Ethical Considerations for Mandating COVID-19 Vaccines - A discussion following FDA Approval

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Disclosure

- I am a clinical pharmacologist and in my work consult with various pharmaceutical and biologics organizations
- The opinions expressed herein are my own

Overview

- Vaccines and mRNA vaccines explained
- Pfizer Vaccine
  - FDA label review and data gaps
  - Safety Information
  - Comparisons with other health authorities
- Emergency Use Authorization vs Approval
- Inducement, Undue Influence and Coercion and COVID-19 Vaccine Administration
- Protecting your rights

What is a Vaccine?

- A biological preparation that provides active acquired immunity to a particular infectious disease.
- Typically contains an agent that resembles a disease-causing microorganism
  - Often made from weakened or killed forms of the microbe, its toxins, or one of its surface proteins.
- Intended for general population, including healthy individuals of all ages

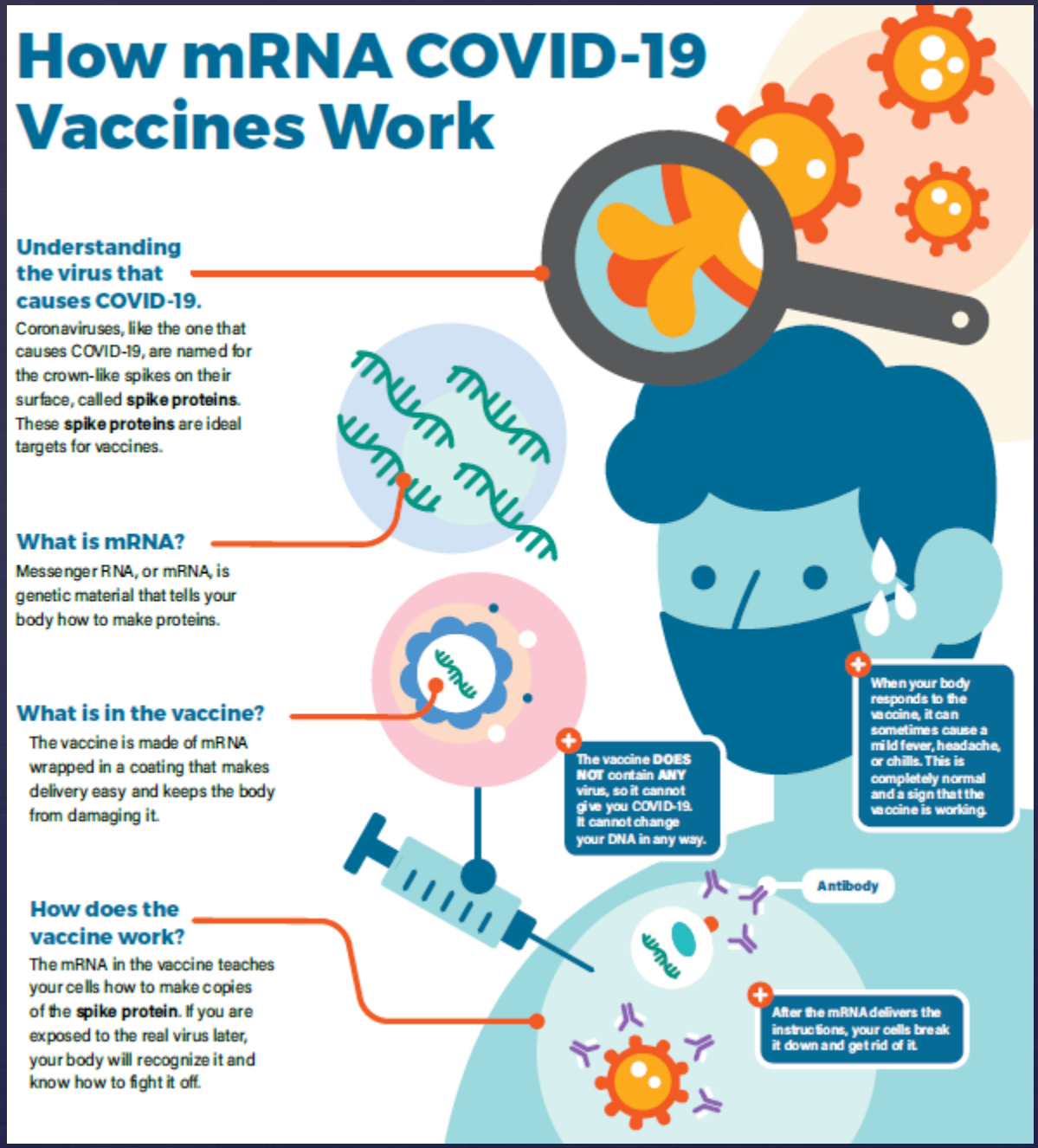
To learn more about the different types of vaccines visit:
https://www.vaccines.gov/basics/types

What are mRNA Vaccines?

- mRNA vaccines are a new type of vaccine to protect against infectious diseases.
- mRNA vaccines teach our cells how to make a protein—or even just a piece of a protein—that triggers an immune response inside our bodies.
- Novel mechanism under research for other diseases (e.g. flu, Zika, rabies, etc).
- Pfizer, Moderna, and Johnson & Johnson (Janssen) COVID-19 vaccines are currently authorized for Emergency Use in the USA
  - Pfizer and Moderna are novel mRNA vaccines
  - J & J delivers genetic material from COVID-19 through viral vector delivery

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/different-vaccines/mrna.html

How mRNA COVID-19 Vaccines Work



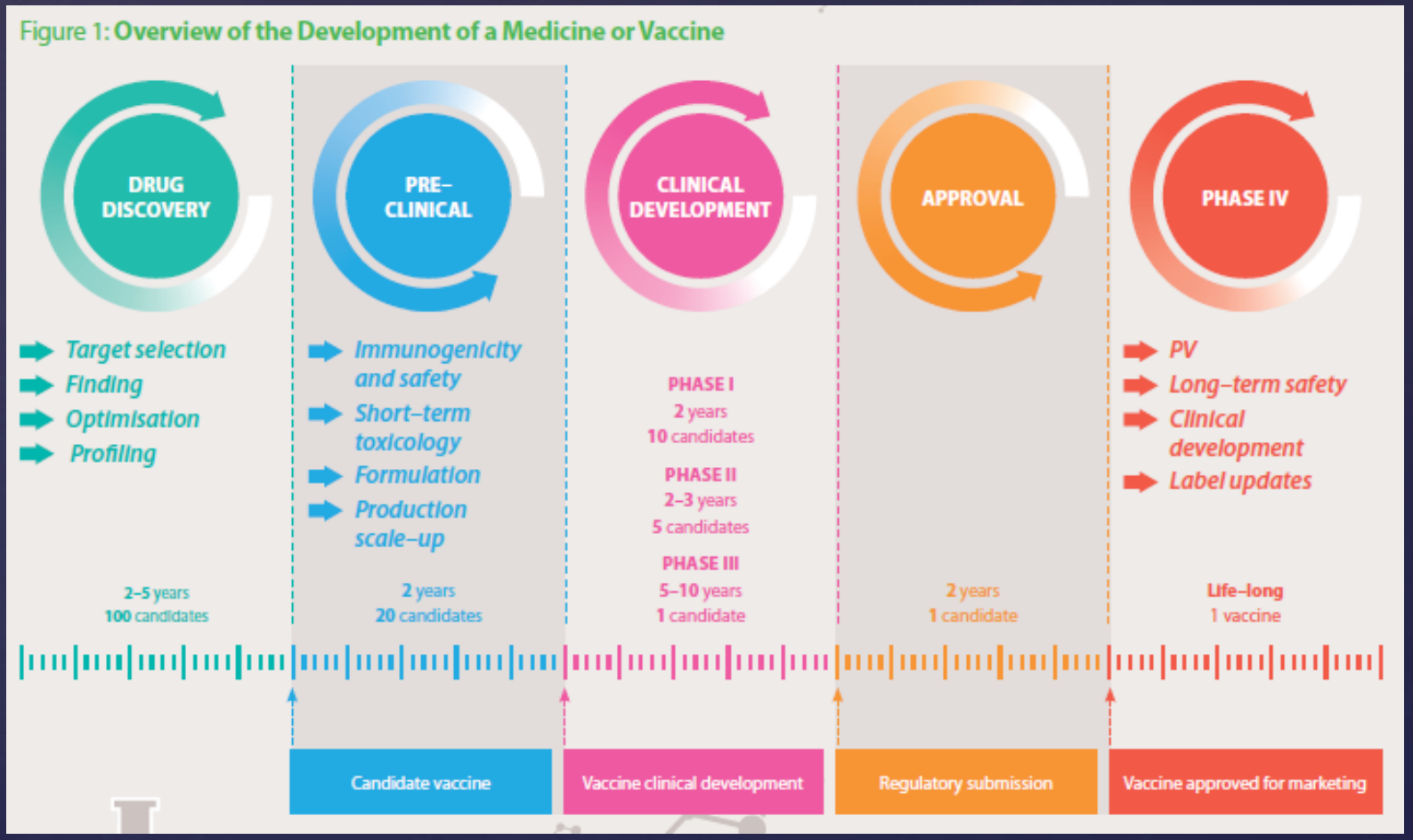
https://www.cdc.gov/coronavirus/2019-ncov/downloads/vaccines/COVID-19-mRNA-infographic_G_508.pdf

