https://www.humetrix.com/powerpoint-vaccine.html

Effectiveness of mRNA COVID-19 Vaccines Against the Delta Variant Among 5.6M Medicare Beneficiaries 65 Years and Older

Weekly update of September 28, 2021

huMETRIX®

Project Salus

JAIC

JAIC
Project Salus

Executive Summary

Basic questions which require data-driven answers

- Is vaccine effectiveness (VE) **waning** over time?
- Is VE **reduced** for the **Delta variant**?
- Does the need vary by **sub-population**?

Project Salus provides answers to these questions

- **VE of both mRNA vaccines appears to wane over time in this large 5.6M US-based 65 & over vaccinated cohort**
- **Risk of breakthrough hospitalization increases with time elapsed since mRNA vaccination with odds ratio increasing to 2.5 at 6 months post vaccination**
- **VE against Delta breakthrough hospitalization (62%) exceeds VE against Delta infection (41%)**
- **Prior COVID-19 infection has a major protective effect against breakthrough hospitalization**
- **Older age groups** (75-84 & 85 and older) **experienced further reduction in vaccine protection against hospitalization**
- **Hospitalization rate (21% vs 32%) and death rate (4% vs 12%) of breakthrough infections lower than rates observed in Covid-19 cases in pre-vaccination pandemic phase in 2020**

Graphic adapted from CDC Presentation ACIP Meeting August 30, 2021
Oliver, S. Framework for Booster Doses of COVID-19 Vaccines

huMETRIX

US 20210082583A1

(19) **United States**

(12) **Patent Application Publication**

EHRLICH et al.

(10) **Pub. No.: US 2021/0082583 A1**

(43) **Pub. Date: Mar. 18, 2021**

(54) **METHODS AND SYSTEMS OF PRIORITIZING TREATMENTS, VACCINATION, TESTING AND/OR ACTIVITIES WHILE PROTECTING THE PRIVACY OF INDIVIDUALS**

(71) Applicants: **Gal EHRLICH**, Ramat-Gan (IL); **Maier FENSTER**, Petach-Tikva (IL)

(72) Inventors: **Gal EHRLICH**, Ramat-Gan (IL); **Maier FENSTER**, Petach-Tikva (IL)

(21) Appl. No.: **17/106,279**

(22) Filed: **Nov. 30, 2020**

(30) **Foreign Application Priority Data**

Aug. 11, 2020	(IL)	276648
Aug. 11, 2020	(IL)	276665
Sep. 1, 2020	(IL)	277083

Publication Classification

(51) **Int. Cl.**

G16H 50/80	(2006.01)
H04W 4/02	(2006.01)
H04W 4/029	(2006.01)
G06N 7/00	(2006.01)
G16H 50/30	(2006.01)

