

## **Covid-19 gene therapy vaccines: Why no review by FDA's Office of Tissues and Advanced Therapies (OTAT) and Cell Therapy Gene Therapy Advisory Committee (CTGTAC)**

Written comments submitted re: FDA- CTGTAC Meeting June 10<sup>th</sup> 2022  
FDA-2022-N-0470

David Wiseman PhD, MRPharmS ([Synechion@aol.com](mailto:Synechion@aol.com))

Hervé Seligmann, PhD, Spiro P. Pantazatos PhD. Columbia University Irving Medical Center, NY  
(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 5)

**June 2<sup>nd</sup> 2022**

<https://www.regulations.gov/comment/FDA-2022-N-0470-0179>

[https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment\\_1.pdf](https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment_1.pdf)

[https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment\\_2.pdf](https://downloads.regulations.gov/FDA-2022-N-0470-0179/attachment_2.pdf)

Oral comments: <https://youtu.be/Eo2BXnGienc?t=11547>

### **Capsule**

We discuss continuing and unanswered safety concerns, particularly with regard to the gene therapy nature of the Covid-19 vaccines. In particular we ask why FDA is not, publicly at least, discussing these concerns through its Office of Tissues and Advanced Therapies (OTAT), [Cellular, Tissue, and Gene Therapies Advisory Committee](#), and its Gene Transfer Branch (GTIB) with six labs researching, inter alia, Covid as well universal flu vaccine.

One of OTAT's stated roles is to *"increase public confidence in and acceptance of novel technologies by addressing concerns."*

As related to the Covid-19 vaccines, FDA is:

- NOT increasing public confidence
- NOT addressing gene therapy concerns of C19 vaccines
- NOT acknowledging C19 vaccines are gene therapies
- NOT affording the public informed consent about the nature and risks of the Covid-19 vaccines.

We need robust and transparent public debate of the kind we have seen at FDA's AMBAC committee when it discussed molnupiravir. Will OTAT insist on having the same debates within its CTGTAC committee?

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# 1. Overview

COVID-19 Vaccines meet FDA's biological definition of a gene therapy product

**COVID-19 Vaccines meet FDA's biological definition of a gene therapy product**

**Long Term Follow-Up After Administration of Human Gene Therapy Products**

[www.fda.gov/media/113768/download](http://www.fda.gov/media/113768/download)  
**Guidance for Industry**

U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research  
January 2020

**Human gene therapy product:** FDA generally considers human gene therapy products to include all products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences. Some examples of gene therapy products include **nucleic acids** (e.g., plasmids, in vitro transcribed **ribonucleic acid** p30 (RNA)), genetically modified microorganisms (e.g., viruses, bacteria, fungi), engineered site-specific nucleases used for human genome editing,<sup>10</sup> and ex vivo genetically modified human

**"mRNA is considered a gene therapy product by the FDA"** (Moderna 2Q2020 SEC Filing)

**"One would expect the classification of an mRNA drug to be a biologic, a gene therapy or a somatic cell therapy."** (Sahin et al. 2014)

**"This guidance does not apply to vaccines for infectious disease indications"**

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However. "This guidance does not apply to vaccines for infectious disease indications" 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<sup>1</sup>](#)) is FDA's Gene Transfer Branch (GTIB).

Despite this "vaccine exclusion" from guidance, OTAT has six labs researching, inter alia, infectious disease (flu) vaccines and Covid.

**Office of Tissues and Advanced Therapies (OTAT)**

**Overview of the Gene Transfer and Immunogenicity Branch**

**Six laboratories focused on:**

- Cell and Gene Therapy
- Immunology
- Virology

**Relevance to FDA's mission**

- Improving safety and efficacy of cell and gene therapy products
- Characterizing complex products
- Mitigating immune responses to products
- Better preclinical models

**Other FDA and HHS priorities**

- Pandemic influenza
- COVID-19

**Relevance of this work to our regulatory mission**

- **Universal influenza vaccine** approach: control of seasonal and **pandemic influenza** is a Center- and Agency-wide public health priority
- Immune responses to recombinant vectors used in this work have major impact on safety and efficacy of gene therapy
- We need to understand these responses – and understand how to measure them – in both preclinical animal models and clinical trials
- In addition, OTAT regulates a variety of immunologically-based products to control viral infections, including influenza

**Relevant vectors studied in this program currently or previously:**

- Plasmid, **adenovirus**, AAV, and poxvirus vectors

**Assays:**

- Mouse, ferret, and human antibody and T cell assays

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FDA has also a Cellular, Tissue, and Gene Therapies Advisory Committee. The [summary minutes<sup>2</sup>](#) for the CTGTAC meeting held September 2-3<sup>rd</sup> 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.

<sup>1</sup> <https://www.fda.gov/media/156771/download>

<sup>2</sup> <https://www.fda.gov/media/154397/download>

FDA U.S. FOOD & DRUG ADMINISTRATION  
 FDA Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting #70  
 September 2-3, 2021  
 Toxicity Risks of Adeno-associated Virus (AAV) Vectors for Gene Therapy (GT)  
[fda.gov/media/151969/download](https://www.fda.gov/media/151969/download)  
 Rosa Sherafat, MD and AC Planning Working Group  
 Office of Tissues and Advanced Therapies (OTAT) CBER, FDA

- Hepatotoxicity
- Thrombotic microangiopathy (TMA)
- Neurotoxicity
  - Dorsalroot ganglia (DRG) toxicity
  - Brain magnetic resonance imaging (MRI) findings
- Oncogenicity

Discussion Questions for the Committee: Hepatotoxicity  
 1. Please discuss the merits and limitations of animal studies to characterize the risk of hepatotoxicity and provide recommendations on preclinical study design elements, such as animal species, disease models, and in-life and post-mortem assessments, including methods for integration analysis.

Discussion Questions for the Committee: TMA  
 1. Please discuss factors that may increase the risk of TMA following AAV vector administration.

Discussion Questions for the Committee: DRG Toxicity  
 1. Based on the published data, please discuss the relevance of the NHP Cases of DRG toxicity to human subjects.

Discussion Questions for the Committee: Oncogenicity  
 1. Please discuss the merits and limitations of animal studies to characterize the risk of AAV vector-mediated oncogenicity, and provide recommendations on specific preclinical study design elements, to include:  
 a. Animal species, healthy vs. disease models, and animal age  
 b. In-life and post-mortem assessments, including methods for integration analysis  
 c. Duration of follow-up, post-dose  
 2. Current literature suggests that various factors may affect AAV-mediated vector genome persistence, vector integration, and the risk of oncogenesis. Please discuss benefit-risk considerations for AAV vector-mediated oncogenesis, such as patient age at the time of treatment, pre-existing liver conditions (e.g., infection with hepatitis B or C virus), and high vector dose.

FDA recently consulted with GTCTAC regarding toxicity of AAV toxicity risks in gene therapy

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How are long term toxicological concerns allayed by ignoring the gene therapy definition and invoking the guidance's exclusion concerning infectious diseases?

Cancer, neurologic, clotting, new infection and autoimmune disease are all concerns of gene therapy products needing a 5-15 year follow up.

SYNECHION  
 What are the concerns?

5-15 year long term follow up for autoimmune, blood, neuro, cancer disease

Long Term Follow-Up After Administration of Human Gene Therapy Products  
[www.fda.gov/media/113768/download](https://www.fda.gov/media/113768/download)  
 U.S. Department of Health and Human Services  
 Food and Drug Administration  
 Center for Biologics Evaluation and Research  
 January 2020

Taking these discussions into consideration, we provided detailed recommendations in the 2006 Delayed Adverse Events guidance document on the duration and design of LTFU observations (Ref. 1). The Agency advised sponsors to observe subjects for delayed adverse events for 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 either in person or by questionnaire.

