CORONAVIRUS
UPDATE
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Update on
COVID-19 vaccines & immune response

THE LATEST ON THE COVID-19
GLOBAL SITUATION & VACCINES

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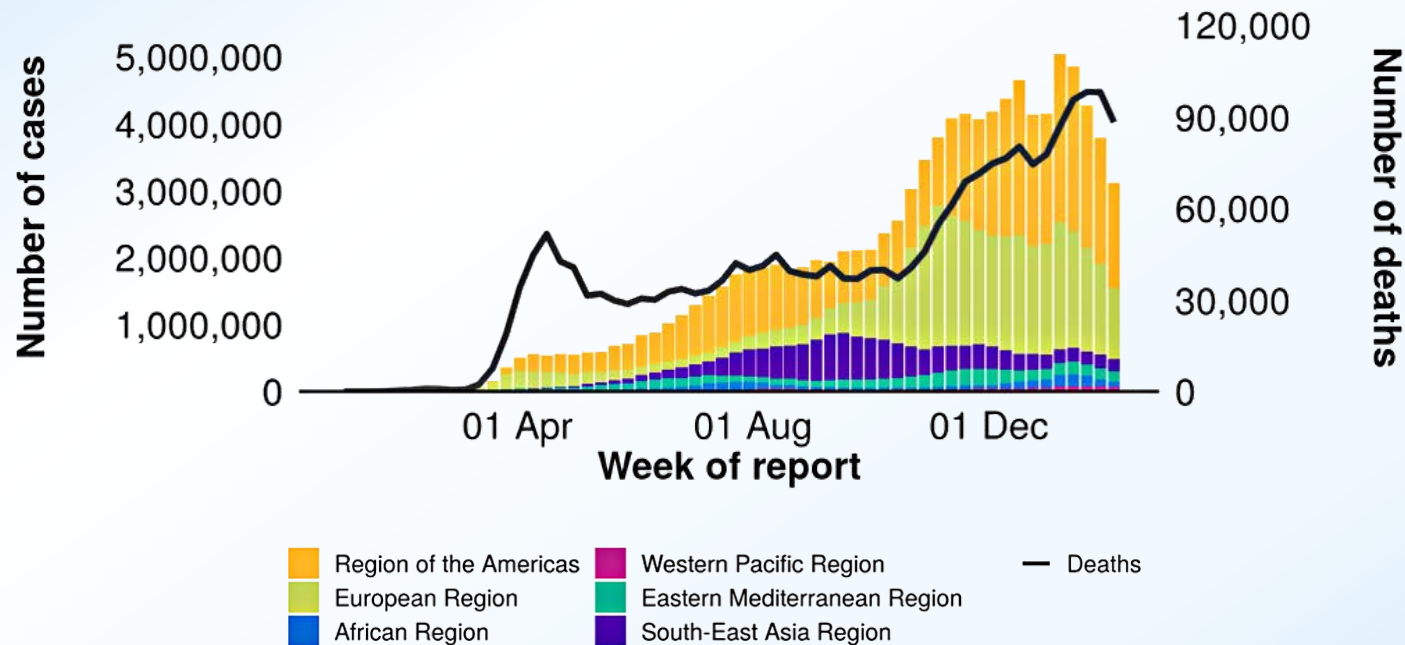
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Current global situation

- **Cases: > 116 million**
- **Deaths: > 2.5 million**

CHECK OUT THE LATEST GLOBAL SITUATION

WHO Coronavirus Disease (COVID-19) Dashboard

Legend:
- Region of the Americas
- European Region
- African Region
- Western Pacific Region
- Eastern Mediterranean Region
- South-East Asia Region
- — Deaths

Data are incomplete for the current week. Cases depicted by bars; deaths depicted by line

Immune response to a viral infection

Two types of immunity are:

- **Innate immunity**
  - ➤ General immediate response to ANY infection

- **Adaptive immunity**
  - ➤ Specific response to an infection
  - ➤ Involves the **cellular response** (T cells) and the **antibody response** (B cells)

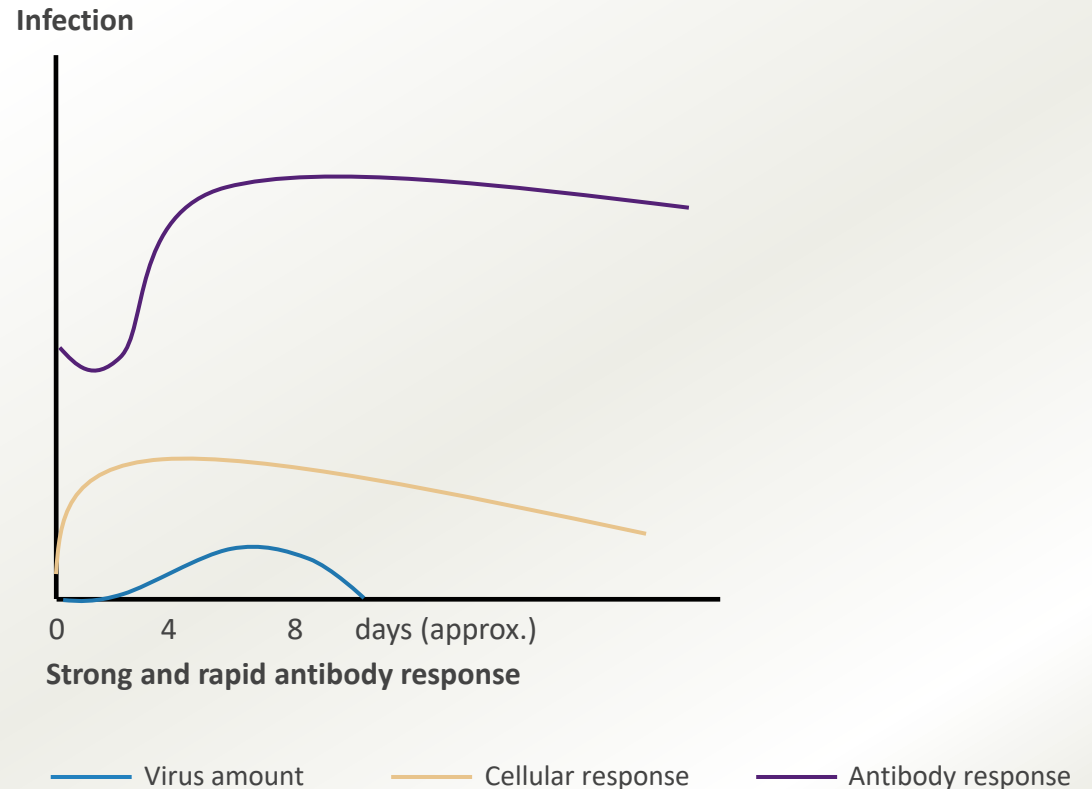- Innate immune response is immediate; whereas cellular & antibody response usually starts after 6 to 8 days