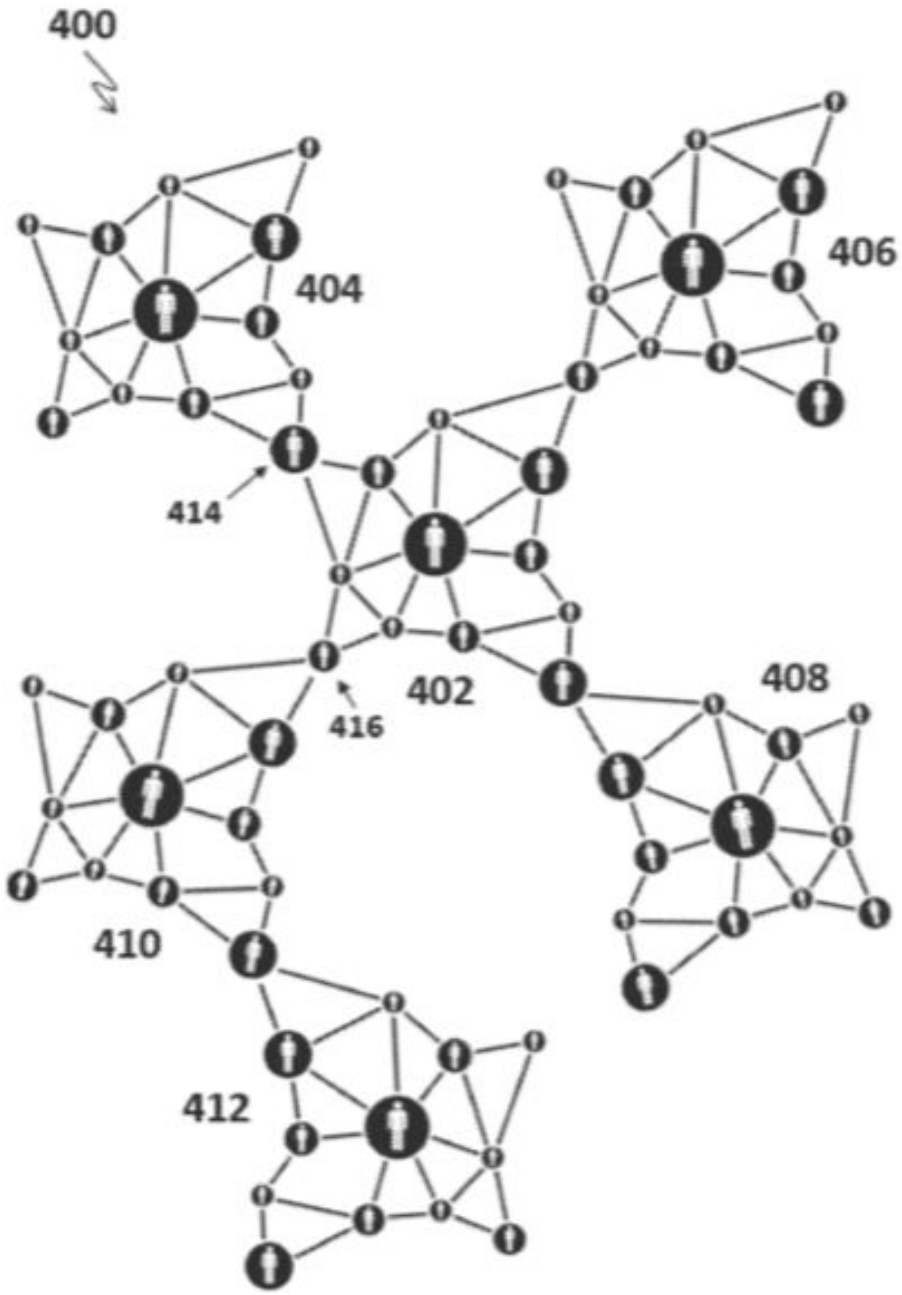
(52) **U.S. Cl.**

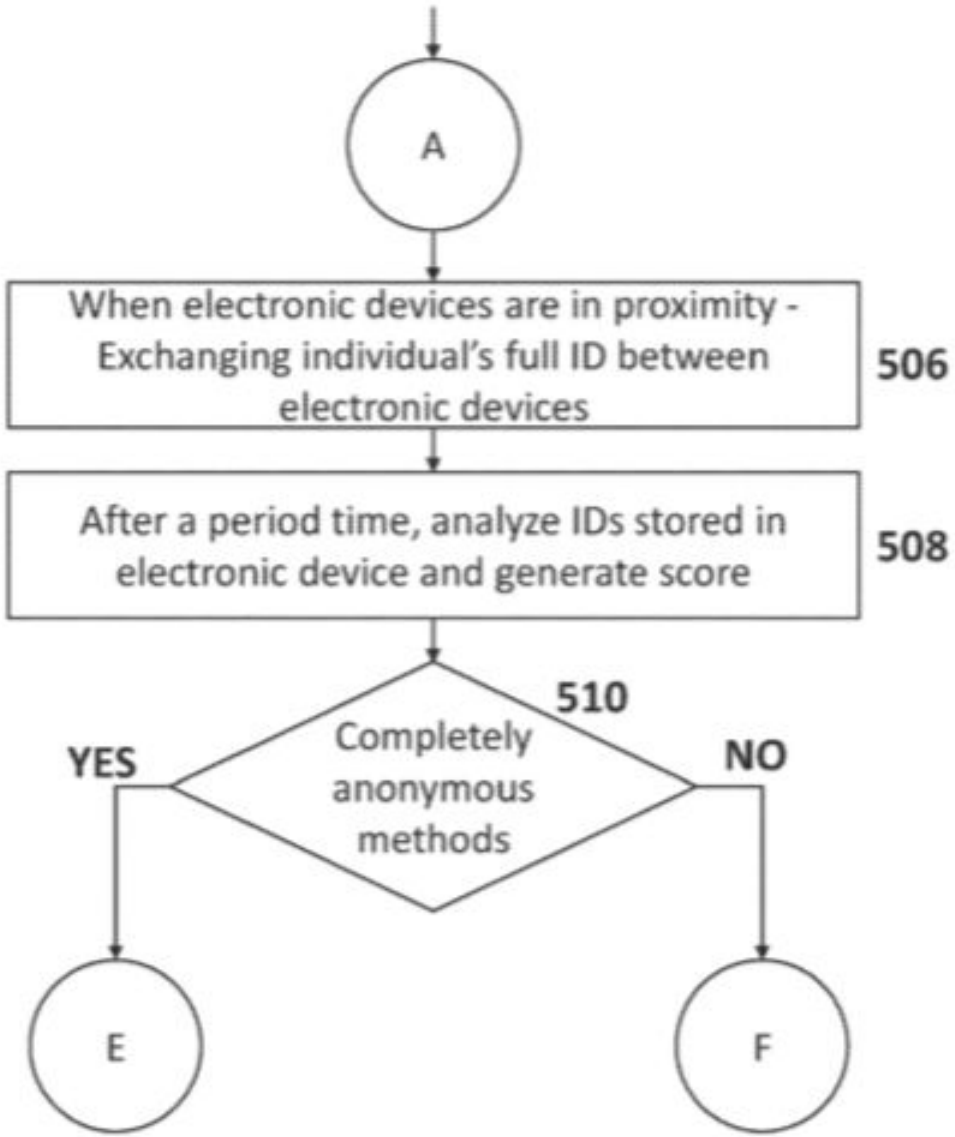
CPC ***G16H 50/80*** (2018.01); ***H04W 4/023*** (2013.01); ***G16H 50/30*** (2018.01); ***G06N 7/005*** (2013.01); ***H04W 4/029*** (2018.02)

(57) **ABSTRACT**

An aspect of some embodiments of the invention relates to system and methods for anonymously selecting subjects for treatment against an infectious disease caused by a pathogen, comprising: 1. a plurality of electronic devices configured with instructions to generate an ID, when in proximity of another such electronic device, one or both of transmit said ID to said another electronic device and receive an ID from said another electronic device, generating a score based on a plurality of such received IDs, receiving information from a server, displaying relevant treatment instructions to said subjects based on received information; 2. at least one server comprising instructions for sending to said plurality of electronic devices information to display said relevant treatment instructions; where said at least one server or said electronic devices comprise instructions to generate a prediction of likelihood of a subject transmitting said pathogen, based on a score of the subject.

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf





https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

Superspreader

[0352] In some embodiments, vaccines are all compounds as disclosed in in the website of the World Health Organization (https://www[dot]who[dot]int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines), which are all incorporated herein by reference, and which are optionally provided (e.g., as a kit) with software such as described herein and/or provided with instructions for use targeting potential super spreaders detected, for example, using methods and apparatus as described herein, and include the following:

28 candidate vaccines in clinical evaluation

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

COVID-19 Vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Admin-istration	Clinical Stage Phase 1	Phase 1/2	Phase 2	Phase 3
University of Oxford/ AstraZeneca	Non-Replicating Viral Vector	ChAdOx1-S	1		IM		PACTR 202006922165132 2020-001072-15 Interim Report	2020-001228-32	ISR CTN 89951424
Sinovac	Inactivated	Inactivated	2	0, 14 days	IM		NCT04383574 NCT04352608		NCT 04456595
Wuhan Institute of Biological Products/ Sinopharm	Inactivated	Inactivated	2	0, 14 or 0, 21 days	IM		Chi CTR 2000031809		Chi CTR 2000034780
Beijing Institute of Biological Products/ Sinopharm	Inactivated	Inactivated	2	0, 14 or 0, 21 days	IM		Chi CTR 2000032459		Chi CTR 2000034780
Moderna/ NIAID	RNA	LNP-encapsulated mRNA	2	0, 28 days	IM	NCT 04283461 Interim Report		NCT04405076	NCT04470427
BioNTech/ FosunPharma/ Pfizer	RNA	3 LNP-mRNAs	2	0, 28 days	IM		2020-001038-36 Chi CTR 2000034825		NCT 04368728
CanSino Biological Inc./Beijing Institute of Biotechnology	Non-Replicating Viral Vector	Adenovirus Type 5 Vector	1		IM	Chi CTR 2000030906 Study Report		Chi CTR 2000031781 Study Report	

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

COVID-19 Vaccine developer/ manufacturer	Vaccine platform	Type of candidate vaccine	Number of doses	Timing of doses	Route of Admin-istration	Clinical Stage Phase 1	Phase 1/2	Phase 2	Phase 3
Anhui Zhifei Longcom Bio-pharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Protein Subunit	Adjuvanted recombinant protein (RBD-Dimer)	2 or 3	0, 28 or 0, 28, 56 days	IM	NCT 04445194		NCT 04466085	
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	Inactivated	2	0, 28 days	IM	NCT 04412538	NCT 04470609		
Inovio Pharma-ceuticals/ International Vaccine Institute	DNA	DNA plasmid vaccine with electro-poration	2	0, 28 days	ID		NCT 04447781 NCT 04336410		
Osaka University/ AnGes/ Takara Bio	DNA	DNA plasmid vaccine + Adjuvant	2	0, 14 days	IM		NCT 04463472		
Cadila Healthcare Limited	DNA	DNA plasmid vaccine	3	0, 28, 56 days	ID		CTRI/ 2020/07/026352		
Genexine Consortium	DNA	DNA Vaccine (GX-19)	2	0, 28 days	IM		NCT 04445389		
Bharat Biotech	Inactivated	Whole-Virion Inactivated	2	0, 14 days	IM		NCT 04471519		
Janssen Pharma-ceutical Companies	Non-Replicating Viral Vector	Ad26COVS1	2	0, 56 days	IM		NCT 04436276		
Novavax	Protein Subunit	Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M	2	0, 21 days	IM		NCT 04368988		

