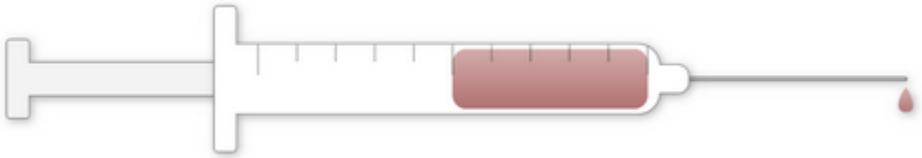
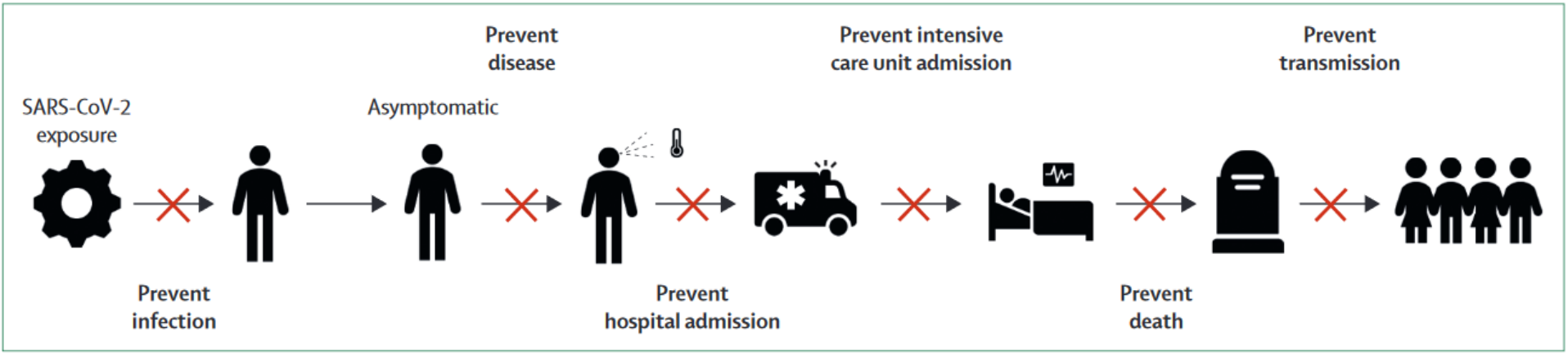
Approfondimento scientifico sulle diverse tipologie di vaccini anti COVID-19

Carlo Federico Perno

Ospedale Pediatrico Bambino Gesù

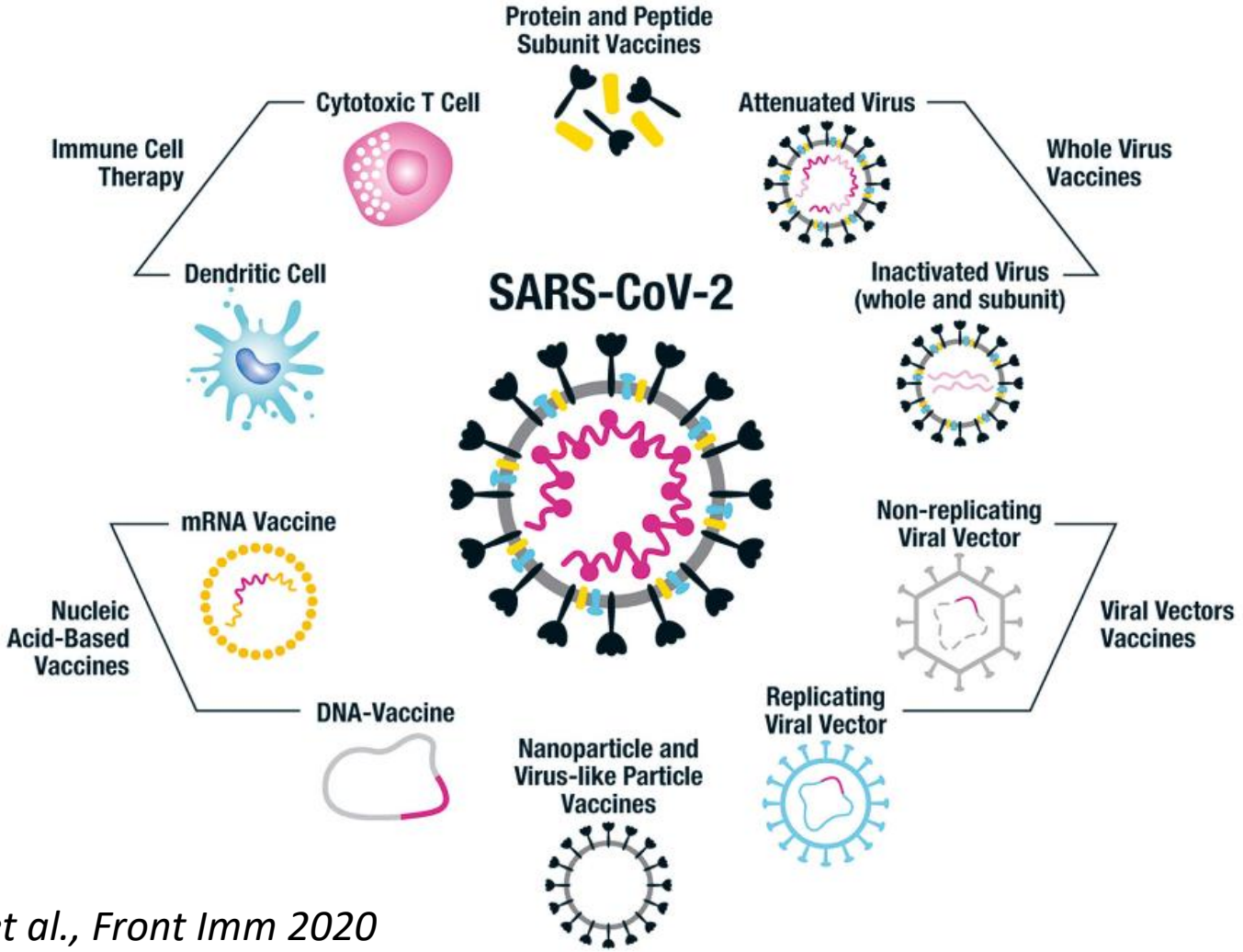


Potential endpoints of an efficacious COVID-19 vaccine



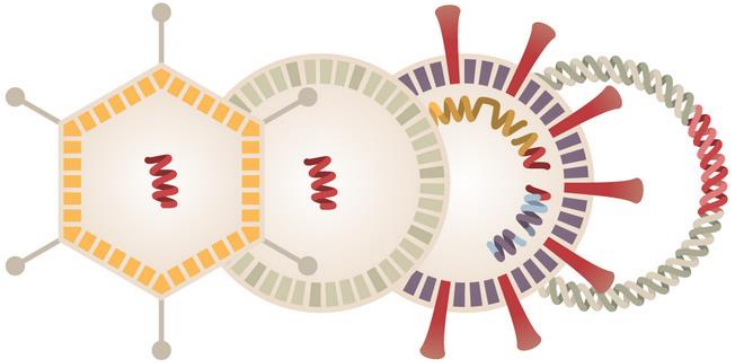
Hodgson SH et al., Lancet Inf Dis 2020

Vaccine platforms being employed for SARS-CoV-2 vaccine design

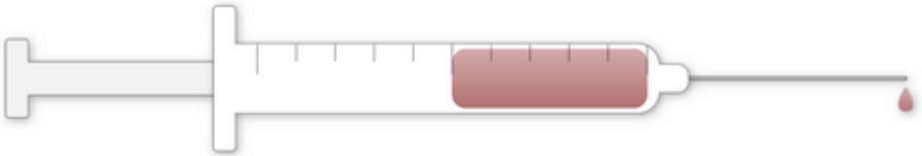


Flanagan KL et al., Front Imm 2020

Various candidate vaccines are being developed and tested



- Nucleic acid vaccines
- Inactivated virus vaccines
- Live attenuated vaccines
- Protein or peptide subunit vaccines
- Viral-vectored vaccines

