

The background of the slide features a microscopic view of COVID-19 virus particles. On the left, a large, detailed cluster of spherical virus particles is shown, each covered in characteristic surface spikes. Several smaller, individual virus particles are scattered across the dark blue background. The overall aesthetic is scientific and clinical.

# COVID-19

Knowledge Translation to Communities:  
Vaccine Safety & Efficacy

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Clinical Immunology, Allergy, Internal Medicine



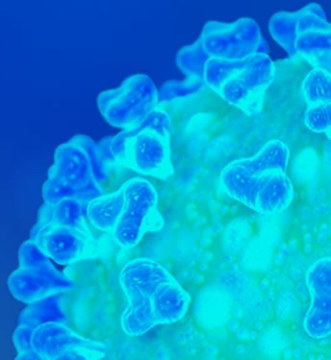
# Disclosures

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.<sup>2</sup>

Why are vaccines so special?

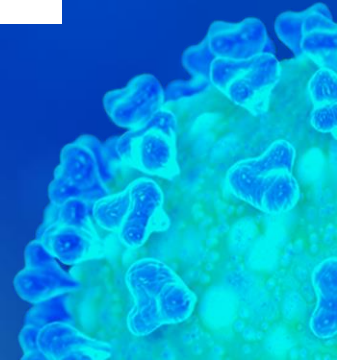
- ❑ **Vaccines promote health:** unlike many other health interventions, they help healthy people stay healthy, removing a major obstacle to human development.
- ❑ **Vaccines have an expansive reach:** they protect individuals, communities, and entire populations (the eradication of smallpox is a case 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).<sup>3</sup>
- ❑ **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.<sup>4</sup>



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



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# Types of Corona Viruses and Strains

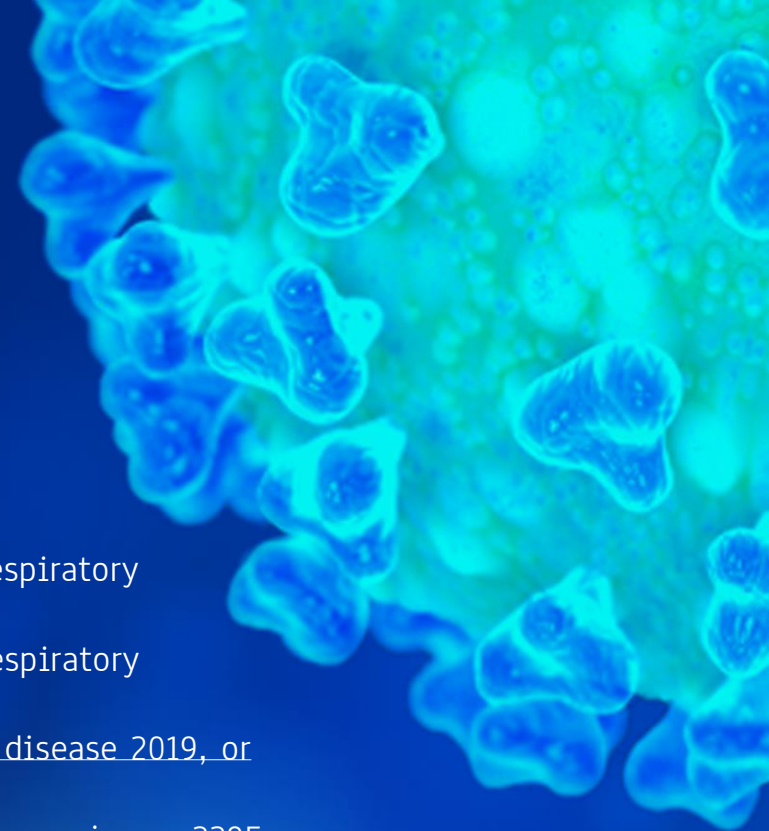
## Common human coronaviruses

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

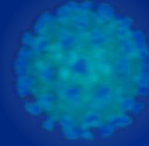
## Other human coronaviruses

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.



# COVID-19 Variants



“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:

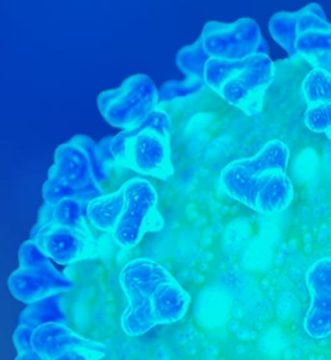
Spread more easily from person to person

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.”



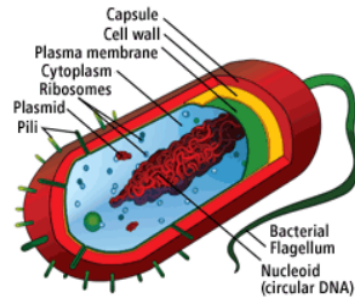
# The Immune Response

## 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.

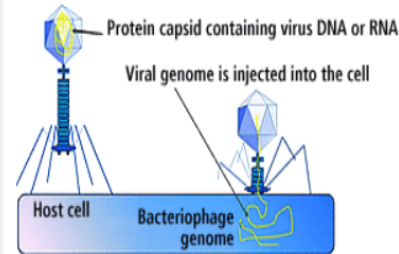
The pathogens causing the vaccine-preventable diseases described in this module are mainly microorganisms such as bacteria or viruses.

- ❑ **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](http://wikipedia.org)



Virus infecting cell.

Source: [wikipedia.org](http://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.



VACCINE SAFETY BASICS  
e-learning course



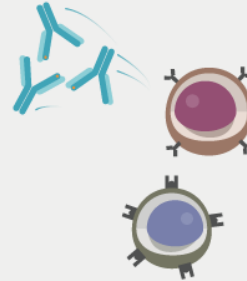
# Knowledge Translation to Communities

## COVID-19, long-term immunity and vaccines

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.

# What's in a vaccine?

## Water

The main ingredient.