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

-continued

Platform	Type of candidate vaccine	Developer	Coronavirus target	Current stage of clinical evaluation/ regulatory status- Coronavirus candidate	Same platform for non-Coronavirus candidates
DNA	DNA vaccine	Ege University	SARS-CoV2	Pre-Clinical	
DNA	DNA plasmid vaccine RBD&N	Scancell/University of Nottingham/ Nottingham Trent University	SARS-CoV2	Pre-Clinical	
DNA	DNA plasmid vaccine S, S1, S2, RBD&N	National Research Centre, Egypt	SARS-CoV2	Pre-Clinical	
DNA	DNA with electroporation	Karolinska Institute/Cobra Biologics (OPENCORONA Project)	SARS-CoV2	Pre-Clinical	
DNA	DNA with electroporation	Chula Vaccine Research Center	SARS-CoV2	Pre-Clinical	
DNA	DNA	Takis/Applied DNA Sciences/Evvivax	SARS-CoV2	Pre-Clinical	
DNA	Plasmid DNA, Needle-Free Delivery	Immunomic Therapeutics, Inc./EpiVax, Inc./PharmaJet	SARS-CoV2	Pre-Clinical	SARS
DNA	DNA vaccine	BioNet Asia	SARS-CoV2	Pre-Clinical	
DNA	msDNA vaccine	Mediphage Bioceuticals/University of Waterloo	SARS-CoV2	Pre-Clinical	
DNA	DNA vaccine	Entos Pharmaceuticals	SARS-CoV2	Pre-Clinical	
DNA	bacTRL-Spike	Symvivo	SARS-CoV2	Pre-Clinical	
Inactivated	Inactivated + alum	KM Biologics	SARS-CoV2	Pre-Clinical	JE, Zika
Inactivated	Inactivated	Selcuk University	SARS-CoV2	Pre-Clinical	
Inactivated	Inactivated	Erciyes University	SARS-CoV2	Pre-Clinical	
Inactivated	Inactivated whole virus	National Research Centre, Egypt	SARS-CoV2	Pre-Clinical	
Inactivated	Inactivated	Beijing Minhai Biotechnology Co., Ltd.	SARS-CoV2	Pre-Clinical	
Inactivated	TBD	Osaka University/ BIKEN/ NIBIOHN	SARS-CoV2	Pre-Clinical	

Electroporation is a **physical transfection method** that uses an electrical pulse to create temporary pores in cell membranes through which substances like nucleic acids can pass into cells.

https://www.thermofisher.com › home

Electroporation | Thermo Fisher Scientific - CA

Broadly defined, transfection is **the process of artificially introducing nucleic acids (DNA or RNA) into cells**, utilizing means other than viral infection.

https://www.thermofisher.com › home

Introduction to Transfection | Thermo Fisher Scientific - US

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

Dedicated Mandatory App

[0378] In some embodiments, in view of the pandemic, the government may order the citizens to install a dedicated application on their smartphones (or other smart devices like tablets, smart watches, smart glasses, etc.) to help the government with the logistics of the vaccination procedures. In some embodiments, the government (or other body) provides the public with such dedicated smart devices. In some embodiments, the app and/or the smart device is configured to inform on the user's location at all times and to communicate with adjacent smart devices (via Bluetooth for example) to assess the interactions between users, for example vicinity between users, movement of users, etc.). In

[0480]

	John Doe	Jane Smith	Mark Lite
Age (relative weight 1%)	30	35	33
Profession (relative weight 5%)	Teacher	Operator	Unemployed
Known health conditions (relative weight 4%)	None	Chronic coughing	None
Visits religious gathering (relative weight 20%)	No	Yes	Yes

[0482] In view of the results of the Weekly mobility data alone, the order of the treatments will be John Doe, Jane Smith and then Mark Lite.

[0483] The calculation of the overall score is:

criteria		John Doe	Jane Smith	Mark Lite
Age	1%	50	50	50
Profession	5%	80	50	0
Known health conditions	4%	0	90	0
Visits religious gathering	20%	0	80	80
Mobility data	70%	80	60	15
weighted scores	100%	60.5	66.2	14.2

[0484] As can be seen, when taking under consideration all the information data, the order of the treatments will be Jane Smith, John Doe and then Mark Lite.

[0485] It should be understood that the above numeric examples are just examples to help a person having skills in the art to understand the invention. It also should be understood that different weight values, scores and methods of calculating a score could be used.

procedure. In some embodiments, individual data arriving from each user is coupled with their health information (sick, vaccinated, recovered, etc.) to further assess the progression of the vaccination procedures and the efficacy of the vaccination procedure. Optionally, if the persons met by a user are vaccinated or otherwise determined to be immune, such contacts may not count and/or be weighted lower.

[0380] In some embodiments, the app will be also used to send personalized communication to the users, for example, to come and be vaccinated. In some embodiments, in view of the information received from the app, specific actions are taken, for example, send a communication to the user to enhance his awareness to behavioral rules during pandemic, to come and be vaccinated, to avoid certain locations, which are at high risk of contagion.

*"…send a communication to the user to **enhance his awareness to behavioral rules** during pandemic, **to come and be vaccinated**, to avoid certain locations, which are at high risk of contagion."*

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

Home > Department of the Premier and Cabinet > COVID-19 coronavirus: G2G Now frequently asked questions

What is G2G Now?

The G2G Now app is a tool that helps WA Police protect the community by conducting remote, virtual in-app checks on people in quarantine. The app uses facial verification technology and phone location data to ensure people in quarantine remain at their registered address throughout their quarantine period.

When users receive a push notification to check-in, they have a 5-minute window to take a photo of themselves. The app then matches the image and location with the person's registered details to ensure compliance with their quarantine direction.

How do I access the app?

Anyone with a smartphone can download and use the app. It takes less than 2 minutes to set up an account.

https://www.wa.gov.au/organisation/department-of-the-premier-and-cabinet/covid-19-coronavirus-g2g-now-frequently-asked-questions?fbclid=IwAR0WgFPfdYcclGzXmIzJYBn5G49lYLuhYPeo76V9byWuOFNFDKrz3nZm3oc

What if I'm sleeping/showering/gardening when I receive a check-in request and don't respond?

G2G Now is designed to make people's lives easier, not harder. If you miss your check-in window, you will be sent a second check-in request shortly after the first one.

If you miss this second request, the app will prompt you to give a reason. Police will then determine what further action, if any, is required, such as follow-up calls or a physical check-in.

I've missed my check-in window multiple times. Will I get fined?

If you miss your check-in window, the app will prompt you to give a reason. If this happens multiple times, or you do not provide a valid reason, Police may attend your address to check on your compliance with the quarantine direction given to you.

If you have travelled from a high risk jurisdiction and are over the age of 16, you are legally required to comply with instructions from the G2G Now app.

If you consistently fail to comply with check-in requests without a good reason, you may have committed an offence under the Emergency Management Act, which can result in fines of up to $50,000 and imprisonment.

https://www.wa.gov.au/organisation/department-of-the-premier-and-cabinet/covid-19-coronavirus-g2g-now-frequently-asked-questions?fbclid=IwAR0WgFPfdYcclGzXmIzJYBn5G49lYLuhYPeo76V9byWuOFNFDKrz3nZm3oc

Does the app track or record my location?

The app records your location at every check-in request only to validate that you are at your registered address. It does not track your location or movements at any other time.

I'm quarantining at the same address as my partner, but I'm asked to check in much more regularly than he is. Is there something wrong with my app?

G2G Now sends check-ins on randomised schedules and gives authorities the ability to individualise people's check-in requirements. It is not unusual for people to receive check-in requests at different times of the day or more than other people.

Will my photos only be used for this app and quarantine compliance purposes? Or will it be kept on Police records?

The information that is collected through the G2G Now app is collected for monitoring quarantine arrangements. It is not collected for general policing purposes.

The information will be stored and used only as permitted or required by law.

https://www.wa.gov.au/organisation/department-of-the-premier-and-cabinet/covid-19-coronavirus-g2g-now-frequently-asked-questions?fbclid=IwAR0WgFPfdYcclGzXmIzJYBn5G49lYLuhYPeo76V9byWuOFNFDKrz3nZm3oc

Exemplary Use of the System and Methods for Determining Who Will Receive a Certain Type of Vaccination

[0400] In some embodiments, during the development of vaccines for a certain disease, different vaccines comprising different vaccine potencies are developed. In some embodiments, vaccine potency is a quantitative measure of the specific ability of the vaccine product to achieve an intended biological effect defined in a suitable biological assay based on the attribute of the product that is linked to the relevant biological properties. In some embodiments, the system is used to identify which individuals will receive which types of vaccines in relation to their potency. For example, individuals that received and/or were identified as a high superspreading score by the system would be vaccinated with more potent vaccines, when compared with other individuals having lower superspreading scores. In some embodiments, those individuals having lower superspreading scores might either receive later a vaccination or receive a vaccine having a lower potency.

