EURORDIS
RARE DISEASES EUROPE

Monthly update

Research & development of vaccines to prevent SARS-coV2 infection

Updated May 2021

Disclaimer

No vaccine against COVID-19 is approved. This document does not provide guidance on what vaccine or medicines to take. Please avoid self-prescription and always refer to your doctor before making any treatment decision.

This document provides a selection of updates on the research and development of vaccines for the current coronavirus infection. Those highlights are for the information of patient organisations/ groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.

Contents (click to navigate in document)

A 'must-read' introduction

This document provides a selection of updates on the research and development of vaccines to prevent SARS-coV2 infection that causes COVID-19. Those highlights are for the information of patient organisations/ groups, advocates and people living with a rare disease. EURORDIS takes reasonable steps to verify the accuracy of the information presented. This document does not constitute, and shall not be deemed or construed as, any approval or endorsement by EURORDIS of such product or entity.

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EURORDIS has a role in disseminating up-to-date information that could be useful for people living with a rare disease, who are exposed to the SARS-coV2 virus infection. Some rare diseases constitute an aggravated risk when infected by C-19. Some products being studied for C-19 are already approved or used off-label for some rare diseases, with potential information confusion and shortages risks. In other rare diseases, some products being studied for C-19 may have medicinal products interactions with medicines used in the care of these diseases. All good reasons to inform patient advocates with curated though raw information material to empower their respective actions. EURORDIS's Task Force on Drug Information, Transparency and Access (DITA) was tasked to prepare and regularly update this document. This task force is composed of EURORDIS volunteers and staff.

This document is an editorial selection and highlights the most recent developments for products being currently tested in phase III clinical trials, measuring their efficacy and toxicity. It is by no mean an exhaustive list of all therapeutic research. To avoid repeating the same situation than for the last Ebola outbreak, where the evaluation of potential treatments could not be completed (not enough participants as the trials were started too late), clinical trials against COVID-19 were authorised very soon after the epidemic started. The priority is to enrol participants in authorised trials.

For any questions or clarification, please contact François Houÿez: francois.houyez@eurordis.org

Resources

- EUnetHTA Covid-19 Rolling Collaborative Reviews https://eunethta.eu/rcr01-rcrxx/
- Horizon scanning for treatments and vaccines by the Austrian HTA institute GÖG https://eprints.aihta.at/1234/
- World Health Organization: https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1
  All trials for COVID-19: https://www.who.int/docs/default-source/coronaviruse/covid-19-trials.xls?sfvrsn=a8be2a0a_6&ua=1
- The NIH register of clinical trials includes 210 clinicals trials to treat COVID 19 (as of 30 March 2020). You can consult here: https://clinicaltrials.gov

And also

- Other information (infography): https://www.visualcapitalist.com/every-vaccine-treatment-covid-19-so-far
- Video on the pathophysiology of the virus, the dynamic of the pandemic and how to fight it

  https://youtu.be/BtN-goy9VOY

Vaccines in development

This document is a summary of information on vaccines in development to prevent the SARs-coV2 infection, intended for people living with a rare disease. Sources include the European Medicines Agency and EUnetHTA, the European Network of HTA Agencies that publishes rolling collaborative reviews and horizon scanning reports.

Of all vaccines in development to prevent the infection, the EURORDIS's Drug Information, Transparency and Access Task Force decided the following selection for its own review:

1. The most advanced vaccine candidates: products in clinical development already, with emphasis on products in phase II, phase II/III and/or phase III.
2. Products with specific issues on efficacy or safety for some groups of rare diseases

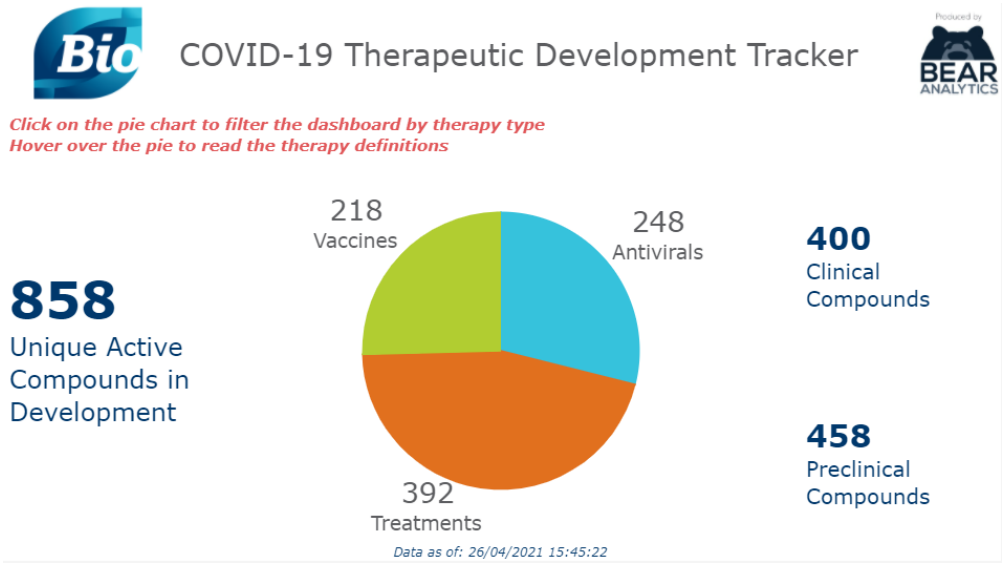


Figure 1: https://www.bio.org

Latest news

EMA rolling reviews in progress

CVnCoV CureVac AG: start of rolling review: 12/02/2021 (https://www.ema.europa.eu/en/news/ema-starts-rolling-review-curevacs-covid-19-vaccine-cvncov)

NVX-CoV2373, Novavax: start of rolling review: 03/02/2021 (https://www.ema.europa.eu/en/news/ema-starts-rolling-review-novavaxs-covid-19-vaccine-nvx-cov2373)

Sputnik V (Gam-COVID-Vac), Russia's Gamaleya National Centre of Epidemiology and Microbiology (https://www.ema.europa.eu/en/news/ema-starts-rolling-review-sputnik-v-covid-19-vaccine)

23 April: AstraZeneca's COVID-19 vaccine: benefits and risks in context, with graphic visualisation

https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

20 April: Vaccine Janssen. EMA finds possible link to very rare cases of unusual blood clots with low blood platelets

https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood

11 March: conditional marketing authorisation for Janssen's vaccines (Johnson & Johnson)

https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen

Vaccine platforms

Platform		Description	Examples
Inactivated		Whole virus, killed (heated or chemically). It cannot cause illness. In general, inactivated viruses do not provide as strong immune response as an attenuated virus vaccine, so repetition of doses needed	Polio virus influenza
Live attenuated		Live attenuated vaccines are made up of whole viruses that have been weakened in a lab (usually through culturing). In general, stronger immune response than inactivated vaccines	Tuberculosis Varicella MMR (Measles, mumps, rubella) Influenza
Subunit		Fragment or portion of the virus introduced into the body. This fragment is enough to be recognised by the immune response and stimulate immunity	Pertussis HPV Hep. B
Viral vector		Viral vector vaccines insert a gene for a viral protein into another, harmless virus (replicating or non-replicating). This harmless virus then delivers the viral protein to the vaccine recipient, which triggers an immune response.	Ebola Veterinary vaccines Recombinant influenza vaccine
mRNA		Work by introducing an mRNA sequence (the molecule that tells cells what to build) coded for a disease specific antigen. Once this antigen is reproduced within the body, it is recognised and triggers an immune response.	None
DNA		Work by inserting synthetic DNA of viral gene(s) into small DNA molecules called plasmids. Cells take in the DNA plasmids and follow their instructions to build viral proteins, which are recognised by the immune system, and prepare it to respond to disease exposure.	None

Regulatory timelines of key vaccine candidates

PRELIMINARY - AS OF APRIL 22

Regulatory timeline of key Vx candidates

https://extranet.who.int/pqweb/key-resources/documents/status-covid-19-vaccines-within-who-eulpq-evaluation-process