I'm a  
vaccine



## Preservatives and stabilisers

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



**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.*



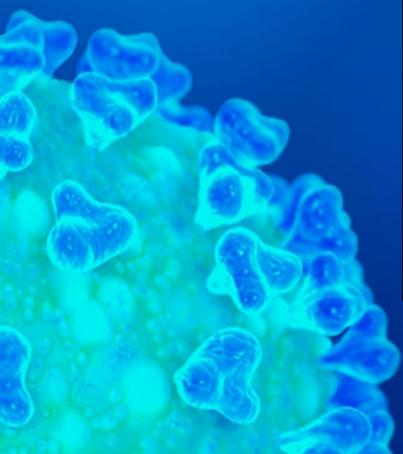
## Active ingredient

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



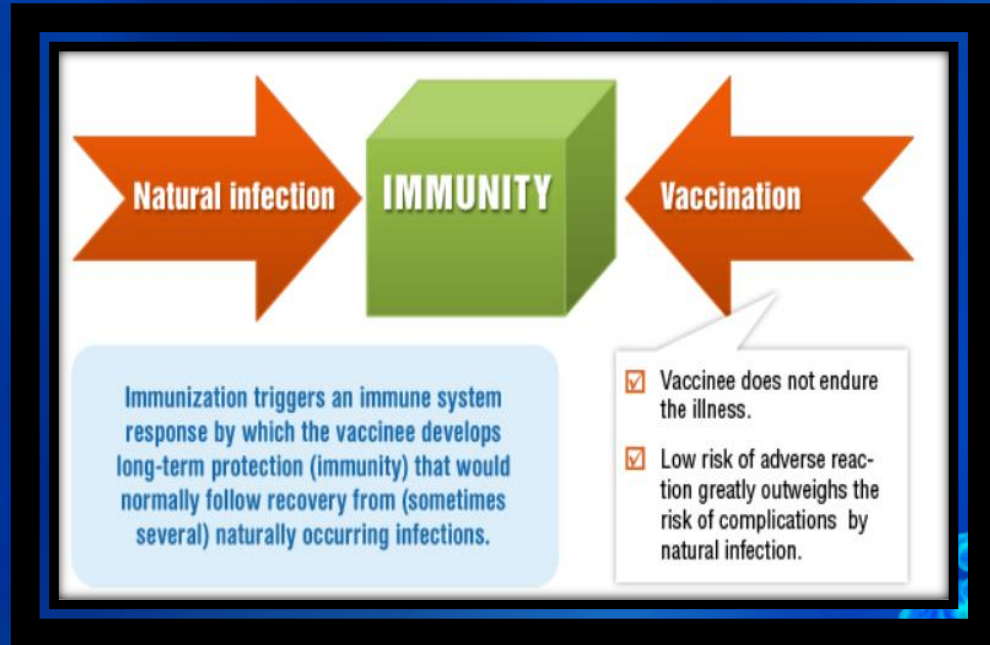
## Adjuvants

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.*










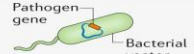



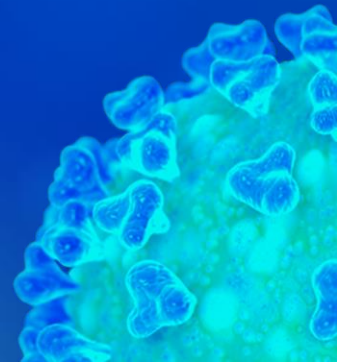
# How do Vaccines Work?

“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”



# 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		<i>Haemophilus influenzae</i> type B, pneumococcal, meningococcal, typhoid	1987 ( <i>H. influenzae</i> type b)
Viral vectored		Ebola	2019 (Ebola)
Nucleic acid vaccine		SARS-CoV-2	2020 (SARS-CoV-2)
Bacterial vectored		Experimental	-
Antigen-presenting cell		Experimental	-



## Types of vaccines for COVID-19

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

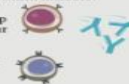
The SARS-CoV-2 virus causes COVID-19 illness. Each type of vaccine for COVID-19 works differently to introduce SARS-CoV-2 antigens, which are unique proteins of the virus and can trigger an immune response. Vaccines stimulate a specific response without causing illness.













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.

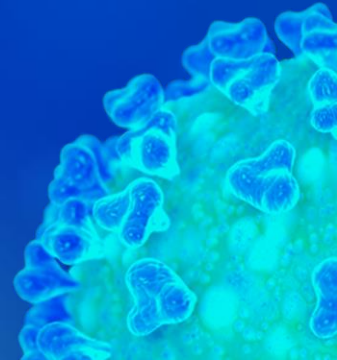
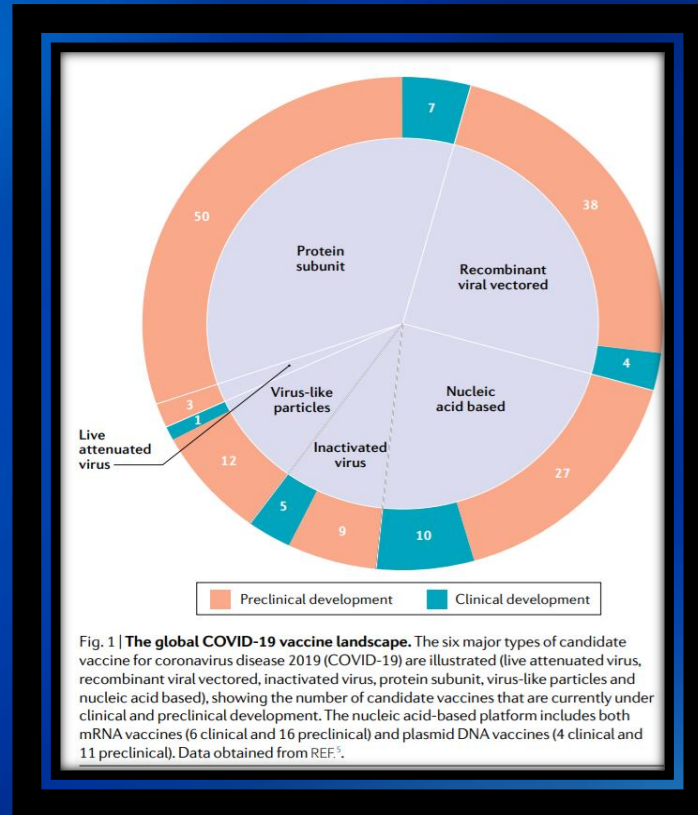
T cells that can help stimulate B cells and kill any infected cells.



*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
<b>Inactivated vaccines</b> 	Contain killed SARS-CoV-2 virus.	May need to be administered with an adjuvant to boost immune response. 	Influenza vaccine	Sinovac, Sinopharm
<b>Attenuated vaccines</b> 	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
<b>Protein vaccines</b> 	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
<b>Viral vector vaccines</b> 	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, Canisius, Gamaleya
<b>Genetic vaccines (nucleic acid vaccines)</b> 	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

# Vaccine Development in COVID 19



# COVID 19 Vaccines

## WHAT ARE RNA VACCINES AND HOW DO THEY WORK?

### WHAT ARE RNA VACCINES?

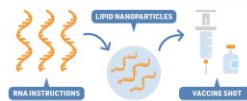
#### SARS-CoV-2

**Viral RNA**  
The virus's genetic material. Contains instructions for making proteins.

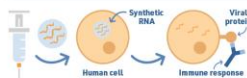
**Spike protein**  
Protein which helps the virus penetrate cells and initiates an infection.



