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# COVID-19 vaccines

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COVID-19 is a pandemic of unprecedented proportions in recent human history. Less than 18 months since the onset of the pandemic, there are close to two hundred million confirmed cases and four million deaths worldwide. There have also been massive efforts geared towards finding safe and effective vaccines. By July 2021 there were 184 COVID-19 vaccine candidates in pre-clinical development, 105 in clinical development, and 18 vaccines approved for emergency use by at least one regulatory authority. These vaccines include whole virus live attenuated or inactivated, protein-based, viral vector, and nucleic acid vaccines. By mid-2021 three billion doses of COVID-19 vaccine have been administered around the world, mostly in high-income countries. COVID-19 vaccination provides hope for an end to the pandemic, if and only if there would be equal access and optimal uptake in all countries around the world.

## Addresses

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## Background

As many countries continue to battle with new infections caused by coronavirus disease 2019 (COVID-19), vaccine development has been accelerated to achieve immunity to the virus and stop transmission [1<sup>••</sup>,2]. The process of vaccine development is usually long and tedious (Figure 1). The recent advances in COVID-19 vaccine development have indicated that research innovations are accumulative, building on already existing knowledge. This allows for the pandemic speed at which the COVID-19 vaccines have

been rapidly developed. Vaccines are biological preparations that provide active acquired immunity to a particular infectious disease. They do so by stimulating an immune response to an antigen, a molecule found on the pathogen [3<sup>•</sup>]. Vaccines date back to the era of Edward Jenner who developed the smallpox vaccine in 1796 [4<sup>••</sup>].

## COVID-19 vaccines

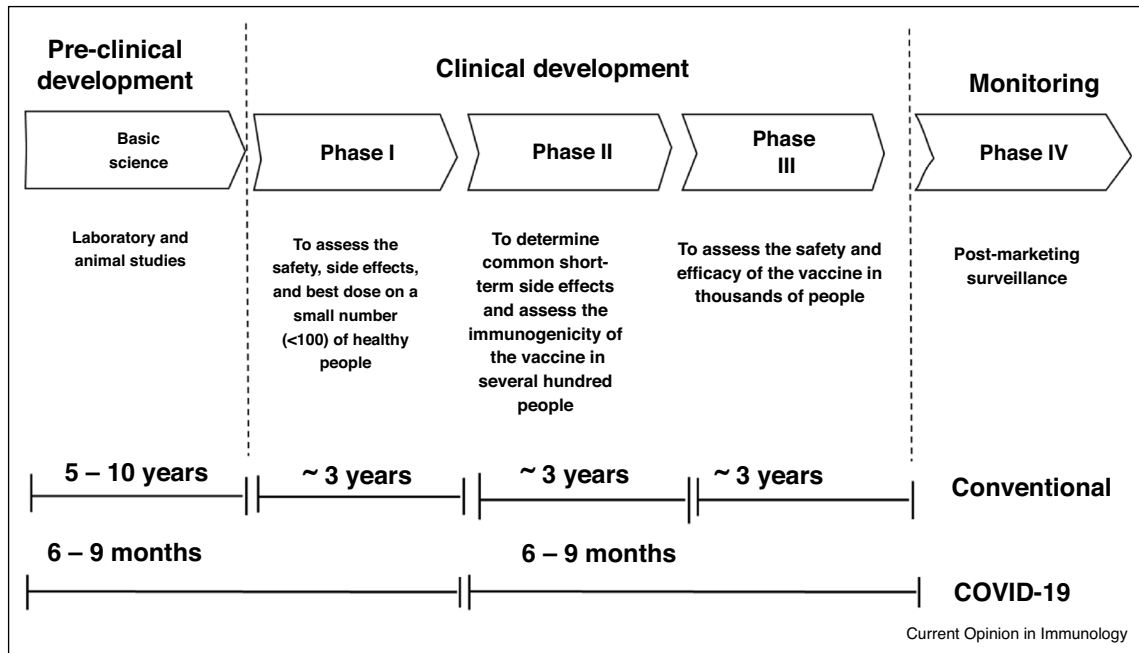
In the history of vaccines, COVID-19 vaccines have accelerated at an unimaginable speed. Currently, there are 184 candidate vaccines in preclinical development and 104 in clinical stages of development [5<sup>••</sup>]. Recent data indicate that there are 18 COVID-19 vaccines approved and are currently in use around the world [5<sup>••</sup>,6<sup>••</sup>]. The COVID-19 vaccines are in four primary categories using different platforms: (1) whole virus vaccines, (2) protein-based vaccines, (3) viral vector vaccines, and (4) nucleic acid vaccines (Appendix A) [7<sup>•</sup>].