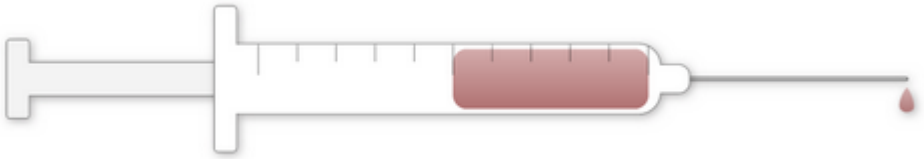


The New York Times

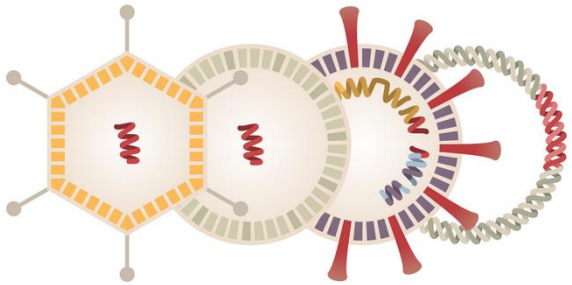
Coronavirus Vaccine Tracker

By Carl Zimmer, Jonathan Corum and Sui-Lee Wee Updated Jan. 5, 2021

PHASE 1	PHASE 2	PHASE 3	LIMITED	APPROVED	ABANDONED
43	20	20	7	3	1
Vaccines testing safety and dosage	Vaccines in expanded safety trials	Vaccines in large-scale efficacy tests	Vaccines in early or limited use	Vaccines approved for full use	Vaccines abandoned after trials



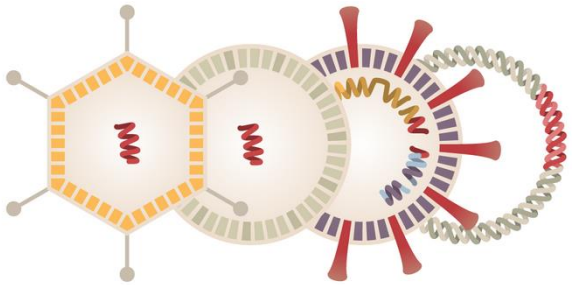
Various candidate vaccines are being developed and tested



	Vaccine type	Location	Trial number
Phase 1 trials only			
Inovio	DNA (INO-4800)	USA	NCT04336410
Genexine	DNA (GX-19)	South Korea	NCT04445389
Academy of Military Sciences; Suzhou Abogen Biosciences; Walvax Biotechnology	mRNA (ARCoV)	China	..
ReiThera; Lazzaro Spallanzani National Institute for Infectious Diseases	Gorilla adenovirus vector (GRAd-CoV2)	Italy	NCT04528641
Clover Pharmaceuticals; Dynavax Technologies	Protein (SCB-2019)	..	NCT04405908
Vaxine	Protein	Australia	NCT04453852
Medicago; GSK; Dynavax Technologies	Virus-like particle	USA	NCT04450004
University of Queensland; CSL	Proteins	Australia	NCT04495933
Kentucky Bioprocessing	Plant	USA	NCT04473690
Medigen; Dynavax Technologies	Protein (MVC-COV1901)	Taiwan	NCT04487210
Adimmune	Protein (AdimrSC-2f)	Taiwan	NCT04522089
West China Hospital of Sichuan University	Protein	China	NCT04470609
Sanofi; GSK	Protein	..	NCT04537208
Merck; Pasteur Institute	Measles vector	France	NCT04497298
Research Institute for Biological Safety Problems	Inactivated virus (QazCovid)	Kazakhstan	NCT04530357
Themis; Merck; University of Pittsburgh Center for Vaccine Research	Vesicular stomatitis virus-vectored (COVID-19–101)	Belgium; France	NCT04497298
Symvivo	Oral (bacTRL-Spike)	USA; Canada	NCT04334980

Poland GA et al., The Lancet 2020

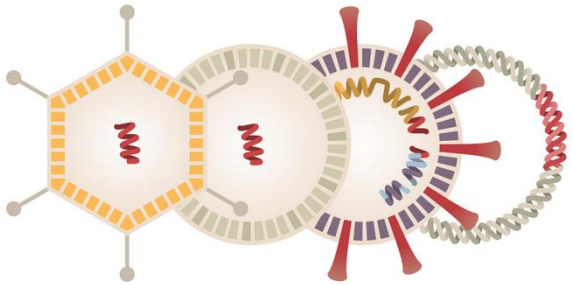
Various candidate vaccines are being developed and tested



	Vaccine type	Location	Trial number
Phase 1 and phase 2 trials			
Imperial College London; Morningside Ventures	Self-amplifying RNA	UK	..
AnGes; Osaka University; Takara Bio	DNA (AG0302-COVID19)	Japan	NCT0452708; NCT04463472
Arcturus; Duke-NUS Medical School	mRNA (LUNAR-COV19)	Singapore	NCT04480957
Johnson & Johnson; Beth Israel Deaconess Medical Center	Adenovirus serotype 26 vector (Ad26.COV2-S)	USA	NCT04436276
Novavax	Nanoparticle (NVX-CoV2373)	USA; South Africa	NCT04533399
Finlay Vaccine Institute	Protein (Soberana 1)	Cuba	..
Vector Institute	Peptide (EpiVacCorona)	Russia	NCT04527575
Bharat Biotech; Indian Council of Medical Research; National Institute of Virology	Inactivated virus (Covaxin)	India	NCT04471519
Anhui Zhifei Longcom Biopharmaceutical; Institute of Microbiology of the Chinese Academy of Sciences	Protein	China	..
Zydus Cadila	DNA (ZyCoV-D)	India	..
Curevac	mRNA (CVnCoV)	Germany, Belgium	NCT04449276, NCT04515147

Poland GA et al., The Lancet 2020

Various candidate vaccines are being developed and tested



	Vaccine type	Location	Trial number
Phase 3 trials			
AstraZeneca; University of Oxford (30 000 participants)	Chimpanzee adenovirus (ChAdOx1/AXD1222)	UK; India; Brazil, South Africa; USA	NCT04516746
Moderna; National Institutes of Health (30 000 participants)	RNA (mRNA-1273)	USA	NCT04470427
Pfizer; BioNTech (44 000 participants)	RNA (BNT162b1 and BNT162b2)	USA	NCT04368728
The Janssen Pharmaceutical Companies of Johnson & Johnson (60 000 participants)	Adenovirus serotype 26 vector (Ad26.COV2.S)	USA; Argentina; Brazil; Chile; Columbia; Mexico; Peru; Philippines; South Africa; Ukraine	NCT04505722
The Gamaleya National Research Centre for Epidemiology and Microbiology; Academy of Military Medical Sciences (40 000 participants)	Adenovirus serotype 5 vector and adenovirus serotype 26 vector (Sputnik V)	Russia	NCT04530396
CanSino Biologics; Academy of Military Medical Sciences (40 000 participants)	Adenovirus serotype 5 vector (Ad5CoV)	China; Pakistan	NCT04526990
Sinovac Biotech (9000 participants)	Inactivated virus (CoronaVac)	Brazil; Indonesia	..
Sinopharm; Wuhan Institute of Biological Products (21 000 participants)	Inactivated virus	The United Arab Emirates; Bahrain; Peru; Morocco; Argentina; Jordan	..
Sinopharm; Beijing Institute of Biological Products (5000 participants)	Inactivated virus (BBIBP-CorV)	The United Arab Emirates	..

Poland GA et al., The Lancet 2020

The New York Times

Leading vaccines

Developer	Type	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in Canada, other countries. Emergency use in U.S., other countries.
Moderna	mRNA	3	Approved in Canada. Emergency use in U.S., Israel.
Gamaleya	Adenovirus	3	Early use in Russia. Emergency use in Belarus, Argentina.
Oxford-AstraZeneca	Adenovirus	2 3	Emergency use in Britain, India, Argentina.
CanSino	Adenovirus	3	Limited use in China.
Johnson & Johnson	Adenovirus	3	
Vector Institute	Protein	3	Early use in Russia.
Novavax	Protein	3	
Sinopharm	Inactivated	3	Approved in China, U.A.E., Bahrain. Emergency use in Egypt.
Sinovac	Inactivated	3	Limited use in China.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

Anti-SARS-CoV-2/COVID-19 vaccines in Italy

1. Nucleic acid vaccines
   - **Pfizer/BioNtech**: lipid nanoparticle-formulated, nucleoside-modified mRNA vaccine encoding the RDB of Spike protein.
   - **Moderna**: sequence-optimised mRNA encoding the Spike glycoprotein encapsulated in lipid nanoparticles.
   - **Curevac**: non-chemically modified mRNA, encoding the prefusion-stabilized full spike protein of the SARS-CoV-2 virus.
2. Viral-vectored vaccines
   - **Oxford/AstraZeneca**: chimpanzee adenovirus-vectored vaccine encoding the spike glycoprotein of SARS-CoV-2.
   - **Janssen Pharmaceutical Companies of Johnson & Johnson**: adenovirus serotype 26-vectored vaccine, expressing full-length spike glycoprotein.
3. Protein vaccines
   - **Sanofi/GSK**: adjuvanted recombinant protein-based vaccine.

