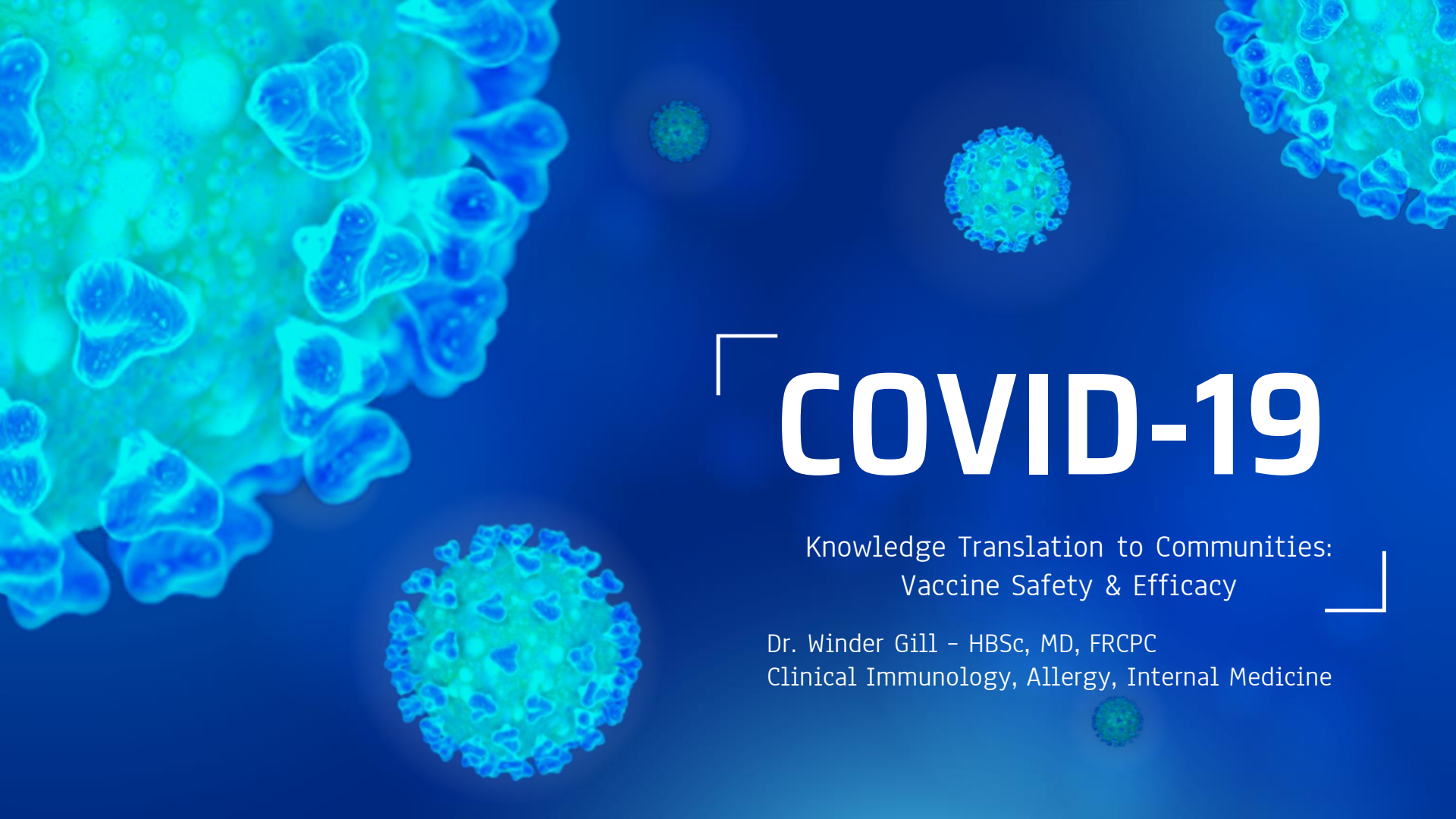
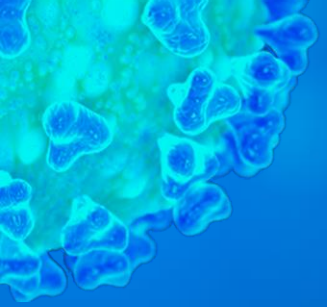


COVID-19

Knowledge Translation to Communities:
Vaccine Safety & Efficacy

Dr. Winder Gill - HBSc, MD, FRCPC
Clinical Immunology, Allergy, Internal Medicine



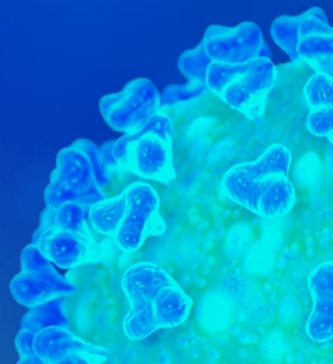
Disclosures

I have no financial interest or affiliation concerning material discussed in this presentation and have not received any endorsements nor compensation.

COVID Prevention in Communities

Objectives:

1) Why are Vaccines important?
2) How do Vaccines work?
3) Vaccine Efficacy
4) Vaccine Safety



The Importance of Vaccination

IMPORTANCE OF IMMUNIZATION PROGRAMMES

Each year, vaccines prevent more than 2.5 million child deaths globally. An additional 2 million child deaths could be prevented each year through immunization with currently available vaccines.[2]

This image shows a child with smallpox, a serious, contagious, and sometimes fatal infectious disease. The only prevention of smallpox is vaccination.

Why are vaccines so special?

- **Vaccines promote health:** unlike many other health interventions, they help healthy people stay healthy, removing a major obstacle to human development.
- **Vaccines have an expansive reach:** they protect individuals, communities, and entire populations (the eradication of smallpox is a case in point).
- **Vaccines have rapid impact:** the impact of most vaccines on communities and populations is almost immediate. For example, between 2000 and 2008, vaccination reduced global deaths from measles by 78% (from 750 000 deaths to 164 000 deaths per year).[3]
- **Vaccines save lives and costs:** recently, a panel of distinguished economists put expanded immunization coverage for children in fourth place on a list of 30 cost-effective ways of advancing global welfare.[4]

World Health Organization

Types of Corona Viruses and Strains

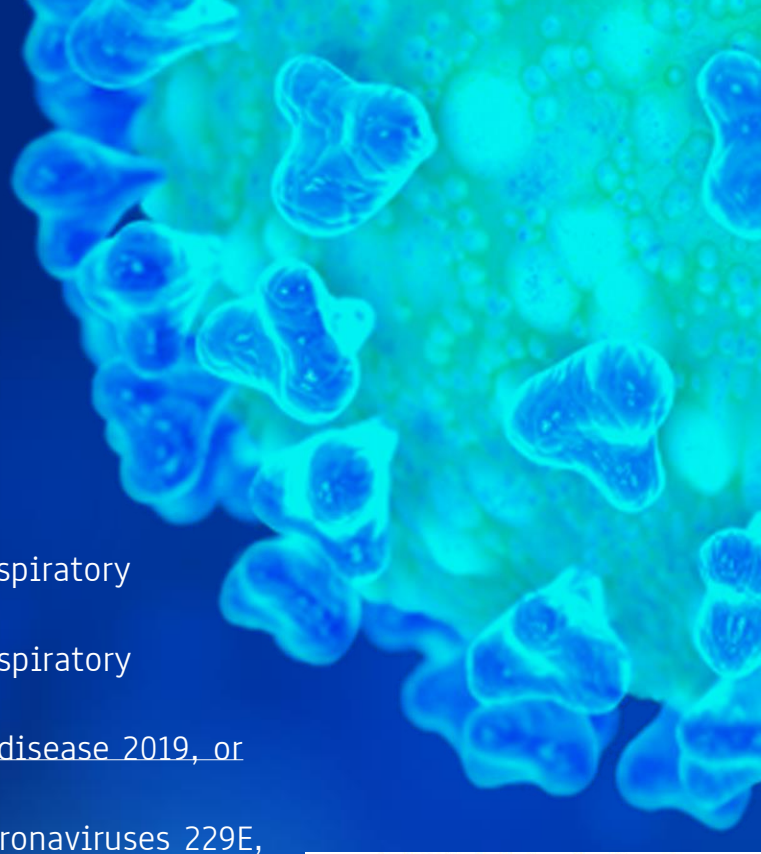
Common human coronaviruses

1. 229E (alpha coronavirus)
2. NL63 (alpha coronavirus)
3. OC43 (beta coronavirus)
4. HKU1 (beta coronavirus)