## Whole virus vaccines

Whole virus vaccines use a weakened (attenuated) or inactivated form of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) to trigger protective immunity. Live attenuated vaccines use a weakened form of the virus, which can still grow and replicate but does not cause illness [7<sup>•</sup>]. Inactivated vaccines contain viruses whose genetic material has been destroyed by heat, chemicals, or radiation, so they cannot infect cells and replicate but can still trigger an immune response [8]. Both types of whole virus vaccines are tried and tested vaccine approaches, which form the basis of many existing vaccines. Existing live attenuated virus vaccines include measles, oral poliovirus, and yellow fever vaccines; and inactivated vaccines include inactivated polio and seasonal influenza vaccines [9].

There are currently 16 inactivated and two live attenuated candidate SARS-CoV-2 vaccines in clinical development [5<sup>••</sup>]. The advantages of live-attenuated SARS-CoV-2 vaccine candidates include targeting and stimulating robust mucosal and cellular immunity, which is essential for protection without the need for adjuvants [10,11]. However, this type of vaccine has some disadvantages. SARS-CoV-2 is excreted in the feces of infected patients [12<sup>•</sup>,13] and there is concern that live-attenuated SARS-CoV-2 vaccines may be excreted in the feces of vaccines, possibly leading to SARS-CoV-2 transmission to unvaccinated individuals. The use of live-attenuated SARS-CoV-2

Figure 1



COVID-19 vaccine development compared to conventional vaccine development.

vaccine may also increase the risk of recombination between the vaccine strain and circulating wild-type virus, generating new viral variants. In addition, production and formulation of a live attenuated SARS-CoV-2 vaccine is labor-intensive and requires rigorous quality control, which would slow down large-scale vaccine production. At least two SARS-CoV-2 inactivated candidate vaccines have been approved for emergency use [5<sup>\*\*</sup>,6<sup>\*\*</sup>].

### Protein-based vaccines

There are two types of protein-based vaccines, that is, subunit and virus-like particle vaccines [14]. Protein subunit vaccines consist of viral antigenic fragments produced by recombinant protein techniques [15]. They are easy to produce, and relatively safe and well-tolerated compared to whole virus vaccines. The limitation of protein subunit vaccines is their low immunogenicity [16<sup>\*</sup>]. Therefore, adjuvants are usually used together with subunit vaccines to improve immunogenicity. Existing subunit vaccines include those against whooping cough, *Streptococcus pneumoniae*, and *Haemophilus influenzae* type b [7<sup>\*</sup>]. There are currently 33 SARS-CoV-2 protein subunit candidate vaccines in clinical development [5<sup>\*\*</sup>], with at least one that has been shown in phase III clinical trials to induce high titers of neutralizing antibodies [17].

Beyond subunit vaccines, other protein-based SARS-CoV-2 candidate vaccines use empty virus shells that mimic the coronavirus structure but are not infectious because they lack genetic material; referred to as ‘virus-like particles’ [14]. There are currently five virus-like particle vaccines in clinical development [5<sup>\*\*</sup>]. Existing vaccines that use this technology include human papillomavirus vaccines [18].

### Viral vector vaccine

Viruses survive and replicate by invading their host’s cells and hijacking their protein-making machinery, so it reads the virus genetic code and makes new viruses [12<sup>\*</sup>]. These virus particles contain antigens, molecules that can trigger an immune response [12<sup>\*</sup>]. A similar principle underpins viral vector vaccines, where the host cells only receive a code to make specific antigens. The viral vector acts as a delivery system, providing a means to invade the cell and insert the code for SARS-CoV-2 antigens. The virus used as a vector is chemically weakened so that it cannot cause disease. In this way, the body can mount an immune response safely, without developing the disease [16<sup>\*</sup>,19]. Viruses that have been used as vectors include the adenovirus (that causes common cold), measles virus, and vaccinia virus. There are two categories of viral vectors; those that can still replicate within cells and those that cannot because key genes have been disabled [7<sup>\*</sup>,9,19]. Before the

onset of SARS-CoV-2, only one viral vector vaccine had been approved for use in human population against Ebola virus disease [20]. The Ebola vaccine uses the vesicular stomatitis virus as a replicating viral vector. One drawback with viral vector vaccines is that if people have been previously exposed to the viral vector and have developed an immune response against it this could potentially blunt the vaccine's effectiveness [14].

There are currently 16 non-replicating and two replicating viral vector candidate SARS-CoV-2 vaccines in clinical development [5\*\*]. Various viral vector SARS-CoV-2 candidate vaccines, all using non-replicating viral vectors, have been approved by regulatory authorities around the world for emergency use [5\*\*,6\*\*].