Vaccine Development

- Complex process
  - 10-15 years of development
  - Viruses/pathogens mutate over time
  - Large database representing various populations/ demographics needed
  - Challenges in activating immune system
  - High failure rate
    - 6% likelihood of reaching market[1]; ~33% success rate once in clinical development[2]
    - Select multiple candidates for testing
    - About 2–10% of healthy individuals fail to mount antibody levels to routine, marketed vaccines[3]
  - Complex manufacturing/supply process

1. Pronker ES, Weenen TC, Commandeur H, Claassen EH, Osterhaus AD. Risk in vaccine research and development quantified. *PLoS One*. 2013;8(3):e57755. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3603987/
2. https://www.acsh.org/news/2020/06/11/clinical-trial-success-rates-phase-and-therapeutic-area-14845
3. Wiedermann U, Garner-Spitzer E, Wagner A. Primary vaccine failure to routine vaccines: Why and what to do?. *Hum Vaccin Immunother*. 2016;12(1):239-243. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4962729/

5 Stages of Development



Vaccine approval by the Food and Drug Administration (FDA) is granted through the Biologics License Application (BLA) Process

Source: International Federation of Pharmaceutical Manufacturers & Associations – The Complex Journey of a Vaccine.

Date 2020	COVID-19 Related Event
December 31, 2019	• World Health Organization (WHO) picks up a media statement on cases of 'viral pneumonia' in Wuhan.
January 2020	• WHO published a comprehensive package of guidance documents for countries, covering topics related to the management of an outbreak of a new disease
January 11-12, 2020	• **Chinese authorities shared the full sequence of the coronavirus genome, as detected in samples taken from the first patients.** [1]
February 3, 2020	• CDC submitted an Emergency Use Authorization (EUA) package to expedite FDA-permitted use of the CDC PCR-based diagnostic panel in the United States. FDA issued the EUA on Feb. 4 and CDC sent the test kits to state and local public health laboratories.[2]
February 2020	• Based on H1N1 and Ebola outbreaks, WHO finalized guidelines for organizers of mass gatherings • February 14, Moderna issues final version of phase I study protocol
March 2020	• Between March 16 and April 14, 2020 Moderna initiates dosing of healthy volunteers in a phase I trial[3] • **Increases in case numbers begin to appear.**
April 2020	• WHO reports 1 M cases of COVID-19 confirmed worldwide
May 2020	• **Moderna initiates phase II trial in a target of 600 subjects (29May)**[4] • **Pfizer enrolls 45 participant in US phase I/II study for BNT162b1 (conducted between 4May – 19 June 2020)**[5] **– amended to a Phase 2.3 study (registration Phase 1/2/3/ Study C459001) of selected candidate BNT162b2**
July 2020	• Moderna initiates phase III trial with their vaccine in a target of 30,000 subjects 27 July 2020[6] • Pfizer initiates Phase I study in China (N=144) for **BNT162b1** conducted from 20July-31Dec 2020[7]
September 29, 2020	• Global death counts at 999,239[8] • 9 Sep- Pfizer starts multi site Phase 1/II study in healthy adults for **BNT162b3** (N=96 (part B cancelled)9
December 2020	• **10 Dec FDA holds advisory meeting to review Pfizer request for Emergency Use Authorization**[10] • **EUA issued for Pfizer 11Dec** • **17 Dec FDA holds advisory meeting to review Moderna request for Emergency Use Authorization**[11] • **EUA issued for Moderna 18 Dec**

Source: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/interactive-timeline#event-0

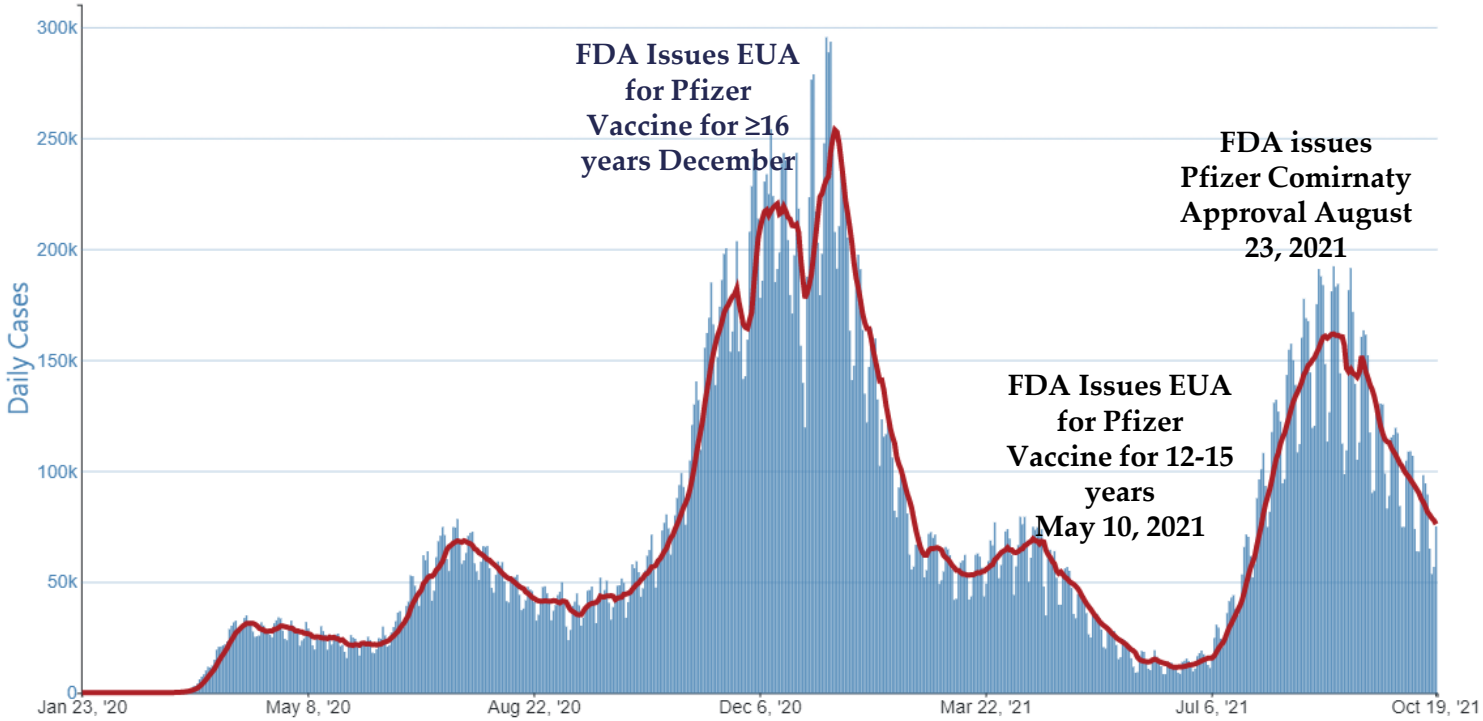
1. https://www.sciencedaily.com/releases/2020/01/200131114748.htm
2. https://www.cdc.gov/coronavirus/2019-ncov/lab/testing.html
3. https://www.nejm.org/doi/full/10.1056/NEJMoa2022483
4. https://clinicaltrials.gov/ct2/show/NCT04405076?term=moderna&cond=covid-19&draw=2
5. https://www.nature.com/articles/s41586-020-2639-4
6. https://clinicaltrials.gov/ct2/show/NCT04470427?term=vaccine&cond=covid-19&draw=5
7. https://www.chictr.org.cn/showprojen.aspx?proj=56834
8. https://covid19.who.int/
9. https://clinicaltrials.gov/ct2/show/NCT04537949?term=vaccine&cond=covid-19&draw=4
10. https://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-10-2020-meeting-announcementhttps://www.fda.gov/advisory-committees/advisory-committee-calendar/vaccines-and-related-biological-products-advisory-committee-december-17-2020-meeting-announcement

