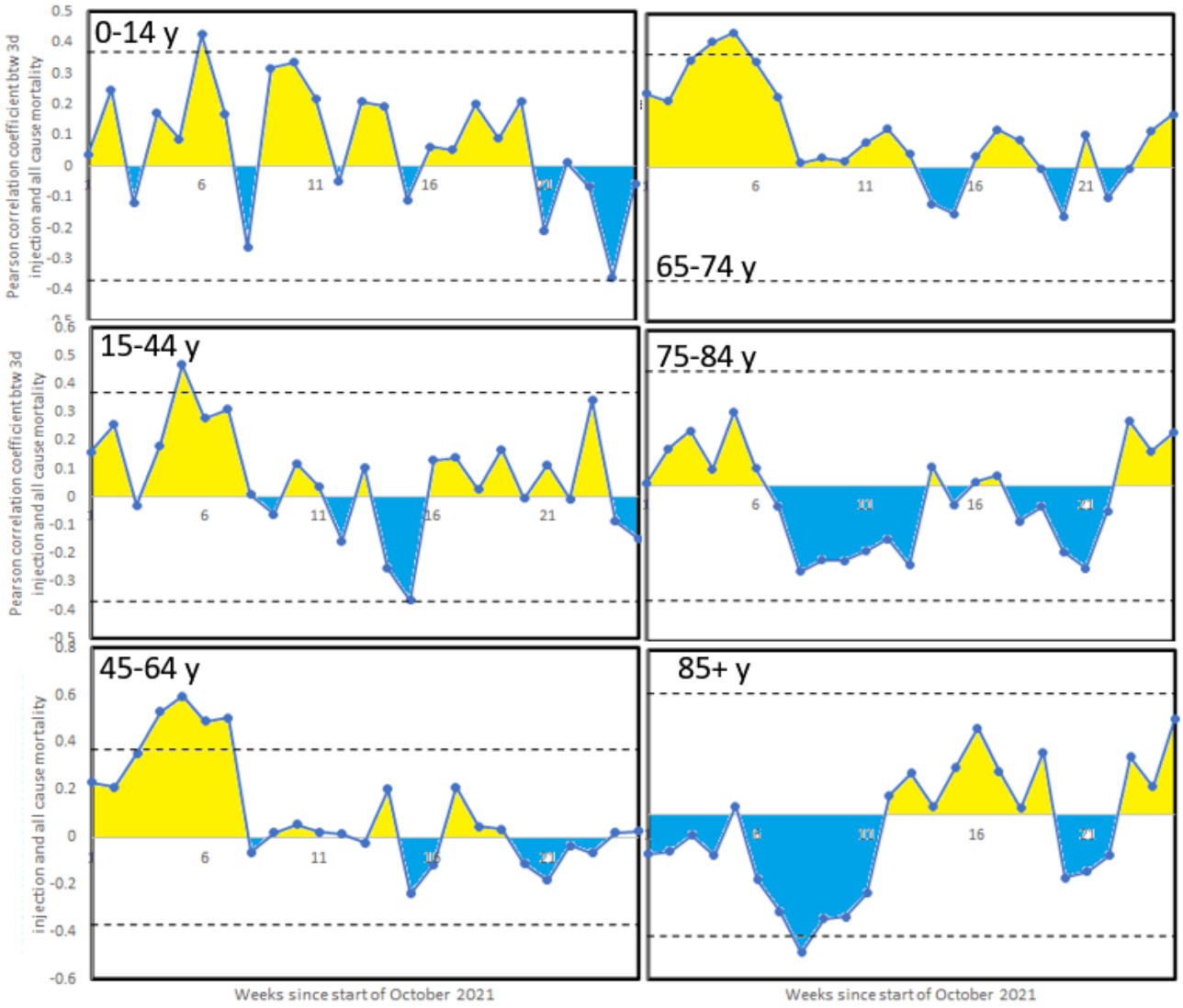
As shown in **Table 2**, there are a total of 150 correlation tests. At $p < 0.05$ (uncorrected for multiple comparisons), there were only two (2/150 =1.33%) negative (i.e. beneficial) associations between all-cause mortality and booster coverage considering all age classes and weeks covered by the analysis. There were eight (8/150 = 5.33%) positive associations (i.e. detrimental). The positive associations observed for ages 0-14 suggest indirect effects of boosters increasing child mortality.