Ministero della Salute

Presidenza del Consiglio dei Ministri
COMMISSARIO STRAORDINARIO PER L'ATTUAZIONE E IL COORDINAMENTO DELLE MISURE DI CONTENIMENTO E CONTRASTO DELL'EMERGENZA EPIDEMIOLOGICA COVID-19

ISTITUTO SUPERIORE DI SANITÀ

agenas

AIFA AGENZIA ITALIANA DEL FARMACO

Vaccinazione anti-SARS-CoV-2/COVID-19

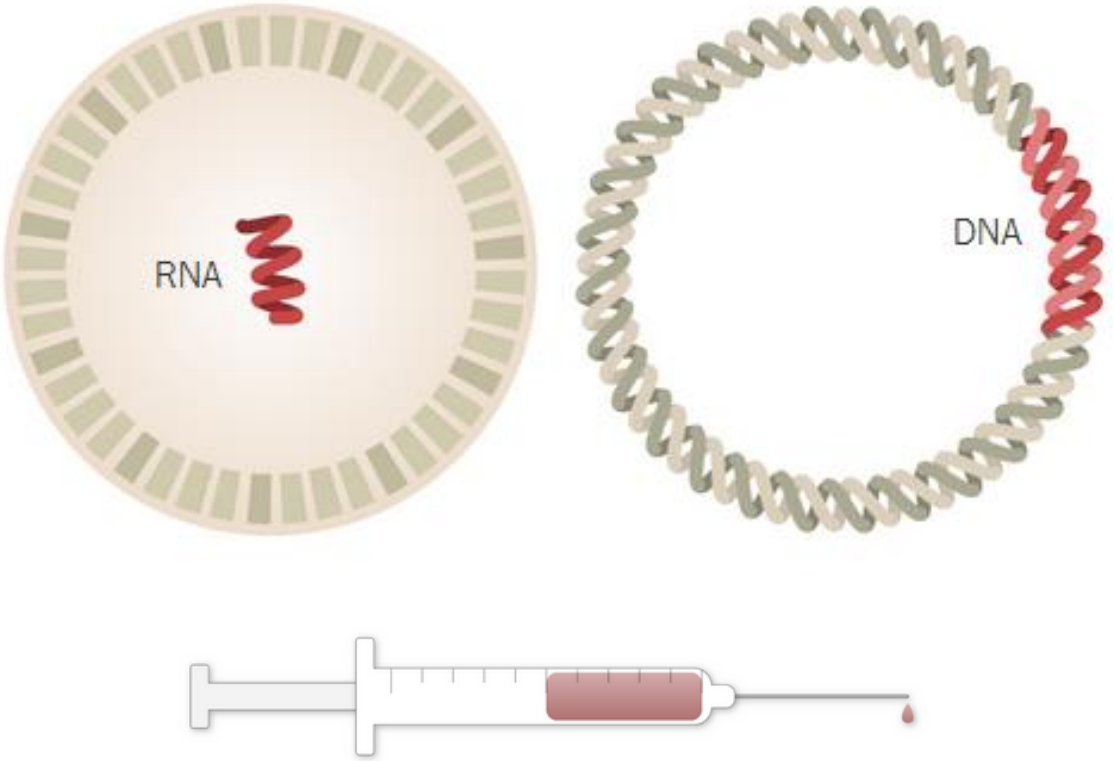
PIANO STRATEGICO

VACCINI (AZIENDA)	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022	TOTALI
Astra Zeneca	16,155	24,225	-	-	-	-	40,38
Pfizer-BioNtech	8,749	8,076	10,095	-	-	-	26,92
Johnson & Johnson	-	14,806	32,304	6,73	-	-	53,84
Sanofi/GSK	-	-	-	-	20,19	20,19	40,38
CureVac	2,019	5,384	6,73	8,076	8,076	-	30,285
Moderna	1,346	4,711	4,711	-	-	-	10,768
TOTALE	**28,269**	**57,202**	**53,84**	**14,806**	**28,266**	**20,19**	**202,573**
media per mese	9,421	19,065	17,947	4,935	9,422	6,73	

https://info.vaccinicovid.gov.it/

Nucleic acid vaccines

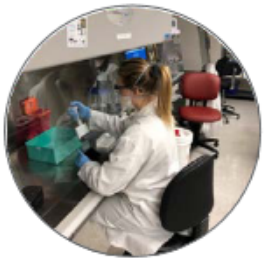
Vaccines that deliver one or more of the coronavirus's own genes into our cells to provoke an immune response.



The New York Times

Advantages of mRNA Vaccine Platform

Safety



Non-infectious, chemically defined, no viral foreign proteins

Efficacy

Broad immune responses, minimal risk of anti-vector immunity, and permits **frequent boosting**

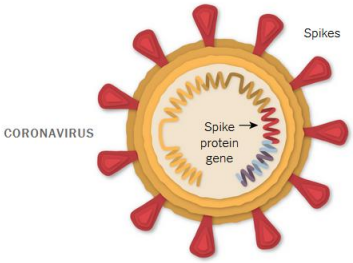
Rapid Response

Technology enables **rapid development** and **quick production scaling**

FDA Vaccines and Related Biological Products Advisory Committee, Dec 2020
https://www.fda.gov/media/144325/download

PHASE 2 | PHASE 3 | COMBINED PHASES

APPROVED IN SEVERAL COUNTRIES | EMERGENCY USE IN U.S., ELSEWHERE



Pfizer BIONTECH

VACCINE NAME: Comirnaty (also known as tozinameran or BNT162b2)

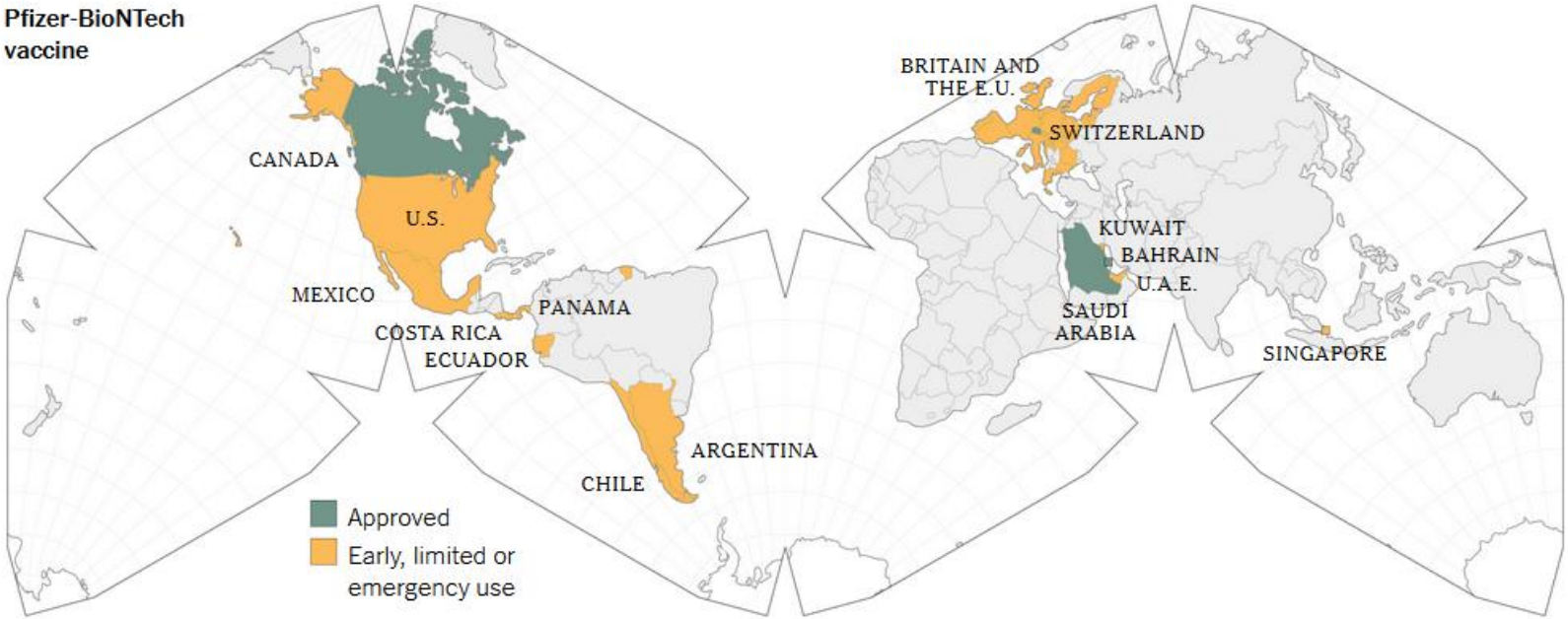
EFFICACY: 95%

DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

STORAGE: Freezer storage only at –94°F (–70°C)