2021 –Pfizer Vaccine Approval

- Monday August 23rd
  - FDA Approves First COVID-19 Vaccine (Comirnaty – Pfizer/BioNTech) for individuals 16 years of age and older
  - Use for 12-15 year olds remains under Emergency Use Authorization (EUA)
- Issues Package Insert and Approval Level (stipulates post-marketing requirements)
- October 26, 2021
  - FDA Advisory Committee Panel votes to approve EUA for 5-11 year olds

https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine

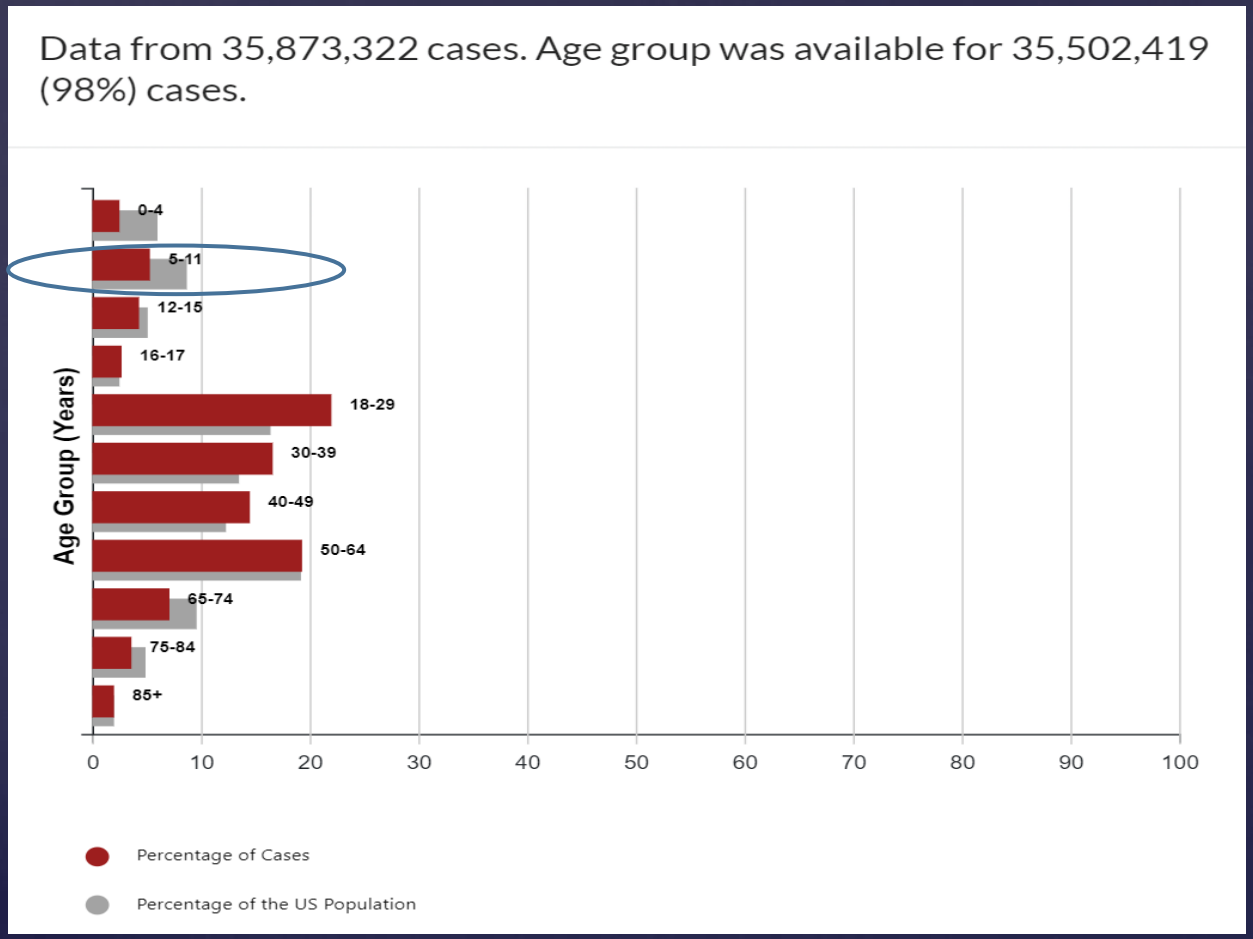
Daily COVID-19 Cases – USA (Jan 23, 2020 –October 19, 2021)



EUA = Emergency Use Authorization

Source: https://covid.cdc.gov/covid-data-tracker/#trends_dailycases

COVID-19 Cases by Age Group – USA (Data as of October 20, 2021)

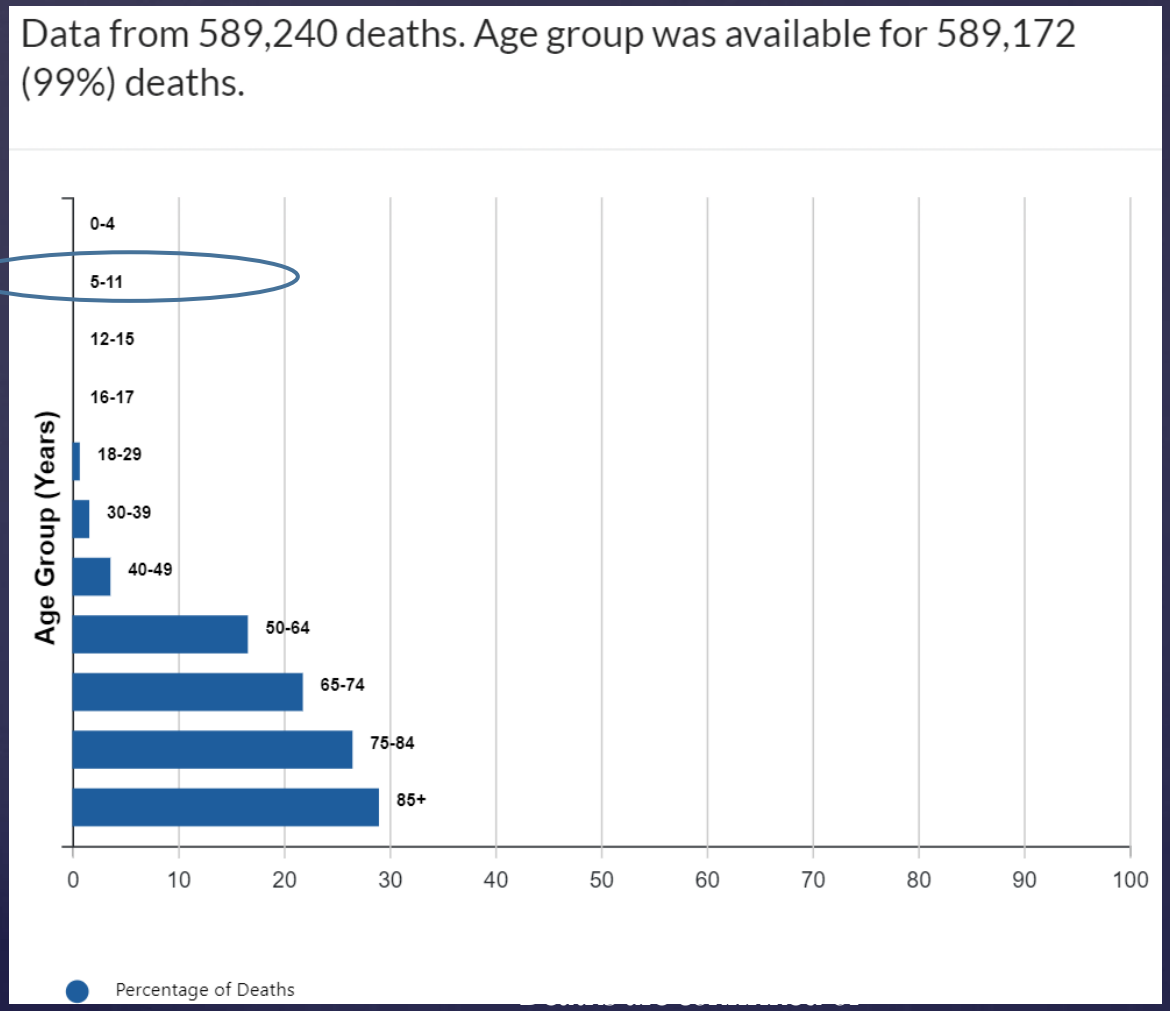


Age Group 5-11 years

- Percentage of **Cases 5.3%** (**N=1,889,815**)
- Represent 8.7% of US Population **(29,016,855** / 333,527,197)
- (**0-11 years age group**) Consistently lowest % Emergency Department Visits with Diagnosed Covid-19 (**1.2** % in October 2021)

Source: https://covid.cdc.gov/covid-data-tracker/#demographics
https://covid.cdc.gov/covid-data-tracker/#ed-visits_separated_by_age_group

COVID-19 Deaths by Age Group



Age Group 5-11 years

- **0.03%** Deaths (**N=156)** by total COVID-19 deaths
- **0.008%** Deaths by total COVID-19 Cases (5-11 years)
- **0.0005%** Deaths by US population (5-11 years)

Age Group 0-17 years

- **0.12%** Deaths **(n=718)** by total Covid-19 Deaths
- **0.014%** Deaths by total COVID-19 Cases (0-17 years)

- Survival 99.99%

"presumed"

Data as of October 21, 2021: https://covid.cdc.gov/covid-data-tracker/#demographics
https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/

Vaccine Adverse Event Reporting System (VAERS) - Pfizer/BioNtech COVID-19 Data (October 21,2021)