Figure. Immune response to viral infection

INCUBATION PERIOD (DAYS)   6   8

Symptoms
Innate immune response
Virus detectable
Cellular response
Early antibodies (IgM) response
Late antibodies (IgG) response

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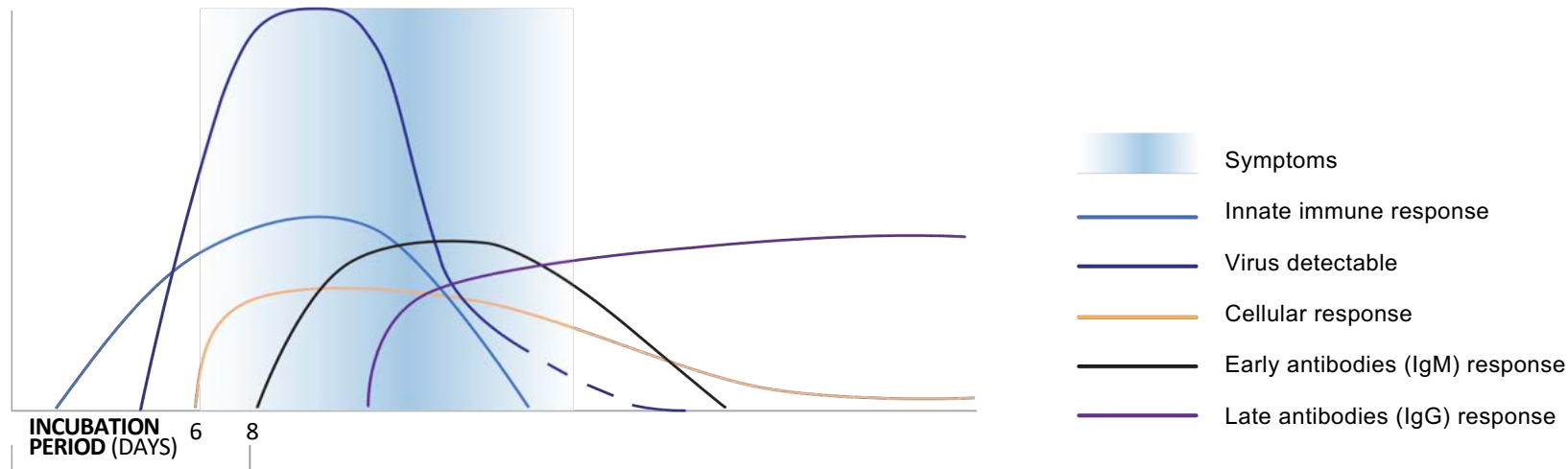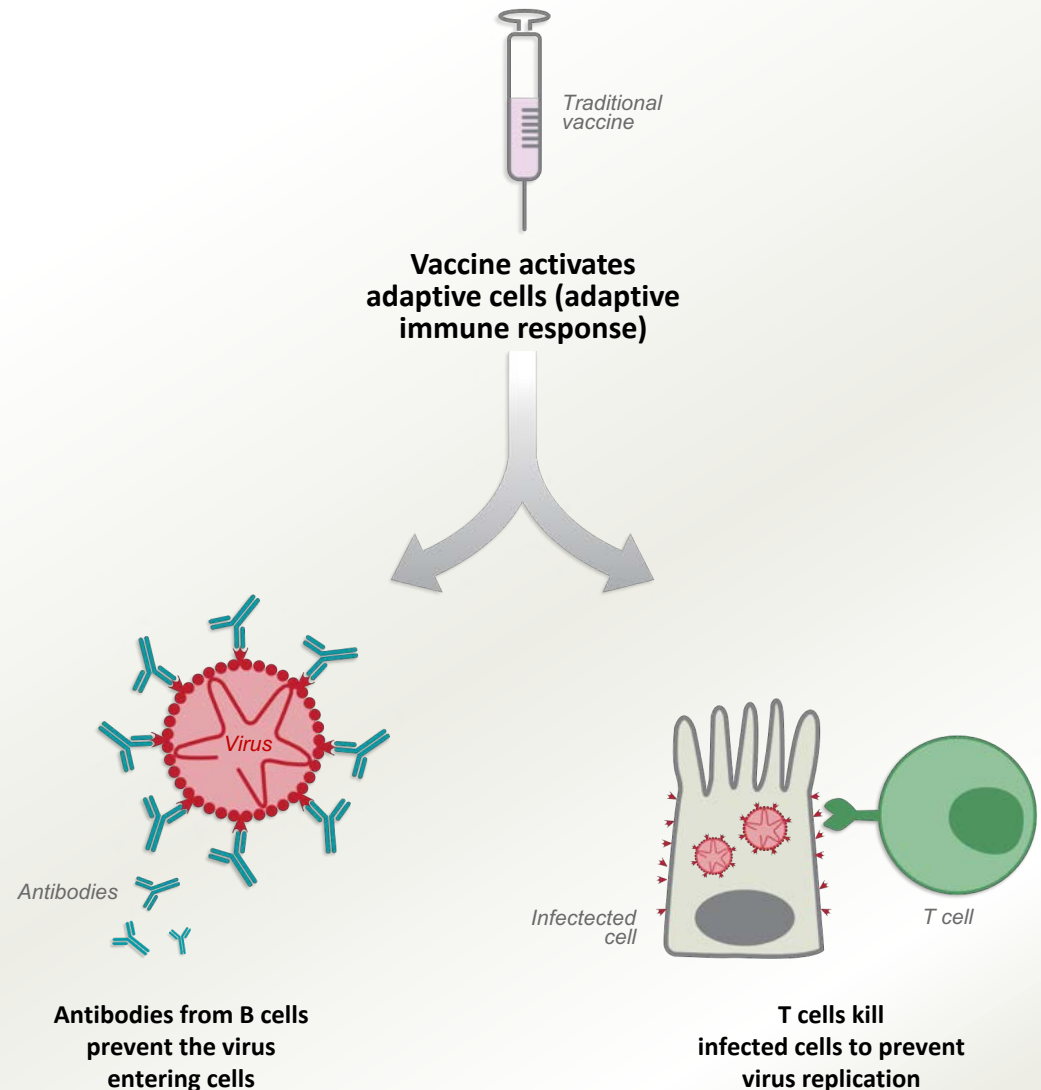
Response in an immunized person