Updated Jan. 2

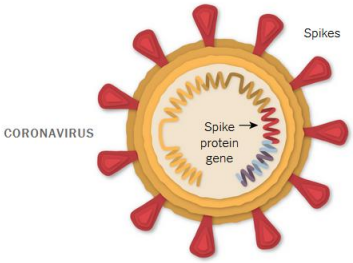


The New York Times

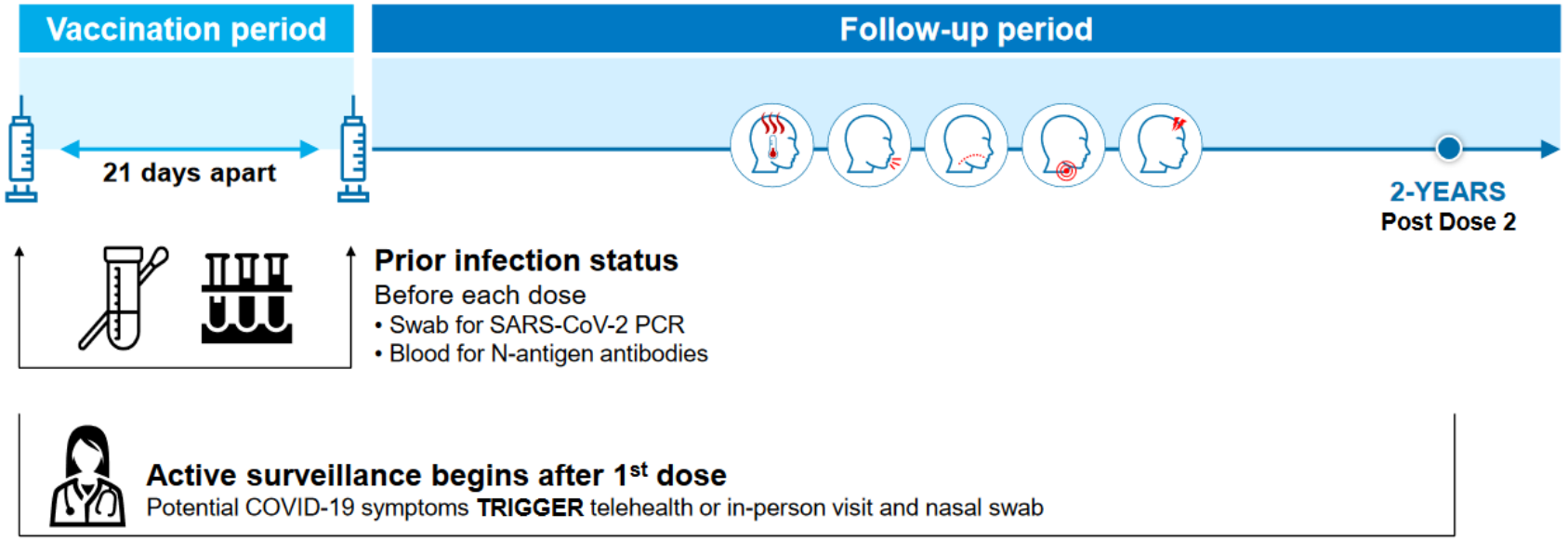
PHASE 2 | PHASE 3 | COMBINED PHASES

APPROVED IN SEVERAL COUNTRIES | EMERGENCY USE IN U.S., ELSEWHERE

Pfizer BIONTECH



- Phase 1/2 trial in 45 participants with BNT162b1 and BNT162b2 vaccines.
- The participants, aged 18-55 years, were randomly assigned to receive two intramuscular doses, separated by 21 days.

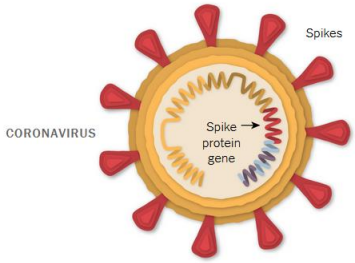


FDA Vaccines and Related Biological Products Advisory Committee, Dec 2020
https://www.fda.gov/media/144325/download

PHASE 2 | PHASE 3 | COMBINED PHASES

APPROVED IN SEVERAL COUNTRIES | EMERGENCY USE IN U.S., ELSEWHERE

Pfizer BIONTECH



- Early results indicate that two vaccines elicited RBD-binding IgG and neutralising antibodies.
- Mostly mild side-effects (eg, injection site pain, fatigue, headache, chills, muscle pain, and joint pain).

First COVID-19 Occurrence From 7 Days After Dose 2

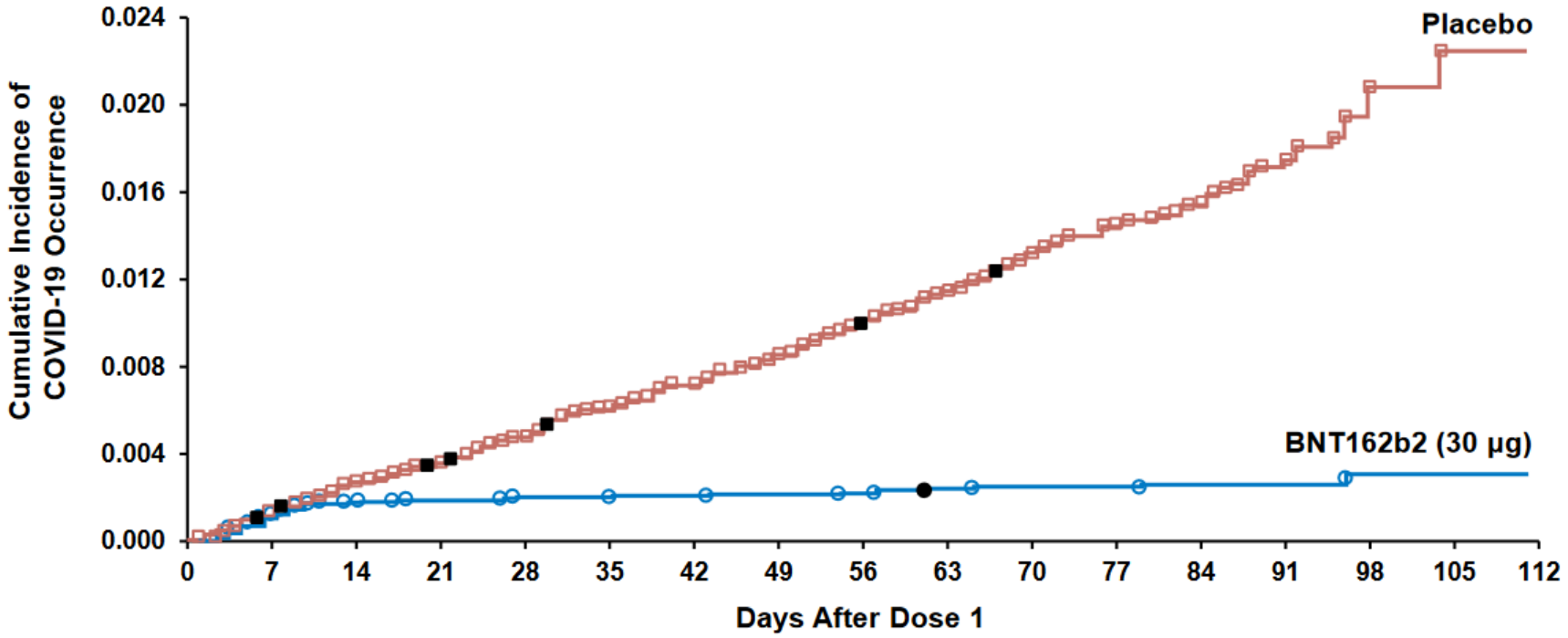
Phase 2/3 Efficacy – Final Analysis

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

		BNT162b2 N=18,198 n	Placebo N=18,325 n	VE (%)	(95% CI)
Overall		8	162	95.0	(90.0, 97.9)
Age	18-64 years	7	143	95.1	(89.6, 98.1)
	65-74 years	1	14	92.9	(53.1, 99.8)
	≥75 years	0	5	100.0	(-13.1, 100.0)
Sex	Male	3	81	96.4	(88.9, 99.3)
	Female	5	81	93.7	(84.7, 98.0)
Race	White	7	146	95.2	(89.8, 98.1)
	Black or African American	0	7	100.0	(31.2, 100.0)
	All Others	1	9	89.3	(22.6, 99.8)
Ethnicity	Hispanic/Latino	3	53	94.4	(82.7, 98.9)
	Non-Hispanic/Non-Latino	5	109	95.4	(88.9, 98.5)
Country	Argentina	1	35	97.2	(83.3, 99.9)
	Brazil	1	8	87.7	(8.1, 99.7)
	USA	6	119	94.9	(88.6, 98.2)