The genetic code of the SARS-CoV-2 virus is made up of RNA. Scientists isolated the part of this genetic code that contains the instructions for making the virus's spike protein.



Synthetic RNA which codes for the virus spike protein is packed in lipid nanoparticles (very small fat droplets). This stops our bodies' enzymes breaking it down and helps our cells take it in.



Once the synthetic RNA is inside one of our cells, the cell follows the RNA instructions to produce the virus spike protein. Its production then triggers an immune response in our bodies.



### RNA VACCINES: BENEFITS AND CHALLENGES



#### VACCINE PRODUCTION

RNA is easy to make in a lab, so RNA vaccines can be developed quicker than other vaccines.



#### SAFETY OF THE VACCINES

RNA can't cause infection and is broken down by normal processes in our cells. An RNA vaccine hasn't been licensed for use in humans before but they've been under development for several years for other viruses, including influenza, HIV, and Zika.



#### STORAGE AND TRANSPORT

Some RNA vaccines must be stored at low temperatures to remain stable, which makes storage and transport more challenging.

### RNA VACCINES FOR COVID-19

Several proposed vaccines for COVID-19 are RNA vaccines. They can be based on two different types of RNA.

#### mRNA vaccines

Moderna  
Pfizer & BioNTech  
CureVac

#### saRNA vaccine

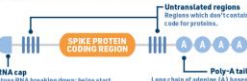
Imperial College  
Arcurus

### mRNA AND saRNA: WHAT'S THE DIFFERENCE?

The structures of mRNA and saRNA are similar but have a key difference, as the diagrams below show.

#### mRNA

mRNA stands for messenger ribonucleic acid



#### saRNA

saRNA stands for self-amplifying ribonucleic acid



As saRNA produces more copies of itself once it's in a cell, it can be given in smaller doses than mRNA vaccines. This makes the cost per dose lower and means higher numbers of doses can be produced from the same volume of vaccine.



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## WHAT ARE VIRAL VECTOR VACCINES AND HOW DO THEY WORK?

### WHAT ARE VIRAL VECTOR VACCINES?

#### SARS-CoV-2

**Genetic material**  
The virus's genetic material. Contains instructions for making proteins.

**Spike protein**  
Protein which helps the virus penetrate cells and initiates an infection.

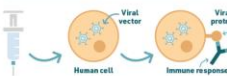
**Spike protein gene**  
The instructions the virus uses to make the spike protein.



The SARS-CoV-2 virus contains a gene which the virus uses to make its spike protein. Scientists have identified this gene and can alter the genetic material of other viruses to contain it.



The gene for the SARS-CoV-2 spike protein is added to the genetic material of another virus: a viral vector. The viral vectors are genetically altered so they can't cause disease.



The vaccine contains viral vector particles. Once the viral vector is inside our cells, it produces the virus spike protein. This then triggers an immune response in our bodies.



### VIRAL VECTORS: BENEFITS AND CHALLENGES



#### VACCINE PRODUCTION

These vaccines can be made relatively quickly. Knowing the genetic code for the viral protein is all that's needed to start development.



#### SAFETY OF THE VACCINES

The viral vectors used in these vaccines are modified so that they can't cause disease. The genetic instructions for making the SARS-CoV-2 spike protein are broken down in our cells after the protein has been produced.



#### MINOR SIDE EFFECTS

Viral vectors cause a strong immune response. This can mean that minor side effects such as headache and fever are more common.

### VIRAL VECTOR VACCINES FOR COVID-19

There are two types of viral vector vaccines: replicating viral vector vaccines or non-replicating viral vector vaccines. The vaccines for COVID-19 are non-replicating, which require higher doses but are safer than replicating viral vectors.

#### REPLICATING



Produce new viral vector particles inside the target cells.

#### NON-REPLICATING



Don't produce new viral vector particles inside the target cells.

### WHAT VIRUSES ARE BEING USED AS VECTORS?

Different viruses can be used as viral vectors in these vaccines. The COVID-19 viral vector vaccine candidates use a range of different viral vectors to deliver their genetic cargo.

#### HUMAN ADENOVIRUS (Ad) VECTORS

Geneveva Research Institute (EUR): Ad5 & Ad26  
Johnson & Johnson (USA): Ad26  
Cansino Biologics (CHN): Ad5

#### PRIMATE ADENOVIRUS (Ad) VECTORS

Oxford/AstraZeneca (UK): Chimp Ad  
ReliThera (ITA): Gorilla Ad

Some people may have some immunity to human adenoviruses, which cause a small proportion of common colds. This immunity means the vector produces an immune response, potentially reducing vaccine effectiveness.



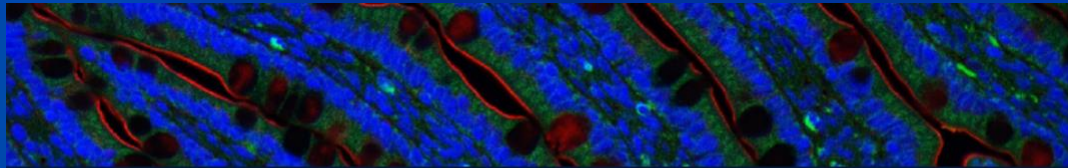
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# Additional Resources

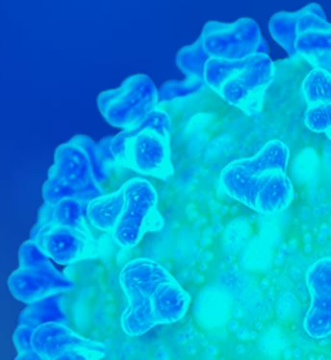
Video Series from the University of Edinburgh