Other human coronaviruses

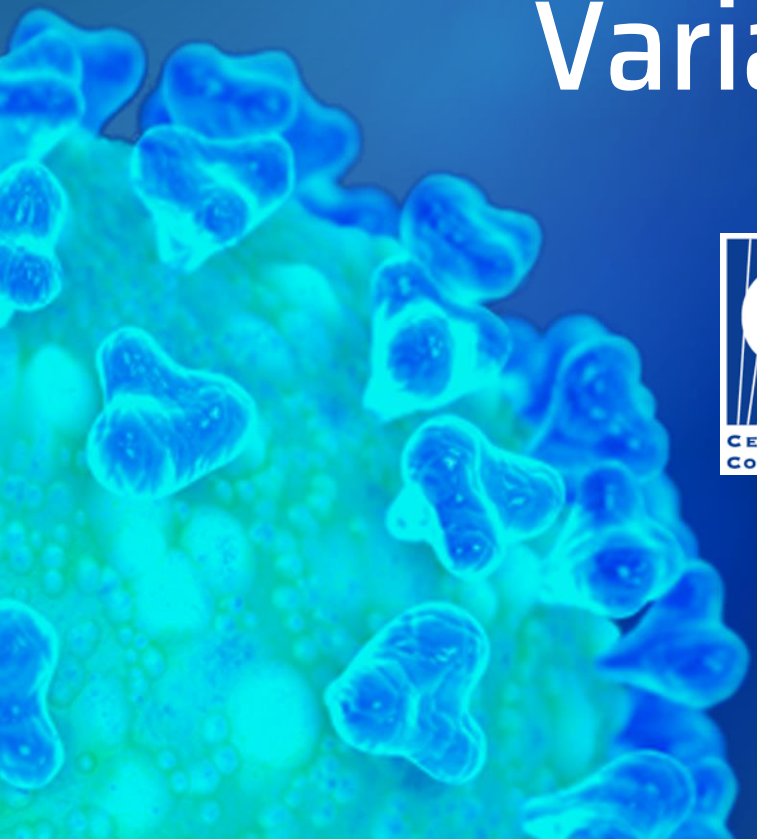
5. MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS)
6. SARS-CoV (the beta coronavirus that causes severe acute respiratory syndrome, or SARS)
7. SARS-CoV-2 (the novel coronavirus that causes coronavirus disease 2019, or COVID-19)

People around the world commonly get infected with human coronaviruses 229E, NL63, OC43, and HKU1.



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

COVID-19 Variants



CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

"Scientists monitor changes in the virus, including changes to the spikes on the surface of the virus. These studies, including genetic analyses of the virus, are helping us understand how changes to the virus might affect how it spreads and what happens to people who are infected with it"

"Viruses constantly change through mutation, and new variants of a virus are expected to occur over time. Sometimes new variants emerge and disappear. Other times, new variants emerge and persist"

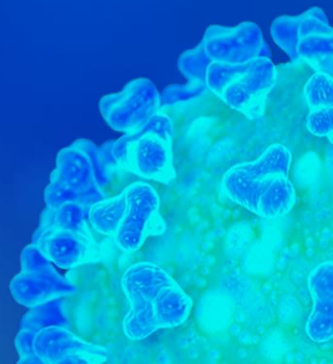
What impact will the new strains have?

“Scientists are working to learn more about these variants, and more studies are needed to understand:

How widely these new variants have spread
How the new variants differ
How the disease caused by these new variants differs from the disease caused by other variants that are currently circulating

Public health officials are studying these variants quickly to learn more to control their spread. They want to understand whether the variants:

Spread more easily from person to person
Cause milder or more severe disease in people
Are detected by currently available viral tests
Respond to medicines currently being used to treat people for COVID-19
Change the effectiveness of COVID-19 vaccines. There is no evidence that this is occurring, and most experts believe this is unlikely to occur because of the nature of the immune response to the virus.”



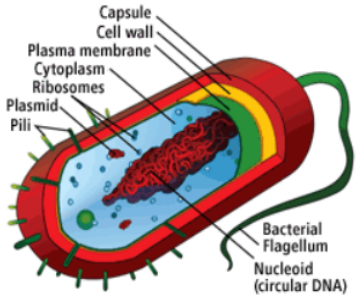
The Immune Response

HOW THE IMMUNE SYSTEM WORKS

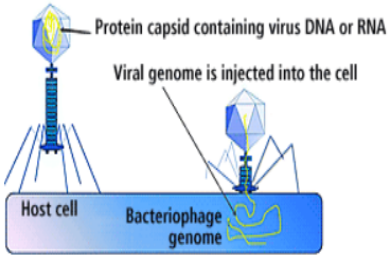
To understand how and why vaccine reactions occur, it is first necessary to understand how the immune system helps to protect the body against infection. It is designed to identify and destroy harmful foreign organisms (pathogens) from the body, and neutralize the toxins (poisons) that some bacteria produce.

The pathogens causing the vaccine-preventable diseases described in this module are mainly microorganisms such as bacteria or viruses.

- **Bacteria** are single-celled life-forms that can reproduce quickly on their own.
- **Viruses**, on the other hand, cannot reproduce on their own. They are ultramicroscopic infectious agents that replicate themselves only within cells of living hosts.



Bacterium (example).
Source: wikipedia.org



Virus infecting cell.
Source: wikipedia.org

The immune system responds to bacteria and viruses in a very complex way: it recognizes unique molecules (antigens) from bacteria and viruses and produces antibodies (a type of protein) and special white blood cells called lymphocytes that mark the antigens for destruction.

During the primary immune response to the first encounter with a specific pathogen, some lymphocytes called memory cells develop with the ability to confer long-lasting immunity to that pathogen, often for life. These memory cells recognize antigens on the pathogens they have encountered before, triggering the immune system to respond faster and more effectively than on the first exposure.

World Health Organization
VACCINE SAFETY BASICS
e-learning course

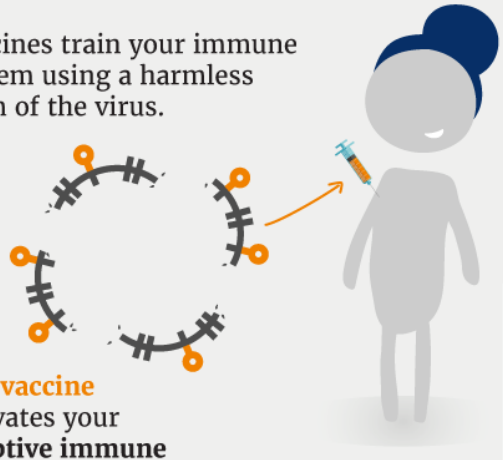
Knowledge Translation to Communities

British Society for immunology
www.immunology.org

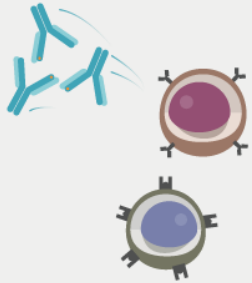
COVID-19, long-term immunity and vaccines

Celebrate Vaccines
with the British Society for Immunology

Vaccines train your immune system using a harmless form of the virus.



The **vaccine** activates your **adaptive immune response**.



The adaptive immune response involves:

B cells that make highly specific **antibodies** to stop the virus getting into your cells.

T cells that can help stimulate the B cells and kill any infected cells.

These cells remember the virus and remain in the body. This is **immune memory**.

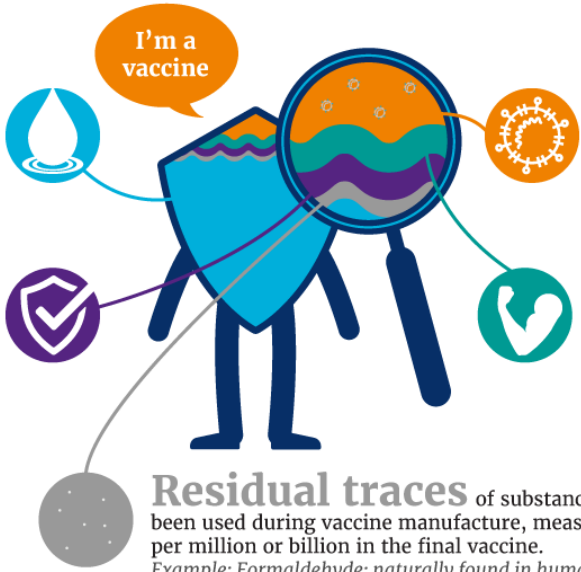
If you encounter the real virus in the future, your immune system responds faster and more effectively to prevent infection. This is **long-term immunity**.

An effective COVID-19 vaccine will produce a strong, long-term, adaptive immune response. It might stimulate B cells and specific antibodies or T cells or a combination of both.

Celebrate Vaccines
with the British Society for Immunology

What's in a vaccine?

British Society for immunology
www.immunology.org



Water

The main ingredient.

Active ingredient

A very small amount of a harmless form of the bacteria or virus you are immunising against.

Preservatives and stabilisers

Maintain vaccine quality, safe storage and prevent contamination.
Example: Sorbitol; naturally found in fruit in larger amounts.

Adjuvants

Create a stronger immune response to the vaccine. Pose no significant risk to health in the very small quantities used.
Example: Aluminium; naturally found in drinking water at higher levels.