Age Group	# of Deaths	# of Life Threatening Events	# of Permanent Disability	Congenital Anomaly/ Birth Defect	Hospitalized	Emergency Room
< 6 months	**1**				**2**	5
6-11 months					**1**	
1-2 years	**1**			**1**	**1**	5
3-5 years						1
6-17 years	**25**	**245**	**105**	**4**	**1,291**	**2,799**
18-29	54	355	349	26	1,317	5,467
30-39	99	625	707	191	1,671	7,276
40-49	128	743	930	32	1,892	7,172
50-59	281	862	1,022	10	2,589	6,649
60+	3,617	2,154	1,983	37	12,591	13,287
TOTAL	4,206	4,984	5,096	211	21,355	42,641

https://wonder.cdc.gov/vaers.html

Serious Events by Vaccine Type – VAERS 28 Oct 2021 – All Ages

Event	Janssen	Moderna	Pfizer/ BioNtech	Unknown Manufacturer	Total
Deaths	858	3,817	4,299	36	**9,010**
Life Threatening	1,142	4,042	5,101	48	**10,333**
Permanent Disability	938	3,904	5,248	34	**10,124**
Hospitalized	4,006	16,129	22,050	168	**42,353**

Additional events not shown
https://wonder.cdc.gov/controller/datarequest/D8;jsessionid=26952BA4E1990FF305B6556737B0

Pfizer Vaccine Adverse Events Reported in Canada

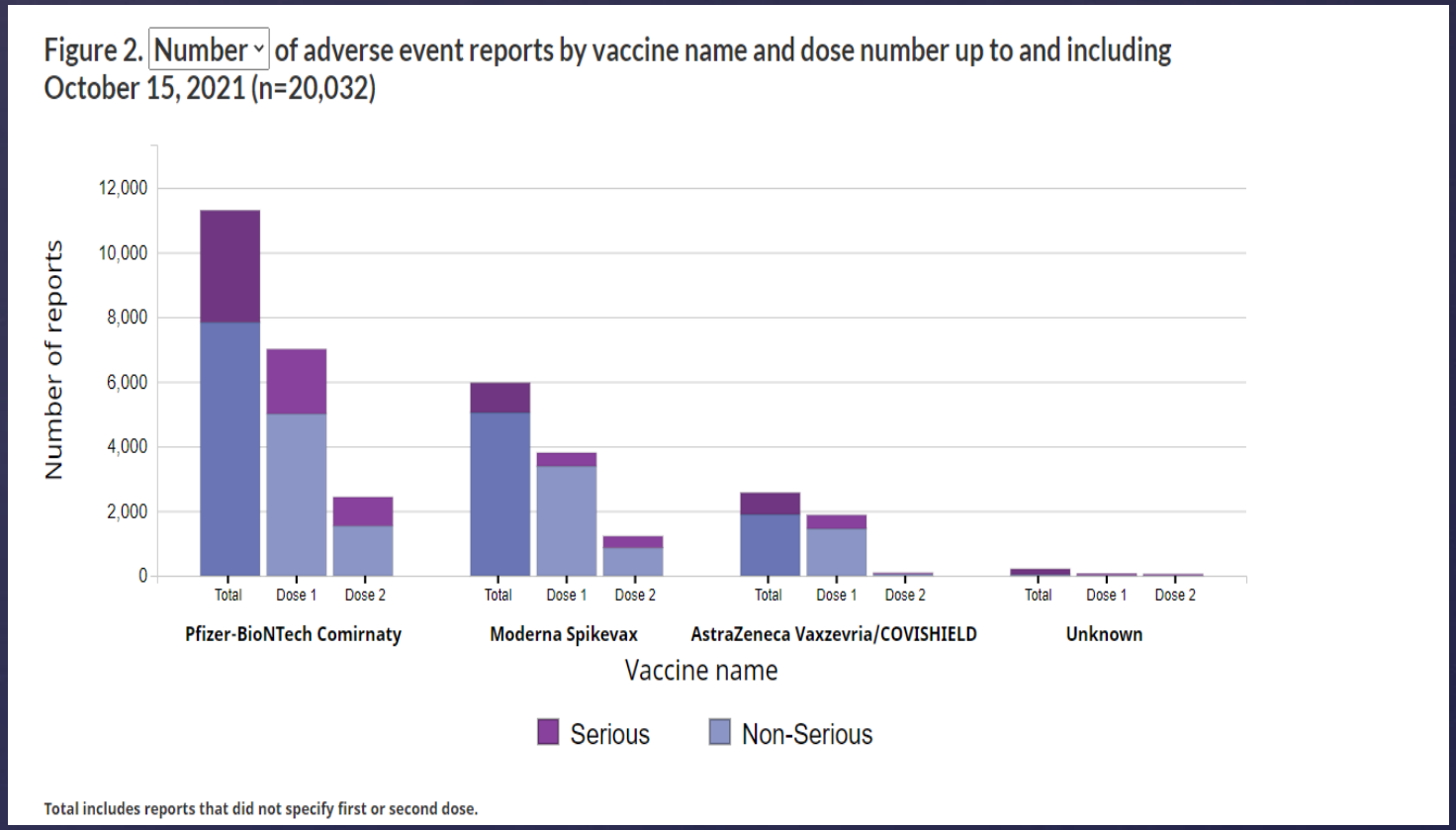
Number and report rate (per 100,000 doses administered) of adverse event reports by vaccine name and dose number up to and including October 8, 2021 (n=19,061)

Vaccine name	Non-serious reports[2]	Serious reports[2]	Total reports[2]	Total number of doses administered	Non-serious report rate[3]	Serious report rate[3]	Total report rate[3]
Pfizer-BioNTech Comirnaty (Total)[1]	**7,380**	**3,293**	**10,673**	39,491,561	18.69	**8.34**	27.03
Pfizer-BioNTech Comirnaty (Dose 1)	4,724	1,993	6,717	20,940,177	22.56	9.52	32.08
Pfizer-BioNTech Comirnaty (Dose 2)	1,444	841	2,285	18,291,975	7.89	4.60	12.49

https://health-infobase.canada.ca/covid-19/vaccine-safety/#a4

Health Canada – Serious and non-Serious Adverse Events by Vaccine Type

(Total 29,460,580 administered at least 1 dose ; Population = 38,176,026)



https://health-infobase.canada.ca/covid-19/vaccine-safety/

https://health-infobase.canada.ca/covid-19/vaccine-safety/

Highlights of Prescribing Information

Contents of the Full Prescribing Information - COMIRATY

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

What relevant sections are missing? **SECTION 7. Drug Interactions**

Section 9 - Drug Abuse and Dependence is not applicable
Section 10 – Overdose (may be relevant in cases of dosing errors)
Section 15 - References

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRATY – Studies Referenced in Prescribing Information

- 1 Preclinical (animal) Study:
  - A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on 4 occasions; twice prior to mating and twice during gestation.
- 2 Clinical (human) Studies:
  1. Study BNT162-01 (Study 1) was a Phase 2-part, dose-escalation trial that **enrolled 60 participants, 18 through 55 years of age and 36 participants, 56 through 85 years of age.** (Germany)
  2. Study C4591001 (Study 2) is a Phase 1/2/3 multicenter, multinational, randomized, saline placebo-controlled, double-blinded (Phase 2/3), dose-finding, vaccine candidate-selection and efficacy study that has enrolled approximately **44,047 participants (22,026 COMIRNATY; 22,021 placebo)** 16 years of age or older **(including 378 and 376 participants 16 through 17 years of age in the vaccine and placebo groups, respectively**). (US, Argentina, Brazil, Turkey, South Africa & Germany)
- Postmarketing Experience:
  - Source undefined

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRNATY® (Covid-19 Vaccine, mRNA)

- INDICATIONS AND USAGE
  - Indicated for active immunization to prevent coronavirus disease 2019 (COVID-29) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in individuals 16 years of age and older.
- DOSAGE AND ADMINISTRATION
  - For intramuscular injection only.
  - COMIRNATY is administered intramuscularly as a series of 2 doses (0.3 mL each) 3 weeks apart.
- DOSAGE FORMS AND STRENGTHS
  - Suspension for injection. After preparation, a single dose is 0.3 mL.

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRNATY® (Covid-19 Vaccine, mRNA)

- CONTRAINDICATIONS
  - Known history of a severe allergic reaction (e.g. anaphylaxis) to any component of COMIRNATY.