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



*Edinburgh Medical School: Clinical Sciences*

**CENTRE FOR INFLAMMATION RESEARCH**



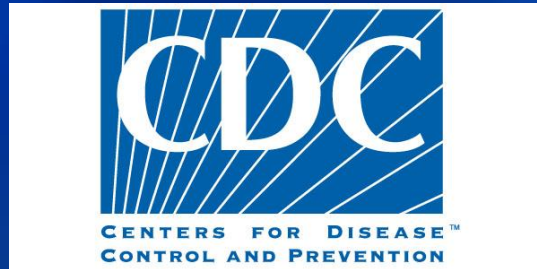


# Vaccine 'Efficacy' and 'Effectiveness'

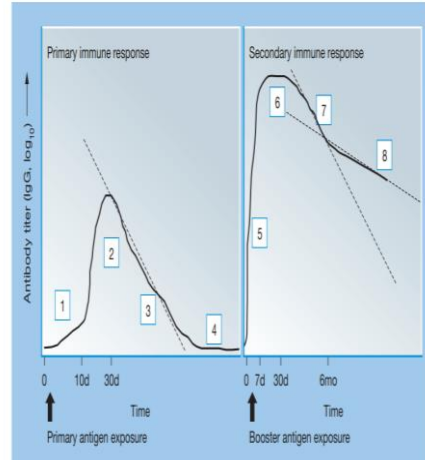
"Vaccine efficacy and vaccine effectiveness measure the proportionate reduction in cases among vaccinated persons"

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

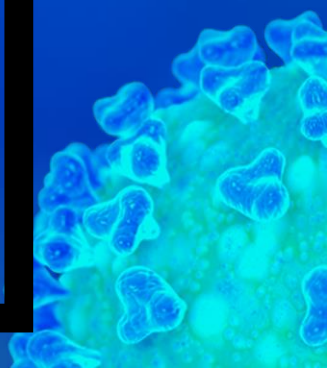
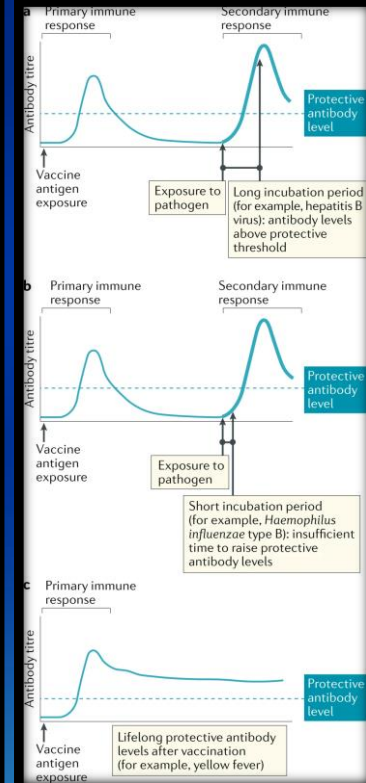
"Vaccine effectiveness is used when a study is carried out in the 'real world'"



# Phases of the Immune Response

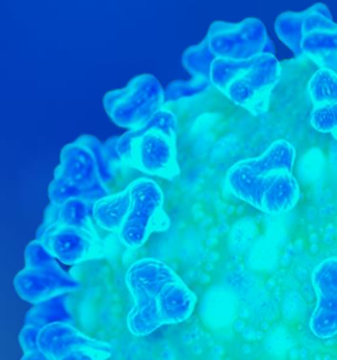
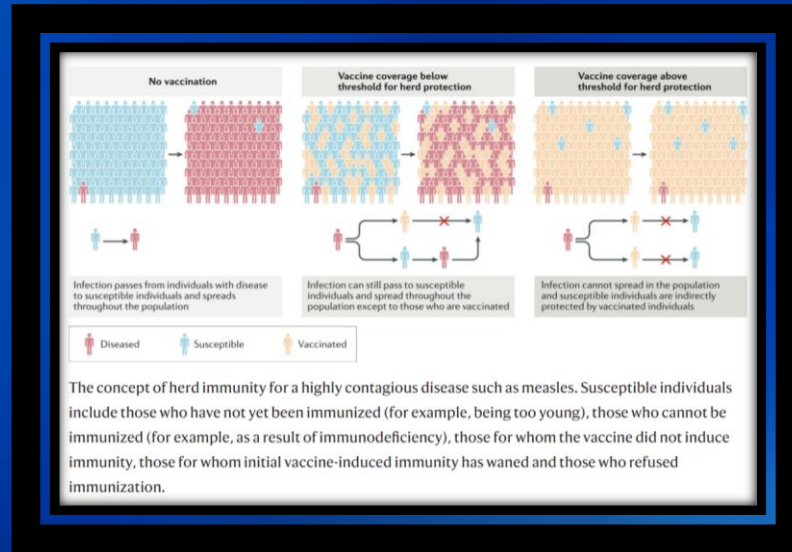


**Figure 23.** Correlation of antibody titers to the various phases of the vaccine response. The initial antigen exposure elicits an extracellular response (1) that results in the rapid appearance of low IgG antibody titers. As B cells proliferate in germinal centers and differentiate into plasma cells, 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



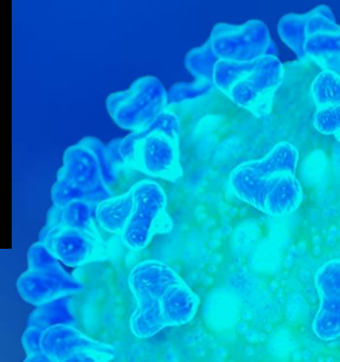
# Vaccine Responses in Healthy Individuals

**TABLE 2.4** Determinants of Primary Vaccine Antibody Responses in Healthy People

Determinants	Mechanisms (Presumed)
<b>VACCINE TYPE</b>	
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 T <sub>H</sub> responses (immunomodulator) may support or limit Ab responses.
<b>ANTIGEN NATURE</b>	
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 T <sub>H</sub> , 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.
<b>VACCINE SCHEDULE</b>	
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; T <sub>H</sub> , follicular T-helper cells.	



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# Determinants of the Duration of Antibody Responses

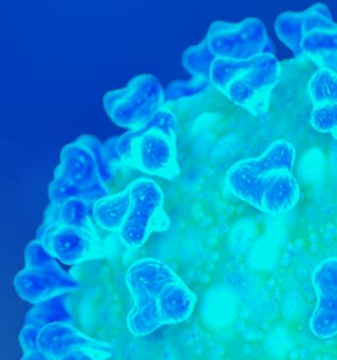
**TABLE 2.5** Determinants of the Duration of Vaccine Antibody Responses in Healthy People

Determinants	Mechanisms (Presumed)
<b>VACCINE TYPE</b>	
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.
<b>VACCINE SCHEDULE</b>	
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

# Vaccine Safety

## How a new vaccine is developed, approved and manufactured

The Food and Drug Administration (FDA) sets rules for the three phases of clinical trials to ensure the safety of the volunteers. Researchers test vaccines with adults first.

### PHASE 1



**20-100  
healthy volunteers**

- Is this vaccine safe?
- Does this vaccine seem to work?
- Are there any serious side effects?
- How is the size of the dose related to side effects?