- When **adaptive immune cells (B cells and T cells)** encounter the same virus again, they respond rapidly and the immune system can effectively clear an infection before it causes disease

- Vaccines use this **immune memory** to protect us from infection

- Immune memory can result from a prior infection or from an effective vaccine

Figure. Immune response to an immunized person

Infection

0   4   8   days (approx.)

Strong and rapid antibody response

—— Virus amount   —— Cellular response   —— Antibody response

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An immune response is induced by vaccines

- **Vaccines safely deliver an immunogen** (antigen able to elicit an immune response) to the immune system in order to train it to recognize the pathogen when it is encountered naturally by activating:

- **CD4+ helper T cells** that in turn stimulate:
  - ➤ **B-cells** to produce neutralizing antibodies specific to the virus
  - ➤ **CD8+ cytotoxic T cells** to recognize and kill cells infected by the virus

Kylie Quinn; https://theconversation.com/could-bcg-a-100-year-old-vaccine-for-tuberculosis-protect-against-coronavirus-138006

Traditional vaccine

Vaccine activates adaptive cells (adaptive immune response)

Virus

Antibodies

Infectected cell

T cell

Antibodies from B cells prevent the virus entering cells

T cells kill infected cells to prevent virus replication

Immunogens used in COVID-19 vaccines

- An **immunogen is a specific type of antigen** that is able to elicit an immune response

- The choice of immunogen for vaccines impacts what type of immune response is induced; as well as safety, development time, production time, costs and access to vaccines

- **Immunogens used** in current COVID-19 vaccines or COVID-19 vaccines in development:
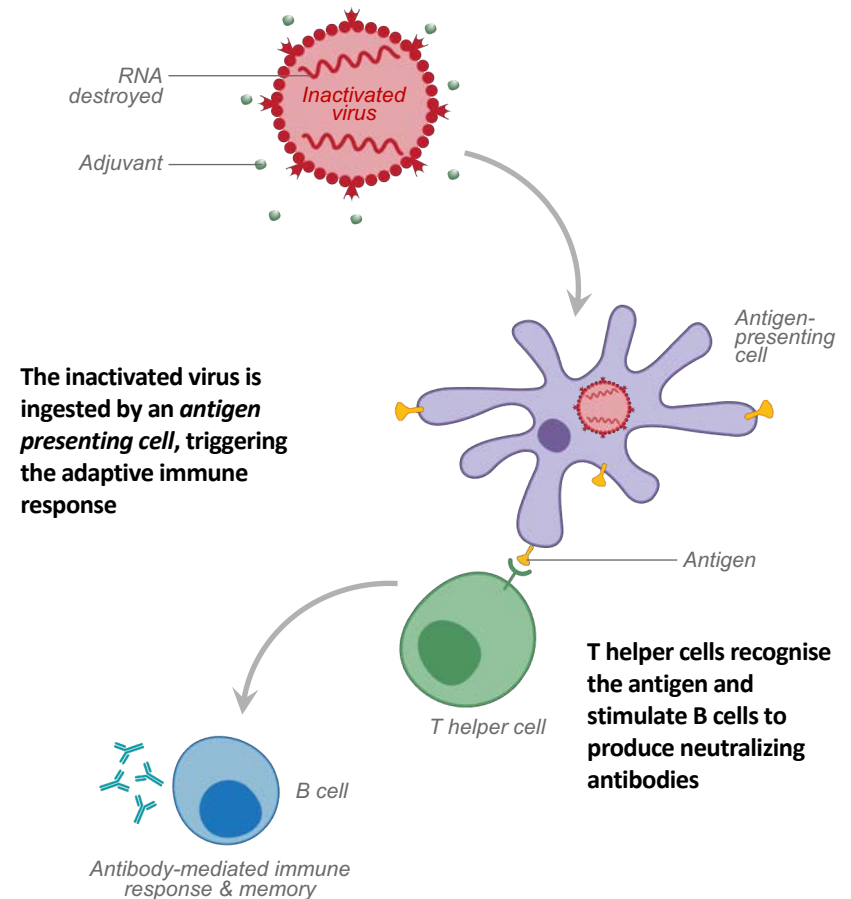
| Inactivated virus | Viral subunit | Viral vector | RNA vaccines |