FDA Vaccines and Related Biological Products Advisory Committee, Dec 2020
https://www.fda.gov/media/144325/download

Cumulative Incidence of COVID-19 After Dose 1



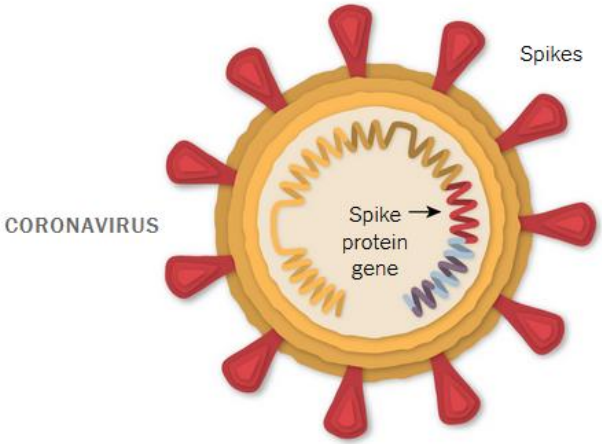
FDA Vaccines and Related Biological Products Advisory Committee, Dec 2020
https://www.fda.gov/media/144325/download

PHASE 3

APPROVED IN CANADA | EMERGENCY USE IN U.S., ISRAEL

moderna

NIH National Institutes of Health
Turning Discovery Into Health



VACCINE NAME: mRNA-1273

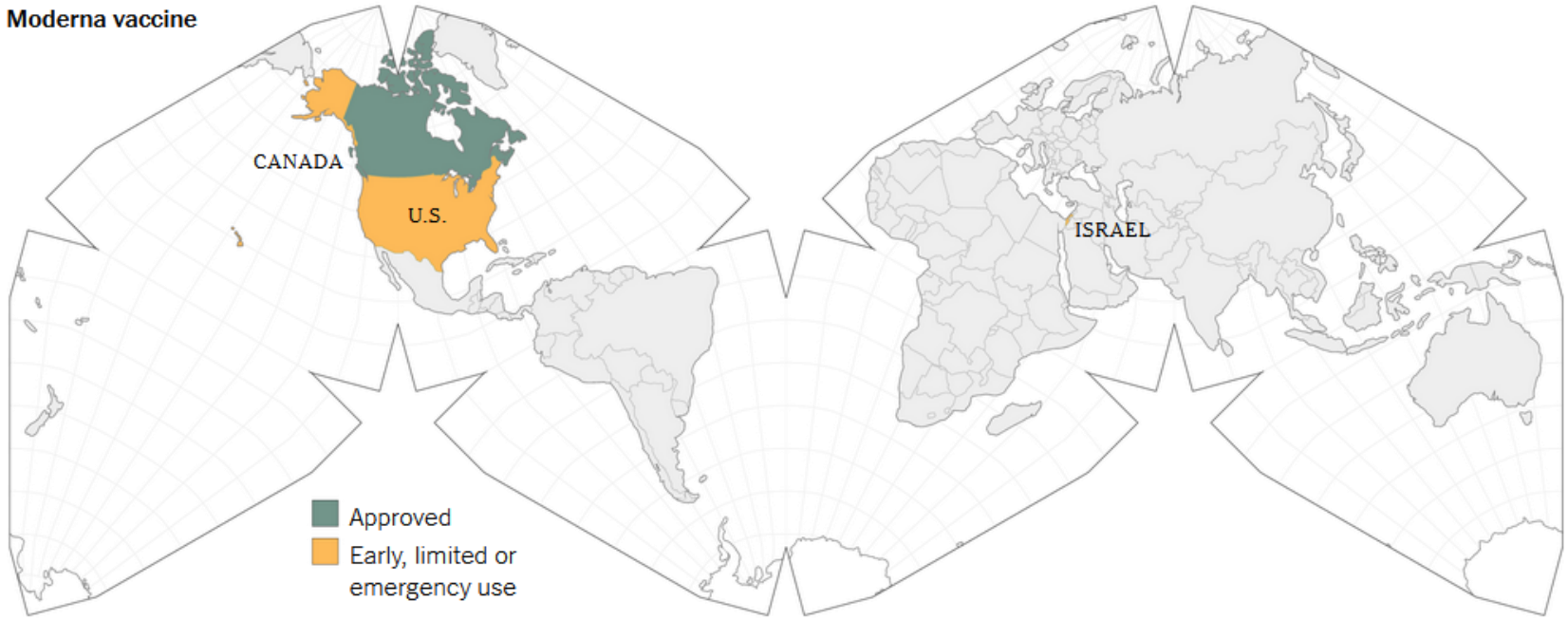
EFFICACY: 94.5%

DOSE: 2 doses, 4 weeks apart

TYPE: Muscle injection

STORAGE: 30 days with refrigeration, 6 months at –4°F (–20°C)