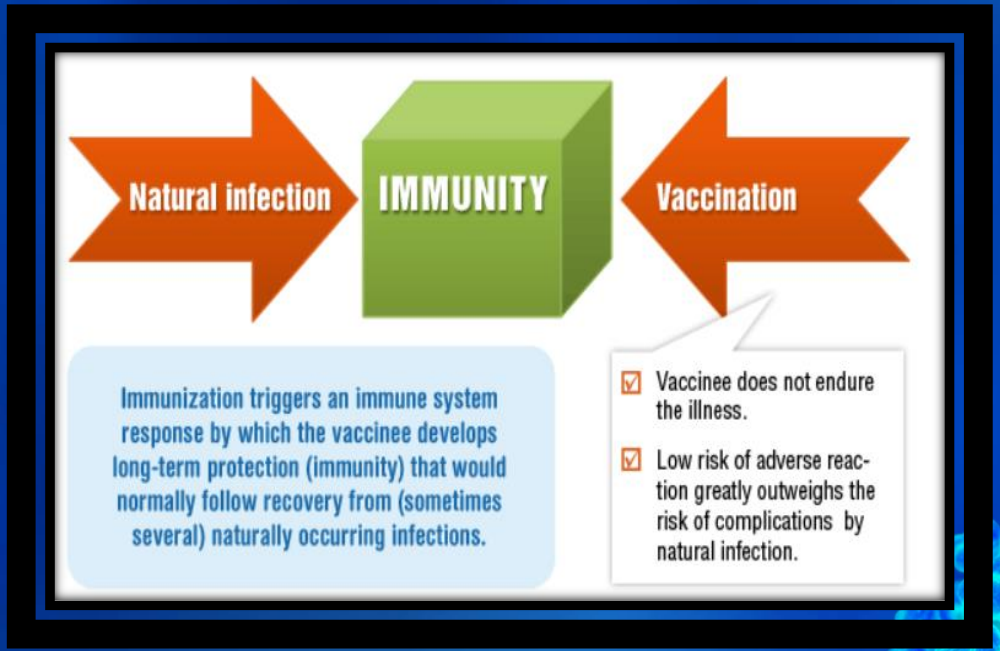
Residual traces

of substances that have been used during vaccine manufacture, measured as parts per million or billion in the final vaccine.
Example: Formaldehyde; naturally found in human body.

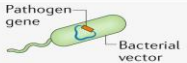
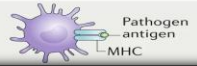
How do Vaccines Work?

"There are two ways of acquiring immunity to a pathogen – by natural infection and by vaccination. Natural infections and vaccines produce a very similar end result – immunity – but the person who receives a vaccine does not endure the illness and its potential life-threatening complications"

World Health Organization
VACCINE SAFETY BASICS
e-learning course



Vaccine Types

Type of vaccine		Licensed vaccines using this technology	First introduced
Live attenuated (weakened or inactivated)		Measles, mumps, rubella, yellow fever, influenza, oral polio, typhoid, Japanese encephalitis, rotavirus, BCG, varicella zoster	1798 (smallpox)
Killed whole organism		Whole-cell pertussis, polio, influenza, Japanese encephalitis, hepatitis A, rabies	1896 (typhoid)
Toxoid		Diphtheria, tetanus	1923 (diphtheria)
Subunit (purified protein, recombinant protein, polysaccharide, peptide)		Pertussis, influenza, hepatitis B, meningococcal, pneumococcal, typhoid, hepatitis A	1970 (anthrax)
Virus-like particle		Human papillomavirus	1986 (hepatitis B)
Outer membrane vesicle		Group B meningococcal	1987 (group B meningococcal)
Protein–polysaccharide conjugate		*Haemophilus influenzae* type B, pneumococcal, meningococcal, typhoid	1987 (*H. influenzae* type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	–
Antigen-presenting cell		Experimental	–

https://www.nature.com/articles/s41577-020-00479-7

Types of vaccines for COVID-19

Vaccines train your immune system using a harmless form of the virus

The SARS-CoV-2 virus causes COVID-19 illness.

Each type of vaccine for COVID-19 works differently to introduce SARS-CoV-2 antigens, which are unique proteins of the virus and can trigger an immune response. Vaccines stimulate a specific response without causing illness.

An effective vaccine for COVID-19 might involve a specific immune response, which includes:

- B cells that make highly specific antibodies to stop the virus getting into your cells.
- T cells that can help stimulate B cells and kill any infected cells.

This response builds immune memory, so your body can fight off SARS-CoV-2 in future.

Type of vaccine	How they work	Considerations	Examples in human use	In clinical trials for COVID-19
Inactivated vaccines	Contain killed SARS-CoV-2 virus.	May need to be administered with an adjuvant to boost immune response.	Influenza vaccine	Sinovac, Sinopharm
Attenuated vaccines	Contain weakened SARS-CoV-2 virus.	A well-known approach which requires time and extensive testing. The immune response resembles the natural infection.	Oral Polio vaccine	Codagenix
Protein vaccines	Contain proteins from the SARS-CoV-2 virus. Can be whole proteins, protein fragments or many protein molecules packed into nanoparticles.	Have good previous safety records. Usually administered with an adjuvant to boost immune response.	Hepatitis B vaccine	Novavax, Sanofi/GSK
Viral vector vaccines	Use an unrelated harmless virus, modified to deliver SARS-CoV-2 genetic material. The delivery virus is known as a viral vector. Our cells use the genetic material to make a specific SARS-CoV-2 protein.	Generate strong immune responses. May need to be stored at specific low temperatures.	Ebola vaccine	University of Oxford/ AstraZeneca, Janssen, Cansino, Gamaleya
Genetic vaccines *(nucleic acid vaccines)*	Contain a segment of SARS-CoV-2 virus genetic material that codes for a specific protein. Can be DNA or RNA. Our cells use the genetic material to make the SARS-CoV-2 protein.	Low cost and fast to develop. May need to be stored at specific low temperatures.	None	Pfizer/ BioNTech, Moderna, Imperial College London

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Vaccine Development in COVID 19

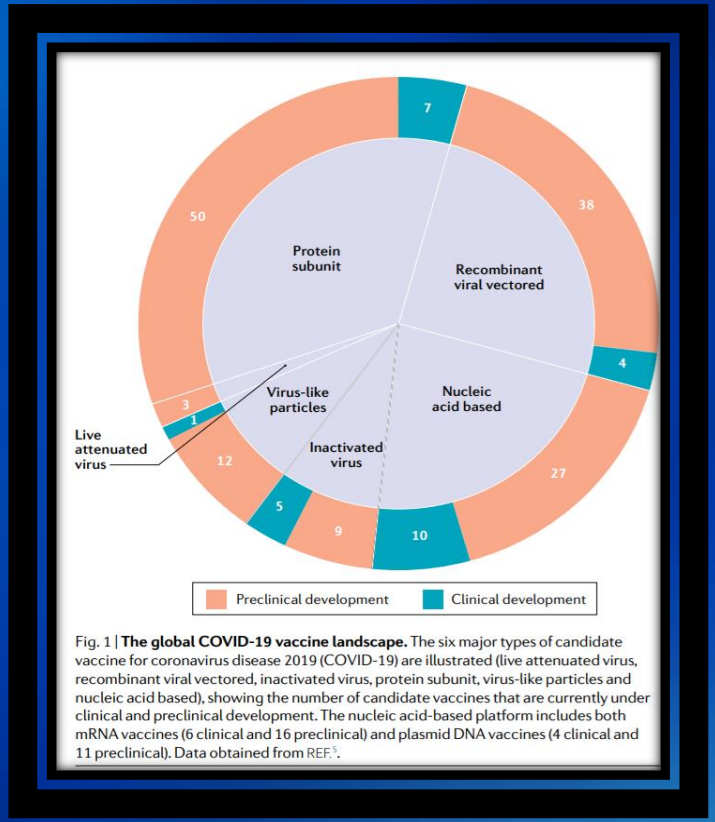
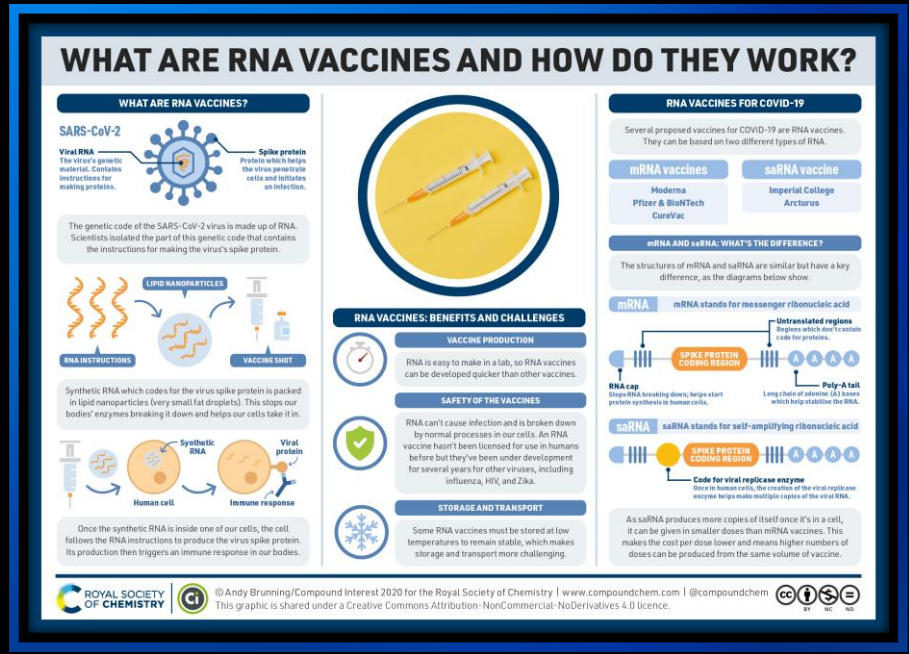