Vaccine POTENCY is Based on Super-Spreader BEHAVIOR

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

Healthcare Privacy: So private…
you may not even be informed if your health is at risk.

[0408] In some embodiments, the notification for getting treatment may or may not contain information regarding the results of the calculations. For example, an individual that was identified as a superspreader may or may not receive information about the fact that he/she was identified as such. In some embodiments, the potential advantage of not providing such information is to further enhance the privacy protection of the user. For example, an onlooker may not be able to tell if a user received a high score due to his own behavior, the behavior of those he meets and/or an underlying health condition, which may put them at higher risk.

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

[0004] Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It was first identified in December 2019 in Wuhan, Hubei, China, and has resulted in an ongoing pandemic. The first confirmed case has been traced back to 17 Nov. 2019 in Hubei. As of 6 August 2020, more than 18.7 million cases have been reported across 188 countries and territories, resu
deaths. More than 11.3 million
virus is primarily spread betw
tact, most often via small dro
sneezing, and talking. The drop
or onto surfaces rather than tra
distances. However, the tra
through smaller droplets that a
the air for longer periods of time in enclosed spaces, as typical for airborne diseases. Less commonly, people may become infected by touching a contaminated surface and then touching their face. It is most contagious during the first three days after the onset of symptoms, although spread is possible before symptoms appear, after they disappear and from people who show very mild or do not show symptoms at all.

It is most contagious during the first three days after the onset of symptoms, although spread is possible before symptoms appear, after they disappear and from people who show very mild or do not show symptoms at all.

[0409] In some embodiments, dedicated codes, for example in the form of coupons, will be provided to individuals having important/relevant professions (like doctors, police, etc.). In some embodiments, insertion of the codes into their personal electronic devices will inform the system that that encrypted/anonymized user needs a correction in their score. In some embodiments, the correction can be either increasing the score or decreasing the score. In some embodiments, when the electronic device detects certain behavior, like an increase in the movements of the user, the electronic device (for example via the dedicated app) will warn the user that his score will be changed if the behavior is not changed. In some embodiments, changing the score can be either increasing or decreasing the score.

Warning Notices and Coupon Codes

Profession in Record of the Individual

[0361] In some embodiments, the profession of the individual is correlated with a potential number of people the person might be in contact with during a regular day of operation. In some embodiments, individuals that potentially must meet many people due to their profession will receive a high score. For example, cashiers at the supermarket, vendors in markets, bus drivers, delivery people, technicians, librarians, etc. In some embodiments of the invention, the profession information is used to estimate a contact quality score, for example, doctors being more careful with PPE than teachers. It is a particular feature of some embodiments of the invention, that differences within such a group, such as between different doctors, are determined. In some embodiments of the invention, a subject's score is modified according to the profession, for example, to compensate for criticality of the subject and/or to lack of control of the subject (e.g., a bus driver) over number of contacts.

"…must meet many people due to their profession will receive a high score. For example, cashiers at the supermarket, market, vendors in markets, bus drivers, delivery people, technicians, librarians, etc."

"…a subject's score is modified according to profession…to compensate for criticality of the subject."

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

[0006] A research article by Straetemans et. al. called "*Prioritization strategies for pandemic influenza vaccine in 27 countries of the European Union and the Global Health Security Action Group: a review*" discussed vaccine prioritization strategies during pandemic times, but its conclusions are limited to the critical groups, for example, health care providers (e.g., doctors, nurses, laboratories, hospitals, etc.), essential service providers (e.g., police, fire fighters, public sector personnel, governmental personnel, etc.) and high risk individuals (e.g., people with high risk of complications, pregnant women, children, etc.). These obvious groups usually amount to less than 2-10% of the total population, which still leaves the government with the question of what is the best order to vaccinate the rest of the population, namely prioritizing vaccinations.

2007: Vaccine Prioritization Strategies for 27 Countries of the EU and Global Health Security Action Group:

- Healthcare providers
- Essential service providers
- Police
- Firefighters
- Government personnel
- High Risk Complications
- Pregnant women
- Children

https://patentimages.storage.googleapis.com/04/24/12/7c8e8238f4ae9d/US20210082583A1.pdf

https://pubmed.ncbi.nlm.nih.gov/17825095/

Lynne Parker

Director of the National Artificial Intelligence Initiative Office - The White House

OECD.AI Policy Observatory

Korean delegation AI event – The OECD Principles on Artificial Intelligence, Progress over the Past Two years and Future Directions

October 4, 2021 1:40PM to 4:05PM

OR EN FR

To Advance Trustworthy Ai and Prioritize Training of an Ai Ready Workforce

"We must prepare the future and the present US workforce for integration of Ai systems across all sectors of the economy and society."

*"Our goal is to **fill the Ai talent gap** and **prepare US workers for jobs of the future by implementing policies that ensure a diverse, inclusive and knowledgeable workforce**. We would like to see the integration of Ai related concepts of schooling, from kindergarten, and even pre-kindergarten through doctoral positions, including community colleges…"*

32:52 VIDEO START
https://oecdtv.webtv-solution.com/6c38401bbfabe96c963ede85620cab98/or/Korean-delegation-AI-event-The-OECD-Principles-on-Artificial-Intelligence-Progress-over-the-Past-Two-years-and-Future-Directions.html

July 7. 2020 – Moderna's Patent

Lipid Nanoparticles (LNPs) for mRNA Vaccines

(57) **ABSTRACT**

A pharmaceutical composition which has a plurality of lipid nanoparticles that has a mean particle size of between 80 nm and 160 nm and contains a modified mRNA encoding a polypeptide. The lipid nanoparticles include a cationic lipid, a neutral lipid, a cholesterol, and a PEG lipid. The mRNA contains a 5'-cap, 5'-UTR, N1-methyl-pseudouridine, a 3'-UTR, and a poly-A region with at least 100 nucleotides.

https://www.modernatx.com/sites/default/files/US10703789.pdf

US010703789B2

(12) **United States Patent**
De Fougerolles et al.

(10) **Patent No.: US 10,703,789 B2**
(45) **Date of Patent: *Jul. 7, 2020**

(54) **MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF SECRETED PROTEINS**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Antonin De Fougerolles**, Waterloo (BE); **Justin Guild**, Framingham, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/438,978**

(22) Filed: **Jun. 12, 2019**

(65) **Prior Publication Data**

US 2020/0017565 A1 Jan. 16, 2020

Related U.S. Application Data

(63) Continuation of application No. 14/987,328, filed on Jan. 4, 2016, now Pat. No. 10,385,106, which is a (Continued)

(51) **Int. Cl.**

A61K 48/00	(2006.01)
A61K 38/17	(2006.01)
A61K 47/54	(2017.01)
A61K 9/127	(2006.01)
C07K 14/535	(2006.01)
C12N 15/88	(2006.01)
A61K 9/50	(2006.01)
C07K 14/47	(2006.01)
A61K 31/7088	(2006.01)
C07K 19/00	(2006.01)
C12N 15/85	(2006.01)
A61K 38/18	(2006.01)
A61K 38/19	(2006.01)
A61K 38/48	(2006.01)
A61K 9/14	(2006.01)
A61K 47/10	(2017.01)
A61K 38/21	(2006.01)
A61K 38/36	(2006.01)
A61K 38/44	(2006.01)
A61K 39/395	(2006.01)

(Continued)