### PHASE 2



**several hundred  
volunteers**

- What are the most common short-term side effects?
- How are the volunteers' immune systems responding to the vaccine?

### PHASE 3



**hundreds or thousands  
of volunteers**

- How do people who get the vaccine and people who do not get the vaccine compare?
- Is the vaccine safe?
- Is the vaccine effective?
- What are the most common side effects?

**FDA licenses the vaccine only if:**

- It's safe and effective
- Benefits outweigh risks

Vaccines are made in batches called lots.



Manufacturers must test all lots to make sure they are safe, pure and potent. The lots can only be released once FDA reviews their safety and quality.

The FDA inspects manufacturing facilities regularly to ensure quality and safety.



FOR MORE INFORMATION, VISIT [HTTPS://WWW.FDA.GOV/CBER](https://www.fda.gov/cber)

# Vaccine Safety Programs

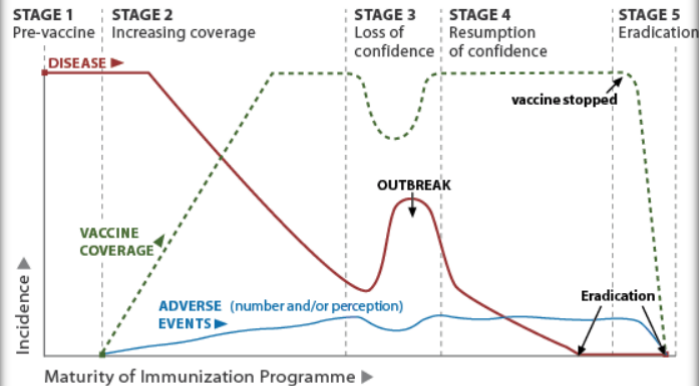


World Health Organization

## 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*

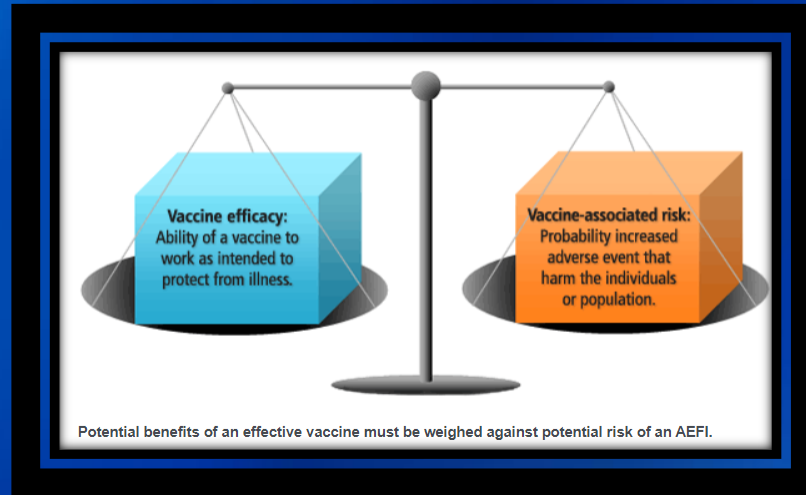
Frequency	Occurrence among persons vaccinated in percent	Severity of reactions
Very common	$\geq 10\%$	<b>Common and usually minor reactions:</b> <ul style="list-style-type: none"><li>• Are part of the immune response to vaccine,</li><li>• Reactions settle on their own,</li><li>• Examples include:<ul style="list-style-type: none"><li>◦ Fever,</li><li>◦ Malaise.</li></ul></li></ul>
Common (frequent)	$\geq 1\%$ and $< 10\%$	
Uncommon (infrequent)	$\geq 0.1\%$ and $< 1\%$	<b>Rare, usually more severe reactions:</b> <ol style="list-style-type: none"><li>1. Usually require clinical management,</li><li>2. Examples include:<ul style="list-style-type: none"><li>• Severe allergic reaction (e.g., anaphylaxis) including an exaggerated response to the vaccine antigen or component,</li><li>• Vaccine specific reactions, such as BCG osteitis.</li></ul></li></ol>
Rare	$\geq 0.01\%$ and $< 0.1\%$	
Very rare	$< 0.01\%$	



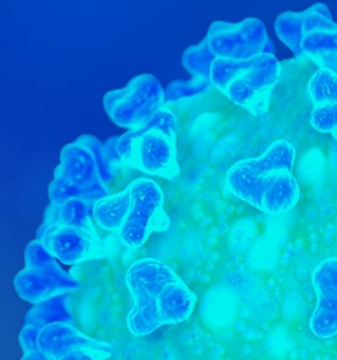
**VACCINE SAFETY BASICS**  
e-learning course

Anaphylaxis is RARE: ~1/1.3 million doses

# How does this impact public confidence?



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

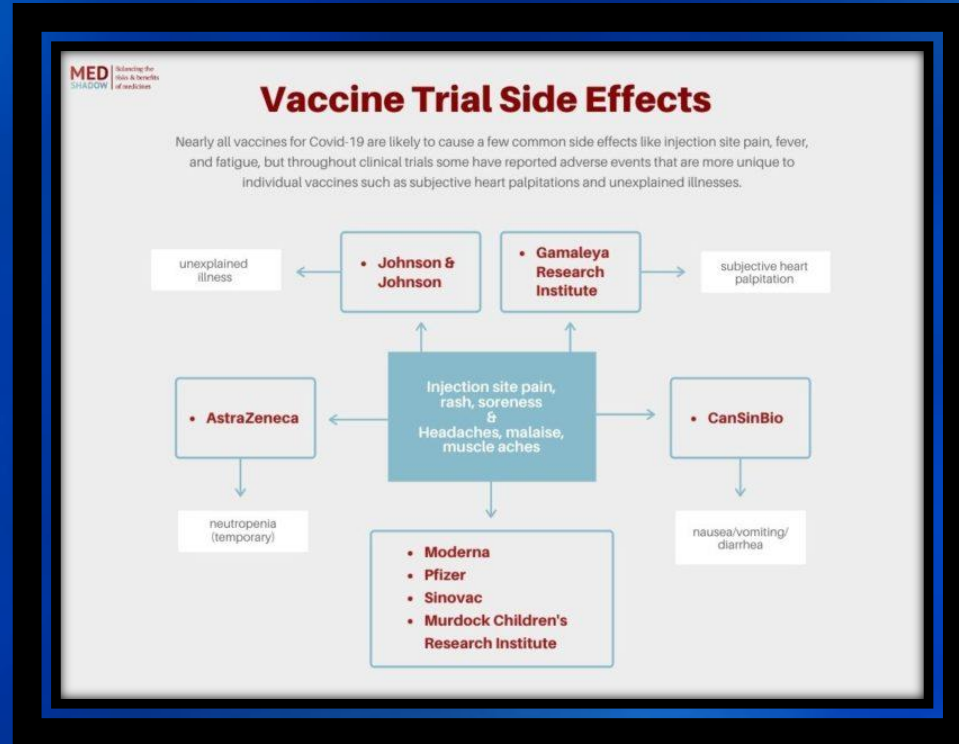


Trials: Participants with 'severe adverse reactions with a vaccine/anaphylaxis to any study component' excluded

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?