Legend (timing of approval)

- Approval / Emergency use
- Decision expected date
- No info
- COVAX Facility product

Vx candidates		Estimated dates of approval / Emergency use: FDA	MHRA	EMA	WHO EUL/PQ	Regulatory authority of record
Pfizer BioNTech	Pfizer BioNTech - Comirnaty	Dec. 12, 2020 Emergency Use	Dec. 2, 2020 Emergency Use	Dec. 21, 2020 Cond. Authorization[1]	Dec. 31, 2020 Emergency use	EMA
AstraZeneca: AZ with EMA as authority of reference	AstraZeneca - Vaxzevria	*No FDA approval*	Dec. 30, 2020 Emergency Use[2]	Jan. 29, 2021 Cond. Auth.[1] (non-Covax)	Apr. 15, 2021 (donations only)	EMA
AstraZeneca: AZ with EMA as authority of reference	AstraZeneca – AZD1222	*No FDA approval*	*Not applicable*	1 COVAX node	Apr. 15, 2021, 1 COVAX node	EMA
Serum Institute of India: AZ South Korea w/ MFDS Korea as authority of record	AstraZeneca – AZD1222	*Not applicable*	*Not applicable*	*Not applicable*	Feb. 15, 2021 Emergency use	MFDS (Rep. Korea)
SII /AZ vaccine (Covishield) with DCGI India as authority of record	SII - Covishield	-	-	-	Feb. 15, 2021 Emergency use	DCGI (India)
Sinopharm / BIBP[4]	Beijing CNBG - BBIBP-CorV				April 2021 (Earliest)	NMPA
Sinovac	Sinovac - CoronaVac	*No FDA approval*		*No EMA approval*	May 2021 (Earliest)	NMPA
Moderna	Moderna – mRNA-1273	Dec. 18, 2020 Emergency Use	Jan. 8, 2021 Emergency Use	Jan. 6, 2021 Cond. Authorization[1]	April 2021 (Earliest)	EMA
Janssen	Janssen – Ad26.COV 2.5	Feb. 27, 2021 Emergency Use		Mar. 11, 2021 Cond. Authorization[1]	Mar. 12, 2021 Emergency use	EMA
Gamaleya	Gamaleya – Sputnik V				*Rolling submission started - Add. data awaited*	Russian NRA
CanSinoBIO	CanSino – Ad5-nCOV				*Rolling submission of data from April 2021*	NMPA
Sinopharm / WIBP[3]	Wuhan CNBG - Inactivated					NMPA
Novavax	Novavax – Covavax*				Novavax submitted EOI on 23 Feb	EMA

Key messages

- **WHO EUL:** Pfizer BioNTech – Comirnaty, SII – Covishield, Janssen - Ad26.COV 2.5, AstraZeneca – Vaxzevria/AZD1222
- **AstraZeneca:** WHO EUL for European nodes (1 COVAX node and non-COVAX for donations)
- Focus on assessment of Beijing CNBG - BBIBP-CorV, Sinovac - CoronaVac and Moderna - mRNA-1273
- **Gamaleya**: Additional data (NonCLIN, CLIN, CMC) required. Inspections in April, May and June 2021. EUL decision after inspections
- **Novavax** pre-submission meeting on May 7
- **Bharat and CureVac / Bayer** submitted EOI
- **BioCubaPharma** is in discussions to submit EOI

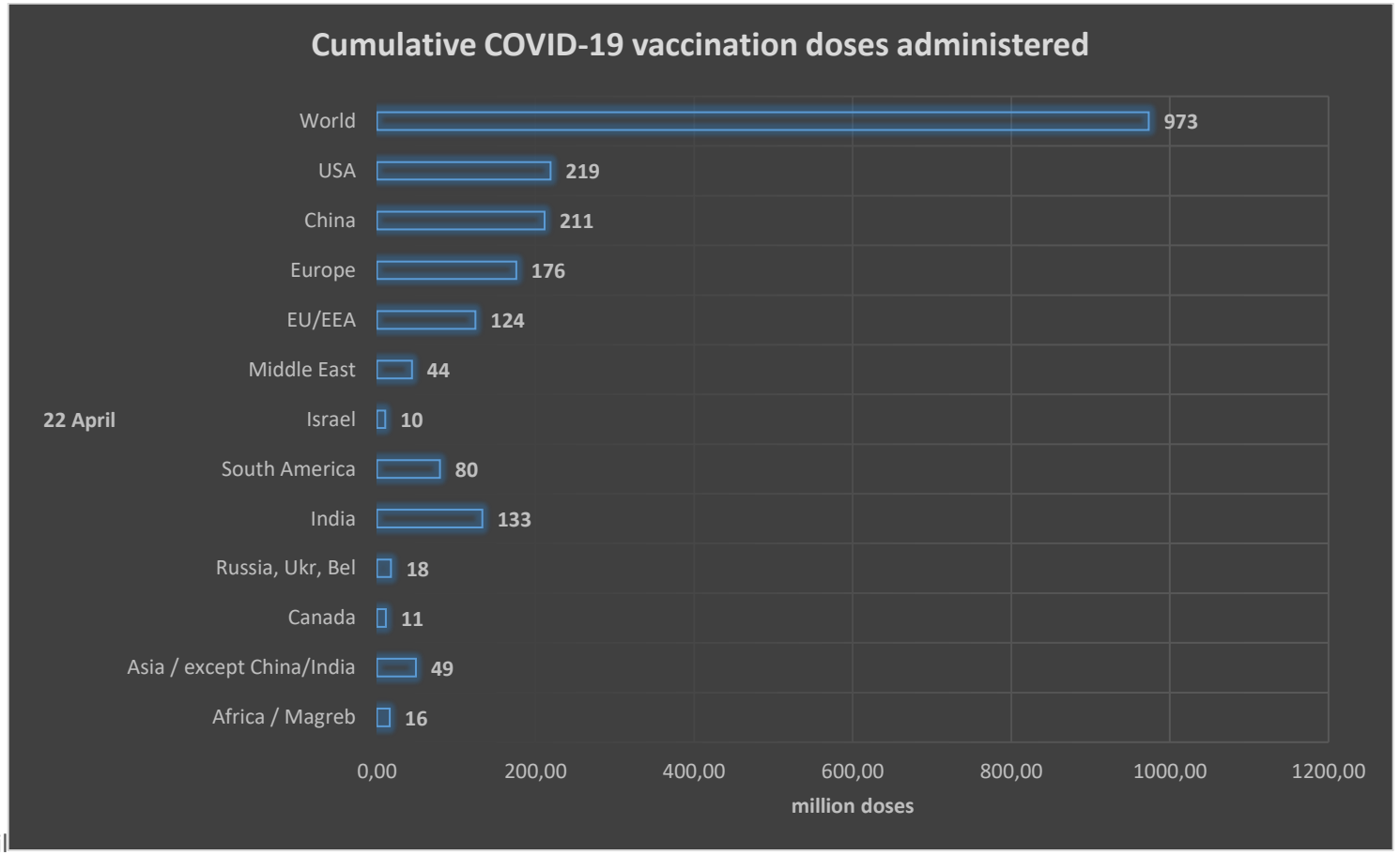
*. SII/Novavax needs to be specified

1. Conditional marketing authorization 2.Temporary authorisation of supply of the vaccine in the emergency use setting (which is distinct from a marketing authorisation) 3. Wuhan Institute of Biological Products Co Ltd 4. Beijing Bio-Institue of Biological Products Co-Ltd

SOURCE: https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_08Feb2021.pdf; https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution/