(52) **U.S. Cl.**

CPC ***C07K 14/535*** (2013.01); ***A61K 9/1271*** (2013.01); ***A61K 9/1272*** (2013.01); ***A61K 9/1277*** (2013.01); ***A61K 9/14*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/7088*** (2013.01); ***A61K 38/1767*** (2013.01); ***A61K 38/1816*** (2013.01); ***A61K 38/1866*** (2013.01); ***A61K 38/191*** (2013.01); ***A61K 38/193*** (2013.01); ***A61K 38/212*** (2013.01); ***A61K 38/215*** (2013.01); ***A61K 38/36*** (2013.01); ***A61K 38/363*** (2013.01); ***A61K 38/44*** (2013.01); ***A61K 38/4833*** (2013.01); ***A61K 38/4846*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/54*** (2017.08); ***A61K 47/542*** (2017.08); ***A61K 48/0033*** (2013.01); ***A61K 48/0066*** (2013.01); ***A61K 48/0075*** (2013.01); ***C07K 14/47*** (2013.01); ***C07K 14/475*** (2013.01); ***C07K 14/505*** (2013.01); ***C07K 14/525*** (2013.01); ***C07K 14/56*** (2013.01); ***C07K 14/565*** (2013.01); ***C07K 14/745*** (2013.01); ***C07K 14/75*** (2013.01); ***C07K 16/2887*** (2013.01); ***C07K 16/32*** (2013.01); ***C07K 19/00*** (2013.01); ***C12N 9/0069*** (2013.01); ***C12N 9/644*** (2013.01); ***C12N 15/85*** (2013.01); ***C12N 15/88*** (2013.01); ***C12Y 113/12007*** (2013.01); ***C12Y 304/21005*** (2013.01); ***C12Y 304/21022*** (2013.01); ***A61K 9/0019*** (2013.01); ***A61K 48/00*** (2013.01); ***C12N 2840/00*** (2013.01)

(58) **Field of Classification Search**

CPC C07H 21/02; C12N 15/67; C12N 15/11

See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,489,677 A	2/1996	Sanghvi et al.
5,591,722 A	1/1997	Montgomery et al.

(Continued)

FOREIGN PATENT DOCUMENTS

CA	2028849 A1	9/1991
CA	2473135 A1	6/2003

(Continued)

OTHER PUBLICATIONS

Anderson et al., "Incorporation of pseudouridine into mRNA enhances translation by diminishing PKR activation," Nucleic Acids Res. 38(17):5884-92 (2010).

(Continued)

Primary Examiner — Antonio Galisteo Gonzalez
(74) *Attorney, Agent, or Firm* — Clark & Elbing LLP

(57) **ABSTRACT**

A pharmaceutical composition which has a plurality of lipid nanoparticles that has a mean particle size of between 80 nm and 160 nm and contains a modified mRNA encoding a polypeptide. The lipid nanoparticles include a cationic lipid, a neutral lipid, a cholesterol, and a PEG lipid. The mRNA contains a 5'-cap, 5'-UTR, N1-methyl-pseudouridine, a 3'-UTR, and a poly-A region with at least 100 nucleotides.

14 Claims, 14 Drawing Sheets

Specification includes a Sequence Listing.

In another embodiment, the polynucleotides, primary constructs, or the mmRNA may be encapsulated into a lipid nanoparticle or a rapidly eliminated lipid nanoparticle and the lipid nanoparticles or a rapidly eliminated lipid nanoparticle may then be encapsulated into a polymer, hydrogel and/or surgical sealant described herein and/or known in the art. As a non-limiting example, the polymer, hydrogel or surgical sealant may be PLGA, ethylene vinyl acetate (EVAc), poloxamer, GELSITE® (Nanotherapeutics, Inc. Alachua, Fla.), HYLENEX® (Halozyme Therapeutics, San Diego Calif.), surgical sealants such as fibrinogen polymers (Ethicon Inc. Cornelia, Ga.), TISSELL® (Baxter International, Inc Deerfield, Ill.), PEG-based sealants, and COSEAL® (Baxter International, Inc Deerfield, Ill.).

In another embodiment, the lipid nanoparticle may be encapsulated into any polymer known in the art which may form a gel when injected into a subject. As another non-limiting example, the lipid nanoparticle may be encapsulated into a polymer matrix which may be biodegradable.

In one embodiment, the polynucleotide, primary construct, or mmRNA formulation for controlled release and/or targeted delivery may also include at least one controlled release coating. Controlled release coatings include, but are not limited to, OPADRY®, polyvinylpyrrolidone/vinyl acetate copolymer, polyvinylpyrrolidone, hydroxypropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose, EUDRAGIT RL®, EUDRAGIT RS® and cellulose derivatives such as ethylcellulose aqueous dispersions (AQUACOAT® and SURELEASE®).

In one embodiment, the controlled release and/or targeted delivery formulation may comprise at least one degradable polyester which may contain polycationic side chains. Degradeable polyesters include, but are not limited to, poly(serine ester), poly(L-lactide-co-L-lysine), poly(4-hydroxy-L-proline ester), and combinations thereof. In another embodiment, the degradable polyesters may include a PEG conjugation to form a PEGylated polymer.

Sustained Release of Compound/Biological Agent May be Programmed over Hours, Days, Weeks, Months or Years

In one embodiment, therapeutic nanoparticle may be formulated for sustained release. As used herein, "sustained release" refers to a pharmaceutical composition or compound that conforms to a release rate over a specific period of time. The period of time may include, but is not limited to, hours, days, weeks, months and years. As a non-limiting example, the sustained release nanoparticle may comprise a polymer and a therapeutic agent such as, but not limited to, the polynucleotides, primary constructs, and mmRNA of the present invention (see International Pub No. 2010075072 and US Pub No. US20100216804, US20110217377 and US20120201859, each of which is herein incorporated by reference in their entirety).

https://www.modernatx.com/sites/default/files/US10703789.pdf

US 20100216804A1

(19) **United States**

(12) **Patent Application Publication**

Zale et al.

(10) **Pub. No.: US 2010/0216804 A1**

(43) **Pub. Date: Aug. 26, 2010**

(54) **LONG CIRCULATING NANOPARTICLES FOR SUSTAINED RELEASE OF THERAPEUTIC AGENTS**

(76) Inventors: **Stephen E. Zale**, Hopkinton, MA (US); **Greg Troiano**, Pembroke, MA (US); **Mir M. Ali**, Woburn, MA (US); **Jeff Hrkach**, Lexington, MA (US); **James Wright**, Lexington, MA (US); **Susan Low**, Cambridge, MA (US)

Correspondence Address:
GOODWIN PROCTER LLP
PATENT ADMINISTRATOR
53 STATE STREET, EXCHANGE PLACE
BOSTON, MA 02109-2881 (US)

(21) Appl. No.: **12/638,297**

(22) Filed: **Dec. 15, 2009**

Related U.S. Application Data

(60) Provisional application No. 61/122,479, filed on Dec. 15, 2008, provisional application No. 61/249,022, filed on Oct. 6, 2009, provisional application No. 61/260,200, filed on Nov. 11, 2009.

Publication Classification

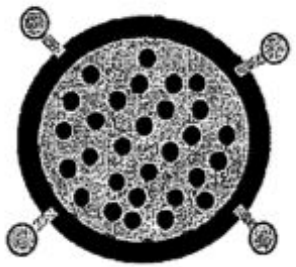
(51) **Int. Cl.**

A61K 9/14	(2006.01)
A61K 31/337	(2006.01)
A61K 31/4745	(2006.01)
A61K 31/519	(2006.01)
A61K 31/436	(2006.01)
A61P 35/00	(2006.01)

(52) **U.S. Cl.** **514/249**; 514/449; 514/283; 977/773;

(57) **ABSTRACT**

The present disclosure is directed in part to a biocompatible nanoparticle composition comprising a plurality of non-colloidal long circulating nanoparticles, each comprising a α-hydroxy polyester-co-polyether and a therapeutic agent, wherein such disclosed compositions provide a therapeutic effect for at least 12 hours.