Each dose of COMIRNATY contains:
- 30 mcg of a nucleoside-modified messenger RNA (mRNA) encoding the viral spike (S) glycoprotein of SARS-CoV-2.
- Lipids:
  - (0.43 mg ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)
  - 0.05 mg 2-(polyethylene glycol 2000)-N,N ditetradecylacetamide
  - 0.09 mg 1,2-distearoyl-sn-glycero-3-phosphocholine
  - 0.2 mg cholesterol
- 0.01 mg potassium chloride
- 0.01 mg monobasic potassium phosphate
- 0.36 mg sodium chloride
- 0.07 mg dibasic sodium phosphate dihydrate
- 6 mg sucrose

COMIRNATY does not contain preservative.
The vial stoppers are not made with natural rubber latex.
The diluent (0.9% Sodium Chloride Injection,USP) contributes an additional 2.16 mg sodium chloride per dose

- Determining *a priori* sensitivity to ingredients not possible – lipid and mRNA components (including translated spike protein) not part of standard allergy panels

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRNATY® (Covid-19 Vaccine, mRNA)

ADVERSE REACTIONS

- In clinical studies of participants **16 through 55 years of age**, the most commonly reported adverse reactions (≥10%):
  - pain at the injection site (88.6%),
  - fatigue (70.1%),
  - headache (64.9%),
  - muscle pain (45.5%),
  - chills (41.5%),
  - joint pain (27.5%),
  - fever (17.8%), and
  - injection site swelling (10.6%).
- In clinical studies of participants **56 years of age and older**, the most commonly reported adverse reactions (≥10%):
  - pain at the injection site (78.2%),
  - fatigue (56.9%),
  - headache, (45.9%),
  - muscle pain (32.5%),
  - chills (24.8%),
  - joint pain (21.5%),
  - injection site swelling (11.8%),
  - fever (11.5%), and
  - injection site redness (10.4%).

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRNATY® (Covid-19 Vaccine, mRNA)

- WARNINGS AND PRECAUTIONS
  - Postmarketing data demonstrate increased risks of myocarditis {inflammation of the heart muscle} and pericarditis {inflammation of the lining outside the heart}, particularly within 7 days following the second dose.
  - Syncope (fainting) may occur in association with administration of injectable vaccines, including COMIRNATY. Procedures should be in place to avoid injury from fainting.

- RISKS of Bell's Palsy NOT included in warning and precautions (FDA)
  - Information limited to reports in the clinical trial (4 participants in the COMIRNATY group and 2 participants in the placebo group)
  - Label concludes "Currently available information is insufficient to determine a causal relationship with the vaccine."

{text added for clarification}
COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

Health Canada

- August 6, 2021 Canada added Bell's Palsy Warning to Pfizer Covid Shot
  - As of July 30, 2021, Health Canada had received 206 reports of Bell's palsy after receiving the Comirnaty shot.

- Bell's Palsy is an immune mediated neurological disorder characterized by {usually} temporary muscle weakness or paralysis on one side of the face

1. https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2021/76203a-eng.php
2. https://thevaccinereaction.org/2021/08/canada-adds-bells-palsy-warning-to-pfizer-covid-shot/
3. https://covid-vaccine.canada.ca/info/pdf/pfizer-biontech-covid-19-vaccine-pm1-en.pdf

European Medicines Agency (EMA)

- **Special warnings and precautions for use – general recommendations**
  - **Hypersensitivity and anaphylaxis**
    - Events of anaphylaxis have been reported. Appropriate medical treatment and supervision should always be readily available in case of an anaphylactic reaction following the administration of the vaccine. Close observation for at least 15 minutes is recommended following vaccination. A second dose of the vaccine should not be given to those who have experienced anaphylaxis to the first dose of Comirnaty.
  - **Myocarditis and pericarditis**
    - Very rare cases of myocarditis and pericarditis have been observed following vaccination with Comirnaty. These cases have primarily occurred within 14 days following vaccination, more often after the second vaccination, and more often in younger men. Available data suggest that the course of myocarditis and pericarditis following vaccination is not different from myocarditis or pericarditis in general.
  - **Anxiety-related reactions**
    - Anxiety-related reactions, including vasovagal reactions (syncope), hyperventilation or stress-related reactions (e.g. dizziness, palpitations, increases in heart rate, alterations in blood pressure, tingling sensations and sweating) may occur in association with the vaccination process itself. Stress-related reactions are temporary and resolve on their own. Individuals should be advised to bring symptoms to the attention of the vaccination provider for evaluation. It is important that precautions are in place to avoid injury from fainting.
- The above precautions correspond to those mentioned in the FDA prescribing information

Summary of product characterisitics: https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

COMIRNATY

EUROPEAN MEDICINES AGENCY

- **Special warnings and precautions for use – general recommendations**
  - **Concurrent illness**
    - Vaccination should be postponed in individuals suffering from acute severe febrile illness or acute infection. The presence of a minor infection and/or low-grade fever should not delay vaccination.
  - **Thrombocytopenia and coagulation disorders**
    - As with other intramuscular injections, the vaccine should be given with caution in individuals receiving anticoagulant therapy or those with thrombocytopenia or any coagulation disorder (such as haemophilia) because bleeding or bruising may occur following an intramuscular administration in these individuals.
  - **Immunocompromised individuals**
    - The efficacy, safety and immunogenicity of the vaccine has not been assessed in immunocompromised individuals, including those receiving immunosuppressant therapy. The efficacy of Comirnaty may be lower in immunosuppressed individuals.

- **The above precautions are <u>NOT</u> mentioned in the FDA prescribing information**
  - FDA only states: "Immunocompromised persons, including individuals receiving immunosuppressant therapy, may have a diminished immune response to the COMIRNATY."

Summary of product characteristics:
https://www.ema.europa.eu/en/documents/product-information/comirnaty-epar-product-information_en.pdf

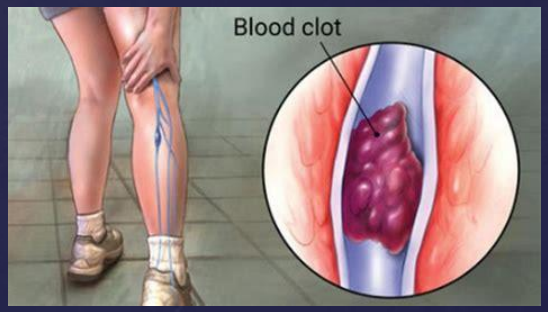
Thrombocytopenia and Coagulation Disorders

- FDA Prescribing Information – only mention of thrombotic events (Section 6.1 Clinical Trials Experience):
  - "In the analysis of blinded, placebo-controlled follow-up, there 13 were no other notable patterns or numerical imbalances between treatment groups for specific categories of non-serious adverse events (including other neurologic or neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to COMIRNATY."

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

Thrombosis Defined

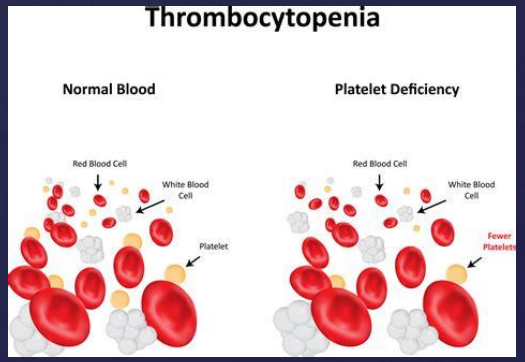
- Thrombosis occurs when blood clots block blood vessels
  - can be venous or arterial
  - Complications include heart attack, stroke, and other infarctions
  - Causes and risk factors include: Trauma, immobility, inherited disorders (genetic), autoimmune disease, obesity, hormone therapy or birth control pills, pregnancy, smoking, cancer, older age
  - Symptoms may include: Pain and swelling in an extremity, chest pain, numbness or weakness on one side of the body, sudden change in mental status
  - Diagnosed mainly through imaging (e.g., CT, MRI, ultrasound) with blood tests (e.g., D-dimer)



Presented in: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf
Source: https://www.hopkinsmedicine.org/health/conditions-and-diseases/thrombosis
Image: https://www.newtimes.co.rw/section/read/220945

Thrombocytopenia Defined

- Platelets and Thrombocytopenia (low platelets)
  - Platelets (thrombocytes) are colorless blood cells that help blood clot; normal platelet count is 150,000–450,000 per microliter
  - Platelets stop bleeding by clumping and forming plugs in blood vessel injuries
  - Thrombocytopenia is a condition in which you have a low blood platelet count (<150,000 per microliter)
  - Dangerous internal bleeding can occur when your platelet count falls below 10,000 per microliter
  - Though rare, severe thrombocytopenia can cause bleeding into the brain, which can be fatal



Presented in: https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-05-12/07-COVID-Shimabukuro-508.pdf
Source: https://www.mayoclinic.org/diseases-conditions/thrombocytopenia/symptoms-causes/syc-20378293
Image: https://www.mfmnyc.com/wp-content/uploads/2017/02/shutterstock_298069364.jpg

Thrombocytopenia and Coagulation Disorders – United Kingdom

- July 29, 2021 - National Institute for Health and Care Excellence (NICE) issues guidance on vaccine induced immune thrombocytopenia and thrombosis (VITT)
  - As of 14 July the Medicines and Healthcare Products Regulatory Agency had received "yellow card" reports of 411 cases of major thromboembolic events with concurrent thrombocytopenia after vaccination with the AstraZeneca vaccine and 15 cases after the Pfizer-BioNTech vaccine.[1]

- VITT is probable in people with:[2]
  - thrombosis and thrombocytopenia with very high D-dimer and low or normal fibrinogen, or
  - thrombosis and thrombocytopenia with high D-dimer and low or normal fibrinogen and strong clinical suspicion