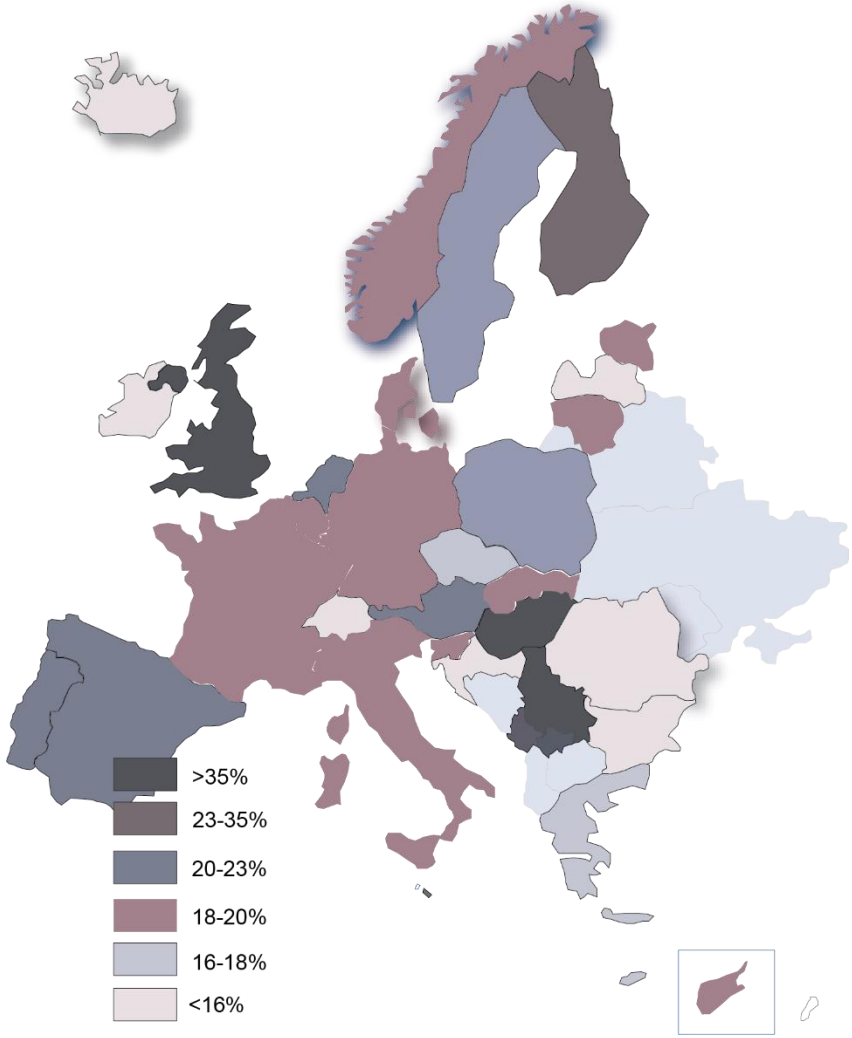
Vaccination campaign

Cumulated number of doses administered, world regions

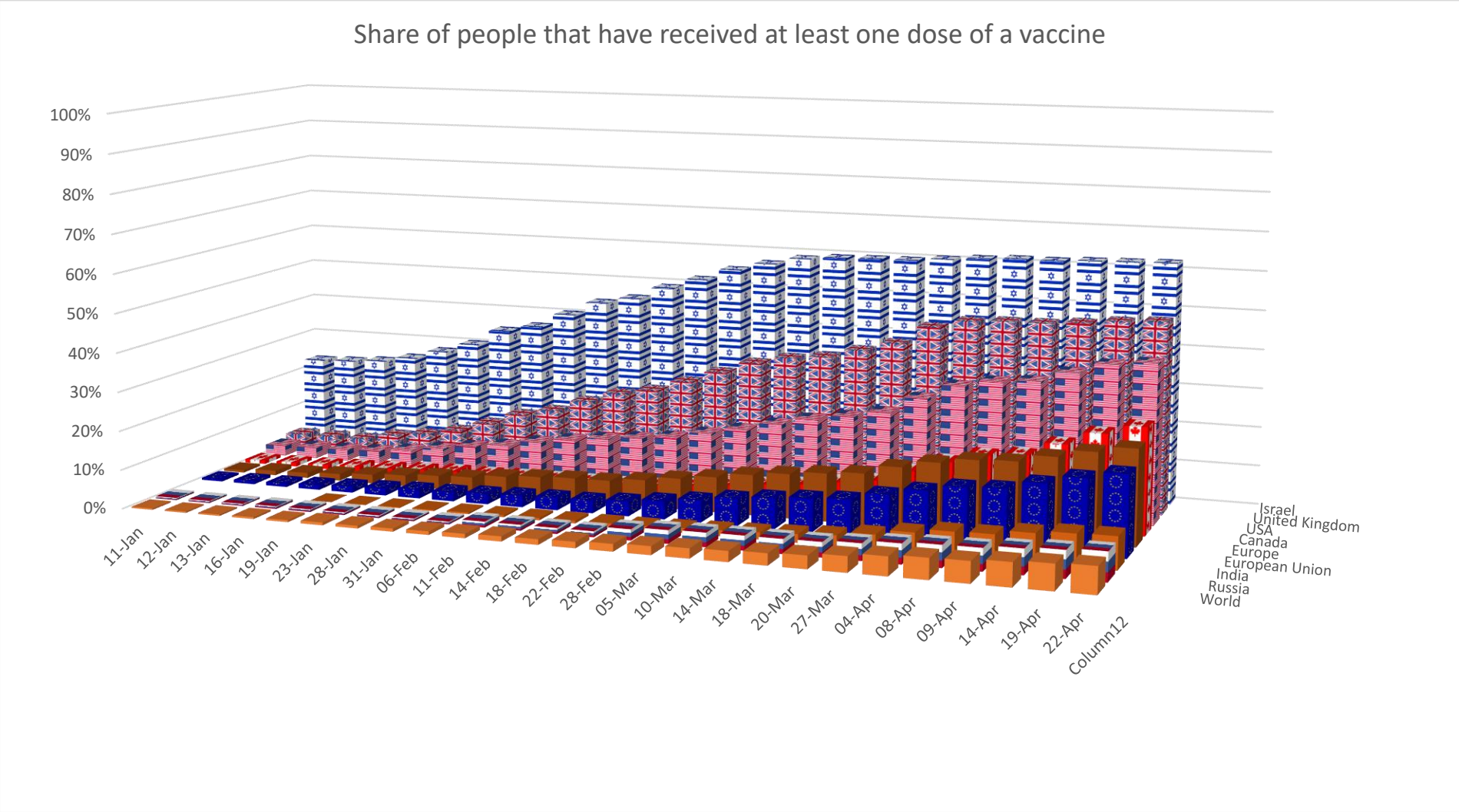


As of 22 April

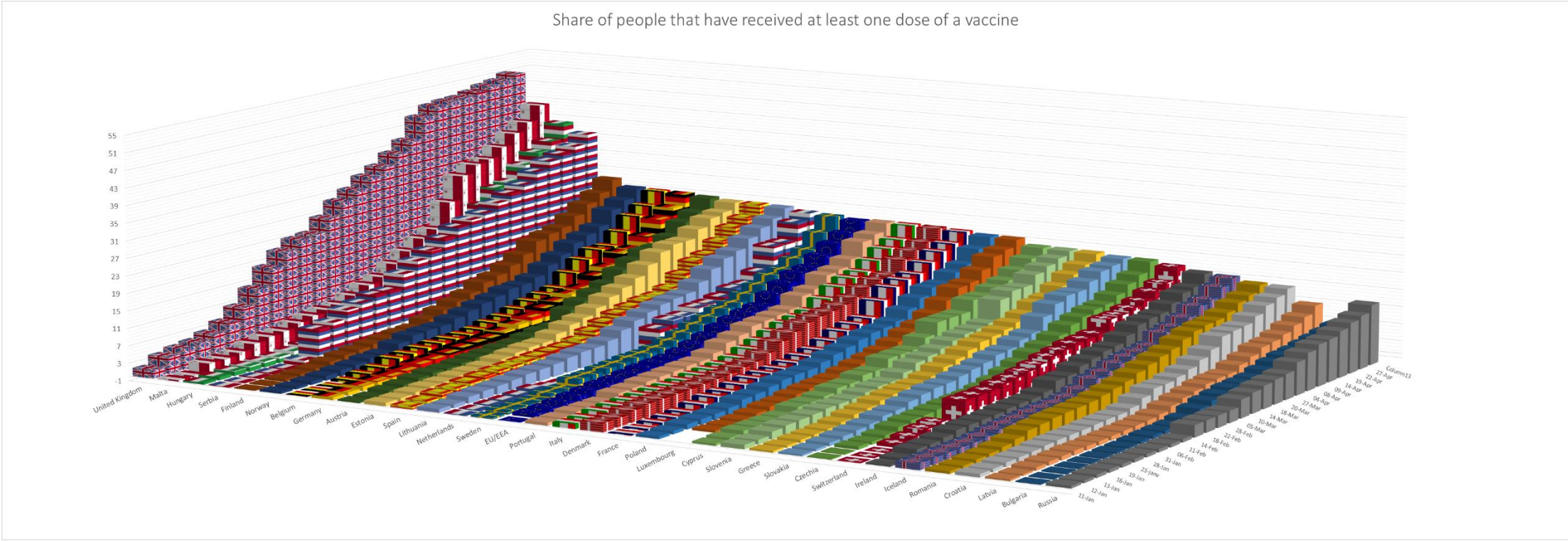
Share of the population that received at least one doses, Europe, by country



Share of the population that received at least one dose, world regions

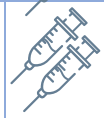
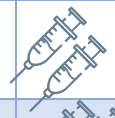
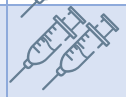
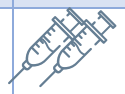


Share of the population that received at least one dose, Europe



Vaccines

Information on authorised vaccines, vaccines undergoing evaluation or rolling review

Company	Brand name	Number of doses	Research status	Investments	Emergency use authorisation or conditional authorisation in	Information
In use in human						
BioNtech/Pfizer Warp Speed Finalist	Comirnaty®		Ph. II/III ongoing: 44,000 volunteers in USA, Argentina, Brazil, Germany, South Africa, Turkey	Pfizer: $500M US Gov.: $1.9B	EU, USA, MHRA (UK), WHO Emergency Validation	See product information (EMA): here
Moderna Warp Speed Finalist COVAX Portfolio	-		Ph. III ongoing: 30,000 USA only	US Gov.: $2.48B CEPI: undisclosed	Canada, USA, United Kingdom, European Union	See product information (EMA): here
AztraZeneca Warp Speed Finalist COVAX Portfolio	Vaxzevria®		Ph. III ongoing: 40,000 in United Kingdom south Africa, and 10,000 in Brazil	US Gov.: $1.2B CEPI/GAVI: $750M EU: $923M	EU, MHRA (UK), WHO Emergency Validation US FDA: not yet	See product information (EMA): here
Johnson & Johson (Janssen) Warp Speed Finalist			Ph III ongoing: 60,000 in USA, Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa	J&J: $500M US Gov.: $1.45B	EU, USA, WHO Emergency Validation	See product information (EMA) here
Sinopharm / Beijing Institute of Biologic Products			Ph III ongoing: 45,000 in UAE, Bahrain, Jordan, Egypt, Argentina, Peru	-	Egypt, Bahrain, China, UAE	
