Update on COVID-19 vaccines & immune response

THE LATEST ON THE COVID-19 GLOBAL SITUATION, VACCINES & IMMUNE RESPONSE
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Current global situation

CASES REPORTED TO WHO AS OF 7 MARCH 2021, 10:00 CEST

• Cases: > 116 million
• Deaths: > 2.5 million

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

WHO Coronavirus Disease (COVID-19) Dashboard
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**

<table>
<thead>
<tr>
<th>INCUBATION PERIOD (DAYS)</th>
<th>Symptoms</th>
<th>Innate immune response</th>
<th>Virus detectable</th>
<th>Cellular response</th>
<th>Early antibodies (IgM) response</th>
<th>Late antibodies (IgG) response</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td></td>
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<tr>
<td>8</td>
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</tr>
</tbody>
</table>
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

- Virus amount
- Cellular response
- Antibody response
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](https://theconversation.com/could-bcg-a-100-year-old-vaccine-for-tuberculosis-protect-against-coronavirus-138006)
THE IMMUNE RESPONSE

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:

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

Table. Advantages and disadvantages of immunogens used in 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
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 a 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 antibody-mediated immunity.

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

- Viral vector vaccines use a non-coronavirus vector (e.g. adenovirus, measles virus, vesicular stomatitis virus) modified to include a gene that encodes a target antigen
- Can be replicating or non-replicating
  - Replicating: upon infection produces SARS-CoV-2 antigen in that cell and new virus, which infects other cells
  - Non-replicating: infects a cell and produces SARS-CoV-2 antigen in that cell but does not produce new virus
- The SARS-CoV-2 antigen inside the cells is seen by the body as if this is a SARS-CoV-2 infection and induces T helper cells and cytotoxic T cells

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

- RNA vaccines are antigen-coding strands of **messenger RNA (mRNA)** delivered inside a lipid coat
- Once inside cells, the mRNA is translated into the **protein antigen**
- The antigen is recognised, inducing an immune reaction
- Seen by the body as if a virus is inside a cell, T-helper, cytotoxic T-cells and antibodies are induced
- mRNA is recognised by cells as a ‘pathogen’ stimulating a strong immune response

https://www.intvetvaccnet.co.uk/blog/covid-19/vaccine-eight-types-being-tested
Preclinical & clinical development of COVID-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**

**Source:** 5 March 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\(^1,2\).

\* An interval of 21-28 days between the doses is recommended for the mRNA vaccines (Pfizer-BioNTech and Moderna).

\(1\) https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00432-3/fulltext

\(\text{Figure. Larger time interval between doses improves vaccine efficacy}

\[\text{Relationship between neutralizing antibody binding 28 days after second dose, and vaccine efficacy against symptomatic COVID-19 of ChAdOx1 nCoV-19}^1\text{ (AstraZeneca COVID-19 vaccine)}\]
## COVID-19 vaccine candidates in phase III or phase IV trials

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

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

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
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

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

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_firstvaccinatedata_preprint.pdf
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
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.
Most discussed topic online: COVID-19 vaccines
25 February to 4 March 2021

Top topics by volume

- Vaccines: 2,624,845
- Measures in Public Settings: 1,090,469
- Unions and Industry: 1,083,265
- Testing: 914,617
- Protection from Transmission: 588,705
- Travel: 587,462
- Supportive Care (Healthcare): 501,392
- Personal Measures: 425,046
- Current Treatment: 356,848
- Confirmed Symptoms: 341,409

Questions on COVID-19
Top key words – excluding ‘COVID’, ‘coronavirus’, ‘pandemic’ and ‘virus’

- vaccine: 2,550
- covid vaccine: 1,427
- questions: 813
- mask: 778
- others: 662
- covid relief bill: 551
- vaccines: 545
- family: 536
- hell: 507
- country: 504
- work: 499
- home: 484
- contact: 478
- world: 470
- money: 464
- benefit: 454
- life: 413
- person: 398
- government: 396
- bars: 392
# Resources on COVID-19 vaccine development

- **COVID-19 vaccine introduction toolkit**
  The COVID-19 vaccine introduction toolbox equips all countries to prepare for and implement COVID-19 vaccination by providing guidance, tools, and training.

- **WHO Target product profile for COVID-19 vaccine**
  This Target Product Profile (TPP) describes the preferred and minimally acceptable profiles for human vaccines for long term protection of persons at high ongoing risk of COVID-19, such as health workers, and for reactive use in outbreak settings with rapid onset of immunity.

- **Vaccine landscape**
  Landscape documents prepared by the WHO for information purposes concerning the 2019-2020 global development of new COVID-19 vaccines.

- **Access to COVID Tools (ACT) Accelerator**
  The vaccines pillar of the ACT Accelerator, convened is speeding up the search for an effective vaccine for all countries.

- **COVAX: Working for global equitable access to COVID-19 vaccines**
  WHO

- **Covax explained**
  GAVI

- **How do vaccines work?**
  This article is part one in a series of explainers on vaccine development and distribution. This article focuses on how vaccines work to protect our bodies from disease-carrying germs.

- **How are vaccines developed?**
  This article is part two in a series of explainers on vaccine development and distribution. This article focuses on the ingredients in a vaccine and the three clinical trial phases.

- **WHO SAGE values framework**
  For the allocation and prioritization of COVID-19 vaccination.

- **WHO SAGE prioritization roadmap**
  An approach to help inform deliberation around the range of recommendations that may be appropriate under different epidemiologic and vaccine supply conditions.

- **Q&A: Coronavirus disease (COVID-19) Vaccines**
  A Q&A including answers to questions on vaccine development, distribution and safety.
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