Establish a method for investigators to record the emergence of new clinical conditions, such as:

- New malignancy(ies)
- New incidence or exacerbation of a pre-existing neurologic disorder
- New incidence or exacerbation of a prior rheumatologic or other autoimmune disorder
- New incidence of a hematologic disorder.
- New incidence of infection (potentially product-related)

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These are some of the concerns already showing up as safety signals in VAERS.

SYNECHION  
 Pfizer-to-Flu Reporting Ratios per Million Fully Vaccinated, Ages 12-17

MedDRA HLGT Category	COVID:Flu Ratio	MedDRA HLGT Category	COVID:Flu Ratio
Menstruation & uterine bleeding disorders	722	Coronary artery disorders	320
Vulvovaginal disorders	442	Cardiac valve disorders	154
Endocrine disorders of gonadal function	372	Myocardial disorders	3,584
Reproductive tract disorders NEC	77	Embolism and thrombosis	180
White blood cell disorders	130	Central nervous system vascular disorders	179
Hepatic and hepatobiliary disorders	68	Arteriosclerosis, stenosis, vascular insufficiency	95
Renal disorders	60	Coagulopathies and bleeding tendencies	33
Autoimmune disorders	13	Vascular haemorrhagic disorders	29

Note: COVID-19 cannot account for higher VAERS reporting rates because reports with indication of COVID-19 infection were excluded from analysis. Comparison includes all reports to VAERS from Pfizer COVID-19 Vaccines through Oct. 8, 2021 to total reports from 5 flu seasons: 2015/16-2019/20.

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And MIS-V is now being recognized by CDC, that can include blood, liver and neurological elements.

**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**

**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, arrhythmia, 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

**System overlap with MIS-V?**

**Blood  
Liver  
Neurological**

BMJ - 10.1136/bcr-2021-243888 Case report

Multisystem inflammatory syndrome in an adult following the SARS-CoV-2 vaccine (MIS-V) PE, d-dimer, Arvind Nune<sup>1</sup>, Karthikeyan P. Iyengar<sup>2</sup>, Christopher Goddard<sup>3</sup>, Ashar E. Ahmed<sup>1</sup>

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Neurological effects of the mRNA Covid-19 vaccines are now being recognized by NIH and CDC.

**medRxiv** THE PREPRINT SERVER FOR HEALTH SCIENCES

**NIH**

**Neuropathic symptoms with SARS-CoV-2 vaccination**

**Conclusions** This observational study suggests that a variety of neuropathic symptoms may manifest after SARS-CoV-2 vaccinations and in some patients might be an immune-mediated process.

**Neurological effects – beginning recognition by NIH and CDC**

**PEDIATRICS**

**Safety of COVID-19 Vaccination in US Children Ages 5–11 Years**

**TABLE 5. Reports of nonserious and serious events to Vaccine Adverse Event Reporting Sys for children ages 5–11 years after receipt of BNT-162b2 COVID-19 vaccine (N = 7,578) — U November 3–February 27, 2022**

Reported events	Number (%) rep
Serious VAERS reports <sup>a, b</sup>	194 (100) <sup>c</sup>
<b>Clinical impression</b>	
Multisystem inflammatory syndrome in children (MIS-C)	26 (13.4)
Seizure <sup>d</sup>	21 (10.8)
Myocarditis <sup>e</sup>	19 (9.8)
Appendicitis	13 (6.7)
Allergic reaction	8 (4.1)
COVID-19	7 (3.6)
Abdominal pain	6 (3.1)
Diabetes mellitus type 1	5 (2.6)
Death	4 (2.1)

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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. (1) Noted also are the presence of human gene sequences in the untranslated regions, whose influence on vaccine toxicity has not been described.

**Anticipated issues**

**Non-natural nucleotides**

- Mitochondrial effects
- Effects after prolonged treatment?
- Reduce immune reaction
- Reduce defence to RNA

**5'-cap modifications:**

- Uncapped, functional when combined with IRES
- Cap analogues mediating binding to eIF4E
- Cap analogues conferring resistance to decapping

**5' UTR:**

- Regulatory sequence elements binding to molecules involved in mRNA trafficking and translation
- Sequences inhibiting 5'-exonucleolytic degradation
- IRESs

**improve translation**

- Optimized base usage to reduce endonucleolytic attack

**Whole IVTmRNA:**

- Use of modified nucleosides for modulating innate immune activation
- Engineering favourable secondary structures by sequence optimization

**3' UTR:**

- Sequence elements mediating binding to proteins involved in mRNA trafficking and translation
- Sequences repressing deadenylation of mRNA

**5' UTR**

- Human genetic sequences
- Improves production
- Inhibit degradation

**Spike protein toxicity**

**Auto-antibodies against mRNA?**

Sahin et al., 2014

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**modRNA** nucleoside-modified messenger RNA

FDA U.S. FOOD & DRUG ADMINISTRATION  
**"Nucleoside modified messenger RNA (modRNA)"**  
<https://cacmap.fda.gov/media/150386/download>  
 October 29, 2021

No cumulative tox data

Pfizer Inc.  
 Attention: Mr. Amit Patel  
 235 East 42<sup>nd</sup> St  
 New York, NY 10017

**4. Pfizer-BioNTech COVID-19 Vaccine (BNT162b2)**  
**Page 11: [fda.gov/media/144245/download](https://www.fda.gov/media/144245/download)**

**4.1. Vaccine Composition, Dosing Regimen**

The Pfizer-BioNTech COVID-19 Vaccine is a white to off-white, sterile, preservative-free, frozen suspension for intramuscular injection. The vaccine contains a **nucleoside-modified messenger RNA (modRNA)** encoding the viral spike glycoprotein (S) of SARS-CoV-2. The vaccine also

**non-natural nucleosides AND human gene sequences**

*Risks associated with non-natural nucleotides:* The highly abundant extracellular RNases have evolved as a powerful

**Uridine → pseudouridine**

down much higher amounts of natural mRNA every day. However, this may not apply to investigational mRNA drugs containing unnatural modified nucleotides. Mechanisms of catabolism and excretion and potential unwanted cross-effects on other toxicity-relevant pathways of unnatural nucleotides in a polynucleotide structure or their metabolites and potential risks associated with these are still unknown.

- "anti-RNA antibodies [...] immune pathology."
- "potential toxicity of nucleoside analogues"
- "metabolites and potential risks [...] unknown."
- "adverse effects [...] prolonged treatment with nucleoside analogues."
- "mitochondrial toxicities"

Sahin et al., 2014

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In the same article, Dr. Sahin expresses concern about genome integration of the DNA vaccines, as well as the transience for the mRNA.

**mRNA-based therapeutics — developing a new class of drugs**

**BioNTech founders:**

- Genome integration
- Transience

Ugur Sahin<sup>1,2</sup>, Katalin Karikó<sup>2,3</sup> and Özlem Türeci<sup>1</sup>

Abstract | *In vitro* transcribed (IVT) mRNA has recently come into focus as a potential new drug class to deliver genetic information. Such synthetic mRNA can be engineered

<sup>1</sup>TRON Translational Oncology at the University Medical Center of the Johannes Gutenberg University, Langenbeckstrasse 1, 55131 Mainz, Germany.  
<sup>2</sup>BioNTech Corporation, Mainz, Germany

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 pharmaceutical applications it is also advantageous that IVT mRNA is only transiently active and is completely degraded via physiological metabolic pathways.

NATURE REVIEWS | DRUG DISCOVERY VOLUME 13 | OCTOBER 2014 | 759

**11**

According to FOIA-released Pfizer documents, we still do not know how the mRNA moves around the body, or the spike protein that it produces.

**How does the mRNA move around the body?**  
 "Pharmacokinetic studies have not been conducted with BNT162b2 and are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005; WHO, 2014)."

**Where is Spike protein produced, and how does it persist?**

Redacted version in FOIA document

**B** Luciferase signal over time

**Luciferase model: Persists at least to 9 days**

**12**

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(2), this should be cause for some concern.