Gamaleya Research Institute	Sputnik V		Ph III ongoing in Russia, Belarus, UAE, Venezuela	-	Argentina, Belarus, Russia, Hungary	
Sinovac Biotech	CoronaVac		Ph III ongoing in 28,000 in Brazil, Indonesia, Bangladesh, Turkey, China	-	China	

Rolling review in progress						
CVnCoV **Curevac**						Read here
NVX-CoV2373 Novavax						Read here
Sputnik V Gamaleya						Read here

WHO is tracking 34 candidates in various stages of development. Here are information on the most advanced candidates (phase I-2, phase 2-3 or phase 3) with their estimated completion date (interim analysis will be performed before the end-date).

Company	Vaccine	Platform	Phase	Completion date*	Country	Reference
Moderna	mRNA-1273	RNA	Phase 3	October 2022	USA	NCT04470427
CansinoBio	Ad5-nCov	Non-replicating viral vector	Phase 2		China	
Inovio	Ino-4800	Synthesised DNA plasmid vaccine	Phase 1		China, South Korea	
Janssen-Cilag J&J	JNJ-78436735	Ad26 vector expressing SARS-CoV-2 spike protein	Phase 3		USA,	NCT04505722
Novavax		VLP recombinant nano-protein	Phase 1-2		Australia, USA	NCT04368988
GSK/Dynavax		molecular clamp	Phase 1		Australia	
CureVac	CVnCoV	mRNA-based vaccine	Phase 1		Belgium, Germany	
BioNtech/Pfizer	BNT-162	mRNA based vaccine	Phase 2-3	November 2022	USA, Germany	NCT04368728
Sinovac Biotech	CoronaVac	Inactivated virus	Phase 3	October 2021	China, Brazil	NCT04456595
GSK / Sanofi		Recombinant protein, adjuvant	Phase 1-2	Ph III delayed, lack of immunogenicity in higher age groups	USA	
AztraZeneca	ChadOx1nCov-19	Non-replicating viral vector	Phase 3	August 2021	GBR	NCT04400838
Shenzen Inst.	LV-SMENP-Dc	Lentivirus	Phase 1-2		China	
Research	BCG vaccine	Live attenuated	Phase 2-3	April 2021	Netherlands	NCT04328441
Murdoch CRI	BCG vaccine	Live attenuated	Phase 2-3	June 2021 or March 2022	Australia	NCT04327206
Sinopharm	Vero-Cell	Inactivated virus	Phase 3	July 2021	China	ChiCTR2000034780
Gamaleya	Gam-COVID-Vac (Sputnik V)	Ad26 vector expressing SARS-CoV-2 spike protein	Phase 3		Russia	