Updated Jan. 4

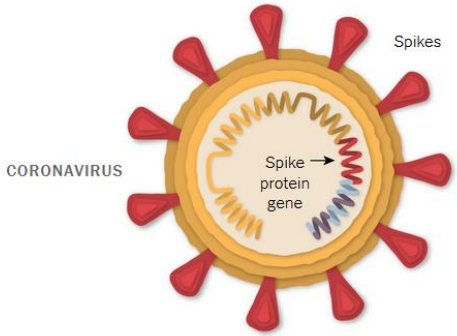


PHASE 3

APPROVED IN CANADA | EMERGENCY USE IN U.S., ISRAEL

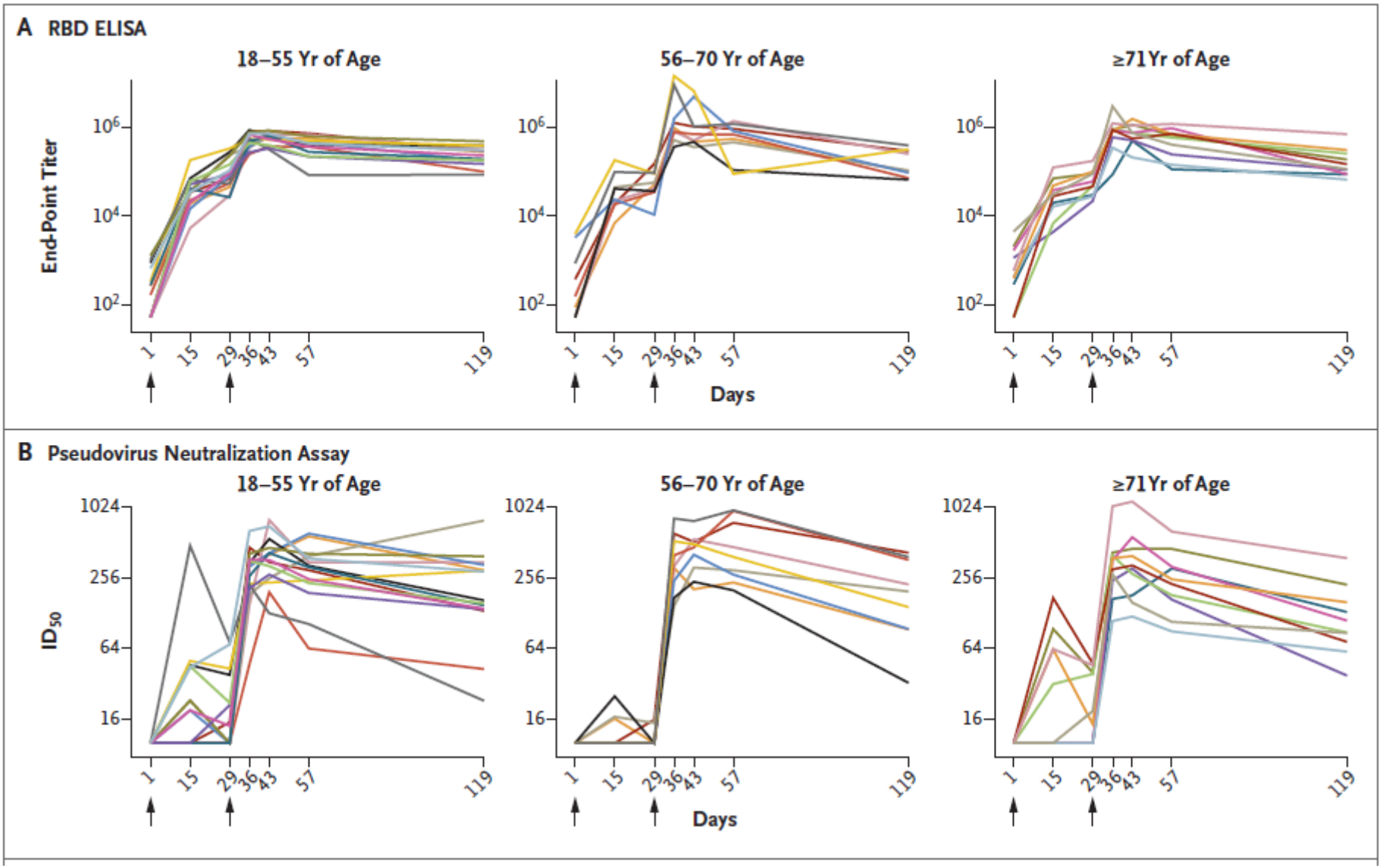
moderna

NIH National Institutes of Health
Turning Discovery Into Health



- Studies in non-human primates have shown the vaccine's immunogenicity and protective efficacy after two doses (10 µg or 100 µg) given 4 weeks apart.
- In two phase 1, dose-escalation trials, this vaccine induced both spike glycoprotein binding and virus-neutralising antibody responses in recipients aged 18–55 years and >65 years.
- These humoral immune responses were similar to those observed in convalescent plasma from patients who had recovered from COVID-19.
  - Vaccine recipients also developed cellular responses, mainly biased towards CD4+ Th1 cells.
  - CD8+T-cell responses were marginal, except for those in recipients of two vaccinations with the higher dose (100 µg).
- No important safety concerns were noted with this vaccine, with mild local and systemic side-effects including pain at the injection site, chills, fatigue, myalgia, and fever occurring within a few days of vaccination.

Despite a slight decline in titers of binding and neutralizing antibodies, mRNA-1273 has the potential to provide durable humoral immunity



Widge AT et al., NEJM 2020

RESEARCH SUMMARY

Efficacy and Safety of mRNA-1273 SARS-CoV-2 Vaccine

L.R. Baden, et al. DOI: 10.1056/NEJMoa2035389

CLINICAL PROBLEM

The Covid-19 pandemic continues and expands. Additional data regarding vaccines to prevent symptomatic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are needed. The mRNA-1273 vaccine is a lipid-encapsulated mRNA vaccine encoding the prefusion stabilized spike protein of SARS-CoV-2.

CLINICAL TRIAL

A randomized, double-blind trial to evaluate the efficacy and safety of mRNA-1273.

30,420 participants ≥18 years old were assigned to receive either the vaccine or placebo in two intramuscular injections 28 days apart. Participants were followed for safety and the development of laboratory-confirmed, symptomatic Covid-19 over a median of 2 months after the second dose.

RESULTS

Safety:
Vaccine recipients had higher rates of local reactions (e.g., pain, erythema, swelling) and systemic reactions (e.g., headache, fatigue, myalgia) than placebo recipients. Most reactions were mild to moderate and resolved over 1–3 days.

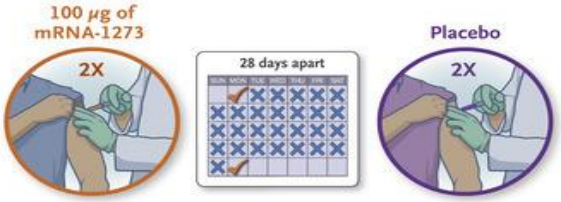
Efficacy:
The incidence of Covid-19 was lower among vaccine recipients than among placebo recipients as early as 14 days after the first dose. Protection in the vaccine group persisted for the period of follow-up.

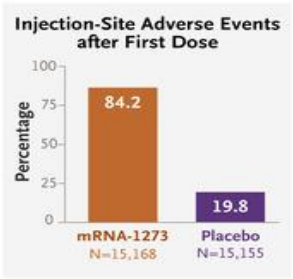
LIMITATIONS AND REMAINING QUESTIONS

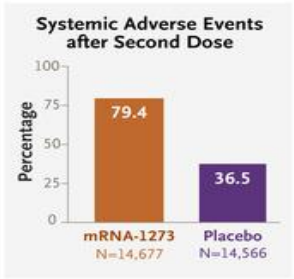
Further study is required to understand the following:

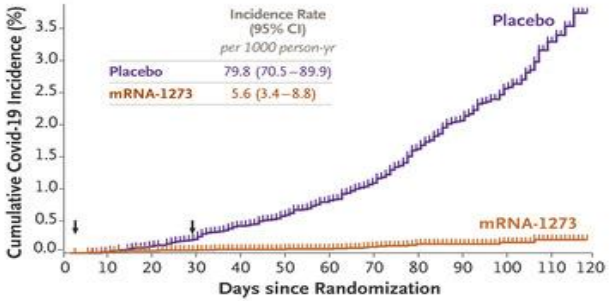
- Safety and efficacy over a longer period of time, in a larger population, and in pregnant women and children.
- Whether the vaccine protects against asymptomatic infection and transmission to unvaccinated persons.
- How to care for those who miss the second vaccine dose.

Links: Full article | NEJM Quick Take | Editorial









	mRNA-1273 Vaccine N=14,550	Placebo N=14,598
Symptomatic Covid-19	11	185
Severe Covid-19	0	30

Vaccine efficacy of 94.1% (95% CI, 89.3–96.8%; P<0.001)

CONCLUSIONS

Two doses of a SARS-CoV-2 mRNA-based vaccine were safe and provided 94% efficacy against symptomatic Covid-19 in persons 18 or older.

PHASE 3

CUREVAC

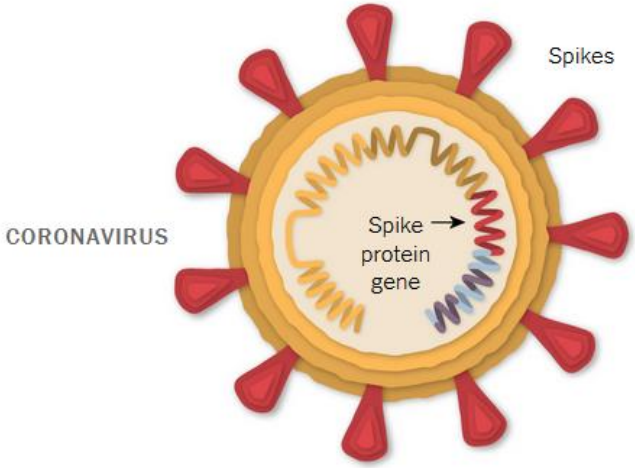
VACCINE NAME: CVnCoV

EFFICACY: Unknown

DOSE: 2 doses, four weeks apart

TYPE: Muscle injection

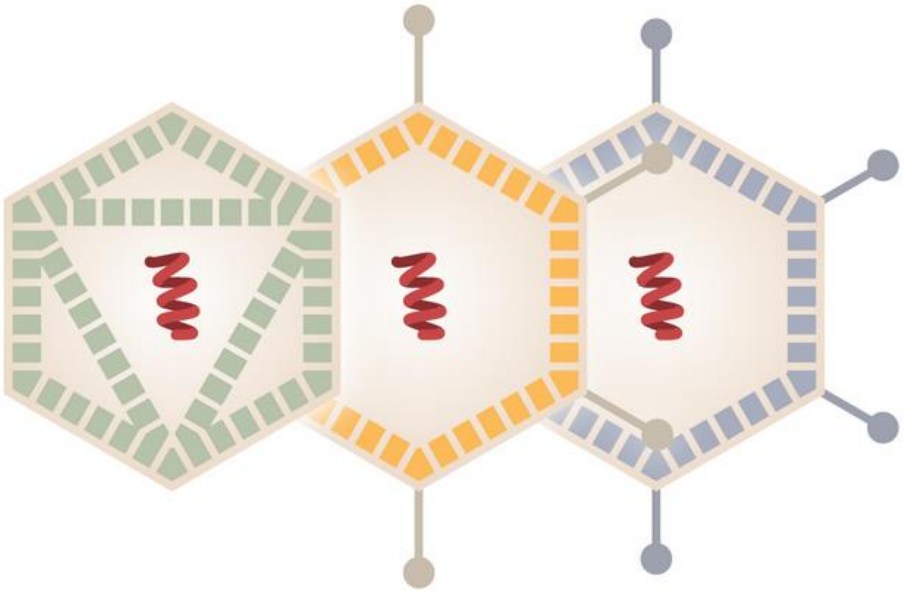
STORAGE: Stable at least 3 months at 36–46°F (2–8°C)



- CVnCoV demonstrated dose-dependent activation of the humoral immune system in mice at doses of 0.25, 1 and 4µg.
- Strong IgG1 and IgG2a binding antibody titers were observed at all doses and translated efficiently into neutralizing antibodies.
- Neutralizing antibodies started to develop 3 weeks after the first vaccination and increased after the second vaccination.
- In December, CureVac launched a Phase 3 trial, recruiting up to 36,500 volunteers in Germany.