1. Wise J. Covid-19 NICE issues guidance on vaccine induced immune thrombocytopenia and thrombosis. *BMJ* 2021;374:n1914
2. NICE COVID-19 rapid guideline: vaccine-induced immune thrombocytopenia and thrombosis (VITT)
https://www.nice.org.uk/guidance/ng200/resources/fully-accessible-version-of-the-guideline-pdf-pdf-51036811744

USE IN SPECIFIC POPULATIONS - COMIRANTY & PREGNANCY

- Pregnancy exposure registry that monitors pregnancy outcomes in women exposed to COMIRNATY during pregnancy.
  - Women who are vaccinated with COMIRNATY during pregnancy are encouraged to enroll in the registry by visiting https://mothertobaby.org/ongoing-study/covid19-vaccines/.
- Risk Summary
  - All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
  - A developmental toxicity study has been performed in female rats administered the equivalent of a single human dose of COMIRNATY on 4 occasions; twice prior to mating and twice during gestation. These studies revealed no evidence of harm to the fetus due to the vaccine
  - **Available data on COMIRNATY administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy.**

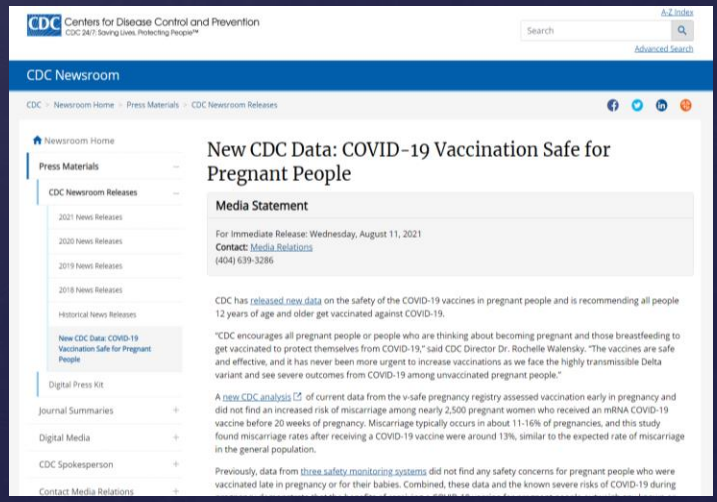
COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

CDC Endorsement- COMIRANTY & PREGNANCY

- August 11, 2021 Centre for Disease Control and Prevention (CDC) announced: COVID-19 Vaccination Safe for Pregnant People.

  "CDC encourages **all pregnant people or people who are thinking about becoming pregnant and those breastfeeding** to get vaccinated to protect themselves from COVID-19. The vaccines are safe and effective, and it has never been more urgent to increase vaccinations as we face the highly transmissible Delta variant and see severe outcomes from COVID-19 among unvaccinated pregnant people." --- said CDC Director Dr. Rochelle Walensky.

CDC makes safety claim despite FDA's admission to insufficient data to establish safety in pregnancy



https://www.cdc.gov/media/releases/2021/s0811-vaccine-safe-pregnant.html

CDC Endorsement- COMIRANTY & PREGNANCY

- CDC Further states "There is currently no evidence that any vaccines, including COVID-19 vaccines, cause fertility problems in women or men"
- In Contrast FDA states: **"COMIRNATY has not been evaluated for the potential to cause carcinogenicity, genotoxicity, or impairment of male fertility. In a developmental toxicity study in rats with COMIRNATY there were no vaccine-related effects on female fertility."**

Animal Data

In a developmental toxicity study, 0.06 mL of a vaccine formulation containing the same quantity of nucleoside-modified messenger ribonucleic acid (mRNA) (30 mcg) and other ingredients included in a single human dose of COMIRNATY was administered to female rats by the intramuscular route on 4 occasions: 21 and 14 days prior to mating, and on gestation days 9 and 20. No vaccine-related adverse effects on female fertility, fetal development, or postnatal development were reported in the study.

https://www.cdc.gov/coronavirus/2019-ncov/vaccines/recommendations/pregnancy.html
COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRANTY & Lactation

- It is not known whether COMIRNATY is excreted in human milk.
- Data are not available to assess the effects of COMIRNATY on the breastfed infant or on milk production/excretion.
  - The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for COMIRNATY and any potential adverse effects on the breastfed child from COMIRNATY or from the underlying maternal condition.
  - For preventive vaccines, the underlying maternal condition is susceptibility to disease prevented by the vaccine.

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRANTY & Pediatric Use

- **Pediatric Use**
- Safety and effectiveness of COMIRNATY in individuals 16 through 17 years of age is based on safety and effectiveness data in this age group and in adults.
- **The safety and effectiveness of COMIRNATY in individuals younger than 16 years of age have not been established.**

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRANTY & DATA GAPS

- Include but not limited to:
  - Biodistribution of the vaccine and location of expression of spike protein
  - Half life of spike protein
  - Toxicity data including genotoxicity, carcinogenicity, male fertility, risks in pregnancy, female fertility
  - Risk factors for myocarditis, pericarditis, thrombocytopenia, thrombosis, Bell's Palsy
  - Safety in pediatric populations, immunocompromised
  - Drug interactions
  - Duration of immune response (i.e. booster shots and safety of additional exposures)
  - Long-term safety and efficacy???

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

COMIRANTY – Postmarketing Requirements

- FDA Approval Label stipulates postmarketing requirements for Pfizer
  - Three pediatric studies in different age ranges (12-15 years, 6 mos - <12 years and < 6mos with expected report dates of 31Oct 2023, 31May2024, and 31 Oct 2024)
  - Six studies to evaluate the risks of myocarditis and pericarditis (including one study C4591036 with at least a 5 year follow up for potential long-term sequelae of myocarditis after vaccination (study completion 31Dec2026).
  - Additional studies in pregnancy (registry study; protocol submitted July 1, 2021 with study completion by June 30, 2025) and immunogenicity, safety, efficacy surveillance.

COMIRNATY Highlights of Prescribing Information: https://www.fda.gov/media/151707/download

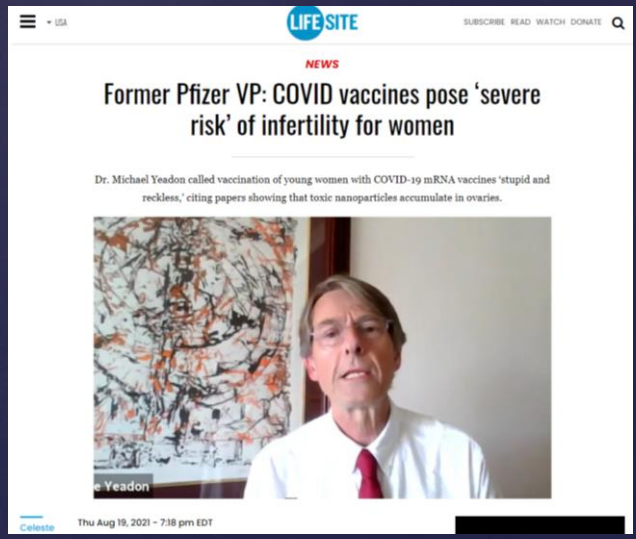
Biodistribution of Lipid Nanoparticles (LPN), encapsulated mRNA (BNT162b) and Expression of Spike Protein

- Not mentioned in prescribing information or in briefing materials from Pfizer (at FDA advisory meeting seeking EUA)
- Leaked Pfizer pharmacokinetic (metabolism) study
  - Radiolabeled lipids or RMA encoding luciferace were used in the study. Examined plasma, urine feces and liver samples - does not mention collection of other organs
  - Study showed rapid distributions from blood to liver
  - Luciferase expression at administration site (observed from 6 hours to 9 days post dose)
  - Radiolabeled lipids highest at administration site and also mainly the liver, spleen, adrenal glands, ovaries and bone marrow. Increasing levels up to 48 hours observed but no further sampling beyond.
  - NLP observed in brain at lower levels; detected in all samples collected

https://www.lifesitenews.com/wp-content/uploads/2021/06/Pfizer-bio-distribution-confidential-document-translated-to-english.pdf

Biodistribution of Lipid Nanoparticles (LPN), encapsulated mRNA (BNT162b) and Expression of Spike Protein

- Based on the fact that the development of vaccines aimed at preventing infectious diseases does not require evaluation of systemic exposure. (WHO, 2005; Non-clinical study guidelines for infectious disease preventive vaccines) 1 , 2 , BNT162b2 Encapsulated LNP muscle No internal PK study was performed. In **addition, two other types of lipids (choleste) contained in this drug Rolls and DSPCs) are naturally occurring lipids that are thought to be metabolized and excreted in the same way as endogenous lipids. available. In addition, BNT162b2 is degraded by ribonucleases in the cells that have taken it up, resulting in nucleic acid charges. Apologize, the S protein from BNT162b2 is expected to undergo proteolysis. From the above, It was considered unnecessary to evaluate the metabolism and excretion of these components again**