Anaphylaxis is highly likely when any one of the following three criteria is fulfilled

**1** Sudden onset of an illness (minutes to several hours), with involvement of the skin, mucosal tissue, or both (e.g. generalized hives, itching or flushing, swollen lips-tongue-uvula)

**AND AT LEAST ONE OF THE FOLLOWING:**

 <p>Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)</p>	 <p>Sudden respiratory symptoms and signs (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)</p>	 <p>Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)</p>
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**OR 2** Two or more of the following that occur suddenly after exposure to a likely allergen or other trigger\* for that patient (minutes to several hours)

 <p>Sudden skin or mucosal symptoms and signs (e.g. generalized hives, itch-flush, swollen lips-tongue-uvula)</p>	 <p>Sudden respiratory symptoms (e.g. shortness of breath, wheeze, cough, stridor, hypoxemia)</p>	 <p>Sudden reduced BP or symptoms of end-organ dysfunction (e.g. hypotonia [collapse], incontinence)</p>	 <p>Sudden gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)</p>
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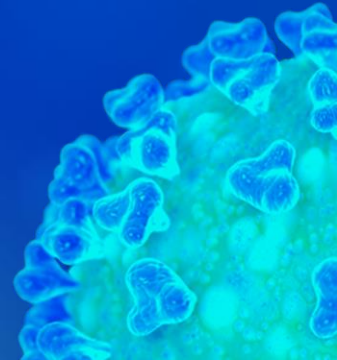
**OR 3** Reduced blood pressure (BP) after exposure to a known allergen\*\* for that patient (minutes to several hours)

 <p>Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP ***</p>	 <p>Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline</p>
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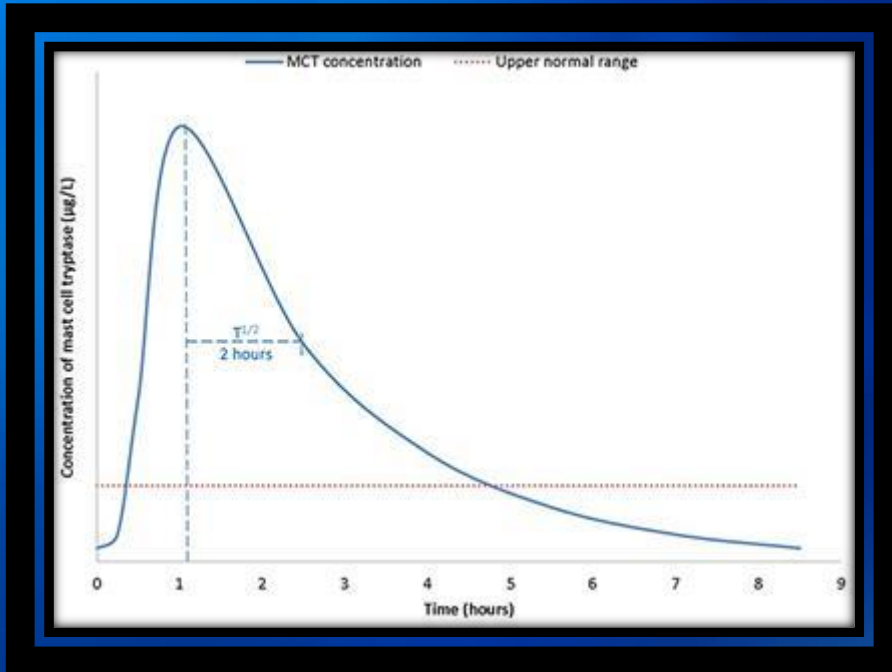
\* For example, immunological but IgE-independent, or non-immunologic (direct mast cell activation)

\*\* For example, after an insect sting, reduced blood pressure might be the only manifestation of anaphylaxis; or after allergen immunotherapy, generalized hives might be the only initial manifestation of anaphylaxis.

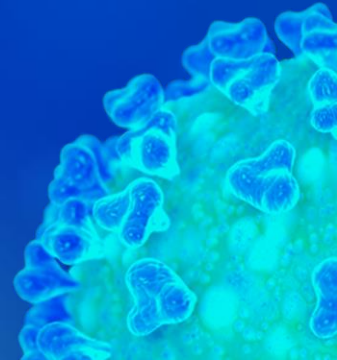
\*\*\* Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years and less than 90 mm Hg from 11 to 17 years. Normal heart rate ranges from 80 - 120 beats/minute at age 3 years; and from 70 - 115 beats/minute after age 3 years. In infants and children, respiratory compromise is more likely than hypotension or shock and shock is more likely to be manifest initially by tachycardia than by hypotension.



# Biomarkers in Anaphylaxis



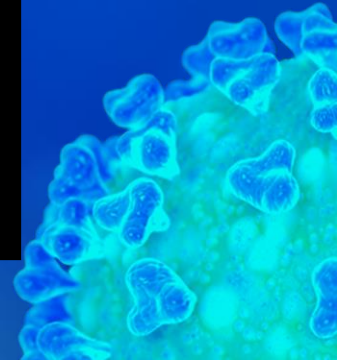
Tryptase is rapidly released from mast cells and peaks ~1-2 h post allergen exposure. T<sub>1/2</sub> is ~2 h. Concentrations return to base line within 24 h after complete resolution of symptoms and signs of anaphylaxis