Table 2:Weekly all-cause mortality and weekly cumulated percentage of individuals with booster injection (Euromomo)

Year	Day	week		0-14	15-44	45-64	65-74	75-84	85+
2021	07-Oct	40	1	4	16	23	24	1	-12
2021	14-Oct	41	2	25	26	21	22	12	-11
2021	21-Oct	42	3	-12	-3	35	35	18	-6
2021	28-Oct	43	4	17	18	53	41	5	-12
2021	04-Nov	44	5	9	47	60	44	24	3
2021	11-Nov	45	6	43	28	49	34	6	-20
2021	18-Nov	46	7	17	31	50	23	-7	-29
2021	25-Nov	47	8	-26	1	-6	2	-27	-42
2021	02-Dec	48	9	32	-6	2	3	-24	-32
2021	09-Dec	49	10	34	12	5	2	-24	-31
2021	16-Dec	50	11	22	4	2	8	-21	-24
2021	23-Dec	51	12	-5	-16	1	13	-17	6
2021	30-Dec	52	13	21	11	-2	4	-25	13
2022	06-Jan	1	14	19	-25	20	-12	6	2
2022	13-Jan	2	15	-11	-37	-24	-15	-6	14
2022	20-Jan	3	16	6	13	-12	4	1	26
2022	27-Jan	4	17	5	14	21	12	4	13
2022	03-Feb	5	18	20	3	5	9	-11	2
2022	10-Feb	6	19	9	17	3	0	-7	19
2022	17-Feb	7	20	21	0	-11	-16	-21	-19
2022	24-Feb	8	21	-21	11	-18	11	-27	-17
2022	03-Mar	9	22	1	-1	-4	-10	-8	-12
2022	10-Mar	10	23	-7	34	-7	0	21	18
2022	17-Mar	11	24	-36	-9	2	12	11	9
2022	24-Mar	12	25	-6	-15	2	17	17	29
			r>0	68	64	68	76	48	48

Pearson correlation coefficients (x100) of associations between weekly all-cause mortality (z-scores from EUROMOMO.EU) and weekly cumulated percentage of individuals with booster injection that week, for six age classes. Highlights indicate correlations with P < 0.05, one tailed tests, blue for protective associations where mortality decreases with injections, and yellow for positive associations where mortality increases with injections.

Figure 2: Euromomo: All-cause mortality and cumulative 3rd dose injection (from Table 2)