- **Authors assume that mRNS is degraded by ribonucleases in the cells that have taken it up and assume that S protein undergoes proteolysis**
- **Therefore it was not necessary to study these components.**

https://www.lifesitenews.com/wp-content/uploads/2021/06/Pfizer-bio-distribution-confidential-document-translated-to-english.pdf
https://www.lifesitenews.com/news/pfizer-vp-vaccination-women-is-stupid-infertility/

Weighing the Risks and Benefits

- Despite COMIRATY approval on August 23, 2001 many data gaps exist regarding the safety and effectiveness of the vaccine
- Postmarketing studies will continue for several years
- COMIRATY continues to be an experimental drug
- Critical studies in the label are missing
- Determining risk/benefit ratios is complex due to lack of safety data and lack of long-term efficacy data
  - Difficult to predict allergic reactions
  - Increased risks to pregnancy and long term effects to fetus/mother
  - No pediatric safety information
  - No long term safety data
  - Medical contraindications may be extensive depending on potential risks for conditions such as myocarditis, pericarditis, thrombosis, thrombocytopenia, Bell's Palsy
  - Activities and co-morbidities may enhance risks (e.g. air travel, smoking, birth control pills)
- Inherent and Natural immunity is also effective and relevant – may be an important risk/benefit determinant
- Certain populations at risk for COVID-19 infections and complications may view the risk:benefit ratio with different weight compared to a population at less perceived risk for COVID-19 complications

https://www.lifesitenews.com/wp-content/uploads/2021/06/Pfizer-bio-distribution-confidential-document-translated-to-english.pdf
https://www.lifesitenews.com/news/pfizer-vp-vaccination-women-is-stupid-infertility/

Coercion -COVID-19 Vaccine

- Threat of:
  - Mandates – removal of freedom of choice
  - Employment loss
  - Loss of access to attend schools/continued mask wearing
  - Barriers to travel (vaccine passports)
  - Barriers to public activities e.g. shopping, entertainment
  - Social isolation/targeting/humiliation
  - Loss of health care coverage
  - Intimidation (e.g. door to door campaign)
  - Fines/imprisonment?

Emergency Use Authorization (EUA)

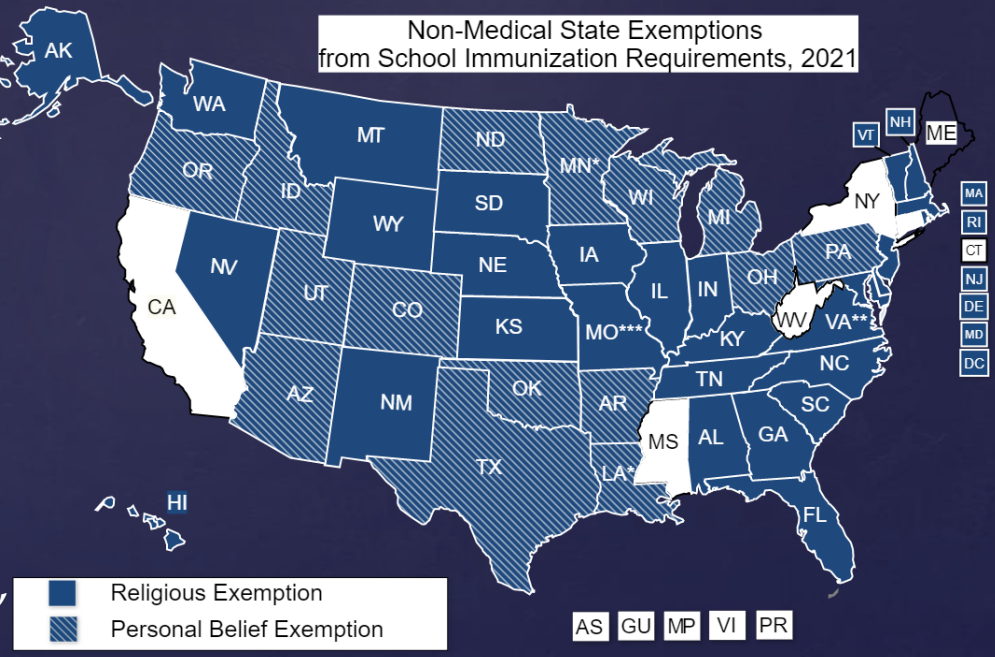
- Although informed consent as generally required under FDA regulations[1] is not required for administration or use of an EUA product, section 564 does provide EUA conditions to ensure that recipients are informed about the MCM they receive under an EUA.

- For an unapproved product (section 564(e)(1)(A)(ii)) and for an unapproved use of an approved product (section 564(e)(2)(A)), the statute requires that FDA ensure that recipients are informed to the extent practicable given the applicable circumstances:
  - That FDA has authorized emergency use of the product;
  - Of the significant known and potential benefits and risks associated with the emergency use of the product, and of the extent to which such benefits and risks are unknown;
  - That they have the option to accept or refuse the EUA product and of any consequences of refusing administration of the product;[2] and
  - Of any available alternatives to the product and of the risks and benefits of available alternatives.

1. See 21 CFR Part 50.
2. The President may under certain circumstances waive the option for members of the armed forces to accept or refuse administration of an EUA product (10 U.S.C. 1107a). In addition, the option to accept or refuse may not be practicable with regard to certain diagnostics because, for example, when a sample is taken from an individual it may be unknown, even to the health care professional, which diagnostic test will be used to test the sample. For this reason, Fact Sheets for both health care professionals and recipients may not accompany an EUA diagnostic product, but instead be publicly posted for reference when receiving test results.

Protecting the Welfare of Individuals -Students

- Vaccine exemptions for religious or medical purposes
- All states and the District of Columbia allow a medical exemption. A medical exemption is allowed when a child has a medical condition that prevents them from receiving a vaccine. There are 44 states and Washington D.C. that grant religious exemptions for people who have religious objections to immunizations. Currently, 15 states allow philosophical exemptions for children whose parents object to immunizations because of personal, moral or other beliefs



https://www.ncsl.org/research/health/school-immunization-exemption-state-laws.aspx

Protecting the Welfare of Individuals – Healthcare Workers

- North Carolina hospitals requiring all hospital employees to be fully vaccinated by September/October deadlines
- If employees choose to request a medical or religious exemption from the vaccine, that exemption must be approved on or before the deadline.

https://carolinapublicpress.org/47632/some-health-care-workers-balk-at-hospitals-covid-19-vaccine-mandates/

Protecting the Welfare of Individuals

- An employer must accommodate an employee with a disability or medical condition under the American with Disabilities Act, as well as a sincerely held religious belief in accordance with Title VII of the Civil Rights Act, unless accommodating either of those poses an undue burden to the employer.
- Some have raised the question as to what role hospitals requiring other vaccines could play in religious exemptions. If an employee has previously been vaccinated but is now balking at getting the COVID-19 vaccine, that could be a factor in the court determining whether the employee's belief is sincere. (Ifeoma Ajunwa, Prof Lay, UNC)
- The situations must be contextualized for each workplace, she said. For instance, because the COVID-19 pandemic is a public health crisis, if someone works in a public-facing role, accommodating a medical or religious exemption could put an undue burden on the employer.

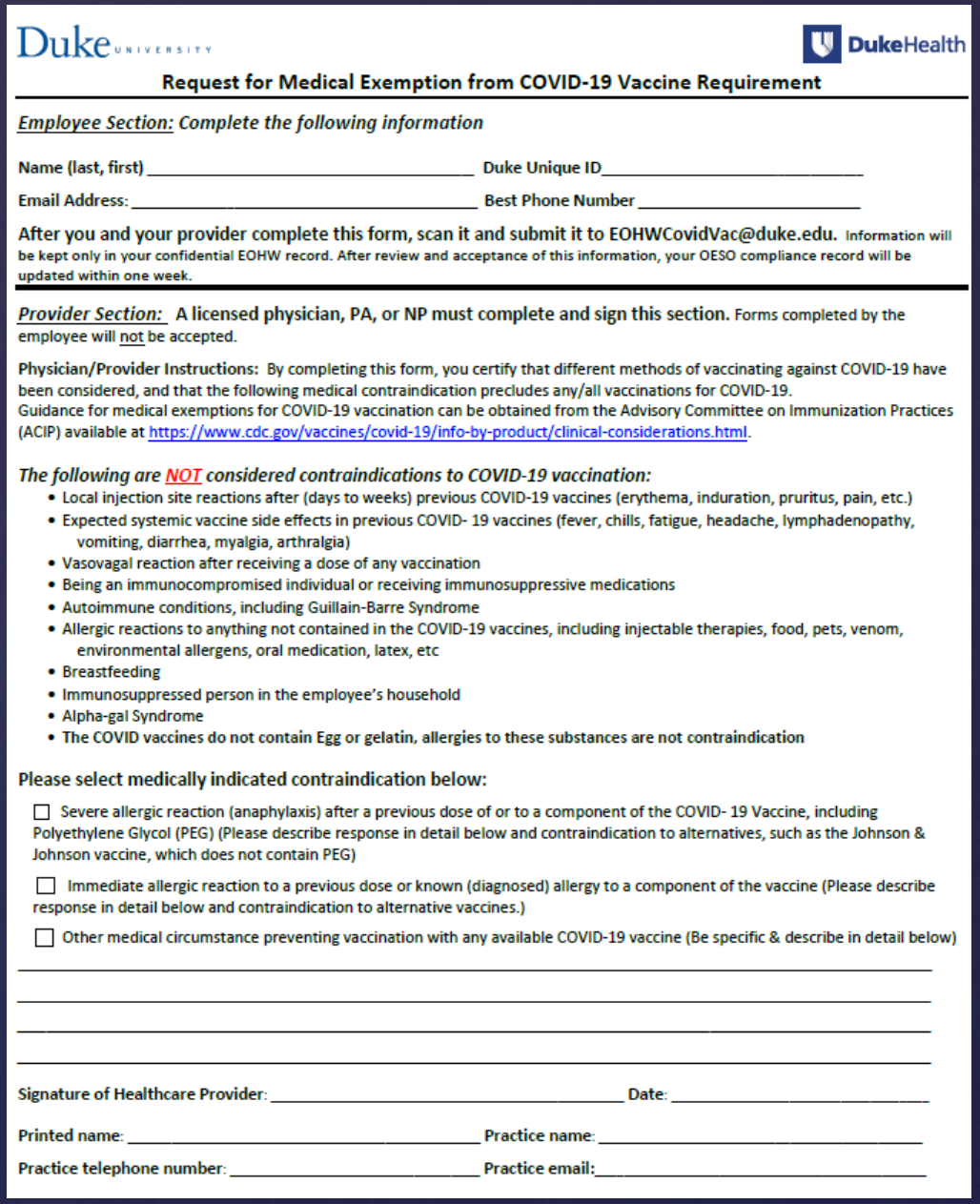
https://carolinapublicpress.org/47632/some-health-care-workers-balk-at-hospitals-covid-19-vaccine-mandates/