# Recommendations on Management of Reactions

## Distinguishing allergic reactions from other types of reactions

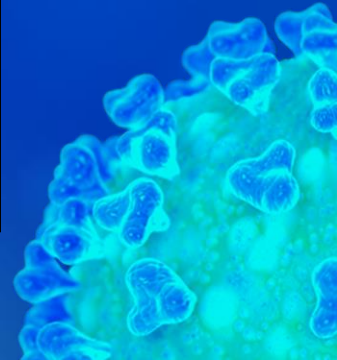
Characteristic	Immediate allergic reactions (including anaphylaxis)	Vasovagal reaction	Vaccine side effects (local and systemic)
<b>Timing after vaccination</b>	Most occur within 15-30 minutes of vaccination	Most occur within 15 minutes	Median of 1 to 3 days after vaccination (with most occurring day after vaccination)
<b>Signs and symptoms</b>			
<b>Constitutional</b>	Feeling of impending doom	Feeling warm or cold	Fever, chills, fatigue
<b>Cutaneous</b>	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
<b>Neurologic</b>	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
<b>Respiratory</b>	Shortness of breath, wheezing, bronchospasm, stridor, hypoxia	Variable; if accompanied by anxiety, may have an elevated respiratory rate	N/A
<b>Cardiovascular</b>	Hypotension, tachycardia	Variable; may have hypotension or bradycardia during syncopal event	N/A
<b>Gastrointestinal</b>	Nausea, vomiting, abdominal cramps, diarrhea	Nausea, vomiting	Vomiting or diarrhea may occur
<b>Musculoskeletal</b>	N/A	N/A	Myalgia, arthralgia
<b>Vaccine recommendations</b>			
Receive 2 <sup>nd</sup> dose of mRNA COVID-19	No	Yes	Yes



# 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



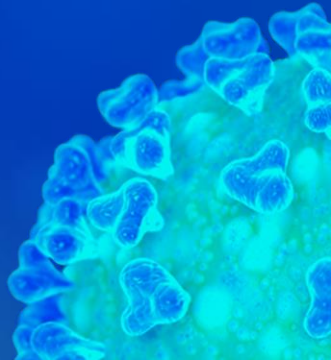


# PEG – Polyethylene Glycol

- 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



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

# Current CDC Recommendations

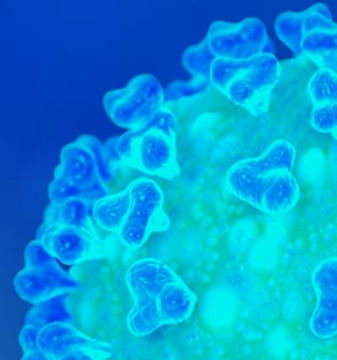
## Contraindications to mRNA COVID-19 vaccination

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



# CDC Recommendations

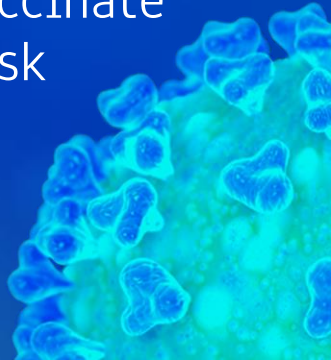
## Neither contraindications nor precautions to vaccination

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

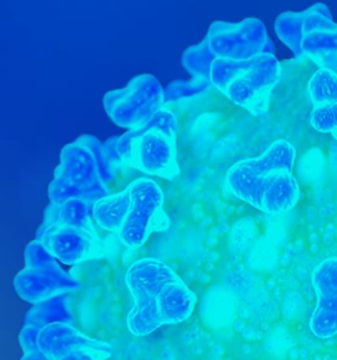
MAY PROCEED WITH VACCINATION	PRECAUTION TO VACCINATION	CONTRAINDICATION TO VACCINATION
<p><b>ALLERGIES</b> History of allergies that are unrelated to components of an mRNA COVID-19 vaccine<sup>‡</sup>, other vaccines, or injectable therapies, such as:</p> <ul style="list-style-type: none"><li>• Allergy to oral medications (including the oral equivalent of an injectable medication)</li><li>• History of food, pet, insect, venom, environmental, latex, etc., allergies</li><li>• Family history of allergies</li></ul> <p><b>ACTIONS</b></p> <ul style="list-style-type: none"><li>• 30 minute observation period: Persons with a history of anaphylaxis (due to any cause)</li><li>• 15 minute observation period: All other persons</li></ul>	<p><b>ALLERGIES</b></p> <ul style="list-style-type: none"><li>• History of any immediate allergic reaction<sup>‡</sup> to vaccines or injectable therapies (except those related to component of mRNA COVID-19 vaccines<sup>‡</sup> or polysorbate, as these are contraindicated)</li></ul> <p><b>ACTIONS:</b></p> <ul style="list-style-type: none"><li>• Risk assessment</li><li>• Consider deferral of vaccination and/or referral to allergist-immunologist</li><li>• 30 minute observation period if vaccinated</li></ul>	<p><b>ALLERGIES</b> History of the following are contraindications to receiving either of the mRNA COVID-19 vaccines:</p> <ul style="list-style-type: none"><li>• Severe allergic reaction (e.g., anaphylaxis) after a previous dose of an mRNA COVID-19 vaccine or any of its components</li><li>• Immediate allergic reaction<sup>‡</sup> of any severity to a previous dose of an mRNA COVID-19 vaccine or any of its components<sup>†</sup> (including polyethylene glycol)<sup>#</sup></li><li>• Immediate allergic reaction of any severity to polysorbate<sup>‡</sup><sup>#</sup></li></ul> <p><b>ACTIONS</b></p> <ul style="list-style-type: none"><li>• Do not vaccinate<sup>#</sup></li><li>• Consider referral to allergist-immunologist</li></ul>

<sup>‡</sup> Refers only to mRNA COVID-19 vaccines currently authorized in the United States (i.e., Pfizer-BioNTech, Moderna COVID-19 vaccines)

<sup>‡</sup> 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.

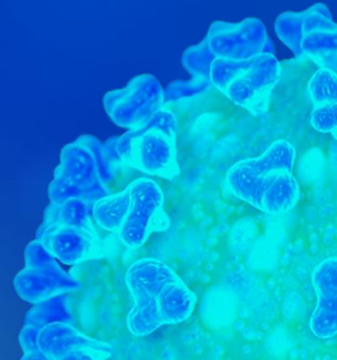
<sup>†</sup> See Appendix A for a list of ingredients. Note: Polyethylene glycol (PEG), an ingredient in both mRNA COVID-19 vaccines, is structurally related to polysorbate and cross-reactive hypersensitivity between these compounds may occur. Information on ingredients of a vaccine or medication (including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

<sup>#</sup> 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).