Table. Advantages and disadvantages of immunogens used in vaccines

IMMUNOGEN	WHAT IT IS	ADVANTAGE	DISADVANTAGE	EXAMPLE OF VACCINES
Inactivated virus	Inactivated dead virus	Induces strong antibody response	Requires large quantities of virus, low or no cellular response	Influenza, rabies hepatitis A
Viral subunit	A protein derived from a pathogen	May have fewer side effects than whole virus (redness, swelling at injection site)	May be poorly immunogenic; complex process	Influenza
Viral vector	Viral pathogen expressed on a safe virus that doesn't cause disease	Rapid development, strong cellular response, relatively easy to produce	Prior exposure to vector virus (eg. adenovirus) may reduce immunogenicity, some vectors require boosting with a different vector	Ebola
Nucleic acid	mRNA coding for a viral protein	Strong cellular immunity; rapid development	Relatively low antibody response	COVID-19

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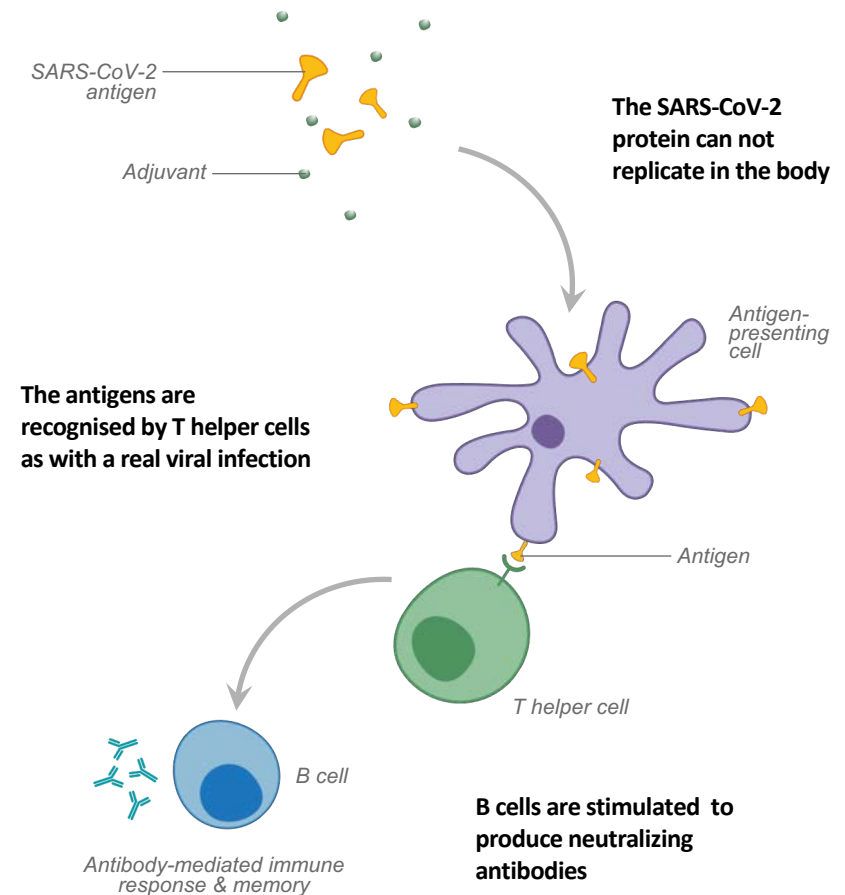
Inactivated virus vaccines

- In inactivated virus vaccines, **the genetic material of the virus has been destroyed to stop disease producing capacity**

- Inactivated virus cannot replicate inside the body, so higher doses are needed

- Sometimes, an **adjuvant** (molecules that stimulate the immune system) is used to help strengthen the immune response

- Inactivated virus vaccines generally only induce **antibody-mediated immunity** (not cell-mediated immunity)

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested

RNA destroyed

Inactivated virus

Adjuvant

Antigen-presenting cell

The inactivated virus is ingested by an *antigen presenting cell*, triggering the adaptive immune response

Antigen

T helper cells recognise the antigen and stimulate B cells to produce neutralizing antibodies

T helper cell

B cell

Antibody-mediated immune response & memory

Viral subunit vaccines

- Subunit vaccines **use the antigen of the virus without any genetic material**, usually with an adjuvant to give a better immune response

- Usually made using **recombinant** expression system (made in a cell without using the virus)

- With the help of antigen-presenting cells, the antigens are recognised by T helper cells as with a real viral infection