**Australian TGA** There are **no data on the kinetics of BNT162b2 mRNA** degradation. In mice injected with the luciferase mRNA, the absence of expressed protein by **9 days** after dosing indicates that **mRNA has been degraded**. [tga.gov.au/sites/default/files/foi-2389-06.pdf](https://www.tga.gov.au/sites/default/files/foi-2389-06.pdf)

> Cell. 2022 Jan 25;S0092-8674(22)00076-9. doi: 10.1016/j.cell.2022.01.018. Online ahead of print.

**Immune imprinting, breadth of variant recognition, and germinal center response in human SARS-CoV-2 infection and vaccination**

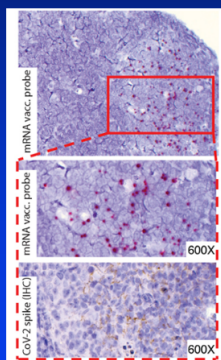
Katharina Röltgen<sup>1</sup>, Sandra C A Nielsen<sup>1</sup>, Oscar Silva<sup>1</sup>, Sheren F Younes<sup>1</sup>, Maxim Zaslavsky<sup>1</sup>, Cristina Costales<sup>1</sup>, Fan Yang<sup>1</sup>, Oliver F Wirz<sup>1</sup>, Daniel Solis<sup>1</sup>, Ramona A Hoh<sup>1</sup>, Aihui Wang<sup>1</sup>, Prabhu S Arunachalam<sup>2</sup>, Deana Colburg<sup>1</sup>, Shuchun Zhao<sup>1</sup>, Emily Haraguchi<sup>1</sup>, Alexandra S Lee<sup>3</sup>, Mihir M Shah<sup>3</sup>, Monali Manohar<sup>3</sup>, Iris Chang<sup>3</sup>, Fei Gao<sup>2</sup>, Vamsee Mallajosyula<sup>2</sup>, Chunfeng Li<sup>2</sup>, James Liu<sup>4</sup>, Massa J Shojanaranbaatar D Dashdorj<sup>1</sup>, R Sharon Chinthrajah<sup>3</sup>, Mark M Davis<sup>1</sup>, Bali Pulendran<sup>1</sup>, Benjamin A Pinsky<sup>1,3</sup>, Ka

**Lymphoid tissue contains “vaccine mRNA and spike antigen up to 8 weeks postvaccination”**

Affiliations: collapse

**Affiliations**

- 1 Department of Pathology, Stanford University, Stanford, CA, USA.
- 2 Institute for Immunity, Transplantation and Infection, Stanford University, Stanford, CA, USA.
- 3 Sean N. Parker Center for Allergy & Asthma Research, Stanford University, Stanford, CA, USA.



12

This contradicts the information provided by CDC.

**SYNECHION**

**CDC** Centers for Disease Control and Prevention  
CDC 24/7. Saving Lives. Protecting People™

Search COVID-19

**COVID-19**

Home Your Health Vaccines Cases & Data Work & School Healthcare Workers Health Depts Science

[www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html](https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html)

Vaccines Understanding mRNA COVID-19 Vaccines

Your Vaccination Updated Jan. 4, 2022 Languages Print

**Data contradict CDC information**

1. First, COVID-19 mRNA vaccines are given in the upper arm muscle. The mRNA will enter the muscle cells and instruct the cells' machinery to produce a **harmless piece of what is called the spike protein**. The spike protein is found on the surface of the virus that causes COVID-19. After the protein piece is made, our cells break down the mRNA and remove it.

The mRNA and the spike protein don't last long in the body.

- Our cells break down mRNA and get rid of it **within a few days** after vaccination.
- Scientists estimate that the spike protein, like other proteins our bodies create, may stay in the body up to a **few weeks**.

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Furthermore, this recent study(3) found evidence of reverse transcription of vaccine mRNA to DNA, invoking Dr. Sahin's fear(1) of insertional mutagenesis for DNA-based vaccines.

current issues in molecular biology

Article

### Intracellular Reverse Transcription of Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 In Vitro in Human Liver Cell Line

**mRNA to DNA reverse transcription**

Markus Aldén<sup>1</sup>, Francisko Olofsson Falla<sup>1</sup>, Daowei Yang<sup>1</sup>, Mohammad Barghouth<sup>1</sup>, Cheng Luan<sup>1</sup>, Magnus Rasmussen<sup>2</sup> and Yang De Marinis<sup>1,\*</sup>

- LINE 1 gene was switched after 6 hours to produce LINE 1 protein.
- LINE 1 protein capable of reverse transcription
- The LINE 1 protein was found in the nucleus
- A DNA copy of the Pfizer vaccine mRNA found.

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-

**Does this raise Sahin's fear of insertional mutagenesis?**

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According to the COMIRNATY package insert,(4) no carcinogenicity or genotoxicity studies have been performed.

An EMA report(5) 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?

### Comirnaty Package Insert: EMA Report

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility [fda.gov/media/151707/download](https://www.fda.gov/media/151707/download)

COMIRNATY has not been evaluated for the potential to cause **carcinogenicity, genotoxicity,** or impairment of male fertility.

**Genotoxicity**

No genotoxicity studies have been provided. This is acceptable as the components of the vaccine formulation are lipids and RNA that are not expected to have genotoxic potential.

The robustness of the DNase digestion step is not considered comprehensively demonstrated although there is routine control of **residual DNA impurities** [...] studies to enhance the robustness of this step are ongoing and these should be reported

**Unreported DNA impurities**

ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report\_en.pdf

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With CDC's own data, there is medium term (3-6month) negative VE. Is this a reflection of the gene therapy guidance document of new infection?



Ruth Link-Gelles, PhD, MPH  
LCDR, US Public Health Service  
Program Lead, COVID-19 Vaccine Effectiveness  
Epidemiology Task Force, CDC

COVID-19 vaccine effectiveness during Omicron for children and adolescents

ACIP  
May 19, 2022

[cdc.gov/vaccines/acip/meetings/downloads/slides-2022-05-19/02-COVID-Link-Gelles-508.pdf](https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-05-19/02-COVID-Link-Gelles-508.pdf)

ICATT: Pfizer-BioNTech 2-dose VE against symptomatic infection, by age group and variant

**Medium term 3-6m negative VE:  
Gene therapy concern- new infection?**

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Other studies are also showing waning and negative efficacy vs. Omicron with VE falling below FDA guidance of 50%, lower CI of 30%, < 4 months.

Other studies: Waning and negative efficacy vs. Omicron  
VE falls below FDA guidance of 50%, lower CI of 30%, < 4 months

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

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And even with boosting, VE wanes just as rapidly as the primary series.