Targeting poly(lactide-*b*-ethylene glycol) (PLA-PEG-lys(urea)glu)

Poly(lactide-*b*-ethylene glycol) (PLA-PEG)

Poly(lactide) (PLA)

Docetaxel

One of the Therapeutic Examples in Patent

https://patentimages.storage.googleapis.com/25/ce/6d/84cb16adb713b2/US20100216804A1.pdf

Docetaxel

What is DOCETAL? A Therapeutic Example in Patent

Drug type: Docetaxel is an anti-cancer ("antineoplastic" or "cytotoxic") chemotherapy drug. This medication is classified as a "plant alkaloid," a "taxane" and an "antimicrotubule agent." (For more detail, see "How this drug works" section below).

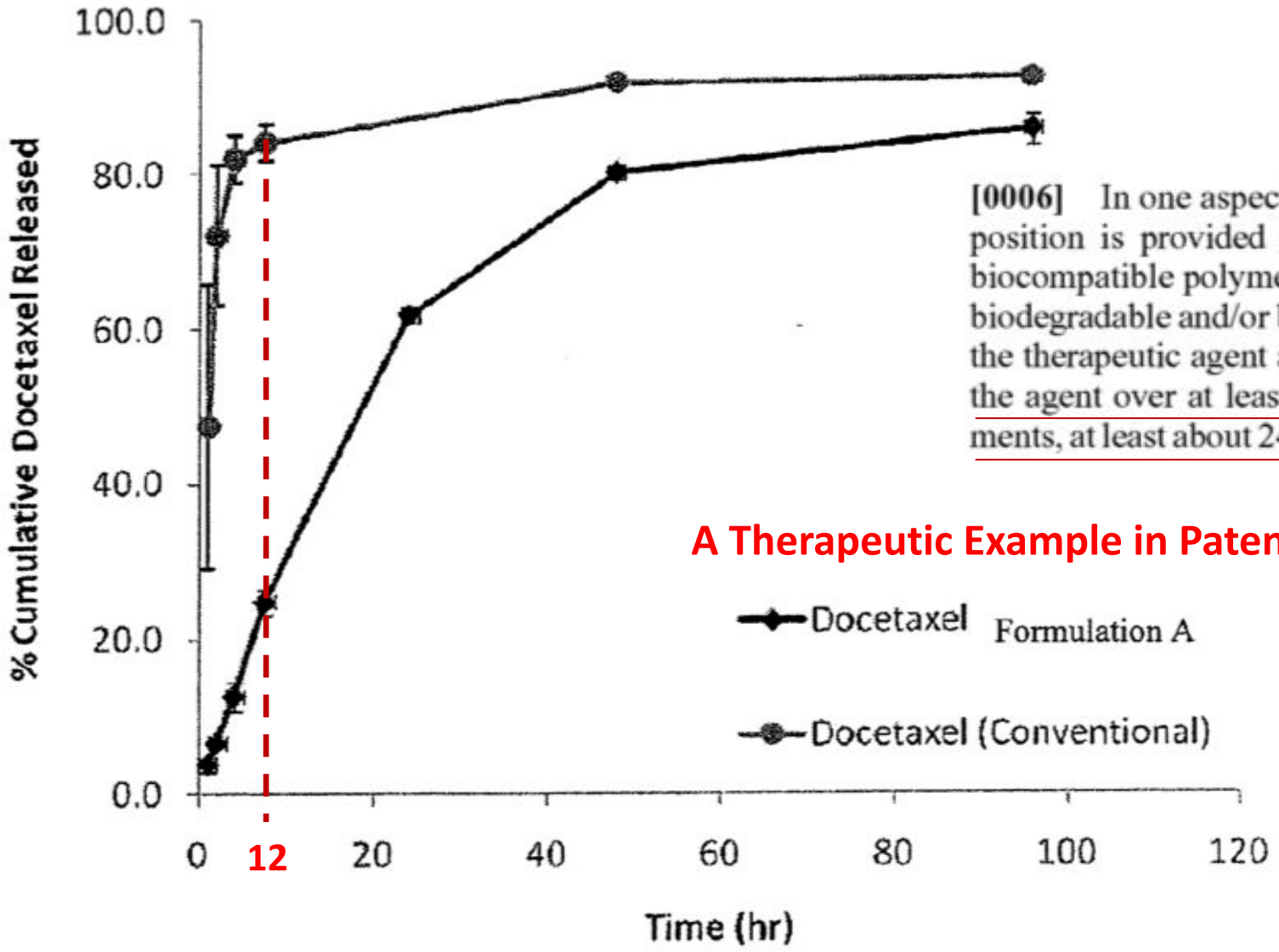
Note: If a drug has been approved for one use, physicians may elect to use this same drug for other problems if they believe it may be helpful.

The following side effects are common (occurring in greater than 30%) for patients taking docetaxel:

- Low white blood cell count. (This can increase your risk for infection)
- Low red blood cell count (anemia)
- Fluid retention with weight gain, swelling of the ankles or abdominal area.
- Peripheral neuropathy (numbness in your fingers and toes) may occur with repeated doses.
- Nausea
- Diarrhea
- Mouth sores
- Hair loss
- Fatigue and weakness
- Infection

https://chemocare.com/chemotherapy/drug-info/docetaxel.aspx

80% of chemotherapy is released in 12 -24hrs, and then a minimal sustained release over next 4 days



[0006] In one aspect of the invention, a nanoparticle composition is provided that includes a biodegradable and/or biocompatible polymer and a therapeutic agent, wherein the biodegradable and/or biocompatible polymer matrix releases the therapeutic agent at a rate allowing controlled release of the agent over at least about 12 hours, or in some embodiments, at least about 24 hours For example, provided herein is

A Therapeutic Example in Patent

https://patentimages.storage.googleapis.com/25/ce/6d/84cb16adb713b2/US20100216804A1.pdf

DETAILED DESCRIPTION

[0030] It is to be understood that the invention is not limited to the particular processes, compositions, or methodologies described, as these may vary. It is also to be understood that the terminology used in the description is for the purpose of describing particular versions or embodiments only and is not intended to limit the scope of the invention. All of the publi-

Circular Nanoparticles Can Deliver Drugs, Gene Therapies, or Toxic Immune Therapies, i.e. Chemotherapy, or be used for Medical Diagnosis

[0046] Disclosed nanoparticles can be used for a variety of applications, such as, without limitation, drug delivery, gene therapy, medical diagnosis, and for medical therapeutics for cancer, pathogen-borne diseases, hormone-related diseases, reaction-by-products associated with organ transplants, and other abnormal cell or tissue growth.

https://chemocare.com/chemotherapy/drug-info/docetaxel.aspx

Circular Nanoparticles Can Have Biomarkers to Target Specific Areas, i.e. Ovaries, Heart, Prostate, et al.

[0074] Disclosed nanoparticles may include optional targeting moieties, which may be selected to ensure that the nanoparticles selectively attach to, or otherwise associate with, a selected marker or target. For example, in some embodiments, disclosed nanoparticles may be functionalized with an amount of targeting moiety effective for the treatment of prostate cancer in a subject (e.g., a low-molecular weight PSMA ligand). Through functionalization of nanoparticle surfaces with such targeting moieties, the nanoparticles are effective only at targeted sites, which minimizes adverse side effects and improves efficacy. Targeted delivery also allows for the administration of a lower dose of therapeutic agent, which may reduce undesirable side effects commonly associated with traditional treatments of disease.