Viral-vectored vaccines

Vaccines that contain viruses engineered to carry coronavirus genes. Some viral vector vaccines enter cells and cause them to make viral proteins. Other viral vectors slowly replicate, carrying coronavirus proteins on their surface.



The New York Times

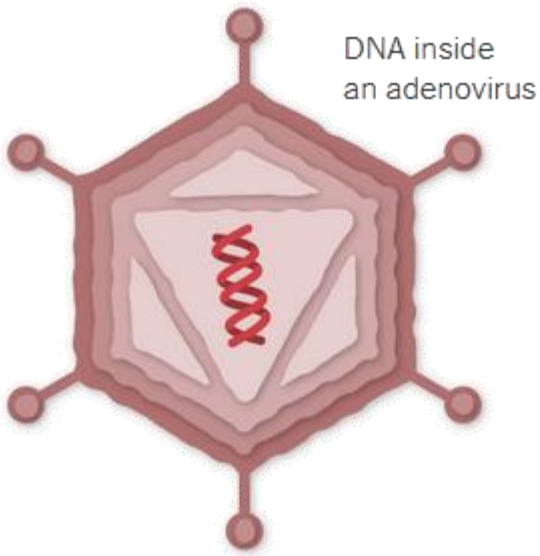
Mode of Action of the Viral-Vectored Vaccine Candidates

The gene for the coronavirus spike protein (in the form of double-stranded DNA) is included within the capsid of another virus, usually an adenovirus.

Adenoviruses are common viruses that typically cause colds or flu-like symptoms.

- The Oxford-AstraZeneca team used a modified version of a chimpanzee adenovirus, known as ChAdOx1.
- The J&J team used an attenuated adenovirus serotype 26.

Both viruses can enter cells, but they can't replicate inside them.



The New York Times

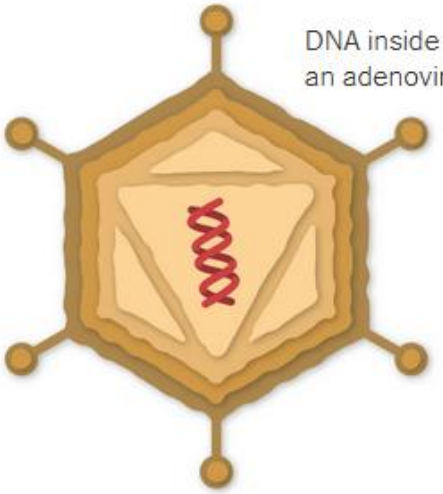
Mode of Action of the Viral-Vectored Vaccine Candidates

- These vaccines are more “resistant” than the mRNA vaccines.
- DNA is not as fragile as RNA, and the adenovirus’s tough protein coat helps protect the genetic material inside.
- As a result, these vaccines do not have to stay frozen.

PHASE 2 | PHASE 3 | COMBINED PHASES

EMERGENCY USE IN BRITAIN, ELSEWHERE

UNIVERSITY OF OXFORD AstraZeneca



VACCINE NAME: AZD1222 (also known as Covishield in India)

EFFICACY: Up to 90%

DOSE: 2 doses, 4 weeks apart

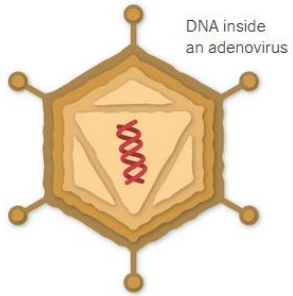
TYPE: Muscle injection

STORAGE: Stable in refrigerator for at least 6 months

Updated Jan. 3

The New York Times

UNIVERSITY OF OXFORD AstraZeneca



VACCINE NAME: AZD1222 (also known as Covishield in India)

- March 2020: pre-clinical efficacy in monkeys.
- April 2020: Phase 1/2 trial. Induction of humoral responses, characterized by anti-spike glycoprotein IgG and neutralising antibodies, and IFNγ T-cell responses in most recipients after the first dose of vaccine and an additional increase in humoral immune outcomes after the second dose of vaccine (28 days).
- Sept. 6, 2020, AstraZeneca halted global trial of the vaccine for a case of transverse myelitis.
  - Within a week, the trials began in all countries except the United States.
  - On Oct. 23, the F.D.A. authorized the restart of the U.S. trial.
- Nov. 19, 2020, researchers published the first findings from the Phase 2/3 trials in the United Kingdom. Encouragingly, the older volunteers produced about as many antibodies against the coronavirus as the younger ones.
- Nov. 23, 2020, AstraZeneca and Oxford announced that the vaccine had good efficacy, based on a study of the first 131 cases of Covid-19 in the trials in the United Kingdom and Brazil.
- Dec. 11, 2020, AstraZeneca announced that it would collaborate with the Russian creators of the Sputnik V vaccine, to combine their and try to deliver a stronger protection.

There were 131 cases of symptomatic COVID-19 more than 14 days after the second dose of vaccine

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0·5%)	44·1 (248 299)	101/5829 (1·7%)	149·2 (247 228)	70·4% (54·8 to 80·6)†
COV002 (UK)	86	18/3744 (0·5%)	38·6 (170 369)	68/3804 (1·8%)	145·7 (170 448)	73·5% (55·5 to 84·2)
LD/SD recipients	33	3/1367 (0·2%)	14·9 (73 313)	30/1374 (2·2%)	150·2 (72 949)	90·0% (67·4 to 97·0)‡§
SD/SD recipients	53	15/2377 (0·6%)	56·4 (97 056)	38/2430 (1·6%)	142·4 (97 499)	60·3% (28·0 to 78·2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0·6%)	56·2 (77 930)	33/2025 (1·6%)	157·0 (76 780)	64·2% (30·7 to 81·5)‡
All SD/SD recipients	98	27/4440 (0·6%)	56·4 (174 986)	71/4455 (1·6%)	148·8 (174 279)	62·1% (41·0 to 75·7)
Other non-primary symptomatic COVID-19 disease¶	18	7/5807 (0·1%)	10·3 (248 299)	11/5829 (0·2%)	16·3 (247 228)	36·4% (−63·8 to 75·3)‡
Any symptomatic COVID-19 disease	149	37/5807 (0·6%)	54·4 (248 299)	112/5829 (1·9%)	165·5 (247 228)	67·1% (52·3 to 77·3)
Asymptomatic or symptoms unknown (COV002)	69	29/3288 (0·9%)	69·8 (151 673)	40/3350 (1·2%)	96·0 (152 138)	27·3% (−17·2 to 54·9)
LD/SD recipients	24	7/1120 (0·6%)	41·4 (61 782)	17/1127 (1·5%)	100·6 (61 730)	58·9% (1·0 to 82·9)‡
SD/SD recipients	45	22/2168 (1·0%)	89·4 (89 891)	23/2223 (1·0%)	92·9 (90 408)	3·8% (−72·4 to 46·3)
Any NAAT-positive swab	221	68/5807 (1·2%)	100·0 (248 299)	153/5829 (2·6%)	226·0 (247 228)	55·7% (41·1 to 66·7)

Vaccine efficacy was calculated from the robust Poisson model. The primary efficacy population (LD/SD and SD/SD) includes randomly assigned participants who were seronegative at baseline and received LD/SD or SD/SD or were in a corresponding control group, and remained on study more than 14 days after their second dose without having had a previous virologically confirmed SARS-CoV-2 infection. In addition, for groups in COV002, only efficacy groups (ie, groups 4, 6, 9, and 10) are included. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. NAAT=nucleic acid amplification test. *CIs are 95% unless indicated otherwise. †95·8% CI used for primary analysis. ‡Vaccine efficacy calculated from a reduced robust Poisson model that was not adjusted for age. All other models included an adjustment for age. §p value for interaction term comparing LD/SD with SD/SD is p=0·010. ¶Other non-primary symptomatic COVID-19 disease includes cases who have symptoms other than the five main symptoms that are required for inclusion in the primary analysis (eg, a participant who has diarrhoea and malaise but no fever, cough, shortness of breath, anosmia, or ageusia).