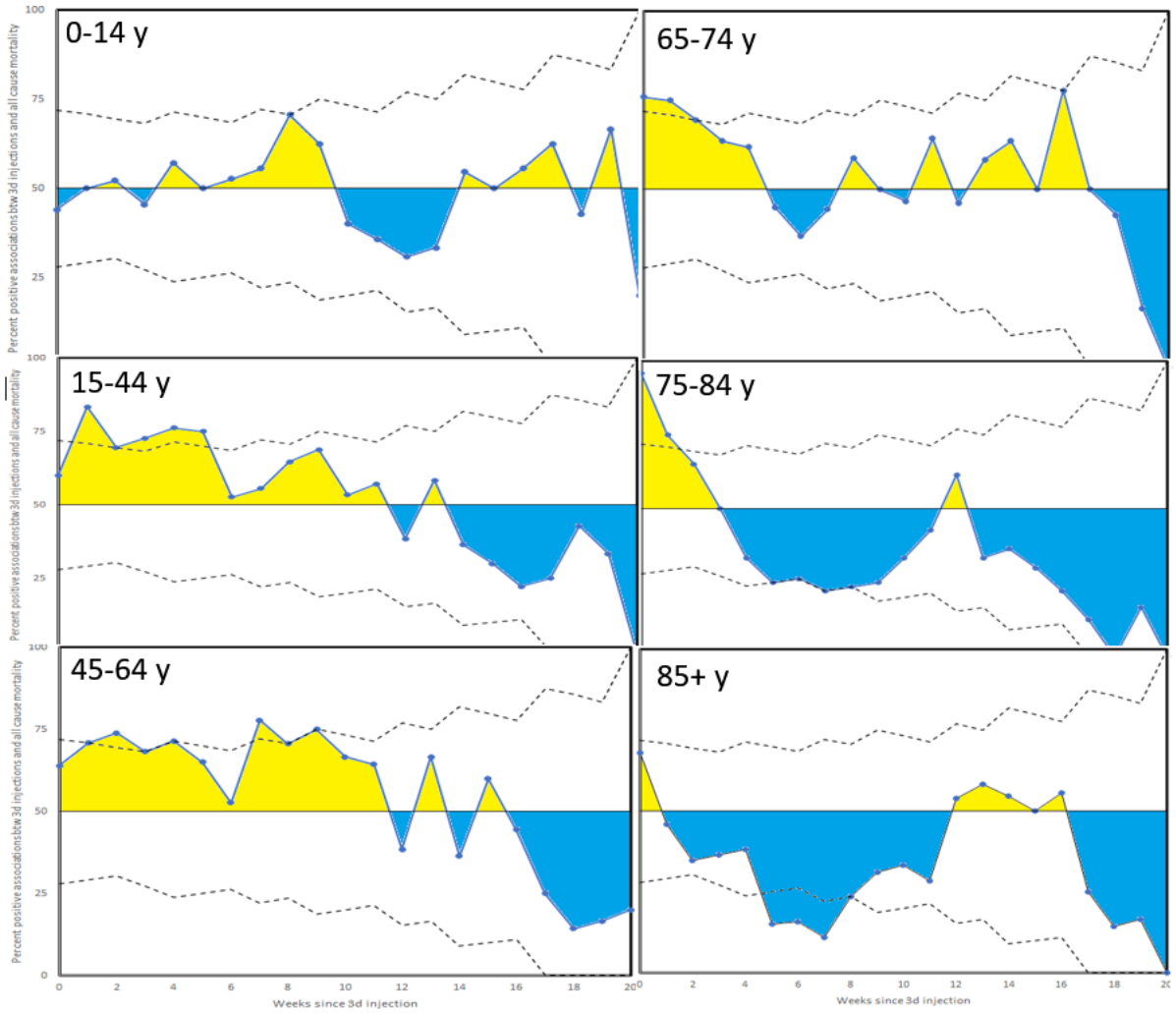
Weekly Pearson correlation coefficient between all-cause mortality from euromomo.eu and cumulated 3d injections, for weeks since start of October 2021 until March 24 2022 function of weeks since start of 2021 in six age classes. Interrupted lines indicate P < 0.05, one tailed tests. Yellow areas correspond to positive associations (detrimental association of boosters with all-cause mortality), blue areas indicate negative associations (beneficial association of boosters with all-cause mortality). The dotted line represents 95% CI and boundary for statistical significance

European Dataset, lag analysis

Figure 3 plots the percentage of positive Pearson correlation coefficients between the weekly increase in percentages of boosted individuals in the population and the weekly all-cause mortality for six age classes, as a function of the lag in number of weeks (up to 20) between injection and mortality data.

Booster injections associate with increased mortality during the first weeks after injections for all ages above 14. The duration of this adverse reaction period varies across age groups and overall decreases with age. There are no significant decreases in mortality associated with boosters for ages below 75. Note that a selection bias may operate for longer lag periods.

Figure 3: Euromomo: All-cause mortality and 3rd dose injection (lag analysis to 20 weeks)



Percentages of positive Pearson correlation coefficients between weekly increase in booster-injected percentage of the population and weekly all-cause mortality as a function of the lag, in number of weeks between injection and mortality in six age classes. Lag 0 means injections and mortality occurred the same week. Interrupted lines indicate P < 0.05, one tailed tests. Yellow areas correspond to positive associations (detrimental association of boosters with all-cause mortality), blue areas indicate negative associations (beneficial association of boosters with all-cause mortality). The dotted line represents 95% CI and boundary for statistical significance.