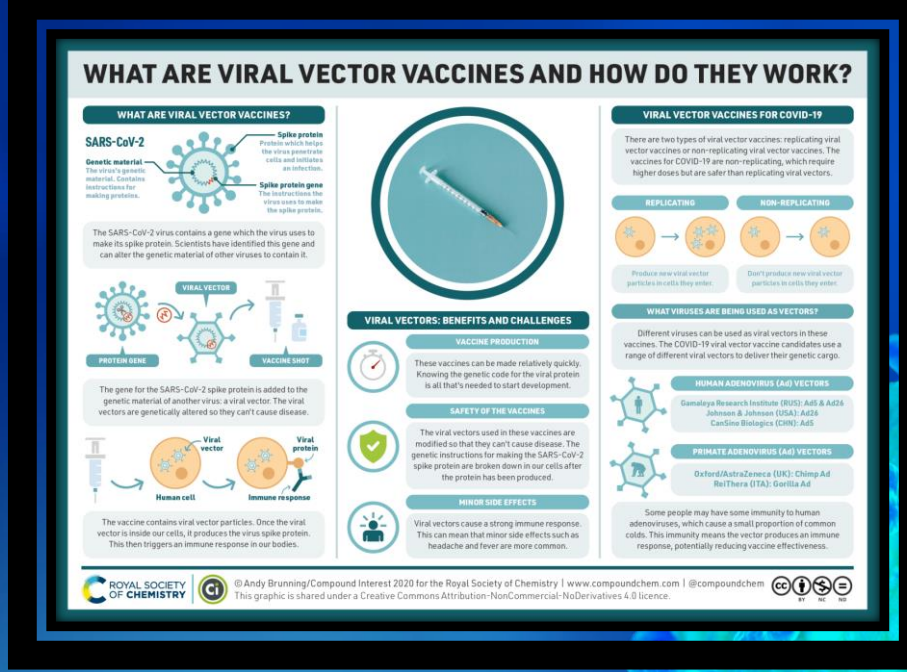
Fig. 1 | **The global COVID-19 vaccine landscape.** The six major types of candidate vaccine for coronavirus disease 2019 (COVID-19) are illustrated (live attenuated virus, recombinant viral vectored, inactivated virus, protein subunit, virus-like particles and nucleic acid based), showing the number of candidate vaccines that are currently under clinical and preclinical development. The nucleic acid-based platform includes both mRNA vaccines (6 clinical and 16 preclinical) and plasmid DNA vaccines (4 clinical and 11 preclinical). Data obtained from REF.[5].

nature REVIEWS IMMUNOLOGY

https://www.nature.com/articles/s41577-020-00434-6

COVID 19 Vaccines

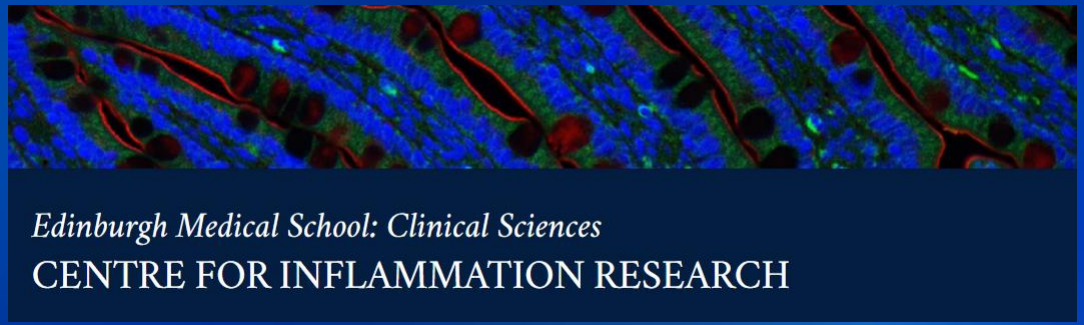




Additional Resources

Video Series from the University of Edinburgh

https://www.ed.ac.uk/inflammation-research/information-public/videos-resources/immune-memory-coronavirus

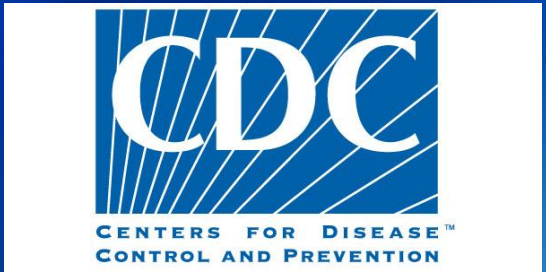


Vaccine ‘Efficacy’ and ‘Effectiveness’

“Vaccine efficacy and vaccine effectiveness measure the proportionate reduction in cases among vaccinated persons”

“Vaccine efficacy is used when a study is carried out under ideal conditions, for example, during a clinical trial”

“Vaccine effectiveness is used when a study is carried out in the ‘real world’”



Phases of the Immune Response

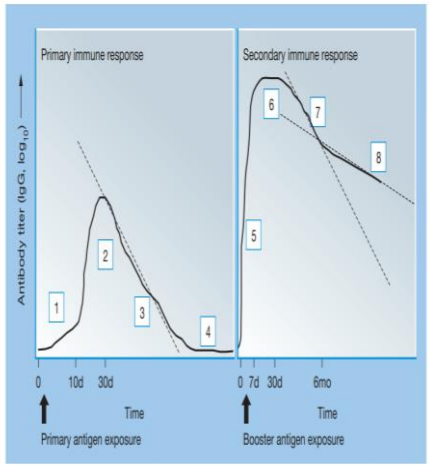
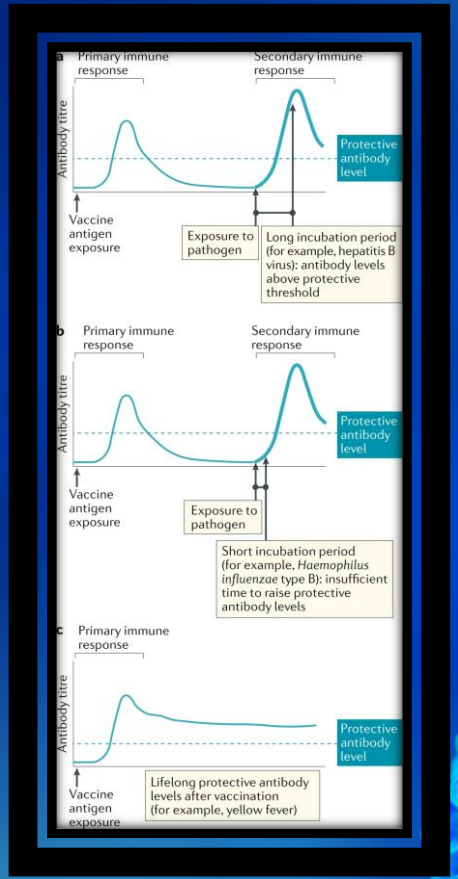
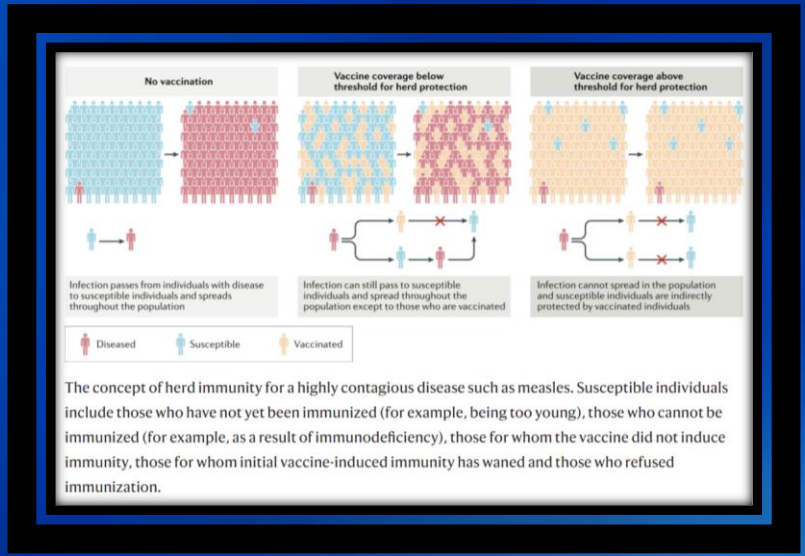


Figure 2.3. Correlation of antibody titers to the various phases of the vaccine response. The initial antigen exposure elicits an extrafollicular response *(1)* that results in the rapid appearance of low IgG antibody titers. As B cells proliferate in germinal centers and differentiate into plasma cells, IgG antibody titers increase up to a peak value *(2)*, usually reached 4 weeks after immunization. The short life span of these plasma cells results in a rapid decline of antibody titers *(3)*, which eventually return to baseline levels *(4)*. In secondary immune responses, booster exposure to antigen reactivates immune memory and results in a rapid (<7 days) increase *(5)* of IgG antibody titer. Short-lived plasma cells maintain peak antibody levels *(6)* during a few weeks—after which serum antibody titers decline initially with the same rapid kinetics as following primary immunization *(7)*. Long-lived plasma cells that have reached survival niches in the bone marrow continue to produce antigen-specific antibodies, which then decline with slower kinetics *(8)*. Note: This generic pattern may not apply to live vaccines triggering long-term IgG antibodies for extended periods.