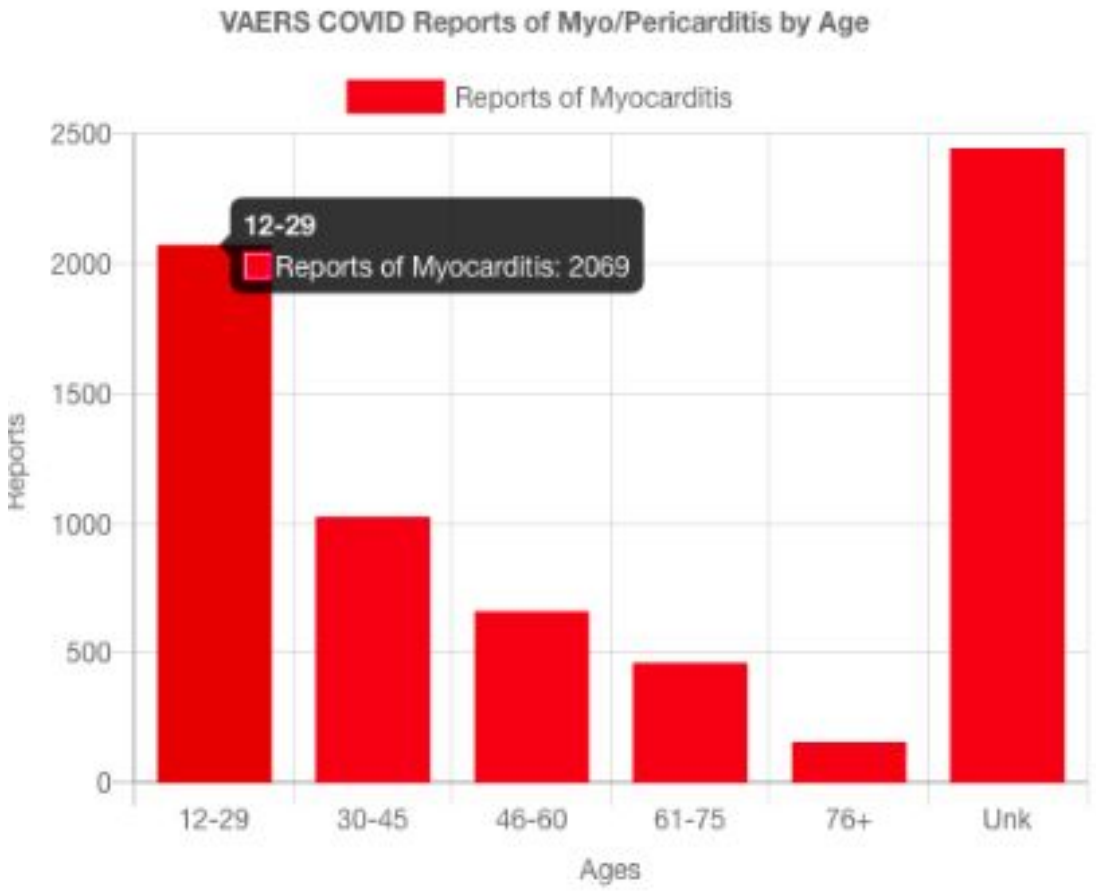
https://chemocare.com/chemotherapy/drug-info/docetaxel.aspx

VAERS COVID Vaccine

miFiGHT

September 17, 2021

Myo/Pericarditis



Myo/Pericarditis Reports post COVID 19 Vaccine VS. All Flu Vaccines

AGE	FLU REPORTS 20 YRS.	COVID19 REPORTS
6-18	16	908
19-29	61	1,161
30-39	28	700

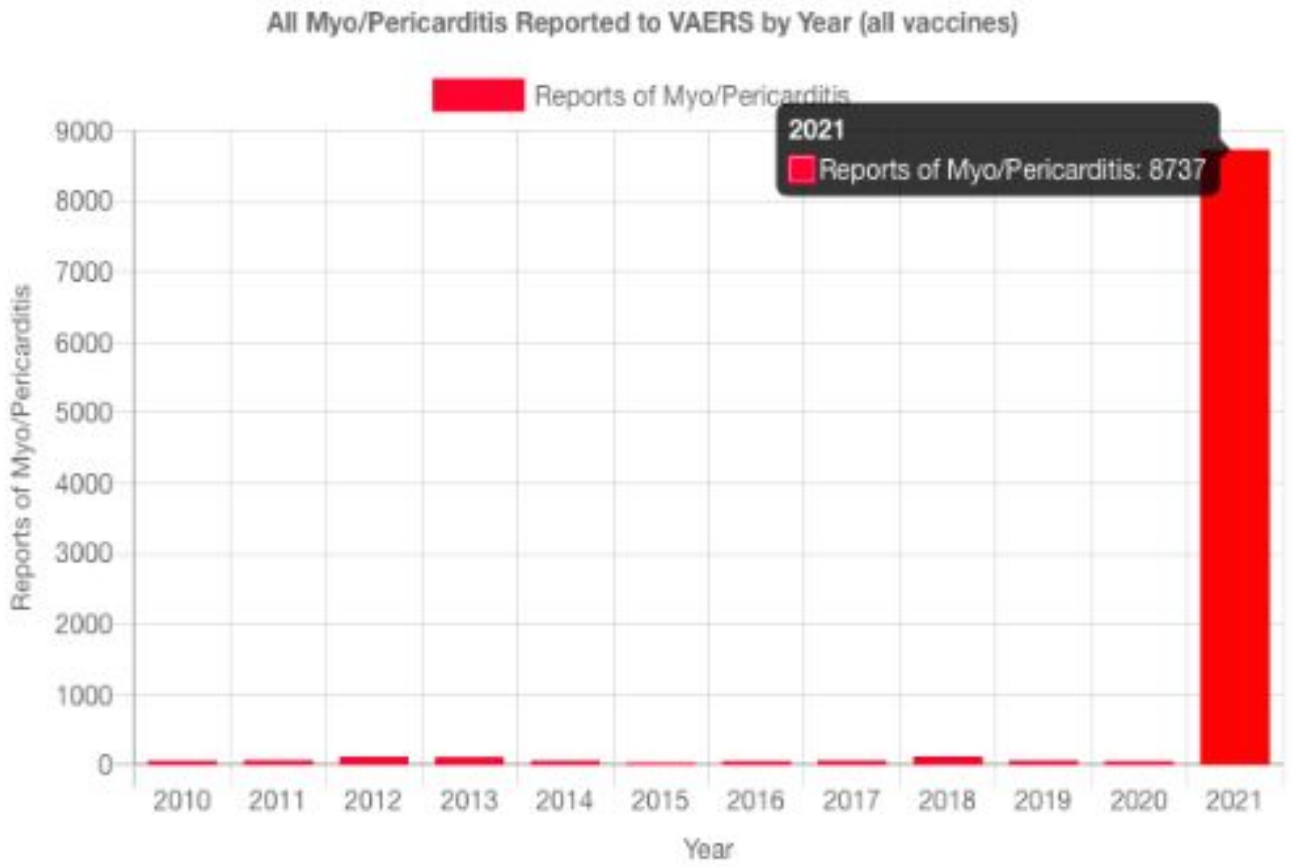
https://openvaers.com/covid-data/cardiac#myocarditis