Data from the UK: VE vs. symptomatic infection comparing Omicron sublineages (BA.1 vs BA.2) by time since booster

- Pfizer-BioNTech, Moderna, or ChAdOx1-5 primary series, Pfizer-BioNTech or Moderna booster
- VE was generally comparable by Omicron sublineage

[www.fda.gov/media/157475/download](https://www.fda.gov/media/157475/download)  
[assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/1063023/Vaccine-surveillance-report-week-12.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1063023/Vaccine-surveillance-report-week-12.pdf)

Figure 2. Vaccine effectiveness against symptomatic disease after 2 doses or a booster dose  
UKHSA Week 12 UK: BA.1 and BA.2 boost waning similar

**Although VE is boosted, it wanes just as rapidly**

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The wisdom of frequent boosting has been questioned in EMA and in CDC's ACIP as "the last whack a mole"

## Boosters: beyond the last whack a mole.

**Dr. Marco Cavaleri (EMA)**  
Jan 18 2022

[www.youtube.com/watch?v=0Gz8MTPV5qs&t=238s](https://www.youtube.com/watch?v=0Gz8MTPV5qs&t=238s)

**Sarah S. Long, MD** ACIP Jan 5<sup>th</sup> 2022

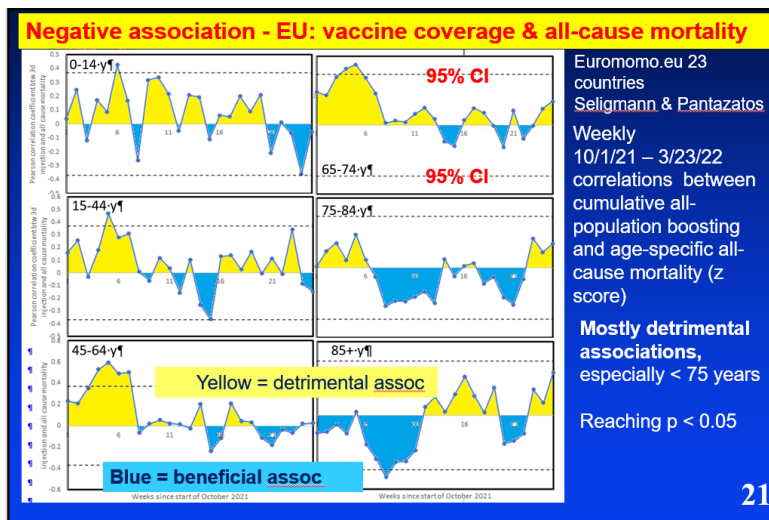
Professor of Pediatrics, Drexel U  
Diseases, St. Christopher's Hosp  
6/30/2024  
[youtu.be/8yIPhOJuX98?t=5208](https://youtu.be/8yIPhOJuX98?t=5208)  
Dr. Long is board certified in ped  
decades of contributions to the f  
committees including as a stand  
Advisory Committee (VRBPAC) of  
Pediatrics (AAP) Committee on IR

"repeated administration of boosters with very short interval might reduce the level of antibodies that can be produced at each administration as our immune system needs a certain amount of time to mature the response "

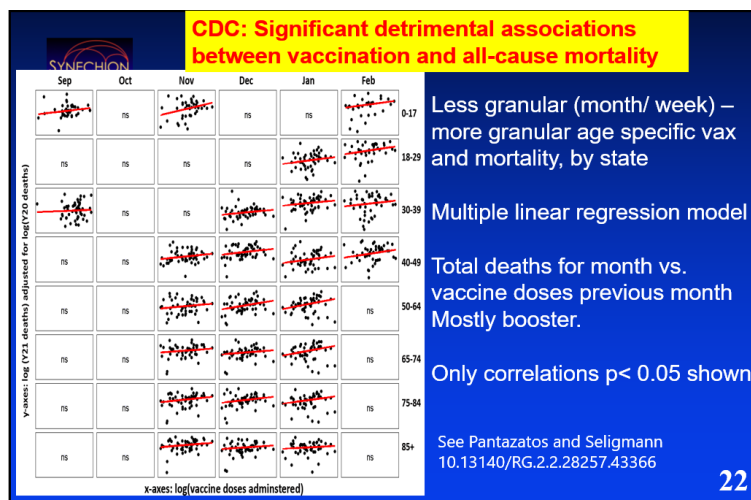
I think it will allow us to whack a mole for another month or two but this is not sustainable and its not smart to think that we have to continue to boost to prevent infection [...] it's the last whack a mole.

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These data are however partly consistent with our European data (see section 5) where 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.



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?

A related question arises from an article(6) in the Wall Street Journal that suggest that FDA is excluding its own experts?

**SYNECHION** **Is FDA hiding gene therapy concerns in plain sight?**

- What are the risks of reverse transcription and delivery of process-derived DNA delivery?
- What is the nature of OTAT's Covid research?
- Why are OTAT and CTGTAC not publicly involved in C19 vax review?

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### FDA Shuts Out Its Own Experts in Authorizing Another Vaccine Booster

Decisions like this only reinforce the perception that Covid policy is driven by groupthink and politics.

By Marty Makary  
April 3, 2022 5:04 pm ET

Dr. Rubin: "hadn't seen enough data"  
Dr. Meissner: "an unanswered scientific question [...] normal immune system."  
Dr. Offit: "advised [...] son to forgo the *third* shot"

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The article quotes three members of FDA's VRBPAC.

Both Moderna and BioNTech expected to see their products regulated as gene therapies.

Moderna, Inc., acknowledged in their 2Q 2020 SEC filing(7)<sup>3</sup> thus "Currently, mRNA is considered a gene therapy product by the FDA." Further, the founder of BioNTech in a 2014 paper(1) stated "One would expect the classification of an mRNA drug to be a biologic, a gene therapy or a somatic cell therap

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.<sup>4</sup>)

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.

<sup>3</sup> 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](https://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](#).

<sup>4</sup> <https://trialsitenews.com/dr-david-wiseman-on-molnupiravir-and-fda-advisory-committee/>

**We need robust public debate: e.g. FDA-AMBAC**

**SYNECHION**

>> JAMES HILDRETH: Thank you, Dr. Baden. This is James Hildreth. I wanted to follow on to the question about the evolution even if it is very low. That this drug would induce an escaped mutant for which the vaccines we have would not cover. That would be catastrophic for the whole world, actually.

So do you have data that you can look at the likelihood of this happening. Please know that transversions as well as transitions are possible as clearly a real possibility that that could happen. So do you have sufficient data to estimate the likelihood of that event happening in your data

SET:

>> NICHOLAS KARTSONIS: So we don't. You know, but we've been able to share with you earlier today that at least proportionately we're not seeing an increase in the phase three population in terms of unusual spike variants being formed relative to placebo. And we will continue to collect

TENNESSEE

**JAMES E.K. HILDRETH, MD, PhD**  
PRESIDENT AND CHIEF EXECUTIVE OFFICER,  
REHARRY MEDICAL COLLEGE

U.S. FOOD & DRUG ADMINISTRATION

November 30, 2021: Antimicrobial Drugs Advisory Committee Meeting Announcement

[youtu.be/fr9ENSjT64M?t=14142](https://youtu.be/fr9ENSjT64M?t=14142)

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FDA's failure to inspire confidence in novel gene technology, as espoused in this slide below from OTAT, does not portend better pandemic management.

One of OTAT's stated roles is to "increase public confidence in and acceptance of novel technologies by addressing concerns."

As related to the Covid-19 vaccines, FDA is:

- NOT increasing public confidence
- NOT addressing gene therapy concerns of C19 vaccines
- NOT acknowledging C19 vaccines are gene therapies
- NOT affording the public informed consent about the nature and risks of the Covid-19 vaccines.

We need robust and transparent public debate of the kind we have seen at FDA's AMBAC committee when it discussed molnupiravir. Will OTAT insist on having the same debates within its CTGTAC committee?

**Summary**

**Roles of Research in OTAT:**

- Provide in-house, hands-on expertise in cutting-edge areas
- Facilitate product development by addressing challenges encountered and helping develop approaches, guidance
- Increase public confidence in and acceptance of novel technologies by addressing concerns

**FDA is:**

- NOT increasing public confidence
- NOT addressing gene therapy concerns of C19 vaccines
- NOT acknowledging C19 vaccines are gene therapies
- NOT affording the public informed consent

25

Additional details are provided below.

## 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,<sup>5</sup>

*“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.<sup>6</sup>

(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.(8) Both this and an earlier guidance (9) 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(7)<sup>7</sup> thus *“Currently, mRNA is considered a gene therapy product by the FDA.”* Further, the founder of BioNTech in a 2014 paper(1) stated *“One would expect the classification of an mRNA drug to be a biologic, a gene therapy or a somatic cell therapy.”*

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.”*(8) 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 (8) was made in FDA’s guidance on development of Covid-19 vaccines(10), 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-

<sup>5</sup> [www.fda.gov/combo-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research](http://www.fda.gov/combo-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research)

<sup>6</sup> [www.fda.gov/combo-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research](http://www.fda.gov/combo-products/jurisdictional-information/transfer-therapeutic-biological-products-center-drug-evaluation-and-research)

<sup>7</sup> 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](http://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](http://clinicaltrials.gov) and for J&J [Sept 7 2020](http://clinicaltrials.gov).