What is ‘Herd Immunity’

'Herd immunity' aka 'population immunity', is the indirect protection from an infectious disease that happens when immunity develops in a population either through vaccination or past infection



The concept of herd immunity for a highly contagious disease such as measles. Susceptible individuals include those who have not yet been immunized (for example, being too young), those who cannot be immunized (for example, as a result of immunodeficiency), those for whom the vaccine did not induce immunity, those for whom initial vaccine-induced immunity has waned and those who refused immunization.

https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination
https://www.nature.com/articles/s41577-020-00479-7

Vaccine Responses in Healthy Individuals

TABLE 2.4 Determinants of Primary Vaccine Antibody Responses in Healthy People

Determinants	Mechanisms (Presumed)
VACCINE TYPE	
Live vs inactivated	Higher intensity of innate responses through the synergistic activation of several PRRs, higher antigen content following replication, and more prolonged antigen persistence generally result in higher Ab responses to live than to inactivated vaccines.
Protein vs polysaccharide	Recruitment of T-cell help and induction of GCs (i.e., memory induction) results in higher and more prolonged Ab responses to protein or glycoconjugate than to PS vaccines.
Adjuvants	Modulation of antigen delivery and persistence (depot or slow-release formulations) and/or enhancement of Tfh responses (immunomodulator) may support or limit Ab responses.
ANTIGEN NATURE	
Polysaccharide antigens	Failure to induce GCs limits immunogenicity.
Protein antigens	Inclusion of epitopes readily recognized by B cells (B-cell repertoire), inclusion of epitopes readily recognized by Tfh, elicitation of efficient follicular T-cell help, and the capacity of antigen to associate/persist in association with FDCs result in higher Ab responses.
Antigen dose	As a rule, higher Ag doses increase the availability of Ag for B-/T-cell binding and activation and for association with FDCs.
VACCINE SCHEDULE	
Interval between doses	A 3-week minimal interval between primary doses avoids competition between successive waves of primary responses.
Genetic determinants	The capacity of Ag epitopes to associate with a large panel of MHC molecules increases the likelihood of responses in the population. MHC restriction may limit T-cell responses. Gene polymorphisms in molecules critical for B- and T-cell activation/differentiation are likely to affect Ab responses.
Environmental factors	Mostly unidentified
Age at immunization	Early life immune immaturity or age-associated immune senescence

Ab, antibody; Ag, antigen; FDC, follicular dendritic cell; GC, germinal center; MHC, major histocompatibility complex; PRR, pattern-recognition response; PS, polysaccharide; Tfh, follicular T-helper cells.

World Health Organization

Determinants of the Duration of Antibody Responses

TABLE 2.5 Determinants of the Duration of Vaccine Antibody Responses in Healthy People

Determinants	Mechanisms (Presumed)
VACCINE TYPE	
Live vs inactivated	Live vaccines generally induce more sustained Ab responses, presumably through Ag persistence within the host.
Polysaccharide antigens	Failure to generate Tfh cells and GCs limits the induction of memory responses and of high-affinity long-lived plasma cells.
VACCINE SCHEDULE	
Interval between primary doses	A minimal interval of 3 weeks between primary doses allows development of successive waves of Ag-specific primary responses without interference.
Interval before boosting	A minimal interval of 4 months between priming and boosting allows affinity maturation of memory B cells and thus higher secondary responses.
Age at immunization	Early life immune immaturity and age-associated immunosenescence limit the induction/persistence of long-lived plasma cells.
Environmental factors	Mostly unidentified.

Ab, antibody; Ag, antigen; GC, germinal center; Tfh, follicular T-helper cells.

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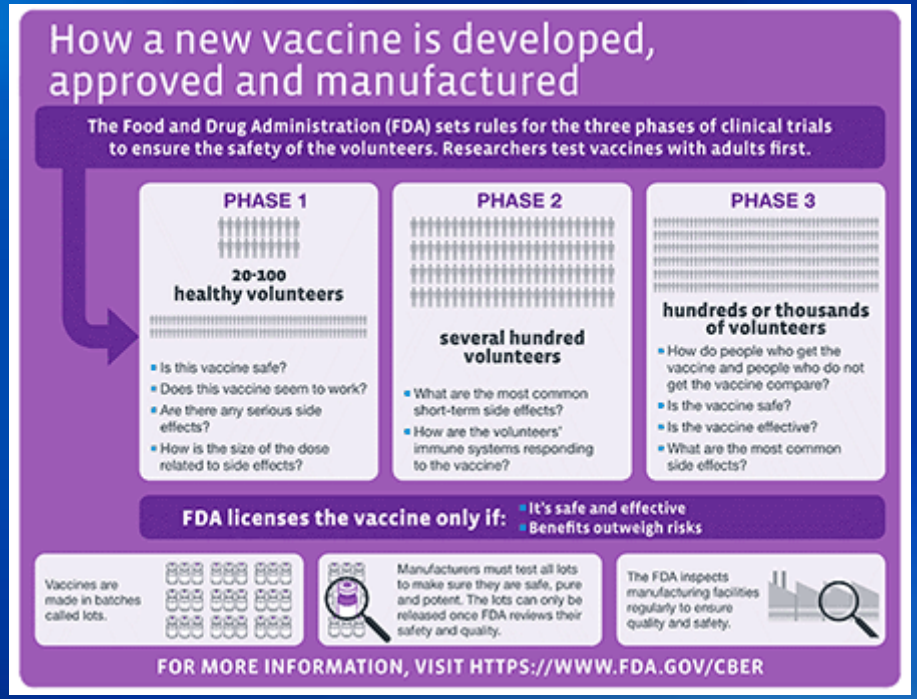
COVID 19 Vaccines and Protective Immunity

- Evidence supports both B and T cell responses to the 3 leading vaccines – Oxford/AZ, Pfizer/BioNTech and Moderna, up to 6 months after infection, and presumed to be similar after vaccination
- Trials of the 2 mRNA vaccines (Pfizer/BioNTech and Moderna) report efficacies of 95% and 94.1% respectively, after 2 dose vaccinations
- The viral vector DNA vaccine by Oxford/AZ reported an average of 70% efficacy, ranging from 62-90% after receiving different dosing regimens
- Johnson and Johnson vaccine: Data to be announced later in January for the late-stage clinical trial, with 45 000 participants enrolled; initial trials showed that 98% of individuals developed antibodies against COVID-19 nearly a month after receiving the vaccination

https://www.bmj.com/content/371/bmj.m4838

Vaccine Safety



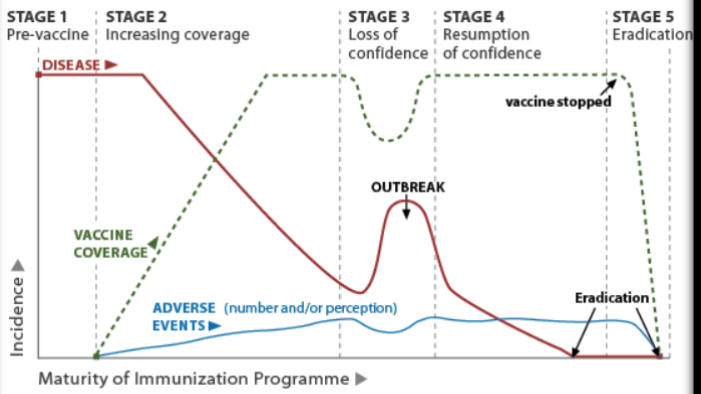
Vaccine Safety Programs

World Health Organization

VACCINE SAFETY IN IMMUNIZATION PROGRAMMES

In the pre-vaccine era, morbidity and mortality caused by infectious diseases that are now preventable were high. Obviously, as vaccines did not exist, there were no adverse events to them yet. The pre-vaccine stage in the graph (**STAGE 1**) is the phase before the vaccine gets introduced.

Pertussis vaccine example



In **STAGE 2**, after an effective vaccine is introduced to prevent a particular disease, an increase in immunization uptake will result in a decrease in disease incidence, but also adverse events (AEFI), real or perceived, may become a major focus. Paradoxically, it is just when vaccine benefits are most apparent and vaccine coverage is highest that vaccine safety concerns are most likely to increase in the general public.

This increased focus on AEFIs, often intensified by media coverage of one or a few case reports, may lead to:

- A loss of confidence in the vaccine by the public,
- A reduction in vaccine coverage,
- A resurgence of the disease to higher or even epidemic levels (**STAGE 3**).

The resurgence of disease or the availability of an alternative vaccine results in renewed public acceptance of vaccination against the disease. Vaccination levels increase and the disease is reduced to earlier low levels (**STAGE 4**).

For vaccine-preventable diseases such as smallpox that can be eradicated, vaccine use can be stopped, thereby removing the risk of any adverse event resulting from its use (**STAGE 5**). To ensure that the cycle displayed in the graph does not repeat, any vaccine safety issue requires timely detection, evaluation, and response efforts to gain and maintain high public confidence.

Reactions to Vaccinations

- Vaccine product-related reaction
- Vaccine quality defect-related reaction
- Immunization error-related reaction
- Immunization anxiety-related reaction
- Coincidental event

Frequency and severity of adverse vaccine reactions

Frequency	Occurrence among persons vaccinated in percent	Severity of reactions

Very common	≥ 10%	**Common and usually minor reactions:**
		• Are part of the immune response to vaccine,
		• Reactions settle on their own,
		• Examples include:
		  ◦ Fever,
		  ◦ Malaise.