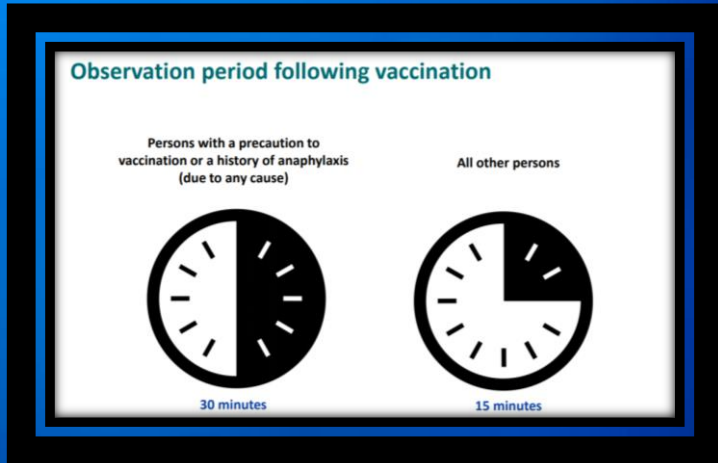


# Health Canada / Government of Canada Resources

<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!

**Preparing for the potential management of anaphylaxis at COVID-19 vaccination sites**

Early recognition of anaphylaxis symptoms	Prompt treatment with epinephrine	Activation of emergency medical services
		

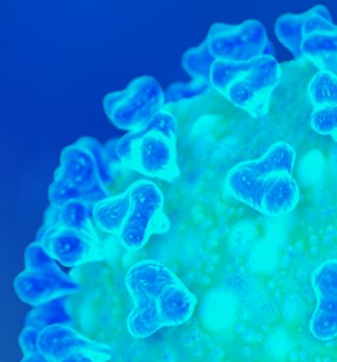
<https://www.cdc.gov/vaccines/covid-19/info-by-product/pfizer/anaphylaxis-management.html>

# 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.”

The logo for the U.S. Food and Drug Administration (FDA), consisting of the letters "FDA" in a bold, white, sans-serif font centered within a teal square.

**FDA**





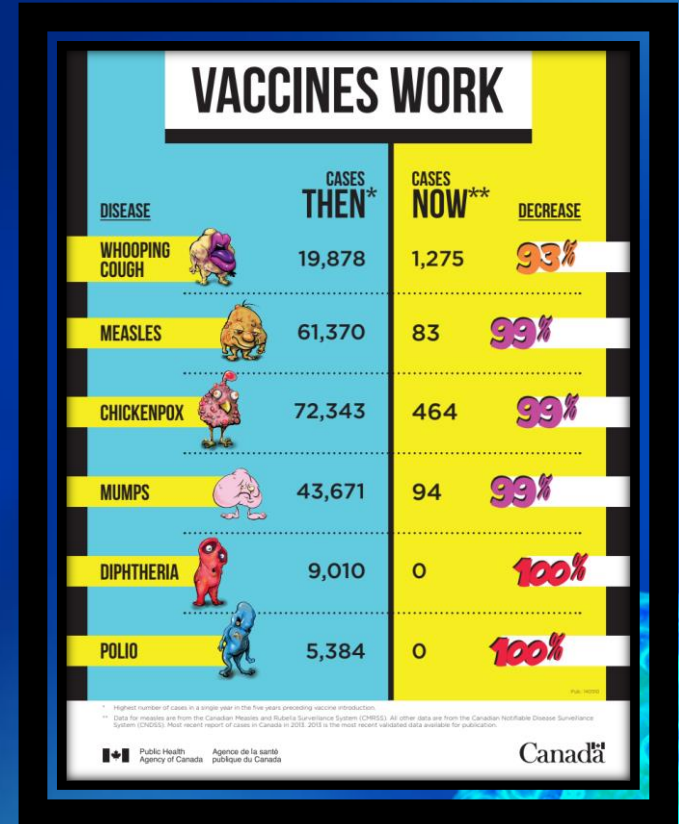
# Take Home Messages

Vaccinations are safe and effective

Current recommendations advise avoidance of vaccination with COVID-19 vaccines in those with known hypersensitivities to any component

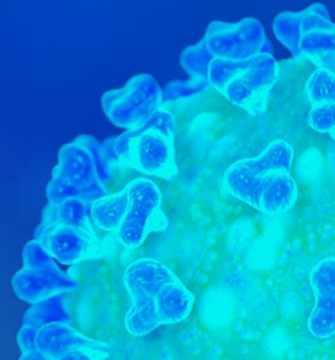
Long term follow up and data is needed and will be gathered in assessing the duration of the immune response

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.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!

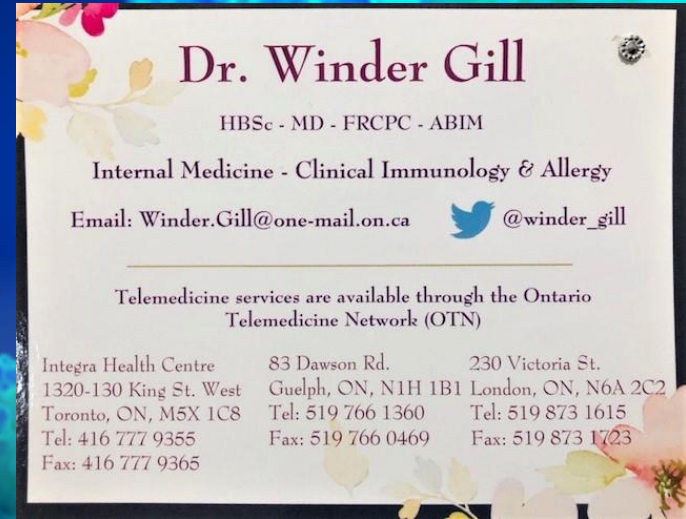


@winder\_gill

Do you have any questions?

Winder.Gill@one-mail.on.ca


CREDITS: This presentation template was created by Slidesgo, including icons by Flaticon, and infographics & images by Freepik

A business card for Dr. Winder Gill. The card has a white background with a decorative floral border on the left and bottom. The text is in a serif font. At the top right is a small circular logo. The card lists her name, credentials, specialty, email, and Twitter handle. It also mentions telemedicine services and provides contact information for three locations: Toronto, Guelph, and London.

**Dr. Winder Gill**

HBSc - MD - FRCPC - ABIM

Internal Medicine - Clinical Immunology & Allergy

Email: [Winder.Gill@one-mail.on.ca](mailto:Winder.Gill@one-mail.on.ca)  [@winder\\_gill](https://twitter.com/winder_gill)

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Telemedicine services are available through the Ontario Telemedicine Network (OTN)

Integra Health Centre 1320-130 King St. West Toronto, ON, M5X 1C8 Tel: 416 777 9355 Fax: 416 777 9365	83 Dawson Rd. Guelph, ON, N1H 1B1 Tel: 519 766 1360 Fax: 519 766 0469	230 Victoria St. London, ON, N6A 2C2 Tel: 519 873 1615 Fax: 519 873 1723
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