US -CDC Dataset Preliminary Results

Prior month vaccinations (number of administered doses) predicted monthly all-cause deaths in all age groups. The beta coefficient for the vaccine term was significant in 15 regression models (p<0.05 FDR corrected, see yellow boxes in **Table 3** and **Figure 4**). All statistically significant regression slopes were positive (i.e. detrimental) while no terms with negative slopes survived p<0.05 corrected nor a more liberal threshold of p<0.05 uncorrected. Independently of p values, the

majority of fitted slopes were positive (detrimental) considering all ages for each individual month from November to February ($p < 0.05$, sign test). A similar relationship was found when considering all months for each specific age group ($p < 0.05$ sign test for age 30-39).

The bulk of the adverse effects from prior month vaccinations begin in November, 2021, consistent with the authorization of boosters by FDA in late September, 2021. Moreover, the results were similar when predicting non-COVID associated deaths (**Figure 5**). Note that because COVID-associated deaths are rarer in younger age groups, the latter analyses had much less power because few states had available data to compute non-COVID deaths in ages 0-49.

Applying our previous modelling methodology (53) to the estimated beta weights, yielded 163,496 (0.085% of vaccination doses) all-cause US deaths associated with prior month vaccinations between September, 2021 and February 2022. This rate is more than twice as high as we estimated for the primary series between February and August, 2021.This is consistent with our findings from the European data, as well as findings of higher serious adverse event rates following second vs. first primary doses.(57)

Table 3: Regression weights and p-values for the vaccination term predicting same or next month all-cause deaths using US CDC data.