Common (frequent)	≥ 1% and < 10%	
Uncommon (infrequent)	≥ 0.1% and < 1%	**Rare, usually more severe reactions:** 1. Usually require clinical management, 2. Examples include: • Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component, • Vaccine specific reactions, such as BCG osteitis.
Rare	≥ 0.01% and < 0.1%	
Very rare	< 0.01%	

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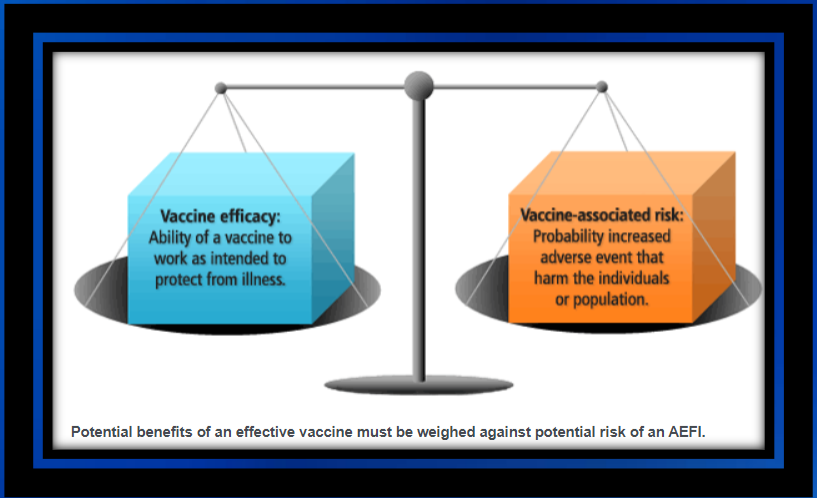
Anaphylaxis is RARE: ~1/1.3 million doses

How does this impact public confidence?

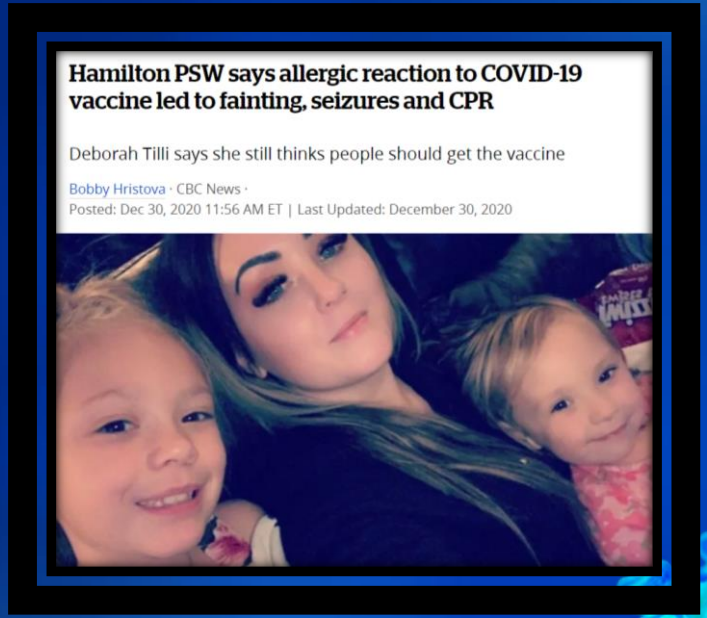


Potential benefits of an effective vaccine must be weighed against potential risk of an AEFI.

World Health Organization

Concerns of Reactions to the COVID Vaccines

- Dec 9, 2020 – UK authorities 'confirmed' 2 cases of anaphylaxis after vaccination
- Dec 19-20 – US CDC had identified 6 case reports of anaphylaxis following Pfizer-BioNTech vaccine (based on clinical criteria)
- As of Jan 6, 29 reported cases in the US (21 between Dec 14-23) out of 5.3 million doses given; the overall 'rate' is 5.5/1 million cases for Pfizer/BioNTech
- Only 2 reported cases secondary to Moderna in the US (although rollout started Dec 21)
- 5 cases (so far) in Canada



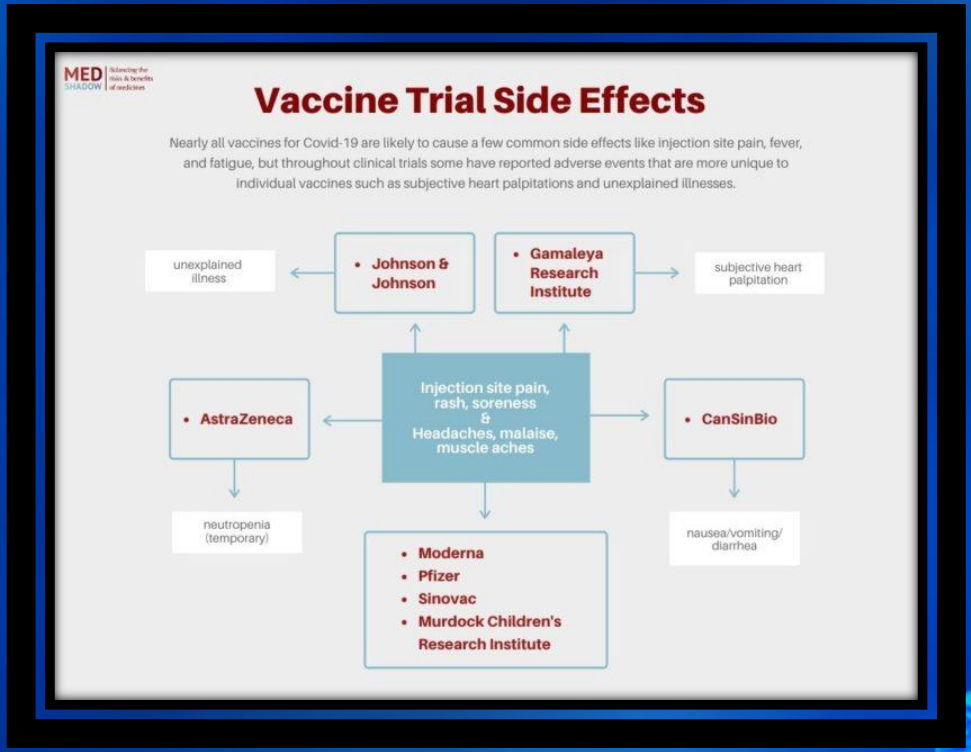
https://www.cdc.gov/mmwr/volumes/70/wr/mm7002e1.htm?s_cid=mm7002e1_w

Trials: Participants with ‘severe adverse reactions with a vaccine/anaphylaxis to any study component’ excluded

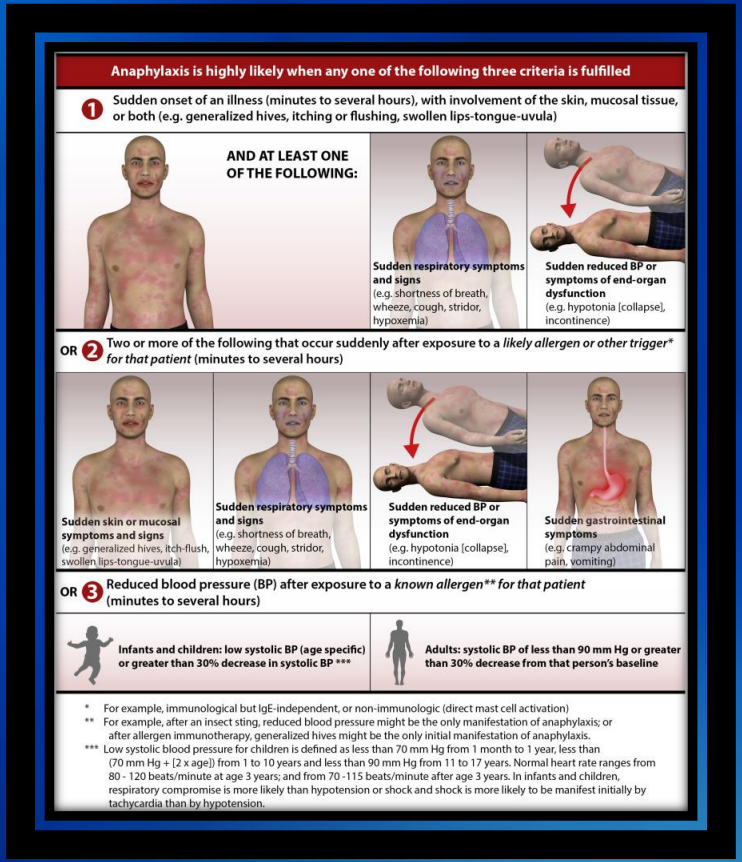
Pfizer/BioNTech (NEJM): Hypersensitivity related adverse events: 0.63% vs placebo 0.51% (137 vs 111), 1 Anaphylactic reaction

Moderna (NEJM): Hypersensitivity adverse events 1.5% vs 1.1% placebo (skin rash/urticaria); 4 reports of Bell’s Palsy, 2 cases of facial swelling in individuals who had received dermal fillers – ‘No anaphylactic reactions’

AstraZeneca/Oxford (Lancet): 1 Anaphylactic reaction in each of the control/study arms