- Subunit vaccines generally induce mainly **antibody-mediated immunity**

- **Adjuvants** can enhance antibody response and also cell-mediated immunity

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested

SARS-CoV-2 antigen

Adjuvant

The SARS-CoV-2 protein can not replicate in the body

Antigen-presenting cell

The antigens are recognised by T helper cells as with a real viral infection

Antigen

T helper cell

B cell

Antibody-mediated immune response & memory

B cells are stimulated to produce neutralizing antibodies

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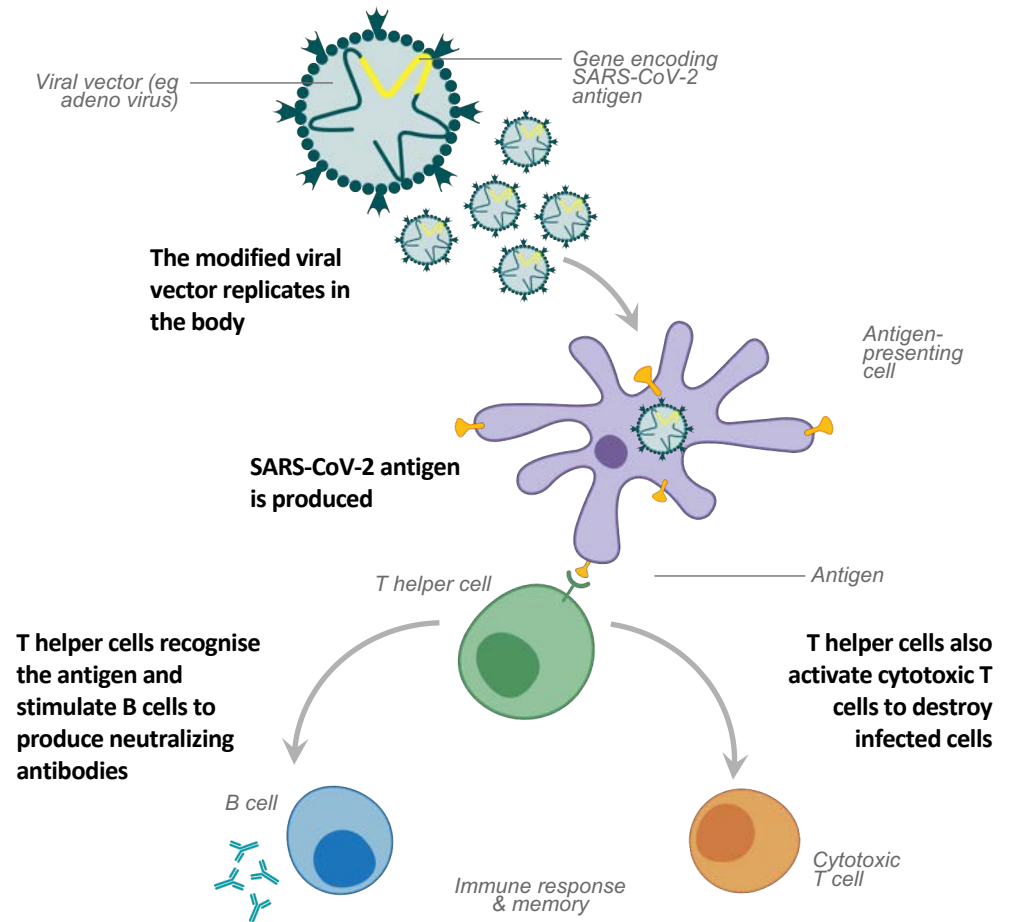
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Viral vector vaccines

- Viral vector vaccines **use a non-coronavirus vector modified to include a gene that encodes a target antigen**

- Examples: adenovirus, measles virus, vesicular stomatitis virus.

- Can be replicating or non-replicating.

- Non-replicating: infects a cell and produces SARS-CoV-2 antigen in that cell but not new virus.

- Replicating: upon infection produces SARS-CoV-2 antigen in that cell and new virus which infects other cells.

- The SARS-CoV-2 antigen inside cells seen by body as if SARS-CoV-2 infection and induces T helper cells and cytotoxic T cells.

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested

Viral vector (eg adeno virus)

Gene encoding SARS-CoV-2 antigen

The modified viral vector replicates in the body

Antigen-presenting cell

SARS-CoV-2 antigen is produced

Antigen

T helper cell

T helper cells recognise the antigen and stimulate B cells to produce neutralizing antibodies