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 (11) or the genetic mRNA vaccines.(12)

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.(13)

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](#):<sup>8</sup> “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.<sup>9</sup> (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.*

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

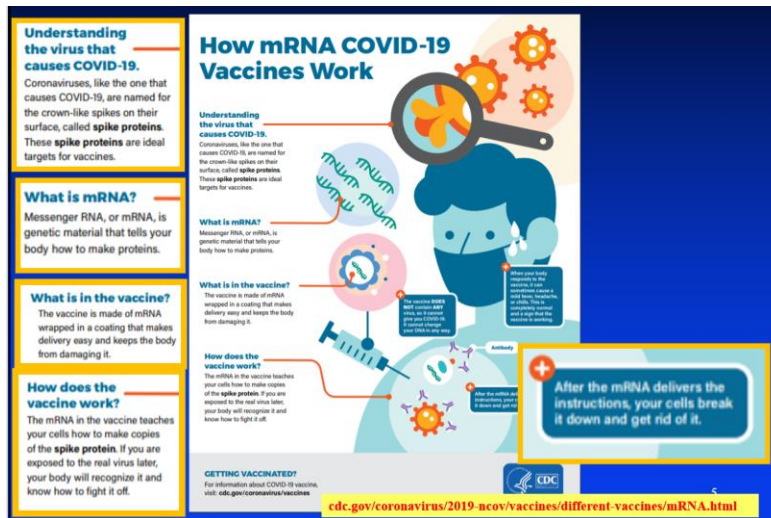
## 2.3. Nucleoside modified mRNA and human gene sequences

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.”

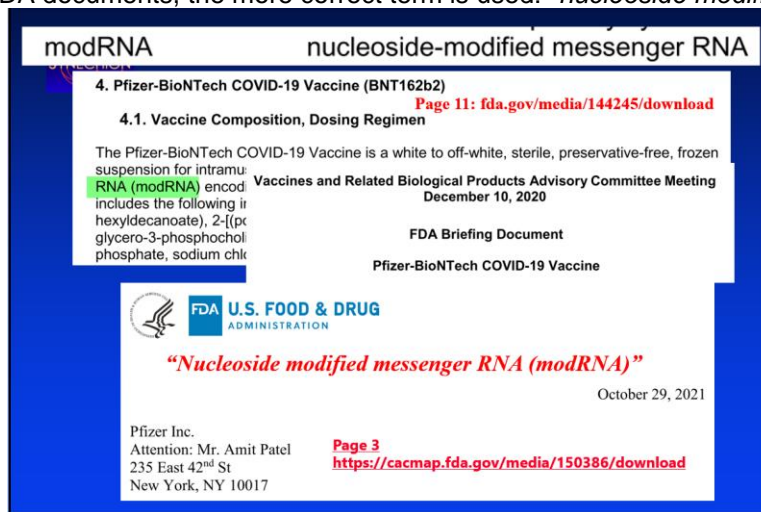
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<sup>8</sup> <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/facts.html>

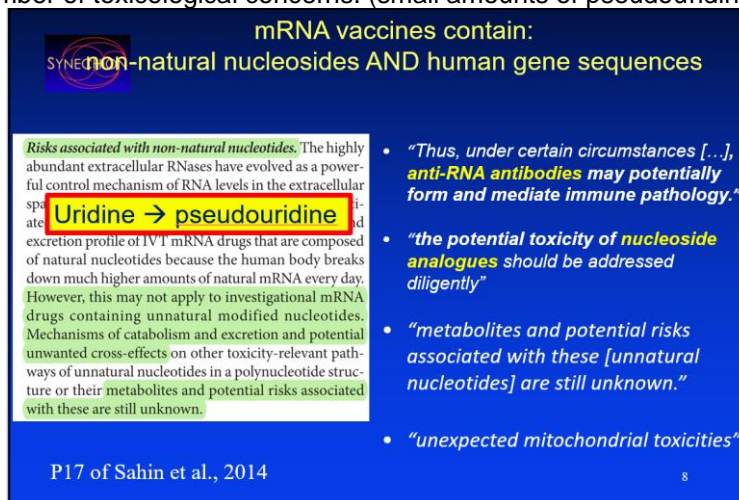
<sup>9</sup> [https://www.washingtonpost.com/video/washington-post-live/wplive/albert-bourla-on-why-mrna-technology-was-counterintuitive-in-producing-an-effective-vaccine/2022/03/10/c397ca8c-afaa-4254-b860-b2cca54b0ecf\\_video.html](https://www.washingtonpost.com/video/washington-post-live/wplive/albert-bourla-on-why-mrna-technology-was-counterintuitive-in-producing-an-effective-vaccine/2022/03/10/c397ca8c-afaa-4254-b860-b2cca54b0ecf_video.html)  
[https://www.youtube.com/watch?v=t9\\_YRw7jBF4](https://www.youtube.com/watch?v=t9_YRw7jBF4)



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**.”<sup>10</sup>



As is discussed by Dr. Sahin,<sup>(1)</sup> 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).



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).

<sup>10</sup> [www.fda.gov/media/150386/download](https://www.fda.gov/media/150386/download)

**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  $\alpha$ - and  $\beta$ -globin mRNAs that harbour several sequence elements that increase the stability and translation of mRNA<sup>30,45</sup>. The stabilizing effect of human  $\beta$ -globin 3'-UTR sequences is further augmented by using two human  $\beta$ -globin 3'-UTRs arranged in a head-to-tail orientation<sup>29</sup>. 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.<sup>(14)</sup> 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. (1) (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<sup>(3)</sup> 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](#),<sup>11</sup> 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 (15-25) 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. (26) Taken with reports of negative VE against Omicron described here (27,28) as well as the doubling of reports of herpes zoster in the Moderna trial,(29) the effect of the q-vaccines on medium to long term immune function must be fully characterized.

The labels for Spikevax(30) and Comirnaty(4) 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*”(30), something similar for lactation. Yet CDC still<sup>12</sup> 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(20) 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.

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<sup>11</sup> [https://phmp.org/wp-content/uploads/2022/03/125742\\_S1\\_M2\\_26\\_pharmkin-tabulated-summary.pdf](https://phmp.org/wp-content/uploads/2022/03/125742_S1_M2_26_pharmkin-tabulated-summary.pdf)

<sup>12</sup> <https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html>

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

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

Booster doses have not been authorized for 5–11-year-olds and their discussion is currently irrelevant to this case. Boosters have been authorized for those 12 years and over (with a 5-month dose interval), and may become authorized for younger children. Booster efficacy wanes just as rapidly as efficacy for the primary series, for both the BA.1 and BA.2 Omicron subvariants (see **Error! Reference source not found.**). An Israeli study found limited initial (Omicron) efficacy of the 3<sup>rd</sup> Pfizer booster of 53%, waning to 16.5% and 3.6% in three or four months respectively, well before FDA’s current boost interval of 5 months.(31) The marginal effectiveness of a 3<sup>rd</sup> dose vs. 2<sup>nd</sup> dose-only vaccinees was 29.1% at 3 months and 18.3% at 4 months.(31)


There discussion of a 4<sup>th</sup> dose (i.e. a second booster dose). Preliminary data from Israel using only a 4 month interval(32) 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%. (10,33) In this case, the confidence intervals indicate that negative efficacy is possible. Consistent with these data are other Israeli data for a 4<sup>th</sup> dose showing waning from 52.9% at one month to 2.6% at 4 months.(31)

Concerns have been expressed about a fourth dose(34) 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](#)<sup>13</sup> (Head of Biological Health Threats and Vaccines Strategy, EMA).