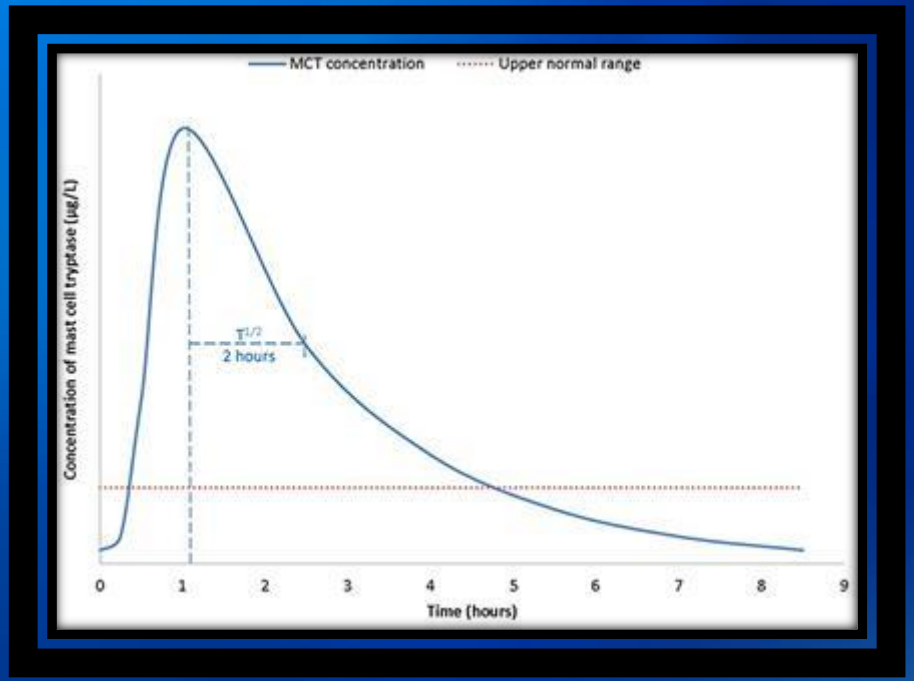


What is Anaphylaxis?



The Journal of Allergy and Clinical Immunology

Biomarkers in Anaphylaxis



Tryptase is rapidly released from mast cells and peaks ~1–2 h post allergen exposure. T1/2 is ~2 h. Concentrations return to base line within 24 h after complete resolution of symptoms and signs of anaphylaxis

frontiers in Immunology

Recommendations on Management of Reactions

Distinguishing allergic reactions from other types of reactions

Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reaction	Vaccine side effects (local and systemic)
Timing after vaccination	Most occur within 15-30 minutes of vaccination	Most occur within 15 minutes	Median of 1 to 3 days after vaccination (with most occurring day after vaccination)
Signs and symptoms			
Constitutional	Feeling of impending doom	Feeling warm or cold	Fever, chills, fatigue
Cutaneous	Skin symptoms present in ~90% of people with anaphylaxis, including pruritus, urticaria, flushing, angioedema	Pallor, diaphoresis, clammy skin, sensation of facial warmth	Pain, erythema or swelling at injection site; lymphadenopathy in same arm as vaccination
Neurologic	Confusion, disorientation, dizziness, lightheadedness, weakness, loss of consciousness	Dizziness, lightheadedness, syncope (often after prodromal symptoms for a few seconds or minutes), weakness, changes in vision (such as spots of flickering lights, tunnel vision), changes in hearing	Headache
Respiratory	Shortness of breath, wheezing, bronchospasm, stridor, hypoxia	Variable; if accompanied by anxiety, may have an elevated respiratory rate	N/A
Cardiovascular	Hypotension, tachycardia	Variable; may have hypotension or bradycardia during syncopal event	N/A
Gastrointestinal	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea may occur
Musculoskeletal	N/A	N/A	Myalgia, arthralgia
Vaccine recommendations			
Receive 2nd dose of mRNA COVID-19	No	Yes	Yes

https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

Product Monographs for the mRNA Vaccines

Ingredients* included in mRNA COVID-19 vaccines

Description	Pfizer-BioNTech	Moderna
mRNA	nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2	nucleoside-modified mRNA encoding the viral spike (S) glycoprotein of SARS-CoV-2
Lipids	2[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide	PEG2000-DMG: 1,2-dimyristoyl-rac-glycerol, methoxypolyethylene glycol
	1,2-distearoyl-sn-glycero-3-phosphocholine	1,2-distearoyl-sn-glycero-3-phosphocholine
	cholesterol	cholesterol
	(4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate)	SM-102: heptadecan-9-yl 8-((2-hydroxyethyl) (6-oxo-6-(undecyloxy) hexyl) amino) octanoate
Salts, sugars, buffers	potassium chloride	Tromethamine
	monobasic potassium phosphate	Tromethamine hydrochloride
	sodium chloride	Acetic acid
	dibasic sodium phosphate dihydrate	Sodium acetate
	sucrose	sucrose

https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

PEG – Polyethylene Glycol

- Primary ingredient in osmotic laxatives and oral bowel preparations for colonoscopy procedures
- Inactive ingredient or excipient in medications
- Used in a process called pegylation to improve therapeutic activity of some medications
- Cross-reactive hypersensitivity between PEG and polysorbates can occur
  - Polysorbates are included as an excipient in some vaccines and other therapeutic agents

Information on whether a medication contains PEG, a PEG derivative, or polysorbates can be found in the package insert. The NIH DailyMed database may also be used as a resource

Medications that contain PEG and/or polysorbate are described in the supplemental materials of Stone CA, et al. "Immediate hypersensitivity to polyethylene glycols and polysorbates: more common than we have recognized." *The Journal of Allergy and Clinical Immunology: In Practice* 7.5 (2019): 1533-1540.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6706272/pdf/nihms-1019221.pdf

https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

Potential Causes of ‘Reactions’

- PEG (Polyethylene Glycol) – Exceedingly rare, according to the FDA, only 4 reported cases/yr
- Based on our knowledge of how allergies develop, we may see more individuals having reactions with the second dose
- Johnson and Johnson vaccine contains polysorbate – There are ‘recommendations’ to test for PEG in advance; however, this is not readily available here or feasible

Allergic Living

https://www.allergicliving.com/2021/01/03/likely-more-than-one-cause-for-covid-19-vaccine-reactions/

Current CDC Recommendations

Contraindications to mRNA COVID-19 vaccination

Pfizer-BioNTech and Moderna COVID-19 vaccines

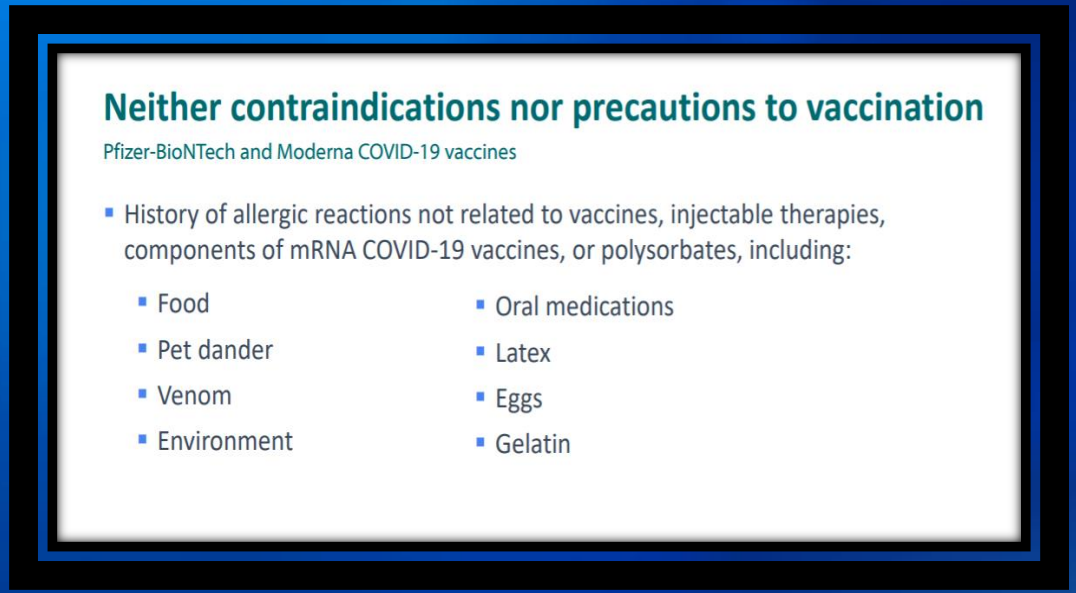
- Contraindications to either of the mRNA COVID-19 vaccines:
  - Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or to any of its components
  - Immediate allergic reaction of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components (including polyethylene glycol [PEG])*
  - Immediate allergic reaction of any severity to polysorbate (due to potential cross-reactive hypersensitivity with the vaccine ingredient PEG)*
- Persons with an immediate allergic reaction to the first dose of an mRNA vaccine should not receive additional doses of either of the mRNA COVID-19 vaccines

* These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available).