VAERS COVID Vaccine Myo/Pericarditis Reports

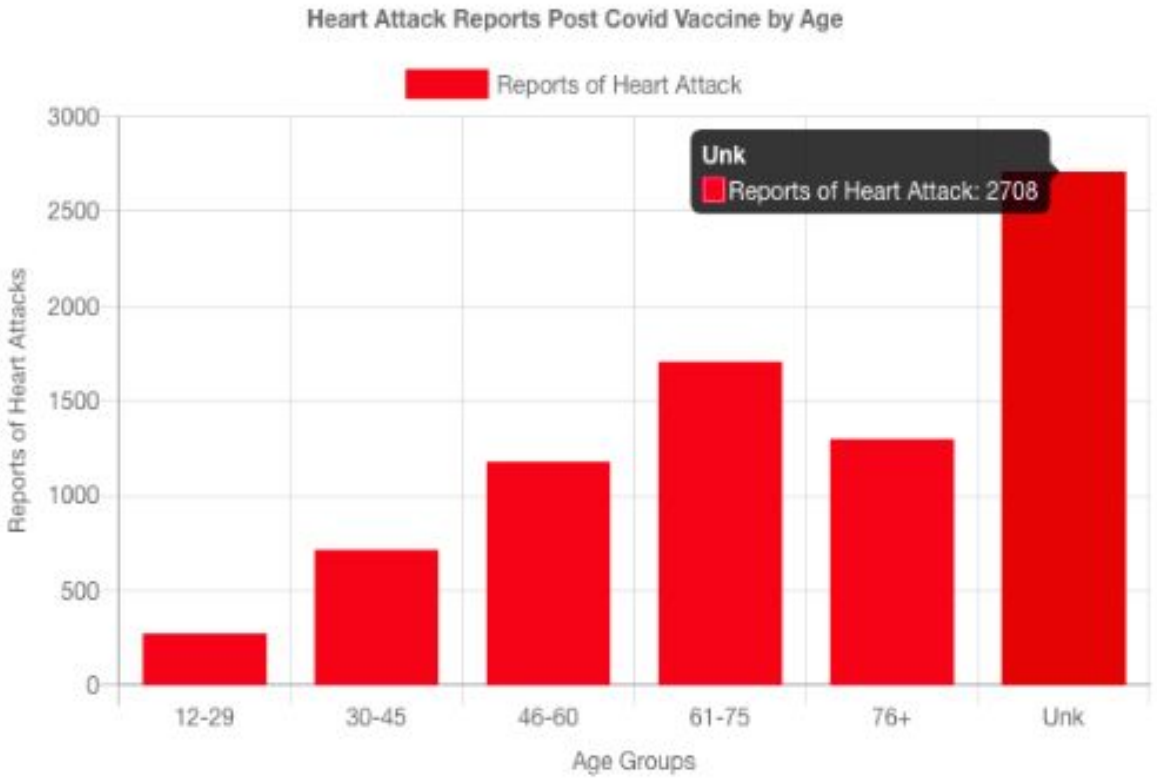
Oct 1. 2021

Through October 01, 2021

8,737 Myo/Pericarditis



7,868 Heart Attacks



https://openvaers.com/covid-data/cardiac#myocarditis

VAERS COVID Vaccine Reproductive Health Related Reports

Oct 1. 2021

Through October 01, 2021

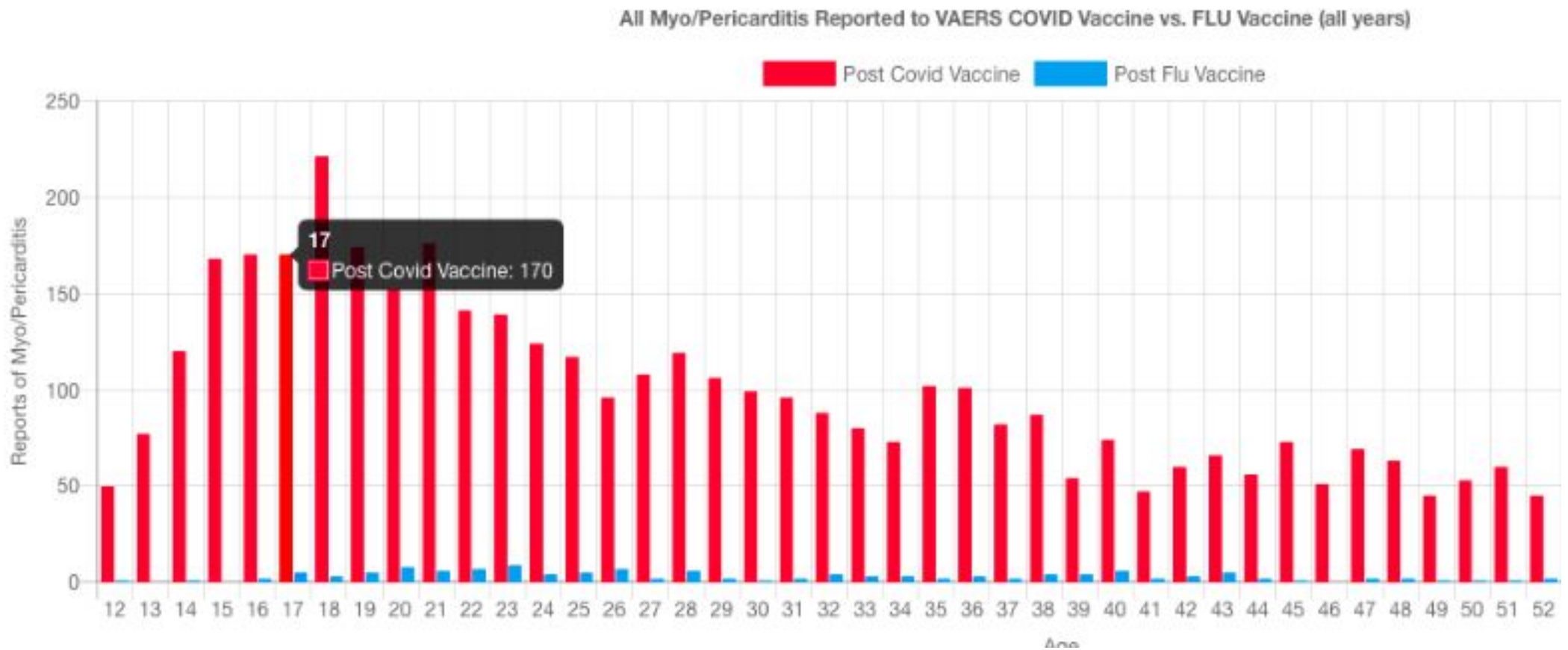
SYMPTOM	CASES
Miscarriage	2,415
Menstrual Disorders	13,480
Vaginal/Uterine Haemorrhage (All Ages)	4,805

SYMPTOM	CASES
Testicular Pain/Swelling	962
Erectile Dysfunction	262

https://openvaers.com/covid-data/cardiac#myocarditis

VAERS COVID Vaccine Myo/Pericarditis Reports

Through October 01, 2021



https://openvaers.com/covid-data/cardiac#myocarditis

8/23/2021 COMIRNATY FDA Approval - Biological License Approval: Page 25

Missing Information: VACCINE EFFECTIVESS

Pharmacovigilance Plan (PVP)

The Applicant's proposed pharmacovigilance plan (version 1.1) includes the following important risks and missing information:

- Important identified risks: Anaphylaxis; Myocarditis and Pericarditis
- Important potential risk: Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Enhanced Respiratory Disease (VAERD)
- Missing information: Use in pregnancy and lactation; Vaccine effectiveness; Use in pediatric individuals <12 years of age

In addition to routine pharmacovigilance, the Applicant will conduct the postmarketing studies listed in Section 11c Recommendation for Postmarketing Activities.

https://www.fda.gov/media/151733/download

“ *Have nothing to do with the fruitless deeds of darkness, but rather expose them…*

Everything exposed by the light becomes visible –
That is why it is said:

‘Wake up, sleeper,
Rise from the dead,
and Christ will shine on you.’

Be careful then on how you live – not as unwise but as wise, making the most of every opportunity because the days are evil. ”

EPHESIANS: 5: 1 - 15