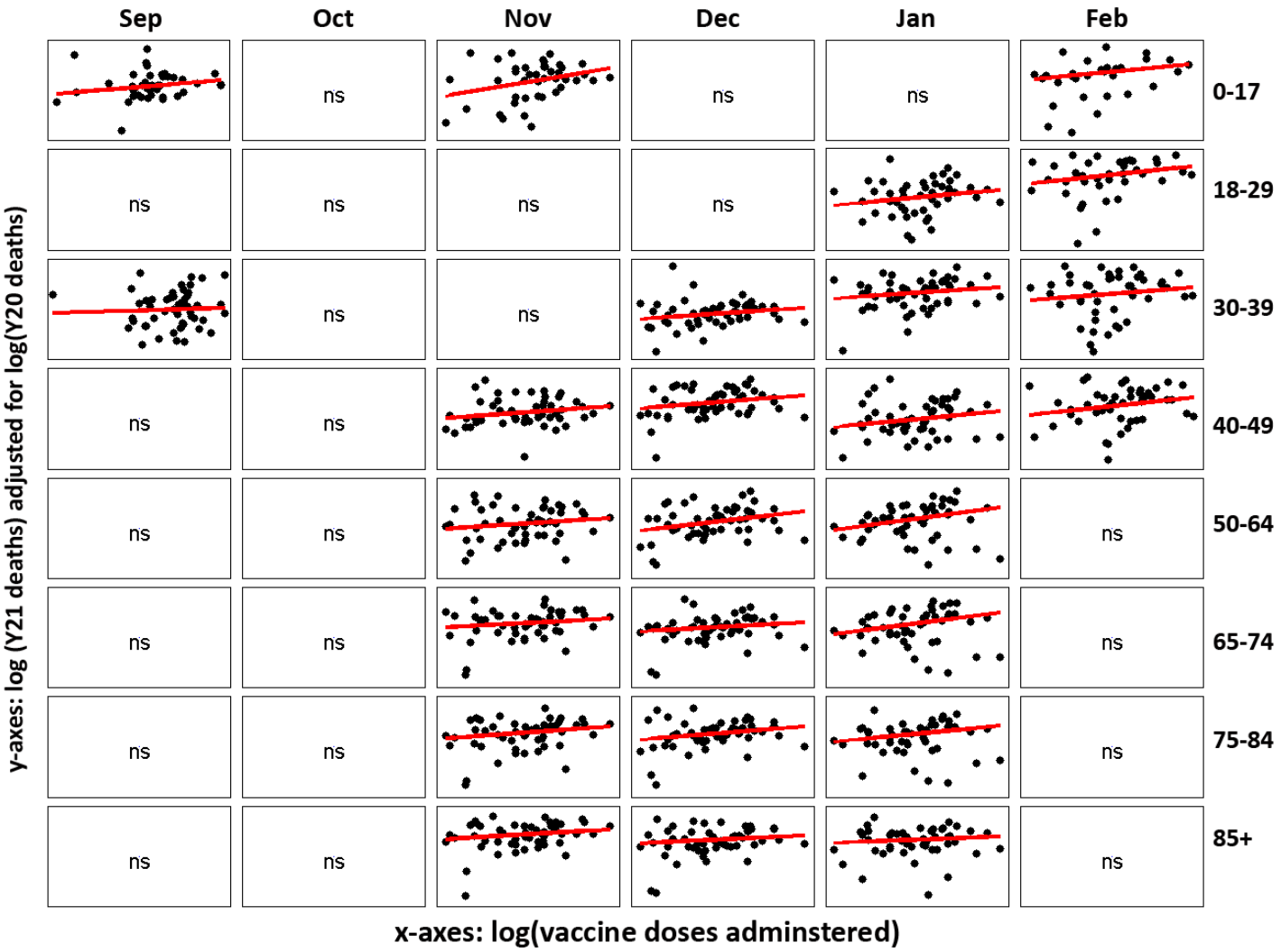
Ages	Sep, 21		Oct, 21		Nov, 21		Dec, 21		Jan, 22		Feb, 22	
	beta	*pval*	*beta*	*pval*	*beta*	*pval*	*beta*	*pval*	*beta*	*pval*	*beta*	*pval*
0-17	**0.154**	0.0234	**0.080**	0.2231	**0.236**	0.0001	**-0.006**	0.9400	**0.195**	0.0686	**0.420**	0.0032
18-29	**0.115**	0.0916	**-0.034**	0.6611	**0.035**	0.5632	**0.085**	0.2235	**0.192**	0.0069	**0.386**	0.0010
30-39	**0.127**	0.0061	**0.096**	0.0860	**0.107**	0.0291	**0.302**	0.0000	**0.214**	0.0036	**0.321**	0.0091
40-49	**0.034**	0.5248	**-0.015**	0.8300	**0.136**	0.0028	**0.206**	0.0001	**0.168**	0.0113	**0.243**	0.0020
50-64	**-0.023**	0.5334	**-0.030**	0.4991	**0.100**	0.0219	**0.237**	0.0000	**0.167**	0.0020	**0.146**	0.0391
65-74	**-0.021**	0.4871	**-0.050**	0.2083	**0.113**	0.0125	**0.154**	0.0006	**0.147**	0.0039	**0.109**	0.0775
75-84	**-0.035**	0.1110	**0.011**	0.7846	**0.168**	0.0001	**0.194**	0.0000	**0.153**	0.0013	**0.094**	0.0919
85-plus	**-0.038**	0.0875	**0.033**	0.4162	**0.217**	0.0000	**0.164**	0.0006	**0.210**	0.0008	**0.057**	0.4628

For each month and age group, beta weights and uncorrected p-values are listed for the vaccination term (β_2) in the fitted equation:

$$log(Y21\_deaths) = \beta_0 + \beta_1 \log(\mathrm{Y20\_deaths}) + \beta_2 \log(\mathrm{Vax}) + \varepsilon$$