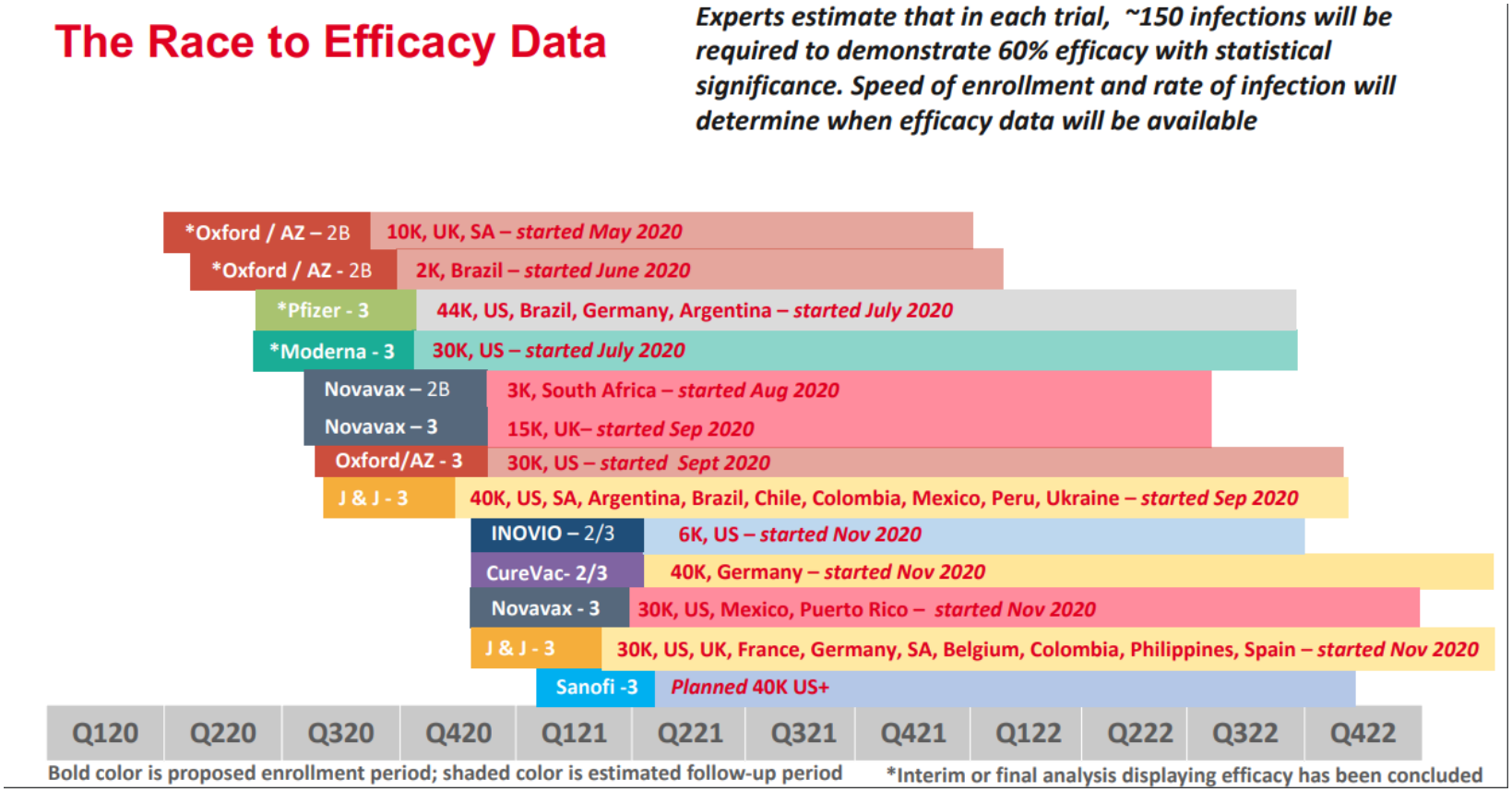


Figure 2: courtesy AVAC. In this graph, Sanofi's phase III trial is still indicated to start during the first quarter 2021, however Sanofi announced it would be delayed to end-2021.

Pfizer/BioNTech

Authorised in EU

Brand name

Comirnaty®

Developer

Developed by BioNTech in collaboration with Fosun Pharma and Pfizer

Description

mRNA platform-based vaccine expressing codon-optimized undisclosed SARS-CoV-2 protein(s)

Development phase

BNT-162 entered clinical testing by the end of April 2020.

A phase 2/3 RCT has started (NCT04368728/EudraCT 2020-002641-42) with aim to describe the safety, tolerability, immunogenicity and efficacy of BNT-162. It enrolled 44,000 participants above 12 years of age in USA, Argentina, Brazil, Germany, South Africa, and Turkey and its primary efficacy endpoint was reached.

Regulatory status

This vaccine can be used in human in the following jurisdictions: EU, USA, Bahrain, Canada, Chile, Costa Rica, India, Japan, Mexico, Philippines, Qatar, Saudi Arabia, Singapore, Switzerland, United Kingdom.

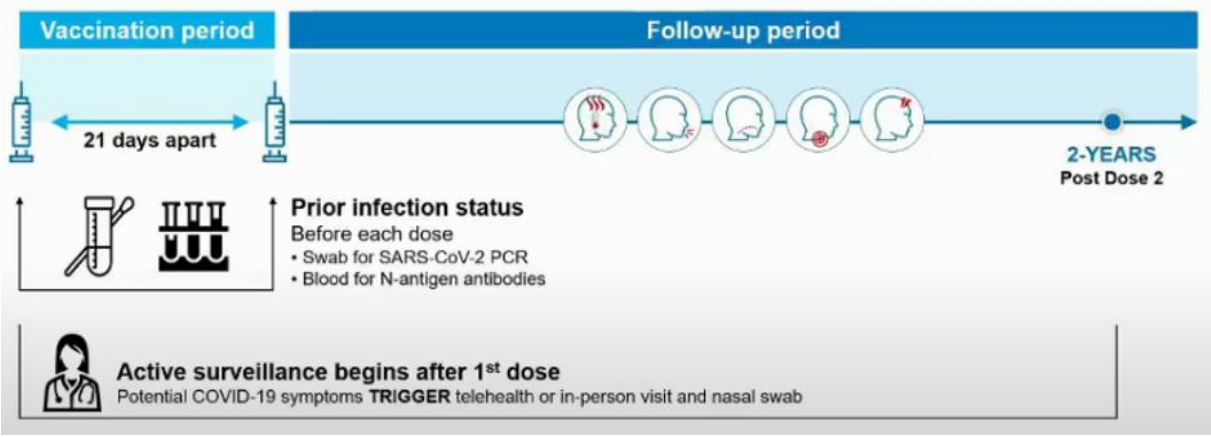
December 24th: Comirnaty®, Pfizer/BioNtech vaccine authorised in the EU. See EMA information here: https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty

Efficacy and safety data

Equally effective for all age groups, effect lasts for at least 3 months after 2nd dose (as of December 2020).

Two doses are needed, all participants were checked for coronavirus infection before each dose via PCR and antibodies detection. Symptoms of COVID-19 were investigated via tele-medicine, in-person visits and nasal swabs.

Participants will be followed-up for up to 2 years after the second dose.



Primary efficacy analysis patrticipants with 2 doses	mRNA	placebo	Comments - interpretation
Number of participants	18,198	18,325	
Confirmed symptomatic COVID-19 cases	8 (0.044%)	162 (0.88%)	
Reduction of the risk	**95%**		For 20 people who had the COVID-19 disease in the placebo group, there was only 1 in the group that received the vaccine
Among adults from 18 to 65 yo			
Confirmed symptomatic COVID-19 cases	7	143	
Reduction of the risk	95.1%		
Among adults above 65 yo			
Confirmed symptomatic COVID-19 cases	1	19	
Reduction of the risk	92.9%		
Among males	3	81	Reduction: 96.4%
Among females	5	81	Reduction: 93.7%

Pfizer/NioNtech vaccine protects against severe forms of COVID-19:

Primary efficacy analysis in participants with at least one dose	mRNA	placebo	Comments - interpretation
Number of participants	21,314	21,259	
Confirmed severe COVID-19 cases	1 (0.0047%)	9 (0.0423%)	
Reduction of the risk		**88.9%**	For 10 people who had a severe COVID-19 disease in the placebo group, there was only 1 in the group that received the vaccine

Side-effects more frequent in the mRNA arm than in the placebo arm included pain (at injection site), fatigue, headache, chills, muscle and joint pain. Globally, more people in the vaccine group had general disorders (18.3% versus 3.9% in the placebo group), or musculo-skeletal and connective tissue disorders (7.3% versus 2%), or nervous system disorders (6.1% versus 2.4%).

More research continues among children, in pregnancy, in immune-compromised patients and on a new formulation that is more stable in the refrigerator.

How it is used

Doses taken 21 days apart. Local storage conditions:

- Freezer at -70°C up to expiration date

Moderna

Authorised in EU

Description

The ModernaTX, Inc.mRNA-1273 vaccine candidate developed by ModernaTX, Inc. in collaboration with NIAID is an encapsulated mRNA-based vaccine (mRNA-1273). It is intended for the prevention of infection through a protein of SARS-CoV-2 that is the key into the human cell. An mRNA-based virus has not been approved for use in humans yet. It is a synthetic RNA strand designed to elicit an immune-response to produce antibodies against SARS-coV2.

To learn more on mRNA vaccines and how they were discovered, an informative video by the NIH Vaccine Research Centre here: https://www.youtube.com/watch?v=uXcA-mByGfw&feature=youtu.be

Development phase

Currently, there is a phase III trial with 30,000 participants (NCT04470427).