T helper cells also activate cytotoxic T cells to destroy infected cells

B cell

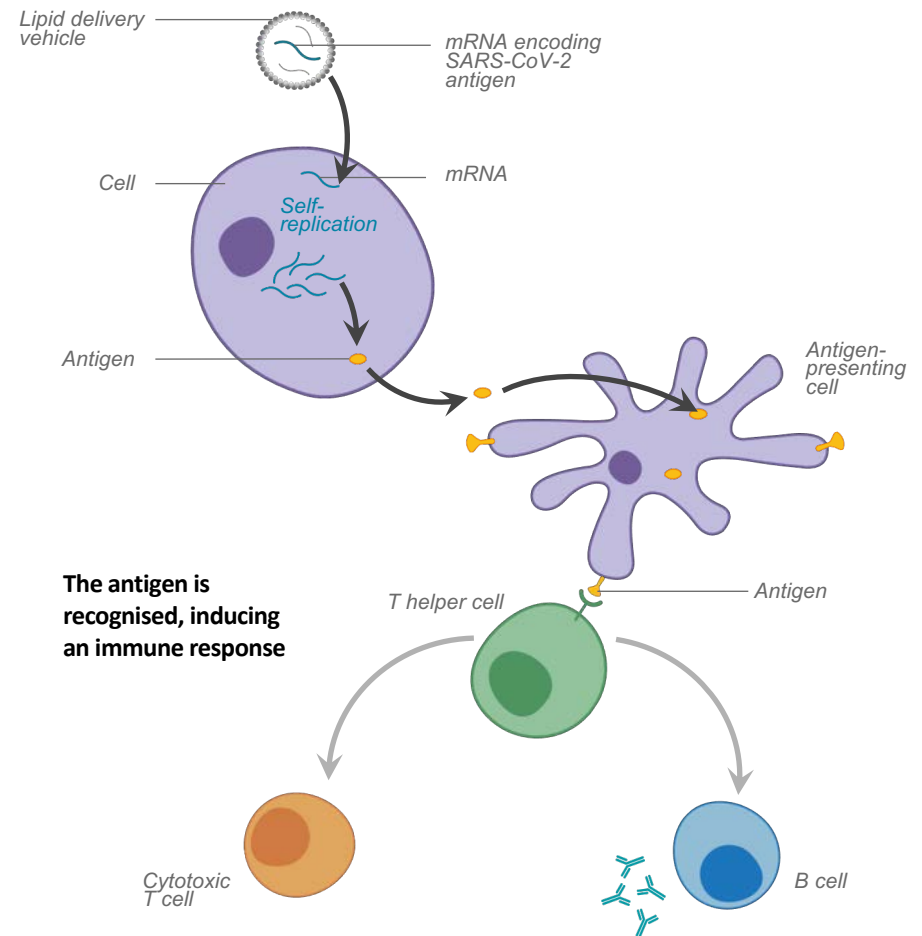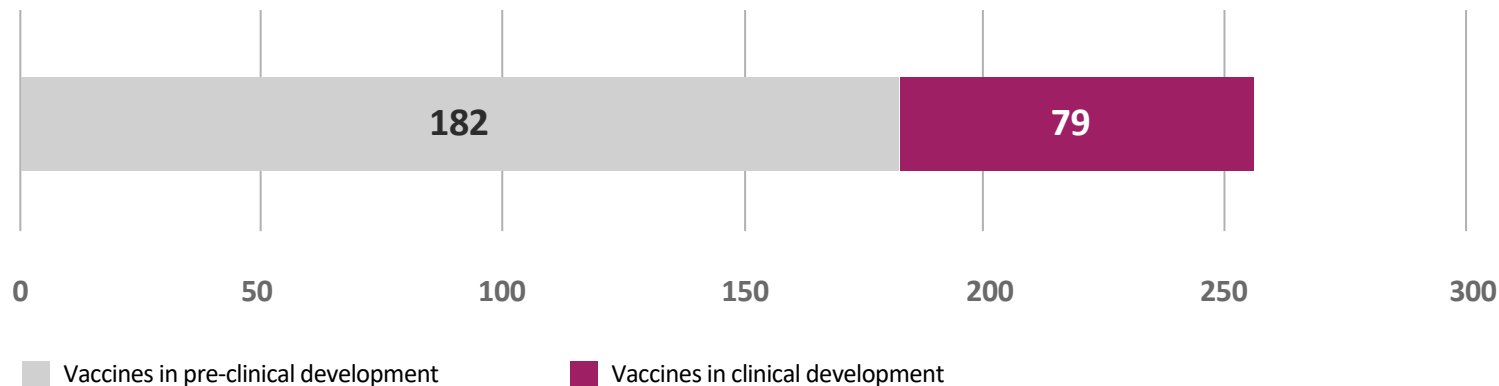Immune response & memory

Cytotoxic T cell

RNA vaccines

- RNA vaccines are antigen-coding strands of **messenger RNA (mRNA)** delivered inside a lipid coat

- Once inside cells, the mRNA is translated **the protein antigen**

- The antigen is recognised, inducing an immune reaction

- Seen by body as if virus inside cell so induces T-helper and cytotoxic T-cells, and antibodies.

- mRNA also recognised by cells as 'pathogen' stimulating strong immune response.

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested

Lipid delivery vehicle

mRNA encoding SARS-CoV-2 antigen

Cell

mRNA

Self-replication

Antigen

Antigen-presenting cell

The antigen is recognised, inducing an immune response

T helper cell

Antigen

Cytotoxic T cell

B cell

Preclinical & clinical development of COIVD-19 vaccines

- As of 5 March 2021, there are **79 COVID-19 candidate vaccines in clinical development** of which **12 are in Phase III trials and 4 are in Phase IV**

- There are another 182 candidate vaccines in preclinical development

- More than 90% of all top candidate vaccines will be delivered through **intra-muscular injection**

Vaccines in pre-clinical development   Vaccines in clinical development

Source: 23 February 2021
https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

Most COVID-19 vaccines are designed for a two-dose schedule

- Two dose vaccination (prime-boost) works by mimicking natural immunity. The first dose primes immunological memory and the second dose solidifies it

- After a first vaccine dose, the immune system needs time to generate a response and to create memory cells that will recognize the pathogen if it is encountered again

- A larger time interval between the first and second dose may induce a stronger immune response compared to a short interval*

  ➢ preliminary data from Astra Zeneca's COVID-19 vaccine trials show that a 12-week prime-boost interval may result in improved vaccine efficacy[1,2]

Fig: Larger time interval between doses improves vaccine efficacy
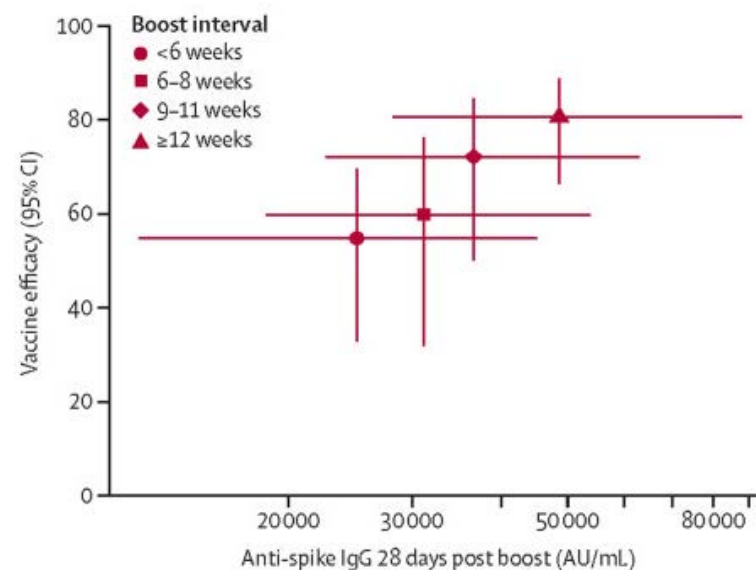
Relationship between neutralizing antibody binding 28 days after second dose, and vaccine efficacy against symptomatic COVID-19 of ChAdOx1 nCoV-19[1] (AstraZeneca COVID-19 vaccine)

1. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00432-3/fulltext
2. https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccines-SAGE_recommendation-AZD1222-2021.1

*An interval of 21-28 days between the doses is recommended for the mRNA vaccines (Pfizer-BioNTech and Moderna)
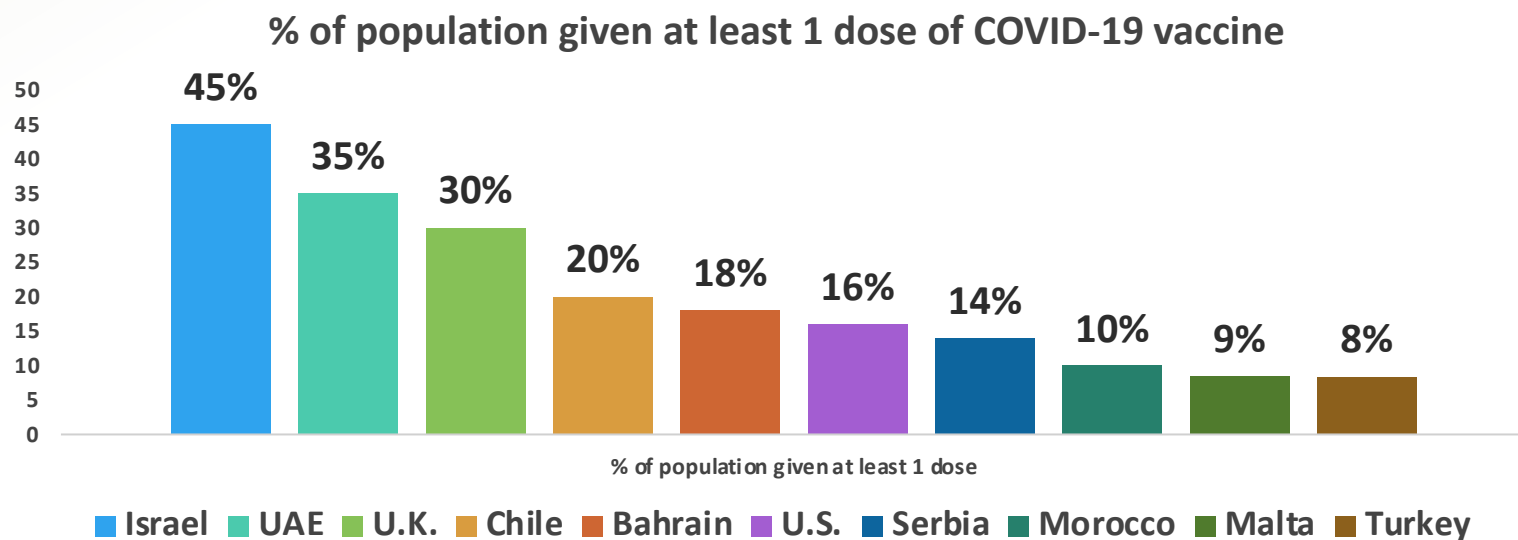
COVID-19 vaccine candidates in phase III or phase IV trials

16 CANDIDATES - VACCINES IN PHASE III CLINICAL EVALUATION	Vaccine platform	WHO EUL	Already in use
Pfizer/BioNTech + Fosun Pharma*	RNA based vaccine	X	X
Moderna + National Institute of Allergy and Infectious Diseases (NIAID)*	RNA based vaccine	X	X
CureVac AG	RNA based vaccine		
AstraZeneca + University of Oxford*	Viral vector (Non-replicating)	X	X
CanSino Biological Inc./Beijing Institute of Biotechnology	Viral vector (Non-replicating)		
Gamaleya Research Institute ; Health Ministry of the Russian Federation	Viral vector (Non-replicating)		X
Janssen Pharmaceutical	Viral vector (Non-replicating)		X
Sinovac Research and Development Co., Ltd	Inactivated virus		X
Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Inactivated virus		X
Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Inactivated virus		X
Institute of Medical Biology + Chinese Academy of Medical Sciences	Inactivated virus		
Research Institute for Biological Safety Problems, Rep of Kazakhstan	Inactivated virus		
Bharat Biotech International Limited	Inactivated virus		X
Novavax	Protein subunit		
Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Protein subunit		
Zydus Cadila	DNA based vaccine		

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COVID-19 vaccine administration

- As of 8 March, more than **349 million vaccine doses have been administered**:

- Different vaccines (3 platforms) have been administered (**Pfizer**, **Moderna**, **Oxford/AZ**, **Gamaleya**, **Sinopharm**, **Sinovac**, **Bharat Biotech**)

Table. WHO COVID-19 vaccines tracker on global distribution (8 March 2021)

% of population given at least 1 dose of COVID-19 vaccine

% of population given at least 1 dose

Israel 45% · UAE 35% · U.K. 30% · Chile 20% · Bahrain 18% · U.S. 16% · Serbia 14% · Morocco 10% · Malta 9% · Turkey 8%

Source: Data retrieved from WHO dashboard on 08 March 2021, https://covid19.who.int/

SARS-CoV-2 variants & COVID-19 vaccines

- Current SARS-CoV-2 variants involve mutations to the gene for the spike protein that is targeted by COVID-19 vaccines