<sup>13</sup> [www.youtube.com/watch?v=OGz8MTPV5qs&t=238s](https://www.youtube.com/watch?v=OGz8MTPV5qs&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](https://ema.europa.eu/en/events/ema-regular-press-briefing-covid-19-12#event-summary-section)

Marco Cavaleri (Head of Biological Health Threats and Vaccines Strategy)




“i would like also to take the opportunity to again clarify our current position on multiple boosted doses the repeated administration of boosters with very short interval might reduce the level of antibodies that can be produced at each administration as our immune system needs a certain amount of time to mature the response to the antigens it is presented with so potentially making the vaccination a little bit less efficient over time ”

EMA regular press briefing on COVID-19  
Jan 18 2022

and by ACIP member [Dr. Sarah Long](#),<sup>14</sup> 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.

Sarah S. Long, MD



Professor of Pediatrics, Drexel University College of Medicine and Attending Physician, Infectious Diseases, St. Christopher's Hospital for Children, Philadelphia, Pennsylvania, Term: 12/24/2020 – 6/30/2024  
<https://youtu.be/8yIPhOJuX98?t=5208>

Dr. Long is board certified in pediatrics and pediatric infectious diseases and has over four decades of contributions to the field of pediatric infectious disease. She has served on numerous committees including as a standing member on the Vaccine and Related Biological Products Advisory Committee (VRBPAC) of the FDA and as a member of the American Academy of Pediatrics (AAP) Committee on Infectious Diseases.

Yes I still couldn't agree more with Dr Kimberlin that this is a hospitalization and death vaccine. Anything else we ask of it is over the top and although a booster dose may get that kind of antibody for a very short period of time that may give some protection against symptomatic infection, that will not last and it will probably get no protection against asymptomatic infection.

So I think that we are enamored of the Israeli study for instance showing where you know a decrease on infection rate and that's not what we're going to be able to accomplish.

However, on the other hand, we're right in the midst of this new phase where children are affected, and children are affected in large numbers, and that I think until we know, until we get past this peak with omicron I'm very much in favor of "should" boosting and that this will help us understand over time whether it does, if there will have been any protection against hospitalization and death for those who are otherwise fully vaccinated.

I think they have no information that that is happening, we do know what the antibody titers look like.

I think it will allow us to whack a mole for another month or two but this is not sustainable and its not smart to think that we have to continue to boost to prevent infection or mildly symptomatic infection, this is just not going to happen unless everybody gets omicron and we then transition to an endemic less severe disease. I'm in favor of "should" for this age group also, it's the last whack a mole.

ACIP  
Jan 5<sup>th</sup>  
2022

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

## 5. 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

<sup>14</sup> <https://youtu.be/8yIPhOJuX98?t=5208> ACIP member - Dr. Sarah Long, Prof Pediatrics, Drexel University.  
<https://youtu.be/8yIPhOJuX98?t=5208>

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(35) 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(36) as well as other estimates of waning vaccine effectiveness.(27,28,37,38) The latter disappear from their blood after week 20 post 1<sup>st</sup> 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% (10,33). According to studies from Denmark(28), Canada(27), USA (CDC) (38,39), and New York (40), 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 (35) 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 1<sup>st</sup> 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)

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

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) 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  $\beta_2$ s for the whole study period, was used to test for significant depletion or excess of positive  $\beta_2$ s, depletion indicating protective effects associated with boosters, and excess indicating adverse effects associated with boosters that increase all-cause mortality.

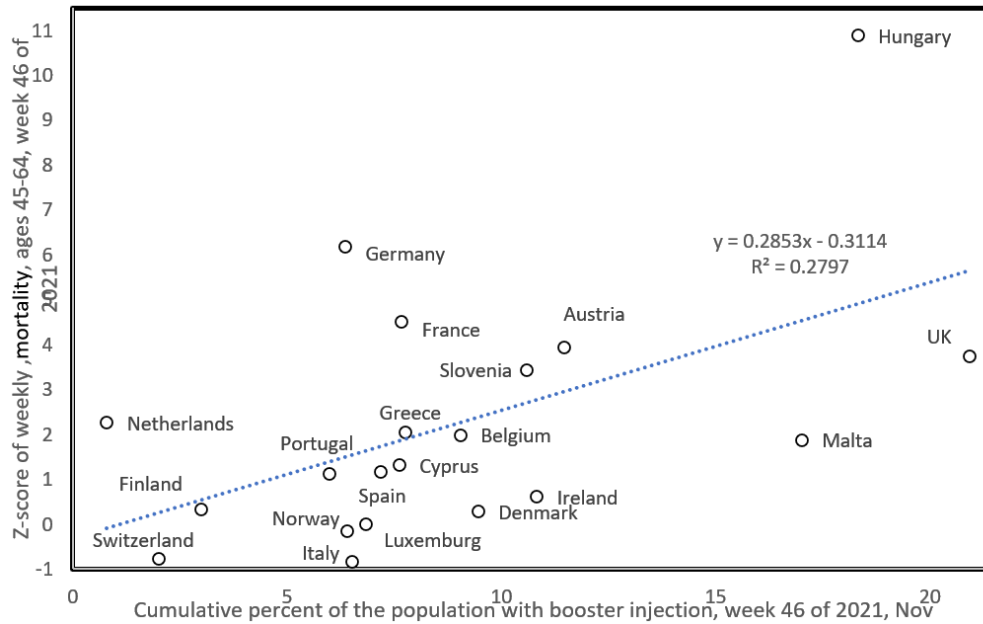
## Results

### 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.

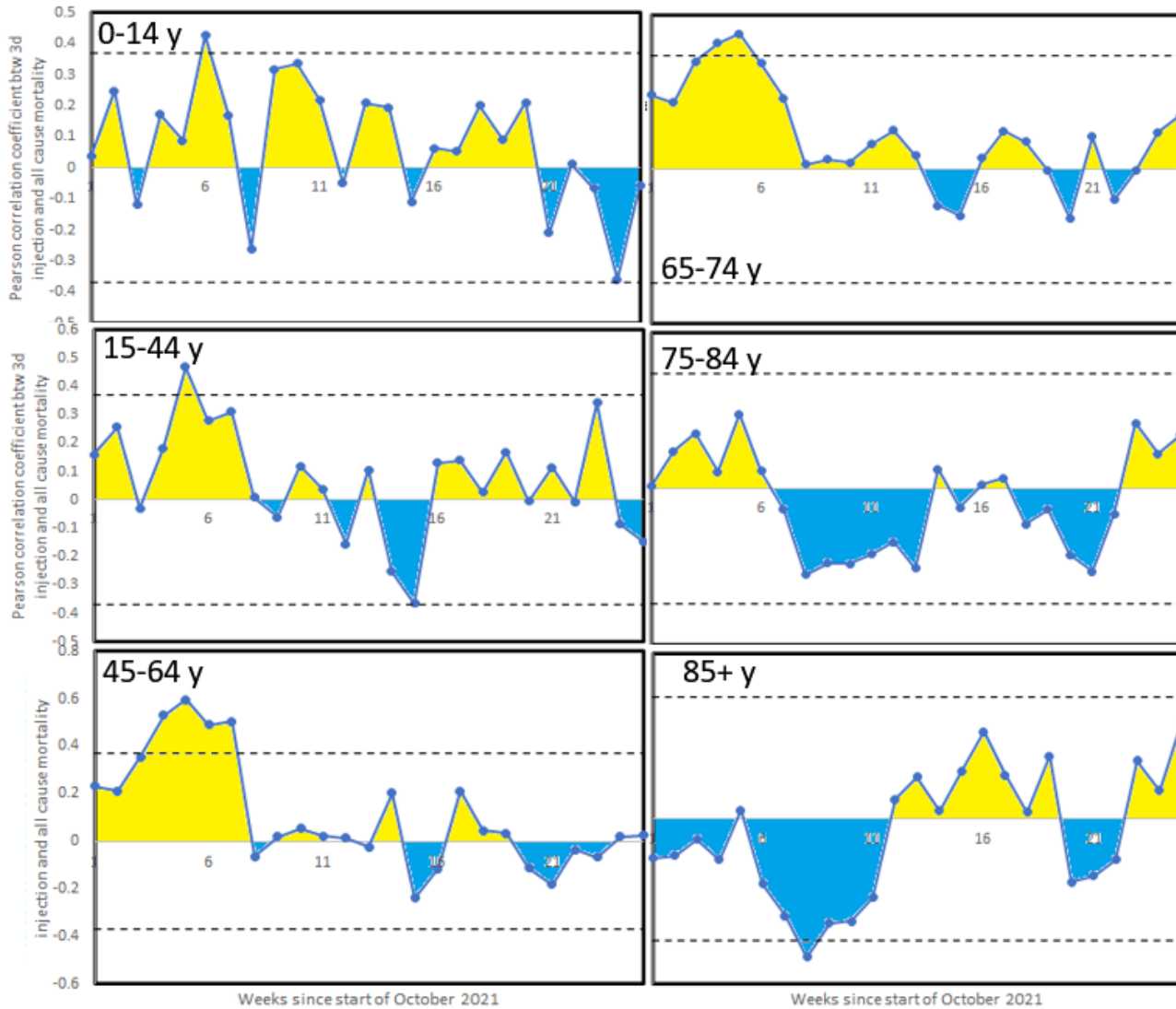
**Table 2: Weekly all-cause mortality and weekly cumulated percentage of individuals with booster injection (Euromomo)**