Table 2: **Efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population**

Vaccine efficacy= 70.4%

Voysey M et al., The Lancet 2020

Surprisingly, an initial half-strength dose led to 90% efficacy, while two standard-dose shots led only to 65.6% percent efficacy

	Total number of cases	ChAdOx1 nCoV-19	Control	Vaccine efficacy (95% CI)	p value for interaction
COV002 (UK), age 18–55 years*	..	..	..	..	0·019
LD/SD recipients	33	3/1367 (0·2%)	30/1374 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	49	14/1879 (0·7%)	35/1922 (1·8%)	59·3% (25·1 to 77·9)	..
COV002 (UK), age 18–55 years with >8 weeks' interval between vaccine doses*	..	..	..	..	0·082
LD/SD recipients	33	3/1357 (0·2%)	30/1362 (2·2%)	90·0% (67·3 to 97·0)	..
SD/SD recipients	34	8/1407 (0·6%)	26/1512 (1·7%)	65·6% (24·5 to 84·4)	..
All SD/SD (UK and Brazil)†	..	..	..	..	0·557
<6 weeks' interval between vaccine doses	28	9/1702 (0·5%)	19/1698 (1·1%)	53·4% (−2·5 to 78·8)	..
≥6 weeks' interval between vaccine doses	70	18/2738 (0·7%)	52/2757 (1·9%)	65·4% (41·1 to 79·6)	..

Cohorts are all subsets of the primary efficacy population. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. LD/SD=low-dose prime plus standard-dose boost. SD/SD=two standard-dose vaccines given. BMI=body-mass index. *Models adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), and ethnicity (white *vs* non-white). †Model adjusted for BMI (<30 *vs* ≥30 kg/m^2), health-care worker status (yes *vs* no), ethnicity (white *vs* non-white), age (<56 years *vs* ≥56 years), and study (COV002 *vs* COV003).

Table 3: Subgroup comparisons of efficacy against SARS-CoV-2 more than 14 days after a second dose of ChAdOx1 nCoV-19 vaccine in the primary efficacy population

Voysey M et al., The Lancet 2020

- The low dose was only tried out on volunteers under 55.
- The researchers speculated that the lower first dose did a better job of mimicking the experience of an infection, promoting a stronger immune response.

PHASE 3

Johnson & Johnson

Beth Israel Lahey Health
Beth Israel Deaconess Medical Center

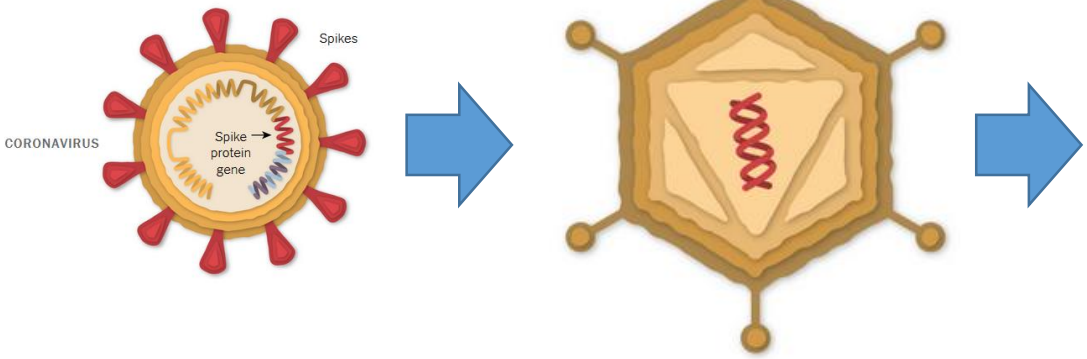
VACCINE NAME: Ad26.COV2.S

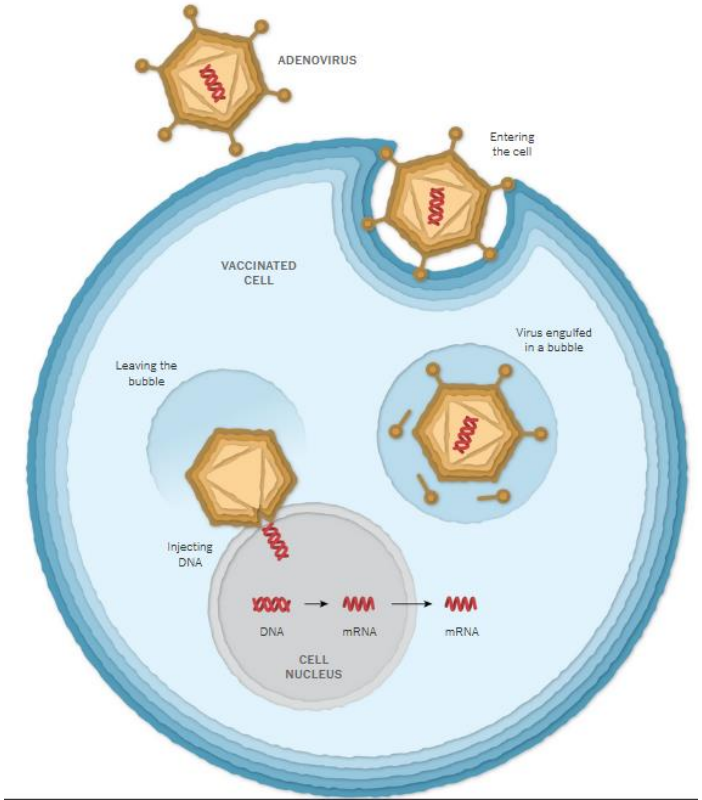
EFFICACY: Unknown

DOSE: 1 dose

TYPE: Muscle injection

STORAGE: Up to two years frozen at –4° F (–20° C), and up to three months refrigerated at 36–46° F (2–8° C).

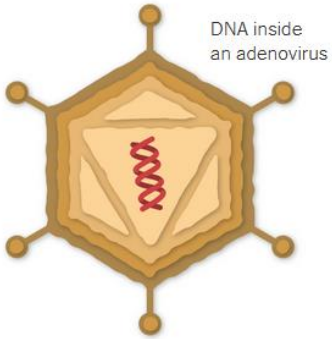




PHASE 3

Johnson & Johnson

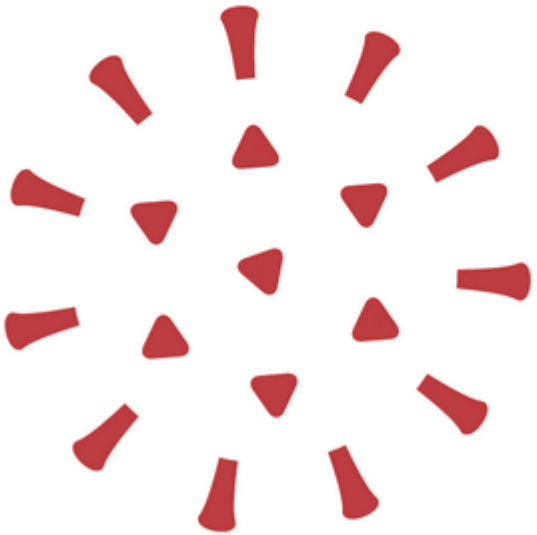
Beth Israel Lahey Health
Beth Israel Deaconess Medical Center



- A single immunisation with this adenovirus serotype 26-vectored vaccine ($1{\cdot}0\times10^{11}$ viral particles by the intramuscular route without adjuvant) induces strong neutralising antibody responses and provides protection against SARS-CoV-2 challenge in rhesus macaques aged 6-12 years.
- The phase 3 trial of this vaccine started on Sept 23, 2020.

Protein vaccines

Vaccines that contain coronavirus proteins but no genetic material. Some vaccines contain whole proteins, and some contain fragments of them. Some pack many of these molecules on nanoparticles.



The New York Times

PHASE 1 | PHASE 2 | COMBINED PHASES

- The Phase 1/2 clinical study is a randomized, double blind and placebo-controlled study designed to evaluate the safety, reactogenicity and immunogenicity (immune response) of the COVID-19 vaccine candidate in 441 healthy adults across 10 investigational sites in the United States.
- The participants received one or two doses of the vaccine candidate, or placebo at 21 days apart.
- Interim results showed a level of neutralizing antibody titers after two doses comparable to sera from patients who recovered from COVID-19, a balanced cellular response in adults aged 18 to 49 years, but insufficient neutralizing antibody titers in adults over the age of 50.
- The Company will start a new Phase 2 trial in February with a different formulation.

Clear and Compelling Data Demonstrating Vaccine's Safety and Efficacy

- Nonclinical data supports vaccine effectiveness and safety
- Phase 1 and 2 data support safety and efficacy and duration of protection
- Meets all safety data expectations for follow up durations and subject number
- Vaccine Safety/COVID-19 outcomes in individuals with prior SARS-CoV-2
- Sufficient cases of severe COVID-19 to support low risk for vaccine-induced ERD
- Final Analysis with a point estimate over 50%
- Vaccine's benefits outweigh its risks based on well-designed Phase 3 clinical trial
- Consistent Manufacturing data with appropriate controls
- Plans for active follow up of safety under EUA