### Nucleic acid vaccines

SARS-CoV-2 nucleic acid vaccines use genetic instructions, in the form of deoxyribonucleic acid (DNA) or ribonucleic acid (RNA), for a SARS-CoV-2 protein that prompts an immune response. Before COVID-19, this platform was unproven, as no existing licensed vaccine used this technology. DNA vaccines use a piece of DNA encoding the antigen, which is first inserted into a bacterial plasmid. Bacterial plasmids are circular pieces of DNA used to store and share genes that may benefit their survival [11]. Plasmids can replicate the main chromosomal DNA independently and provide a simple tool for transferring genes between cells. Because of this, they are already widely used in genetic engineering. This allows for the host machinery to translate the antigen message into protein inside cells [19]. RNA vaccines, on the other hand, encode the antigen of interest in a messenger RNA (mRNA) or self-amplifying RNA, which is a molecular template used by cellular factories to produce proteins [11,19]. The RNA can be injected by itself, encapsulated within nanoparticles, or driven into cells using some of the same techniques developed for DNA vaccines. Once the DNA or RNA is inside the cell and starts producing antigens, these are then displayed on its surface, where they can be detected by the immune system, triggering a response. This response includes killer T cells (which look for and kill infected cells) and antibody-producing B cells and helper T cells that support antibody production [9,16\*].

There are currently at least 10 DNA and 18 RNA candidate vaccines in clinical development [5\*\*]. Several mRNA vaccines against SARS-CoV-2 have been

approved for emergency use around [5\*\*,6\*\*]. This is the first time in the history of vaccinology that a nucleic acid vaccine has been approved for use in public health programs.

### COVID-19 vaccine rollout

By mid-2021 more than three billion doses of COVID-19 vaccines had been administered worldwide, and 24% of the world population had received at least one dose of a COVID-19 vaccine [21]. By the same time, more than 40 million COVID-19 vaccine doses were being administered each day worldwide. Countries that had vaccinated at least 50% of their citizens against COVID-19 by mid-2021 include the United Kingdom, Chile, Uruguay, Israel, Bahrain, Hungary, Italy, Spain, Germany, United States of America, and France. However, only 1% of people in low-income countries had received a COVID-19 vaccine dose by end of June 2021. In Africa, only 53 million vaccine doses had been administered [21].

### Conclusion

Advances in COVID-19 vaccines are encouraging because this is the first time that vaccine development has accelerated at this speed. Research advances incorporating vaccinology have ensured that the most critical public health intervention is developed timeously. Points to consider for future COVID-19 vaccines include the development of heat stable vaccines, which can be administered easily in low resource tropical settings. Countries all over the world, regardless of political ideologies, can unite and work together to achieve fast and successful COVID-19 vaccine rollout worldwide.

### Authors' contributions

Dudzile Ndwandwe conceived and wrote the first draft of the article, Charles S Wiysonge contributed important intellectual input to subsequent versions of the article, and both authors read and approved the final version of the article for submission.

### Conflict of interest statement

Charles S Wiysonge is one of the editors of this themed issue on Vaccines. Dudzile Ndwandwe declares no competing interests.

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## Appendix A

See Table A1.