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 3<sup>rd</sup> 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

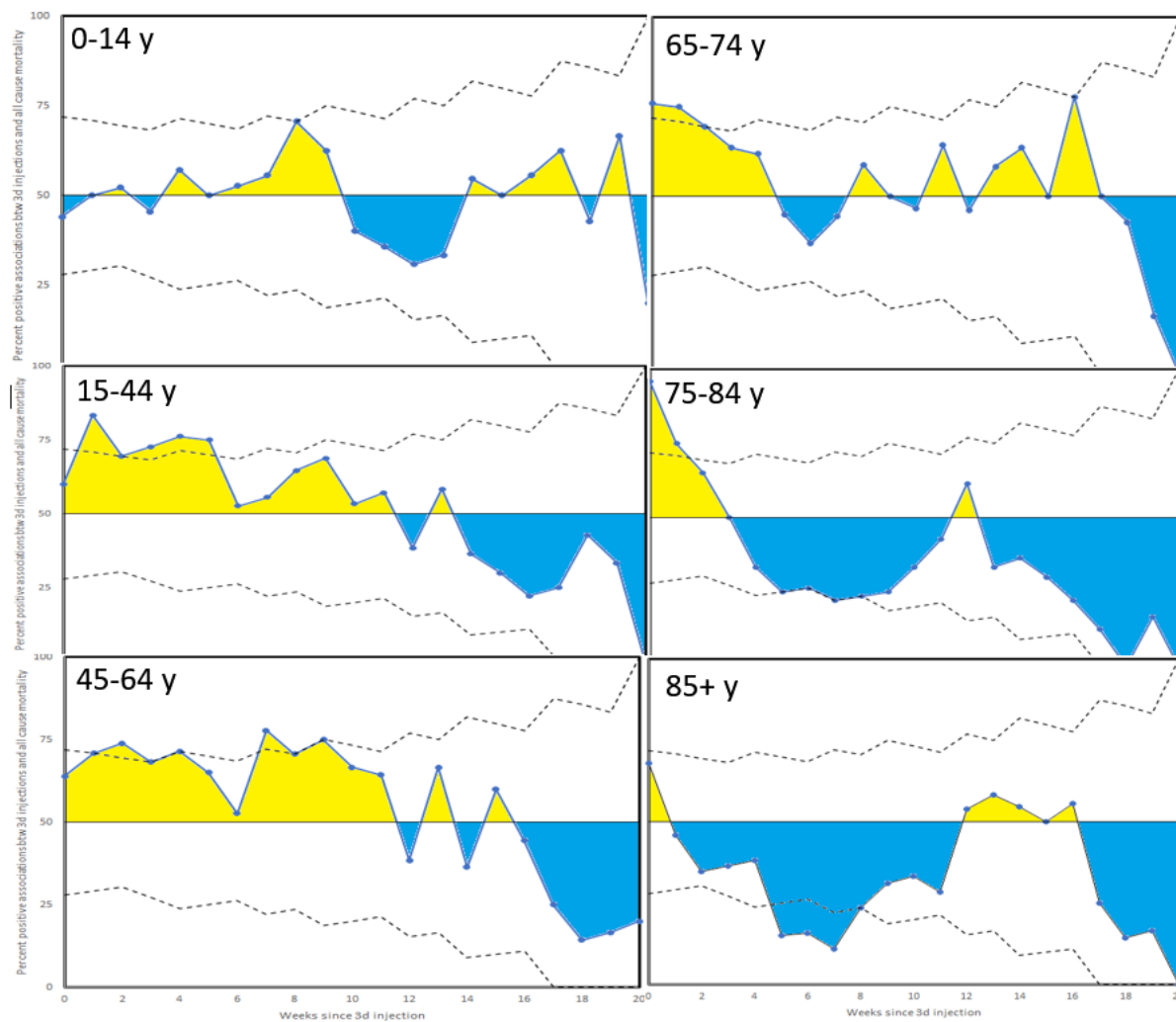


### European Dataset, lag analysis

**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 3<sup>rd</sup> 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 (35) 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.(41)