- Several COVID-19 vaccines have reported reduced efficacy to protect against mild to moderate disease in people infected with SARS-CoV-2 variants, however the vaccines are still expected to protect against severe disease and death

- Studies are ongoing to examine if some vaccines may be more susceptible to effects of variants than others
  - those using smaller epitopes (the **receptor binding domain** on the spike protein) may be more susceptible than those using a larger part of the virus such as the **spike protein** or the **whole inactivated virus**

- Other studies are exploring the development of COVID-19 vaccines that make it difficult for the virus variants to evade immunity, for example:
  - **multivalent vaccines** that include both new (derived from variants) and old forms of the spike protein in a single dose
  - **vaccines that target multiple sites on several viral proteins** in contrast to vaccines that target only the SARS-CoV-2 spike protein

https://www.who.int/publications/m/item/draft-landscape-of-covid-19-candidate-vaccines

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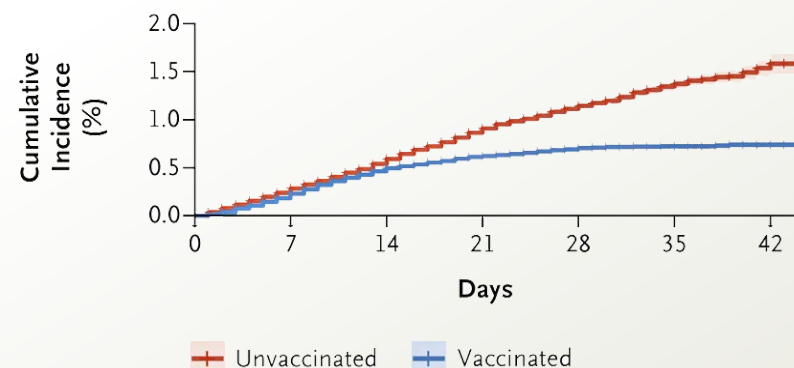
Preliminary COVID-19 vaccination results

- A recent study showed that two doses of the Pfizer BioNTech vaccine **prevented 94% of symptomatic COVID-19 cases**, **87% of hospitalizations** and **92% of severe disease** in 596,618 people vaccinated between 20 December and 1st of February in Israel

- Preliminary results from Scotland, show that four weeks after the first doses of the Pfizer BioNTech and Oxford AstraZeneca vaccines were administered the risk of hospitalization from COVID-19 fell by up to 85% and 94%, respectively. Combined **effectiveness for people over 80 was 81%**

Table. COVID-19 vaccine effectiveness in Israel

Vaccine effectiveness	14-20 days post dose 1	≥7 days post dose 2
Documented infections	46% (40-51%)	92% (88-95%)
Symptomatic COVID-19	57% (50-63%)	94% (87-98%)
Hospitalization	74% (56-86%)	87% (55-100%)
Severe disease	62% (39-80%)	92% (75-100%)

*https://www.bmj.com/content/372/bmj.n523#:~:text=The%20results%2C%20available%20as%20a,73%20to%2099)%2C%20respectively , https://www.ed.ac.uk/files/atoms/files/scotland_firstvaccinedata_preprint.pdf
https://www.nejm.org/doi/full/10.1056/NEJMoa2101765*

Figure. Symptomatic COVID-19 in Israel following vaccination

Source:
https://www.nejm.org/doi/full/10.1056/NEJMoa2101765

Global COVID-19 vaccine allocation

- The allocation of COVID-19 vaccines is guided by public health objectives. For the initial phase these objectives are:
  - ➤ Reduce mortality
  - ➤ Protect health systems

- To maximise the public health impact of a **limited supply of COVID-19 vaccines**, the global vaccines allocation mechanism targets:
  - ➤ **high risk groups** (people over the age of 65, people with cardiovascular diseases, cancer, diabetes, chronic respiratory disease or obese) **to reduce severe disease and mortality**
  - ➤ **health workers to protect the health system**

- These groups correspond to 20% of the global population

- Therefore, the first phase of COVID-19 vaccines allocation will be up to 20% of a country's population

https://www.who.int/publications/m/item/fair-allocation-mechanism-for-covid-19-vaccines-through-the-covax-facility
https://www.who.int/publications/m/item/allocation-mechanism-for-covax-facility-vaccines-explainer

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To keep in mind

Because of the limited supplies, we need to maximize the impact by targeting the high risks groups
WHO recommends prioritization based on the SAGE Prioritization Roadmap
At risk groups to be vaccinated first, such as older adults, persons with underlying conditions, health workforce

In order to:
→ to reduce the severe cases among those populations
→ to relieve congestion in health care settings
→ to leave easy access for the entire population in need of healthcare that is not related to COVID-19
→ to reduce mortality

Vaccination is one tool in our toolbox, we will need to use the other tools as well such as Public Health and Social Measures

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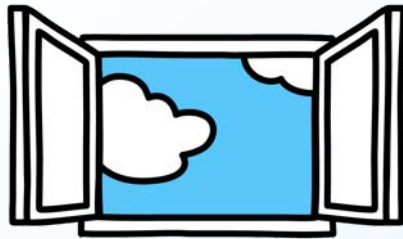# COVID-19 protective measures
Protect yourself & others
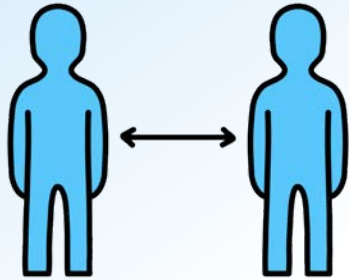
Keep your distance

Wash your hands frequently

Cough & sneeze into your elbow

Ventilate or open windows

Wear a mask