**Table A1**

**Characteristics of COVID-19 vaccines in advanced stage of clinical development**

Developers	Type of candidate vaccine	Vaccine platform description	Number of doses	Schedule	Route of administration	Phase
Inovio Pharmaceuticals + International Vaccine Institute + Advaccine (Suzhou) Biopharmaceutical Co., Ltd	INO-4800 + electroporation	Viral vector (Non-replicating)	2	Day 0 + 28	ID	Phase 2/3
AnGes + Takara Bio + Osaka University	AG0301-COVID19	DNA based vaccine	2	Day 0 + 14	IM	Phase 2/3
ReiThera + Leukocare + Univercells	GRAd-COV2 (Replication defective Simian Adenovirus (GRAd) encoding S)	Viral vector (Non-replicating)	1	Day 0	IM	Phase 2/3
Clover Biopharmaceuticals Inc./GSK/Dynavax	SCB-2019 + AS03 or CpG 1018 adjuvant plus alum adjuvant (Native like Trimeric subunit Spike Protein vaccine)	Protein subunit	2	Day 0 + 21	IM	Phase 2/3
CSL Ltd. + Seqirus + University of Queensland	MF59 adjuvanted SARS-CoV-2 Sclamp vaccine	Protein subunit	2	Day 0 + 28	IM	Phase 2/3
Vaxxinity	UB-612 (Multitope peptide based S1-RBD-protein based vaccine)	Protein subunit	2	Day 0 + 28	IM	Phase 2/3
Medicago Inc.	Coronavirus-like particle COVID-19 (CoVLP)	Virus like particle	2	Day 0 + 21	IM	Phase 2/3
Shifa Pharmed Industrial Co	COVID-19 inactivated vaccine	Inactivated Virus	2	Day 0 + 14	IM	Phase 2/3
Sinopharm + China National Biotec Group Co + Wuhan Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Vero cell)	Inactivated virus	2	Day 0 + 21	IM	Phase 3
Sinopharm + China National Biotec Group Co + Beijing Institute of Biological Products	Inactivated SARS-CoV-2 vaccine (Vero cell), vaccine name BBIBP-CorV	Inactivated virus	2	Day 0 + 21	IM	Phase 3
Gamaleya Research Institute; Health Ministry of the Russian Federation	Gam-COVID-Vac Adeno-based (rAd26-S + rAd5-S)	Viral vector (Non-replicating)	2	Day 0 + 21	IM	Phase 3
Janssen Pharmaceutical	Ad26.COV2.S	Viral vector (Non-replicating)	1–2	Day 0 or Day 0 + 56	IM	Phase 3
Novavax	SARS-CoV-2 rS/Matrix M1-adjuvant (Full length recombinant SARS CoV-2 glycoprotein nanoparticle vaccine adjuvanted with Matrix M) NVX-CoV2373	Protein subunit	2	Day 0 + 21	IM	Phase 3
Anhui Zhifei Longcom Biopharmaceutical + Institute of Microbiology, Chinese Academy of Sciences	Recombinant SARS-CoV-2 vaccine (CHO Cell)	Protein subunit	2–3	Day 0 + 28 or Day 0 + 28 + 56	IM	Phase 3
CureVac AG	CVnCoV vaccine	RNA based vaccine	2	Day 0 + 28	IM	Phase 3
Institute of Medical Biology + Chinese Academy of Medical Sciences	SARS-CoV-2 vaccine (vero cells)	Inactivated virus	2	Day 0 + 28	IM	Phase 3
Research Institute for Biological Safety Problems, Rep of Kazakhstan	QazCovid-in®-COVID-19 inactivated vaccine	Inactivated virus	2	Day 0 + 21	IM	Phase 3
Zydus Cadila	nCov vaccine	DNA based vaccine	3	Day 0 + 28 + 56	ID	Phase 3
Bharat Biotech International Limited	Whole-virion inactivated SARS-CoV-2 vaccine (BBV152); covaxin	Inactivated virus	2	Day 0 + 14	IM	Phase 3
Sanofi Pasteur + GSK	VAT00002: SARS-CoV-2 S protein with adjuvant	Protein subunit	2	Day 0 + 21	IM	Phase 3



**Table A1 (Continued)**

Developers	Type of candidate vaccine	Vaccine platform description	Number of doses	Schedule	Route of administration	Phase
Shenzhen Kangtai Biological Products Co., Ltd.	Inactivated SARS-CoV-2 vaccine (Vero cell)	Inactivated virus	2	Day 0 + 28	IM	Phase 3
Instituto Finlay de Vacunas	FINLAY-FR-2 anti-SARS-CoV-2 vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant)	Protein subunit	2	Day 0 + 28	IM	Phase 3
Federal Budgetary Research Institution State Research Center of Virology and Biotechnology 'Vector'	EpiVacCorona (EpiVacCorona vaccine based on peptide antigens for the prevention of COVID-19)	Protein subunit	2	Day 0 + 21	IM	Phase 3
Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences	SARS-CoV-2 mRNA vaccine (ARCoV)	RNA based vaccine	2	Day 0 + 14 or Day 0 + 28	IM	Phase 3
Center for Genetic Engineering and Biotechnology (CIGB)	CIGB-66 (RBD + aluminium hydroxide)	Protein subunit	3	Day 0 + 14 + 28 or Day 0 + 28 + 56	IM	Phase 3
Valneva, National Institute for Health Research, United Kingdom	VLA2001	Inactivated virus	2	Day 0 + 21	IM	Phase 3
Sinovac Research and Development Co., Ltd	CoronaVac; inactivated SARS-CoV-2 vaccine (vero cell)	Inactivated virus	2	Day 0 + 14	IM	Phase 4
AstraZeneca + University of Oxford	ChAdOx1-S - (AZD1222)	Viral vector (Non-replicating)	1–2	Day 0 + 28	IM	Phase 4
CanSino Biological Inc./Beijing Institute of Biotechnology	Recombinant novel coronavirus vaccine (Adenovirus type 5 vector)	Viral vector (Non-replicating)	1	Day 0	IM	Phase 4
Moderna + National Institute of Allergy and Infectious Diseases (NIAID)	mRNA-1273	RNA based vaccine	2	Day 0 + 28	IM	Phase 4
Pfizer/BioNTech + Fosun Pharma	BNT162b2 (3 LNP-mRNAs), also known as 'Comirnaty'	RNA based vaccine	2	Day 0 + 21	IM	Phase 4

Source: WHO COVID-19 vaccine tracker and landscape [Ref. 5\*\*].

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- of special interest
- of outstanding interest

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The COVID-19 vaccine tracker and landscape compiles detailed information of each COVID-19 vaccine candidate in development by closely monitoring their progress through the pipeline.

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