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

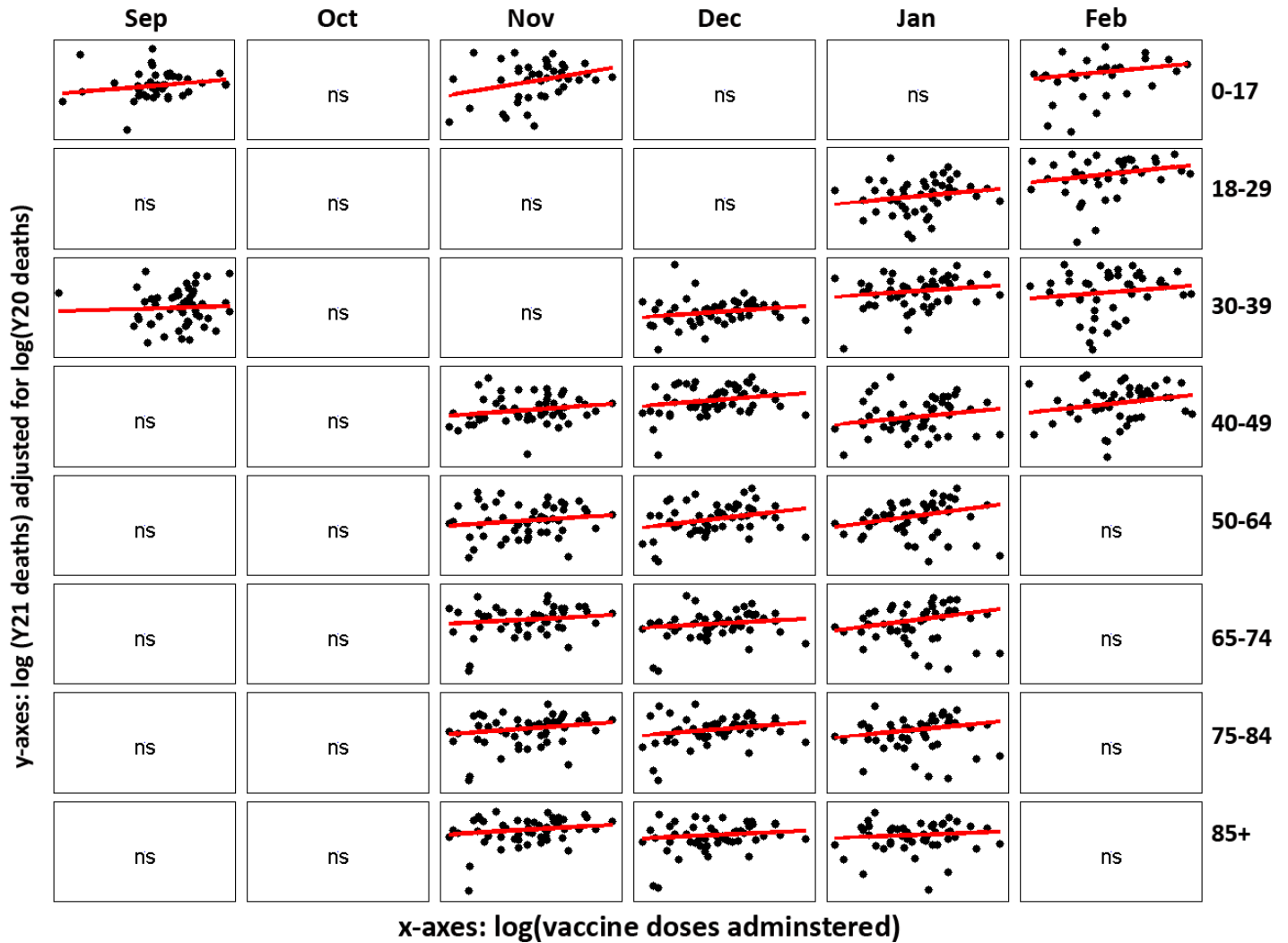
Ages	Sep, 21		Oct, 21		Nov, 21		Dec, 21		Jan, 22		Feb, 22	
	beta	pval	beta	pval	beta	pval	beta	pval	beta	pval	beta	pval
0-17	<b>0.154</b>	0.0234	<b>0.080</b>	0.2231	<b>0.236</b>	0.0001	<b>-0.006</b>	0.9400	<b>0.195</b>	0.0686	<b>0.420</b>	0.0032
18-29	<b>0.115</b>	0.0916	<b>-0.034</b>	0.6611	<b>0.035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

For each month and age group, beta weights and uncorrected p-values are listed for the vaccination term ( $\beta_2$ ) in the fitted equation:

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

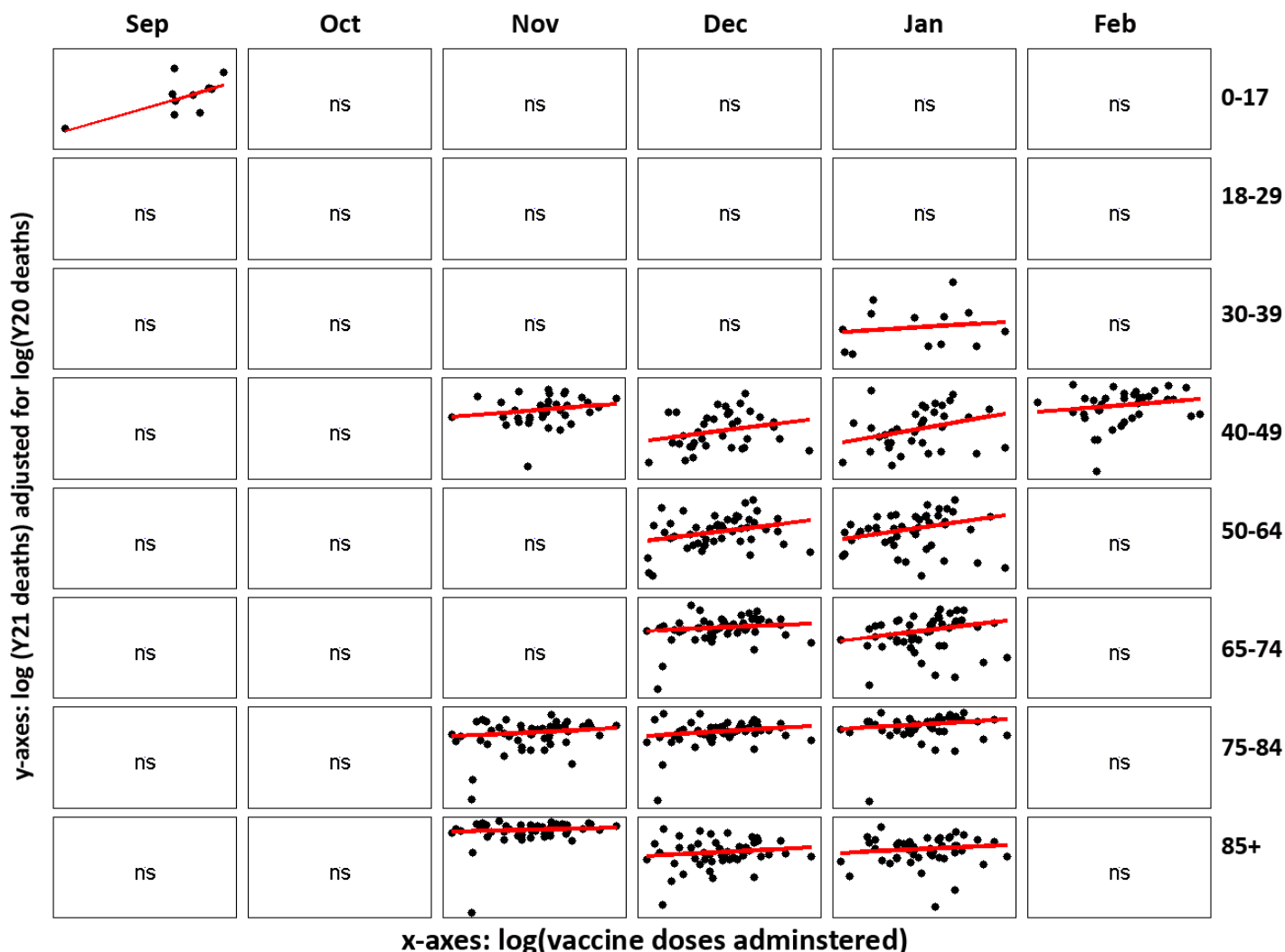
where Vax = vaccine doses administered previous or same month across all US states with available data for that month and age group (~42-52 states for each cell/regression, see Equation 1). Models were fitted using robust regression. Yellow indicates positive beta slopes with p-values < 0.05 FDR corrected. 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  $\beta_2$  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  $\beta_2$  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 (37) 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 4<sup>th</sup> dose (i.e. a second booster dose). Preliminary data from Israel using only a 4 month interval (32) 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%. (10,33) 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 4<sup>th</sup> dose showing waning from 52.9% at one month to 2.6% at 4 months.(31)

Concerns have been expressed about a fourth dose(34) 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](#)<sup>15</sup> (Head of Biological Health Threats and Vaccines Strategy, EMA). and by ACIP member [Dr. Sarah Long](#),<sup>16</sup> 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.(42)
- As cited in a Feb 20 2022 New York Times article, (43) 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: because,*” 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.(44)

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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<sup>15</sup> [www.youtube.com/watch?v=OGz8MTPV5qs&t=238s](http://www.youtube.com/watch?v=OGz8MTPV5qs&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](http://ema.europa.eu/en/events/ema-regular-press-briefing-covid-19-12#event-summary-section)

<sup>16</sup> <https://youtu.be/8ylPhOJuX98?t=5208> ACIP member - Dr. Sarah Long, Prof Pediatrics, Drexel University. <https://youtu.be/8ylPhOJuX98?t=5208>

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