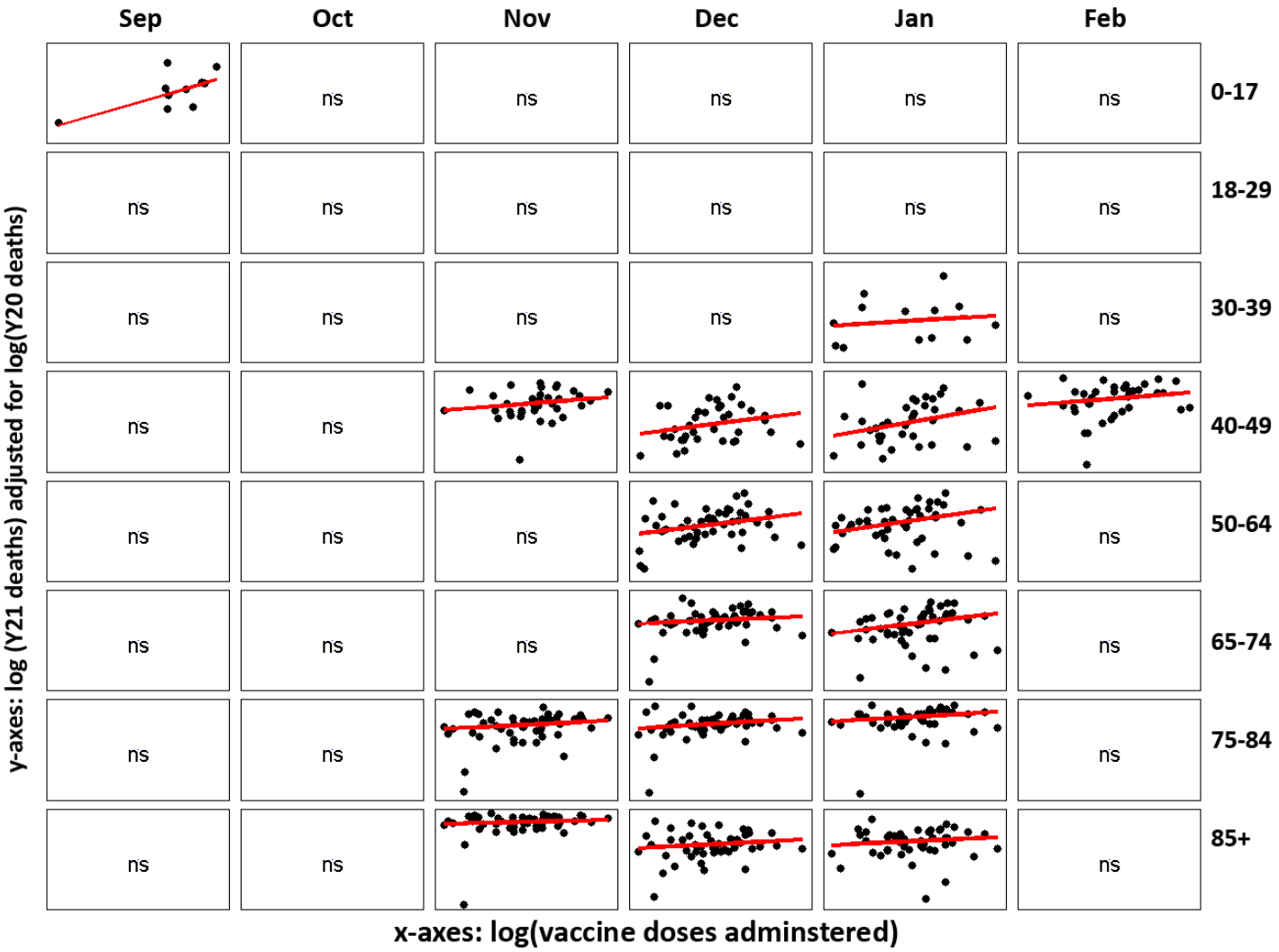
where Vax = vaccine doses administered previous or same month across all US states with available data for that month and age group (~42-52 states for each cell/regression, see Equation 1). Models were fitted using robust regression. Yellow indicates positive beta slopes with p-values < 0.05 FDR corrected. No negative slopes were significant.

Figure 4: USA: Monthly all-cause mortality and vaccination prior month



Scatter plots of monthly vaccination (mostly 3rd booster) doses vs. subsequent month total all-cause deaths with best fit regression lines from the US CDC dataset. For each month (top labels) from September 2021 through February, 2022, the panels plot prior month vaccine doses vs. current month total deaths (adjusted for same month deaths in 2020) for each age group (right), and for each regression model in which the β_2 term survived p<0.05 FDR corrected (see **Table 3**). ns=not significant at p<0.05 FDR corrected. The FDA approved the booster shots for ages 65 and high risk 18 and older on September 22nd, 2021. Eligibility for the booster was expanded to all ages 18 and older on November 19th, 2021.