Exemptions in NC

- Duke Health
- Exemptions
- Students should email immunizations@duke.edu(link sends e-mail) to request a medical or religious exemption form.
- University faculty and staff may apply for a medical or religious exemption. (Note: School of Medicine and DUHS team members should follow the process described on the Duke Health website(link is external)). Individuals granted medial or religious exemptions will be subject to daily symptom monitoring, regular testing, masking while indoors and other protocols applicable to those who have not been vaccinated:
  - All students who have obtained an exemption from vaccination will be required to participate in surveillance testing twice a week. Faculty and staff who have not been vaccinated will be required to participate in surveillance testing once per week.
  - Anyone who has not been vaccinated, regardless of the circumstances, will be required to complete daily symptom monitoring.
  - Anyone who has not been vaccinated will be required to wear a mask indoors at all times.
- Applications for medical or religious exemptions should be submitted by Wednesday, August 25, 2021

https://covidvaccine.duke.edu/requirements

Medical Exemption Form - Example



Duke UNIVERSITY

DukeHealth

Request for Medical Exemption from COVID-19 Vaccine Requirement

***Employee Section:* Complete the following information**

Name (last, first) _____ Duke Unique ID_____

Email Address: _____ Best Phone Number _____

After you and your provider complete this form, scan it and submit it to EOHWCovidVac@duke.edu. Information will be kept only in your confidential EOHW record. After review and acceptance of this information, your OESO compliance record will be updated within one week.

Provider Section: **A licensed physician, PA, or NP must complete and sign this section.** Forms completed by the employee will not be accepted.

Physician/Provider Instructions: By completing this form, you certify that different methods of vaccinating against COVID-19 have been considered, and that the following medical contraindication precludes any/all vaccinations for COVID-19.
Guidance for medical exemptions for COVID-19 vaccination can be obtained from the Advisory Committee on Immunization Practices (ACIP) available at https://www.cdc.gov/vaccines/covid-19/info-by-product/clinical-considerations.html.

The following are NOT considered contraindications to COVID-19 vaccination:

- Local injection site reactions after (days to weeks) previous COVID-19 vaccines (erythema, induration, pruritus, pain, etc.)
- Expected systemic vaccine side effects in previous COVID- 19 vaccines (fever, chills, fatigue, headache, lymphadenopathy, vomiting, diarrhea, myalgia, arthralgia)
- Vasovagal reaction after receiving a dose of any vaccination
- Being an immunocompromised individual or receiving immunosuppressive medications
- Autoimmune conditions, including Guillain-Barre Syndrome
- Allergic reactions to anything not contained in the COVID-19 vaccines, including injectable therapies, food, pets, venom, environmental allergens, oral medication, latex, etc
- Breastfeeding
- Immunosuppressed person in the employee's household
- Alpha-gal Syndrome
- The COVID vaccines do not contain Egg or gelatin, allergies to these substances are not contraindication

Please select medically indicated contraindication below:

☐ Severe allergic reaction (anaphylaxis) after a previous dose of or to a component of the COVID- 19 Vaccine, including Polyethylene Glycol (PEG) (Please describe response in detail below and contraindication to alternatives, such as the Johnson & Johnson vaccine, which does not contain PEG)

☐ Immediate allergic reaction to a previous dose or known (diagnosed) allergy to a component of the vaccine (Please describe response in detail below and contraindication to alternative vaccines.)

☐ Other medical circumstance preventing vaccination with any available COVID-19 vaccine (Be specific & describe in detail below)

_____

_____

_____

_____

Signature of Healthcare Provider: _____ Date: _____

Printed name: _____ Practice name: _____

Practice telephone number: _____ Practice email:_____

https://covidvaccine.duke.edu/sites/default/files/Request%20for%20Medical%20Exemption%20from%20COVID-19%20Vaccine.pdf

Religious Exemption Form - Example

Duke UNIVERSITY

Application for Religious Exemption of COVID-19 Vaccine

All information requested must be provided and all questions must be answered in order for your application to be considered. Information will be kept confidential. If your application is approved, it will be recorded in your compliance record within one week.

Name:

Duke Unique ID:

Job Title:

Work Area:

Best Phone Number:

Supervisor:

Duke Email Address:

Section A:

Do you provide direct patient care?
- ☐ Yes
- ☐ No

Do you work in an area where patient care is provided (example: inpatient unit or clinic)?
- ☐ Yes
- ☐ No

Do you have patient or visitor contact (example: registering, providing directions, praying)?
- ☐ Yes
- ☐ No

Do you provide a service to patients or visitors (example: food preparation, financial counseling, music therapy)?
- ☐ Yes
- ☐ No

Do you understand that you will be required to wear a mask while indoors in Duke owned or leased buildings and may be tested weekly for COVID-19?
- ☐ Yes
- ☐ No

Duke UNIVERSITY

Do you understand that you may be asked to submit an application for religious exemption in the future if vaccination or a booster is recommended more regularly (having been approved for an exemption does not automatically mean your exemption will be approved permanently)?
- ☐ Yes
- ☐ No

Section B: Description of your religious beliefs that are contrary to the COVID-19 vaccine

Section C:

☐ The information I am providing in completing this form accurately reflects my sincerely held religious beliefs.

Signature: _____

Date: _____

Submit this completed form to Staff and Labor Relations by email to hrslrpolicies@duke.edu or by fax to 919-681-7924. **Applications must be received by Wednesday, Aug. 25, 2021.**

https://covidvaccine.duke.edu/sites/default/files/Request%20for%20Religious%20Exemption%20from%20COVID-19%20Vaccine.pdf

Safety of Masks in Children

- Very few studies published
- Goh et al performed a randomized two-period crossover on 106 children aged 7-14 years – wore N95 mask for 5 minutes and during mild activity (walking on treadmill for 5 minutes
- Cardiorespiratory conditions excluded
- When they were resting their mean end-tidal carbon dioxide was 30.9 ± 3.37 mmHg without a mask and 34.3 ± 3.32 mmHg when they were wearing a mask. During mild exercise, their end-tidal carbon dioxide values were 28.2 ± 2.8 mmHg and 32.0 ± 2.9 mmHg.
- All their physiological variables, including their heart rate and respiratory rate, were within acceptable ranges and the children's mean oxygen saturation was at least 99% in all cases. The authors reported that seven of the 106 (6.6%) children experienced mild breathing difficulties
- ETCO2 more sensitive compared to Oxygen saturation
- Respiratory depression defined as ETCO2 >50 mmHg or net increase of 10 mmHg ; O2 sats <92%
- Data not analyzed to show net change in each individual; time frame very short 5 minutes

Goh DYT, Mun MW, Lee WLJ, Teoh OH, Rajgor DD. A randomised clinical trial to evaluate the safety, fit, comfort of a novel N95 mask in children. Sci Rep. 2019;9(1):18952

Conclusions

- COMIRANTY and Other COVID-19 Vaccines continue to be under investigation for safety and prolonged efficacy regardless of approval status
- North Carolina observes religious and medical exemptions for vaccinations
- A strong stance in support of individual medical rights and freedoms are critical from a legal perspective
- Ethical compromise is not acceptable in research and medicine