Regulatory status

This vaccine can be used in human in the following jurisdictions: Canada, USA, United Kingdom, and the European Union (January 6th: Moderna vaccine was authorised in the EU. See here https://www.ema.europa.eu/en/news/ema-recommends-covid-19-vaccine-moderna-authorisation-eu)

Efficacy and safety data

Equally effective for all age groups, effect lasts for at least 3 months after 2nd dose (as of December 2020).

Primary efficacy analysis	mRNA	placebo	Comments - interpretation
Number of participants	14,134	14,073	
Confirmed symptomatic COVID-19 cases	11 (0.077%)	185 (1.3%)	
Reduction of the risk	**94.1%**		For 20 people who had the COVID-19 disease in the placebo group, there was only 1 in the group that received the vaccine
Among adults from 18 to 65 yo with no underlying disease	8,396	8,403	
Confirmed symptomatic COVID-19 cases	5	121	
Reduction of the risk	**95.9%**		Same
Among adults from 18 to 65 yo with underlying diseases	2,155	2,118	
Confirmed symptomatic COVID-19 cases	2	35	
Reduction of the risk	**94.4%**		Same
Among adults older than 65, with or without underlying disease	3,583	3,552	
Confirmed symptomatic COVID-19 cases	4	29	
Reduction of the risk	**86.4%**		For 7 people who had the COVID-19 disease in the placebo group, there was only 1 in the group that received the vaccine

Side-effects more frequent in the mRNA arm than in the placebo arm included pain (at injection site), most often mild, swelling, erythema (red skin), some fatigue, headache, muscle pain, joint pain and some fever.

A few death occurred in both arms, not related to the vaccine: 6 in the vaccine group (1 suicide, 1 cardio-vascular arrest, 1 head injury, 1 myocardial infarction, 1 multisystem organ failure, 1 not specified), and 7 in the placebo group (1 abdominal injury, 1 cardio-vascular arrest, 1 due to COVID-19, 2 myocardial infarctions, 1 dermatitis bullous, 1 not specified).

No participant was excluded from the trial due to allergic reactions prior to entering the trial. 2 anaphylactic reactions occurred (a serious and profound state of shock brought about by hypersensitivity to an allergen such as a drug, foreign protein, or toxin):

- One in the placebo group (10 days after first dose)
- One in the vaccine group (67 days after first dose)

The relation between the reaction and the vaccine is therefore not established.

How it is used

Doses taken 28 days apart. Local storage conditions:

- Freezer at -20°C up to expiration date
- Refrigerator 5°C up to 30 days
- Room temperature up to 12 hours
- Local transport at 5°C.

AztraZeneca vaccine

Authorised in EU

Developer

The ChAdOx1 nCoV-19 (AZD1222) is developed by AstraZeneca, licensed from Oxford University) vaccine candidate developed by the Jenner Institute at Oxford University.

Description

It is based on a non-replicating viral vector. A chimpanzee adenovirus platform is hereby used. This platform was previously utilised in clinical phase I trials for a vaccine against MERS.

The vaccine candidate uses a genetically modified safe adenovirus that may cause a cold-like illness. The intended prevention is through the modified adenovirus producing Spike proteins, eventually leading to the formation of antibodies to the coronavirus's Spike proteins.

Development phase

A Phase 2b/3 study (EUdraCT 2020-001228-32/NCT04400838) determined the efficacy, safety and immunogenicity of ChAdOx1 nCoV-19. The primary endpoint was virologically confirmed (PCR positive) symptomatic COVID-19 infection.

A Phase 3 RCT (ISRCTN89951424) started in Brazil and South Africa, with another country in Africa set to follow, as well as a trial in the US. Participants are randomly allocated to receive the investigational vaccine or a well-established meningitis vaccine. The study is estimated to be completed in July 2021.

Regulatory status

AstraZeneca vaccine is approved in the EU, the UK, and qualifies for WHO. Its brand name is Vaxzevria®. A collaboration between AstraZeneca and the Serum Institute of India was successful, with the authorisation of Covishied, the brand name for this vaccine in India.

It is not yet approved by the US FDA.

Efficacy data

Different results of the same clinical trials were obtained at different moments, so different regulatory agencies had different sets of data and their respective conclusions regarding the overall efficacy of this vaccine might vary. The most recent publication analysed results extracted from these clinical trials in December 2020 and are summarised below.[1]

17,177 trial participants were eligible for inclusion in the efficacy analysis, 8948 in the UK, 6753 in Brazil and 1476 in South Africa.

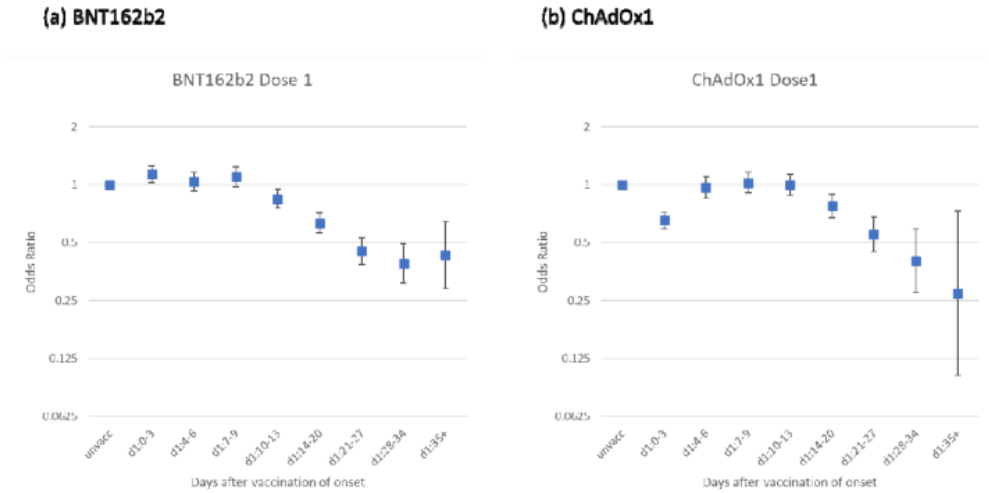
Symptomatic COVID-19 cases more than 14 days after second dose	Number of cases	Vaxzevria	Control (placebo)	Vaccine efficacy
Time between first and second dose				
< 6 weeks	111	35/3900 (0.9%)	76/3860 (2.0%)	54.9%
6-8 weeks	64	20/1103 (1.8%)	44/1004 (4.4%)	59.9%
9-11 weeks	43	11/905 (1.2%)	32/957 (3.3%)	63.7%
12 weeks or more	53	8/1293 (0.6%)	45/1356 (3.3%)	82.4%

[1] Oxford COVID Vaccine Trial, Single Dose Administration, And The Influence Of The Timing Of The Booster Dose On Immunogenicity and Efficacy Of ChAdOx1 nCoV-19 (AZD1222) Vaccine. Available at http://dx.doi.org/10.2139/ssrn.3777268

These results indicate that the longer the interval between the first dose and the booster, the highest the efficacy. When the booster is injected after 12 weeks or more than 12 weeks, the overall efficacy is 82.4% (82.4% fewer symptomatic COVID-19 cases in the vaccine arm). This level of protection is high, and can be compared with vaccine efficacy of 90 to 95% with Moderna's or Pfizer's vaccines.

Vaxzevria's efficacy in older people (above 70 years of age) is documented from a large population study in the UK published in March 2021 (preprint).[2] The study by Public Health England (PHE) compared the rate of vaccination in symptomatic people older than 70 who tested positive for coronavirus with that of those who weren't vaccinated (8 Dec 2020 to 19 Feb 2021). 44,590 participants with available vaccination data tested positive, while 112,340 tested negative.

The investigators found that one dose of the Pfizer vaccine was 57% to 61% effective in preventing symptomatic COVID-19 after 4 weeks and that the AstraZeneca vaccine was 60% to 73% effective.