Figure 5: USA: Monthly non-Covid-19 mortality and vaccination prior month



Scatter plots of monthly vaccination (mostly 3rd booster) doses vs. subsequent month non-Covid-19 total deaths with best fit regression lines from the US CDC dataset. For each month (top labels) from September 2021 through February, 2022, the panels plot prior month vaccine doses vs. current month total deaths (adjusted for same month deaths in 2020) for each age group (right), and for each regression model in which the β_2 term survived p<0.05 uncorrected (see **Table 3**). ns=not significant at p<0.05 uncorrected. An uncorrected threshold was used because fewer states reported COVID deaths (required in order to calculate non-COVID deaths from the CDC data) in younger age groups and so these models had less power than the models predicting all-cause mortality.

Discussion and conclusions

From the European data, below age 75, there is no evidence for overall protective (blue) effects of boosters. On the contrary, for the most part there is cause for concern of a detrimental association between all-population booster usage and age-specific all-cause mortality. This is particularly concerning for those under 14 group, where a cyclical pattern was observed. This may have been the result of confounding related to the introduction of primary series vaccination in the 11 years and younger group starting around the end of October.

For those over 75, there was a period of negative (i.e. beneficial) associations between all-population booster usage and age-specific all-cause mortality, more limited for the 75-84+ group, and flanked (both sides for 75-84; afterwards only for 84+) by **detrimental** periods.

Data are also confounded by the emergence of the Omicron variant in the November 2021 timeframe. These results do not indicate any benefits of booster injections, and strongly suggest adverse effects increasing all-cause mortalities in all ages at various periods. Emerging data elsewhere suggest limited utility of booster doses. Data from the UK (8) suggest that a third (booster) dose of the Pfizer vaccine wanes at about the same rate and to a similar extent as the primary series (against Omicron), with similar effects of the BA1.1 and BA.2 variant.

There is currently discussion of a 4th dose (i.e. a second booster dose). Preliminary data from Israel using only a 4 month interval (11) reported a paltry vaccine efficacy against infection of only 30% (95% confidence interval (–9% to +55%) (Pfizer) and 11% (–43% to +44%) (Moderna). Note that these figures fall well below the FDA target efficacy of 50% with a lower confidence interval of 30%. (3,4) In this case, the confidence intervals indicate that negative efficacy is possible, as results above indicate. Consistent with these data are other Israeli data for a 4th dose showing waning from 52.9% at one month to 2.6% at 4 months.(12)

Concerns have been expressed about a fourth dose(24) in particular and boosters in general.

Since the toxicity of two doses has not been fully explored, even less is known about the toxicity of three doses. The wisdom and sustainability of boosting has been questioned by Dr. Marco Cavaleri[22] (Head of Biological Health Threats and Vaccines Strategy, EMA). and by ACIP member Dr. Sarah Long,[23] who described the use of Pfizer boosting in 12–15-year-olds for Omicron as the "last whack a mole" and neither sustainable nor smart.

Our findings are certainly consistent with these comments and demand more transparent scrutiny availability and scrutiny of public records, particularly by CDC. Several problems are known to exist in CDC-derived data:

- Many of the studies published by CDC are derived from electronic medical records, they are subject to the underreporting error described by FDA for vaccination-status.(58)
- As cited in a Feb 20 2022 New York Times article, (59) CDC is not publishing large portions of its data on Covid. A named spokeswoman was quoted as saying that there was a fear, within CDC, that "the information might be misinterpreted." Particularly, the article stated that "*The agency has been reluctant to make those figures public: beca*use," according to a CDC official, "they might be misinterpreted as the vaccines being ineffective."
- CDC has recently corrected (March 15 2022) the number of children's (0-17 years) deaths attributed to Covid-19 in its Covid-19 Data Tracker from 1755 to 1339, a reduction of 24.7%. The error was attributed to a coding logic error.(60)

This is anathema to the principle of data transparency, sorely needed as the number of deaths attributed to Covid-19 approaches 1 million in the USA (977,495, 3/31/22) and exceeds 6 million (6,137,553, WHO), worldwide. Our analyses are based on all-cause mortality data and do not suffer underreporting biases or biases due to differences in definitions of COVID as cause of death. In addition, they enable to detect detrimental effects associated with injections but unrelated to COVID.

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