1

https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

CDC Recommendations



Neither contraindications nor precautions to vaccination

Pfizer-BioNTech and Moderna COVID-19 vaccines

- History of allergic reactions not related to vaccines, injectable therapies, components of mRNA COVID-19 vaccines, or polysorbates, including:
  - Food
  - Pet dander
  - Venom
  - Environment
  - Oral medications
  - Latex
  - Eggs
  - Gelatin

*NB – No specific guidelines yet on 'special populations' ie pregnancy, <16, immunocompromised individuals
In general, vaccinate if benefit > risk

https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf

COVID Vaccine Recommendations

Summary: Triage of persons presenting for mRNA COVID-19 vaccination

MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
ALLERGIES History of allergies that are unrelated to components of an mRNA COVID-19 vaccine†, other vaccines, or injectable therapies, such as: • Allergy to oral medications (including the oral equivalent of an injectable medication) • History of food, pet, insect, venom, environmental, latex, etc., allergies • Family history of allergies **ACTIONS** • 30 minute observation period: Persons with a history of anaphylaxis (due to any cause) • 15 minute observation period: All other persons	**ALLERGIES** • History of any immediate allergic reaction‡ to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines† or polysorbate, as these are contraindicated) **ACTIONS:** • Risk assessment • Consider deferral of vaccination and/or referral to allergist-immunologist • 30 minute observation period if vaccinated	**ALLERGIES** History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines†: • Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components • Immediate allergic reaction‡ of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components^ (including polyethylene glycol)# • Immediate allergic reaction of any severity to polysorbate^# **ACTIONS** • Do not vaccinate# • Consider referral to allergist-immunologist

† Refers only to mRNA COVID-19 vaccines currently authorized in the United States (i.e., Pfizer-BioNTech, Moderna COVID-19 vaccines)

‡ Immediate allergic reaction to a vaccine or medication is defined as any hypersensitivity-related signs or symptoms consistent with urticaria, angioedema, respiratory distress (e.g., wheezing, stridor), or anaphylaxis that occur within four hours following administration.

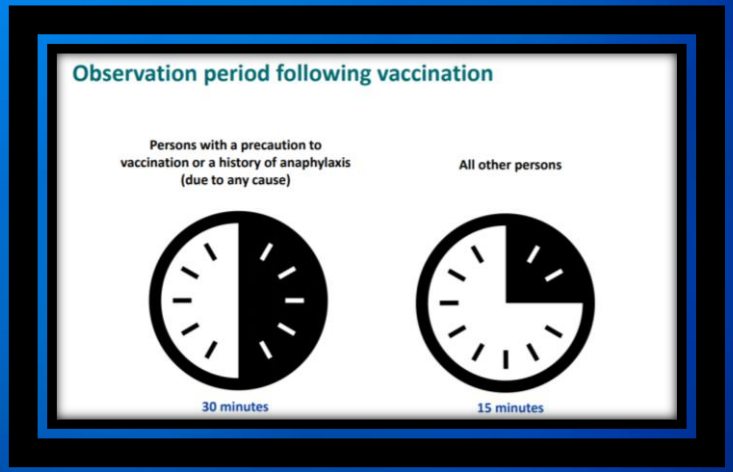
^ See Appendix A for a list of ingredients. Note: Polyethylene glycol (PEG), an ingredient in both mRNA COVID-19 vaccines, is structurally related to polysorbate and cross-reactive hypersensitivity between these compounds may occur. Information on ingredients of a vaccine or medication (including PEG, a PEG derivative, or polysorbates) can be found in the package insert.

These persons should not receive mRNA COVID-19 vaccination at this time unless they have been evaluated by an allergist-immunologist and it is determined that the person can safely receive the vaccine (e.g., under observation, in a setting with advanced medical care available)

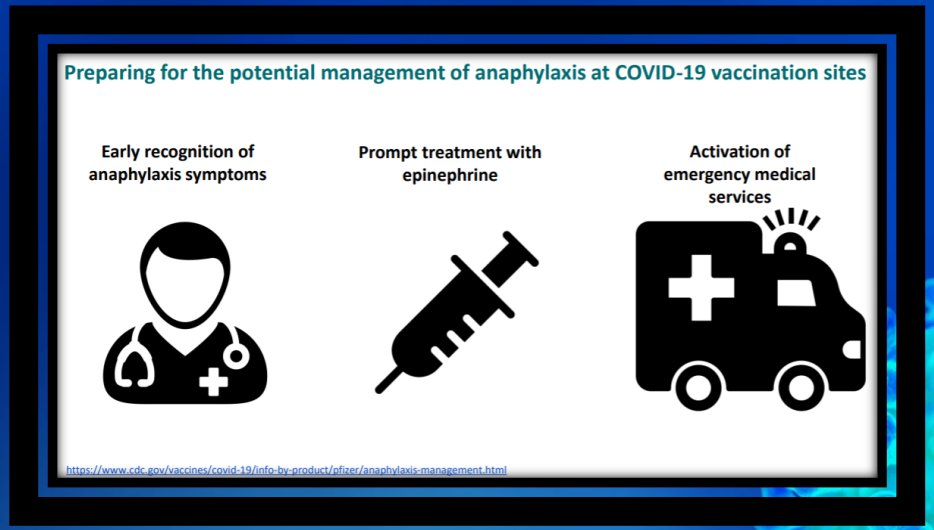
Health Canada / Government of Canada Resources

https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information/page-15-contents-immunizing-agents-available-use-canada.html

Monitoring and Management



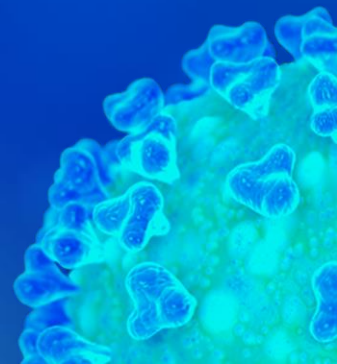
Epinephrine is ALWAYS first-line!



A word on dosing regimens and proposed changes

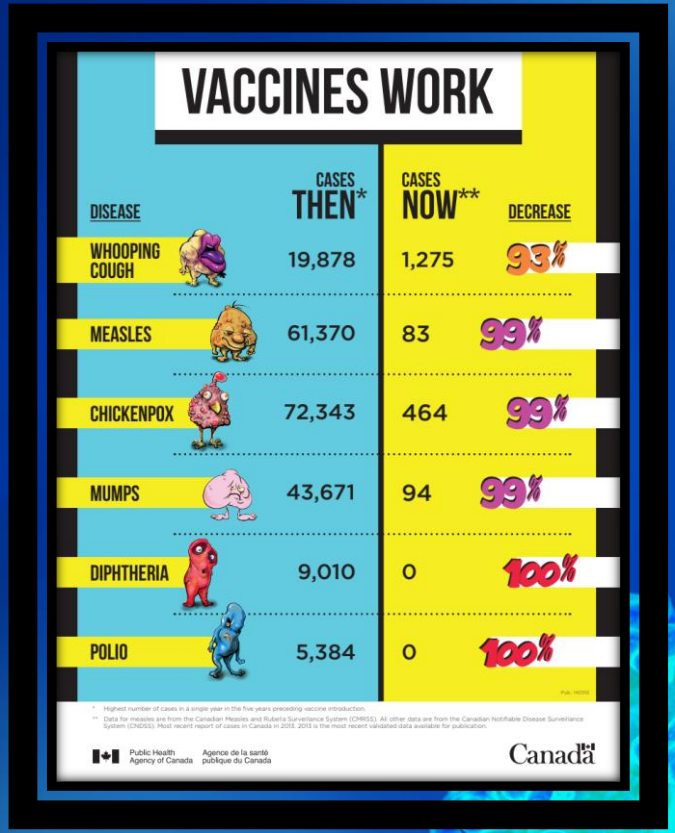
"We know that some of these discussions about changing the dosing schedule or dose are based on a belief that changing the dose or dosing schedule can help get more vaccine to the public faster. However, making such changes that are not supported by adequate scientific evidence may ultimately be counterproductive to public health."

FDA



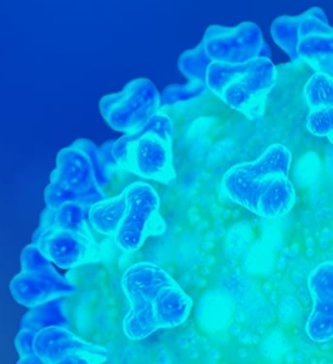
Take Home Messages

- Vaccinations are safe and effective
- Current recommendations advise avoidance of vaccination with COVID-19 vaccines in those with known hypersensitivities to any component
- Long term follow up and data is needed and will be gathered in assessing the duration of the immune response
- Hopefully more vaccines to come!



References and Resources

- WHO - https://vaccine-safety-training.org/
- CDC Emergency Preparedness Guidelines - https://emergency.cdc.gov/coca/ppt/2020/dec-30-coca-call.pdf
- Slides adapted from December 19-20, 2020 ACIP meeting presentation: Anaphylaxis Following m-RNA COVID-19 Vaccine Receipt, by
- Thomas Clark, MD, MPH, https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2020-12/slides-12-19/05-COVID-CLARK.pdf
- https://www.who.int/news-room/q-a-detail/vaccines-and-immunization-what-is-vaccination
- https://www.nature.com/articles/s41577-020-00479-7
- https://www.jacionline.org/article/S0091-6749(20)30105-6/abstract
- https://www.allergicliving.com/2021/01/03/likely-more-than-one-cause-for-covid-19-vaccine-reactions/
- https://www.frontiersin.org/articles/10.3389/fimmu.2019.00494/full



Thank You!

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Do you have any questions?

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