35 days after dose 1

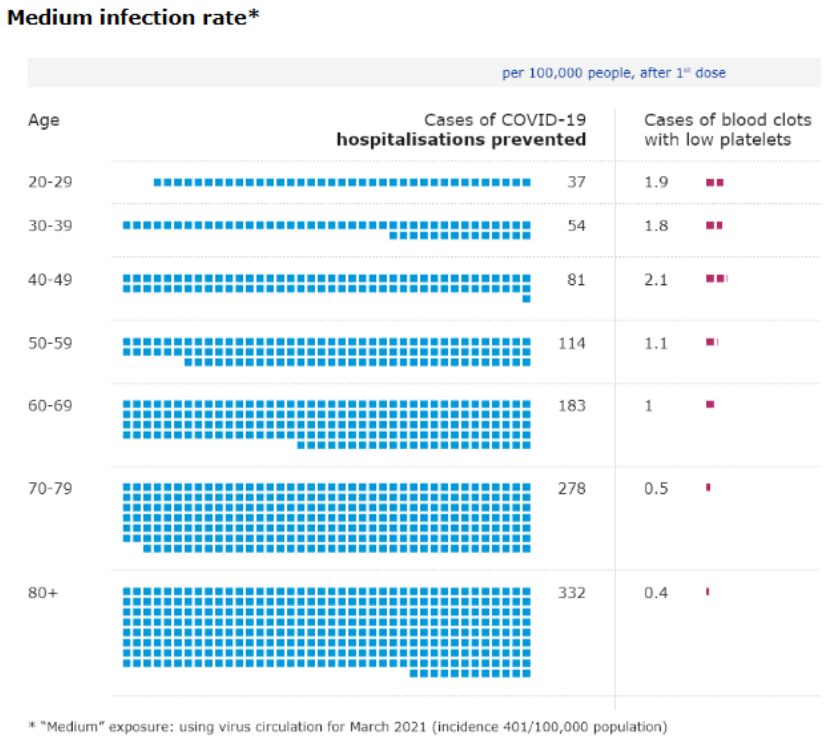
Figure 3: Adjusted odds ratios for confirmed case by interval after vaccination for BNT162b2 and ChAdOx1 vaccines, vaccinations administered since 4th January 2021

Figure 3: this shows the reduction in the likelihood of testing positive for the coronavirus in people vaccinated with Pfizer's vaccine (left) or Astrazeneca's vaccine (right), compared to people who received no vaccine at all

[2] Early effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. Jamie Lopez Bernal et al. https://doi.org/10.1101/2021.03.01.21252652 version posted March 2, 2021

Safety data

The EMA published graphic visualisation on the risk of blood clot, by age group, and depending on the intensity of the epidemic.[3] One example is shown below; in the context of the epidemic in March 2021, the number of hospitalisations that could be prevented thanks to Vaxzevria can be compared to the number of events with blood clots:



Blood clots are more likely to form in younger people, and overall blood clots do not put into question the efficacy of this vaccine, as did EMA scientific committees conclude (the benefits of Vaxzevria continue to outweigh its risks, to a large extent).

[3] https://www.ema.europa.eu/en/documents/chmp-annex/annex-vaxzevria-art53-visual-risk-contextualisation_en.pdf

Janssen-Cilag or Johnson & Johnson vaccine

Authorised in EU

Developer

The Janssen Pharmaceutical Companies of Johnson & Johnson developed Ad.26.COV2.S, a recombinant vector vaccine that uses a human adenovirus to express the SARS-CoV-2 spike protein in cells.

Description

This vaccine does not need to be stored at sub-zero temperatures, and it may require just a single dose. If its efficacy is similar to already authorised vaccines, it could become a champion in its category as much easier to handle.

Development phase

It is currently in phase III with 60,000 participants in USA, Argentina, Brazil, Chile, Colombia, Mexico, Peru and South Africa.

Regulatory status

The US FDA granted emergency use in February 2021, followed by the EMA/European Commission (11 March, conditional authorisation), and then the WHO (12 March).

EMA information can be found here: https://www.ema.europa.eu/en/medicines/human/EPAR/covid-19-vaccine-janssen

Efficacy data

From the EMA Medicines Overview: “Results from a clinical trial involving people in the United States, South Africa and Latin American countries found that COVID-19 Vaccine Janssen was effective at preventing COVID-19 in people from 18 years of age. This study involved over 44,000 people. Half received a single dose of the vaccine and half were given placebo (a dummy injection). People did not know if they had been given COVID-19 Vaccine Janssen or placebo.

The trial found a 67% reduction in the number of symptomatic COVID-19 cases after 2 weeks in people who received COVID-19 Vaccine Janssen (116 cases out of 19,630 people) compared with people given placebo (348 of 19,691 people). This means that the vaccine had a 67% efficacy”.

Safety data

The EMA published an update regarding the risk of blood clots with this vaccine on 22 April.[4]

Cases occurred within the first three weeks following vaccination, and mostly in women under 60 years of age; one had a fatal outcome

Events of thrombosis (blood clots obstructing blood vessels) occurring together with thrombocytopenia (low blood platelets) were reported after vaccination with COVID-19 Vaccine Janssen. The assessment included eight cases reported for COVID-19 Vaccine Janssen from clinical trials (1 case) and vaccination campaigns (7 cases) in the United States. More than 27,000 persons had been vaccinated in clinical trials and about7 million people in the US vaccination campaigns. The allocated frequency category 'very rare (occurring in less than 1 in 10,000 persons)' is the category with the lowest frequency defined for regulatory labelling of any side effect in a product information.

More detailed information from the US Centre for Diseases Control can be found here.[5]

Other vaccines

CansinoBio

Developer

CanSino Biologics Inc. and the Beijing Institute of Biotechnology

Description

The AD5-nCoV vaccine candidate is a replication-defective adenovirus type 5 (viral vector) that expresses SARS-CoV-2 spike proteins (antigens). The platform (non-replicating viral vector) of AD5-nCoV was originally used for an Ebola vaccine (time to market minus 3 years).

[4] https://www.ema.europa.eu/en/documents/covid-19-vaccine-safety-update/covid-19-vaccine-safety-update-covid-19-vaccine-janssen-22-april-2021_en.pdf
[5] https://www.cdc.gov/mmwr/volumes/70/wr/pdfs/mm7017e4-H.pdf?ACSTrackingID=USCDC_921-DM55766&ACSTrackingLabel=MMWR%20Early%20Release%20-%20Vol.%2070%2C%20April%2027%2C%202021&deliveryName=USCDC_921-DM55766

Development phase

The first clinical phase 1 trial (ChiCTR2000030906/ NCT04313127) with 108 healthy adults is a single-centre dose-escalation study to test both the safety and tolerability of AD5-nCoV injections in three intervention groups using different dosages (low, medium and high). Specific T-cell response peaked at day 14 post-vaccination. (See results)[6]

As of 17 August, 2020 the results from the a phase 2 RCT were published:[7]

Both doses of the vaccine induced significant neutralising antibody responses to live SARS-CoV-2.

Severe adverse reactions were reported by 24 (9%) participants in the 1×10^{11} viral particles dose group and one (1%) participant in the 5×10^{10} viral particles dose group. No serious adverse reactions were documented. Authors concluded that the Ad5-vectored COVID-19 vaccine at 5×10^{10} viral particles is safe, and induced significant immune responses in the majority of recipients after a single immunisation.

Inovio Ino-4800

Developer

Inovio Pharmaceuticals Inc.

Description

Ino-4800 is a DNA plasmid vaccine based on a DNA platform. The DNA is hereby synthesised in a laboratory, hence, no actual virus samples are required.

The company's DNA platform was previously utilised for a MERS-CoV vaccine (INO-4700) tested in a phase I trial.

[6] Zhu F et al. Safety, tolerability, and immunogenicity of a recombinant adenovirus type-5 vectored COVID-19 vaccine: a dose-escalation, open-label, non-randomised, first-in-human trial. The Lancet. 2020;395(10240):1845-1854. DOI: 10.1016/S0140-6736(20)31208-3.

[7] Zhu F. et al. Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial. The Lancet. 2020;396(10249):479-488. DOI: 10.1016/S0140-6736(20)31605-6.

Development phase

A phase 1 clinical trial started in April 2020. The results are aimed to be presented and published later (April 2021).

The phase 1, non-randomised, open-label, sequential assignment clinical trial (NCT04336410) in 40 healthy adult volunteers aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using CELLECTRA® 2000 device.

Phase 1/2 trial (NCT04447781) aims to evaluate the safety, tolerability and immunological profile of INO-4800 administered by intradermal (ID) injection followed by electroporation (EP) using the CELLECTRA® 2000 device in 160 healthy adults aged 19 to 64 years in Republic of K

To date, no completed studies in humans are available for the INO-4800 vaccine candidate.

Novavax

Developer

Novavax and co-sponsored by Coalition for Epidemic Preparedness Innovations (CEPI)

Description

Recombinant protein nanoparticle technology platform that is to generate antigens derived from the coronavirus spike (S) protein. Novavax also expects to utilise its proprietary Matrix-M™ adjuvant in order to enhance immune responses.

Development phase

Novavax initiated a Phase 1/2 clinical trial in May/June 2020. Novavax has previous experience with both MERS and SARS.

The phase 1/2, randomised, placebo-controlled, triple-blind, parallel assignment clinical trial (NCT04368988) in 131 healthy adults aims to evaluate the immunogenicity and safety of SARS-CoV-2 rS nanoparticle vaccine with or without Matrix-M adjuvant in healthy participants ≥ 18 to 59 years of age.

An interim analysis of Part 1 safety and immunogenicity data will be performed prior to an optional expansion to Part 2. To date, no completed studies in humans are available for Novavax COVID-19 vaccine.

GSK / Dynavax

Developer

Dynavax, Glaxo Smith Kline and the University of Queensland.

Description

The potential vaccine uses a molecular clamp stabilised Spike proteins. The so-called 'molecular clamp' technology is intended to prevent infection by synthesising surface proteins and „clamping" them into shape. In so doing, the immune system may induce a response, by recognising them as the correct antigen on the surface of the virus, more easily. Initially, this technology was designed to be a platform for generating vaccines against different viruses such as influenza, Ebola, and the MERS coronavirus.

Development phase

A Phase 1 randomised, double blind, placebo-controlled, dosage-escalation trial started on July 13, 2020 (ACTRN12620000674932/NCT04495933). The estimated study completion date is September 2021. To date, no completed studies in humans are available for the candidate vaccine.

CureVax

Description

A protamine-complexed mRNA-based vaccine expressing undisclosed SARS-CoV-2 protein(s). This means that CureVac's technology uses mRNA as a data carrier in order to train the human body to produce ideal levels of proteins. Thereby the immune system is stimulated and can respond to antigens

Development phase

Phase 1 (NCT04449276) study aims to evaluate the safety and reacto-genicity profile after 1 and 2 dose administrations of CVnCoV at different dose levels.

SinoVac

Developer

The private Chinese biopharmaceutical company Sinovac Biotech Ltd.

Description

CoronaVac, an inactivated COVID-19 vaccine candidate.

Development phase

The phase 1 and 2 trials started on April 16, 2020 in Jiangsu Province, China.

According to Sinovac announcement, preliminary phase I/II results showed that there was no serious adverse event after vaccinating a total of 743 volunteers. 90% seroconversion was observed in the phase II clinical trial 14 days after completion of a two-dose vaccination at day 0 and day 14

A Phase II study on elderly adults is being conducted which will be followed by child and adolescent groups. The phase II trial is expected to be completed at the end of 2020. Sinovac registered a new Phase 3 RCT (NCT04456595), aiming at assessing efficacy and safety of the Adsorbed COVID-19 (inactivated) vaccine in health care professionals in Brazil. Estimated number of participants is 8,870. Interim preliminary efficacy analysis can be triggered by reaching the target number of 150 cases. The study is estimated to be completed in October 2021.

China National Pharmaceutical Group Corporation (SINOPHARM)

Developer

Sinopharm is a state-owned Chinese company

Description

Vero-Cell is a β-propiolactone–inactivated whole-virus vaccine against COVID-19.

Development phase

A phase 3 double-blind, placebo controlled RCT has been initiated (ChiCTR2000034780), to evaluate the protective efficacy of inactivated SARS-CoV-2 Vaccine (Vero Cell) after full course of immunisation in healthy subjects aged 18 years old and above. The study is estimated to be completed in July 2021.

Sanofi-GSK

Developer

Sanofi developers a recombinant protein (technology already use for a flu vaccine) while GSK provides an adjuvant.

Development phase

A phase 1-2 randomised, double-blinded, placebo controlled trial is in progress with 440 participants (NCT04537208), recruiting in the USA only. A phase 3 trial could be submitted end 2020.

Development is delayed as the immune response in the elderly population seems to be lower than expected, and more research needs to be done before launching the phase III confirmatory trial.

BCG Vaccine

Developer

Two research groups, one in the Netherlands, and one in Australia.

Description

Live attenuated virus: repurposing thee BCG vaccine, originally for tuberculosis, to fight SARS-CoV2 in healthcare workers at high risk.

Development phase

RCTs in Netherlands (BCG-CORONA phase 3 trial, NCT04328441) and Australia (BRACE phase 3 trial, NCT04327206) aim to assess whether BCG-Danish reduces the incidence and severity of COVID-19 in health-care workers, and the effect this has on days off work. 1,000 healthcare professionals to be enrolled in 8 hospitals to receive the vaccine or placebo.

Sputnik V Vaccine (Russia)

This Russian COVID-19 vaccine Sputnik V is the first in the world with a national authorisation for human use. It was approved for public use even ahead of its Phase III trial.

Developer

Gamaleya Research Institute of Epidemiology and Microbiology

Description

Gam-COVID-Vac is a viral two-vector vaccine based on the human adenovirus, a common cold virus, fused with the spike protein of SARS-CoV-2 to stimulate an immune response.

Development phase

Sputnik V is approved for distribution in Russia, despite having been tested only in a small number of people in early-stage clinical trials that lasted two months, normally a process requiring a year or more of clinical assessment for proof of vaccine safety and efficacy against viral disease.[8]

[8] "Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia". The Lancet: 1–11. 4 September 2020. doi:10.1016/S0140-6736(20)31866-3.

Vaccine initiatives

COVID-19 Prevention Trial Network (COVPN)

NIAID established a new clinical trials network - The COVID-19 Prevention Trials Network (COVPN), that aims to enroll thousands of volunteers in large-scale clinical trials testing a variety of investigational vaccines and monoclonal antibodies intended to protect people from COVID-19.

The first Phase 3 clinical trial that the COVPN is expected to conduct with the investigational mRNA-1273 vaccine, developed by NIAID scientists and their collaborators at Moderna, Inc., based in Cambridge, Massachusetts.[9]

ACCESS (vACcine Covid-19 monitoring ReadinESS)

Utrecht scientists (in close collaboration with RIVM, Netherlands Pharmacovigilance centre LAREB and the PHARMO Institute in the Netherlands) are leading an European project with the aim to create an infrastructure and to prepare European organisations to collaboratively evaluate the benefits, coverage and risks of the novel COVID-19 vaccines in their post-licensure phase. The project is funded by the European Medicines Agency (EMA).[10]

COVAX

The COVAX initiative consists in purchasing distributing fairly two billion vaccine doses in 2021. It emerged from the World Health Organization (WHO), the Coalition for Epidemic Preparedness Innovations (CEPI) and from GAVI, the Vaccine Alliance.

NIAID Vaccine Research Centre

Almost of developments of SARS-coV2 vaccines derive from research for an HIV vaccine.[11]

[9] https://www.nih.gov/news-events/news-releases/nih-launches-clinical-trials-network-test-covid-19-vaccines-other-prevention-tools
[10] https://www.uu.nl/en/news/monitoring-the-benefits-and-safety-of-the-new-corona-vaccines
[11] Barney Graham, Deputy Director, Vaccine Research Centre