بنام خداوند جان و خرد

Inactivated and Protein-based Recombinant COVID-19 Vaccines

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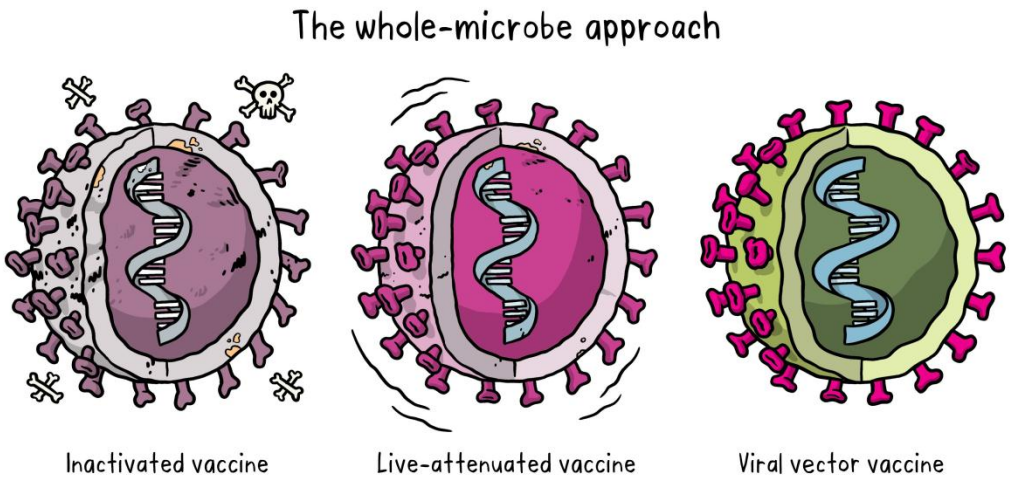
Definition

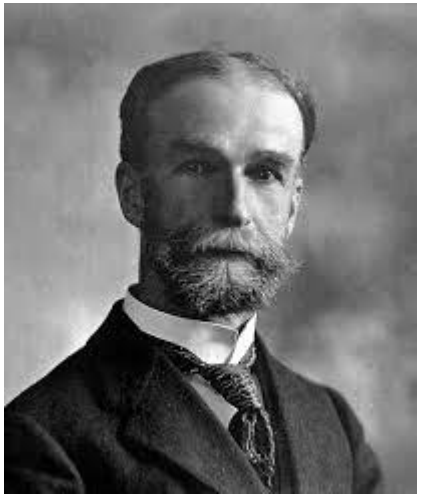
- **Inactivated vaccines(or killed vaccine) :**
  - Is a vaccine consisting of virus particles, bacteria, or other pathogens that have been grown in culture and then killed **to destroy disease producing capacity**.

- **Live attenuated vaccines:**
  - A living virus or bacteria that **has been weakened** so that it **does not cause serious disease** in people with healthy immune systems.



History

- The first inactivated vaccines were developed simultaneously by Salmon and Smith in the United States and the Pasteur Institute group (Roux and Chamberland) in France **(1896-1897).**
- Inactivation was first applied to pathogens such as the **typhoid, plague, and cholera bacilli**.



Theobald Smith

Daniel Elmer Salmon

Emile Roux

Charles Chamberland

Routine inactivated vaccines

Table 1. Outline of the development of human vaccines

Live attenuated	Killed whole organisms	Purified proteins or polysaccharides	Genetically engineered
18th Century			
Smallpox (1798)			
19th Century			
Rabies (1885)	Typhoid (1896)		
	Cholera (1896)		
	Plague (1897)		
Early 20th Century, first half			
Tuberculosis (bacille Calmette–Guérin) (1927)	Pertussis (1926)	Diphtheria toxoid (1923)	
Yellow fever (1935)	Influenza (1936)	Tetanus toxoid (1926)	
	Rickettsia (1938)		

Routine inactivated vaccines

20th Century, second half

Polio (oral) (1963)

Measles (1963)
Mumps (1967)

Rubella (1969)

Adenovirus (1980)
Typhoid (*Salmonella* TY21a) (1989)
Varicella (1995)

Rotavirus reassortants (1999)
Cholera (attenuated) (1994)
Cold-adapted influenza (1999)

Polio (injected) (1955)

Rabies (cell culture) (1980)
Japanese encephalitis (mouse brain) (1992)
Tick-borne encephalitis (1981)

Hepatitis A (1996)
Cholera (WC-rBS) (1991)
Meningococcal conjugate (group C) (1999)

Anthrax secreted proteins (1970)

Meningococcus polysaccharide (1974)
Pneumococcus polysaccharide (1977)

Haemophilus influenzae type B polysaccharide (1985)
H.influenzae type b conjugate (1987)
Typhoid (Vi) polysaccharide (1994)
Acellular pertussis (1996)

Hepatitis B (plasma derived) (1981)

Hepatitis B surface antigen recombinant (1986)
Lyme OspA (1998)
Cholera (recombinant toxin B) (1993)

21st Century

Rotavirus (attenuated and new reassortants) (2006)
Zoster (2006)

Japanese encephalitis (2009) (Vero cell)
Cholera (WC only) (2009)

Pneumococcal conjugates* (heptavalent) (2000)
Meningococcal conjugates* (quadrivalent) (2005)
Pneumococcal conjugates* (13-valent) (2010)

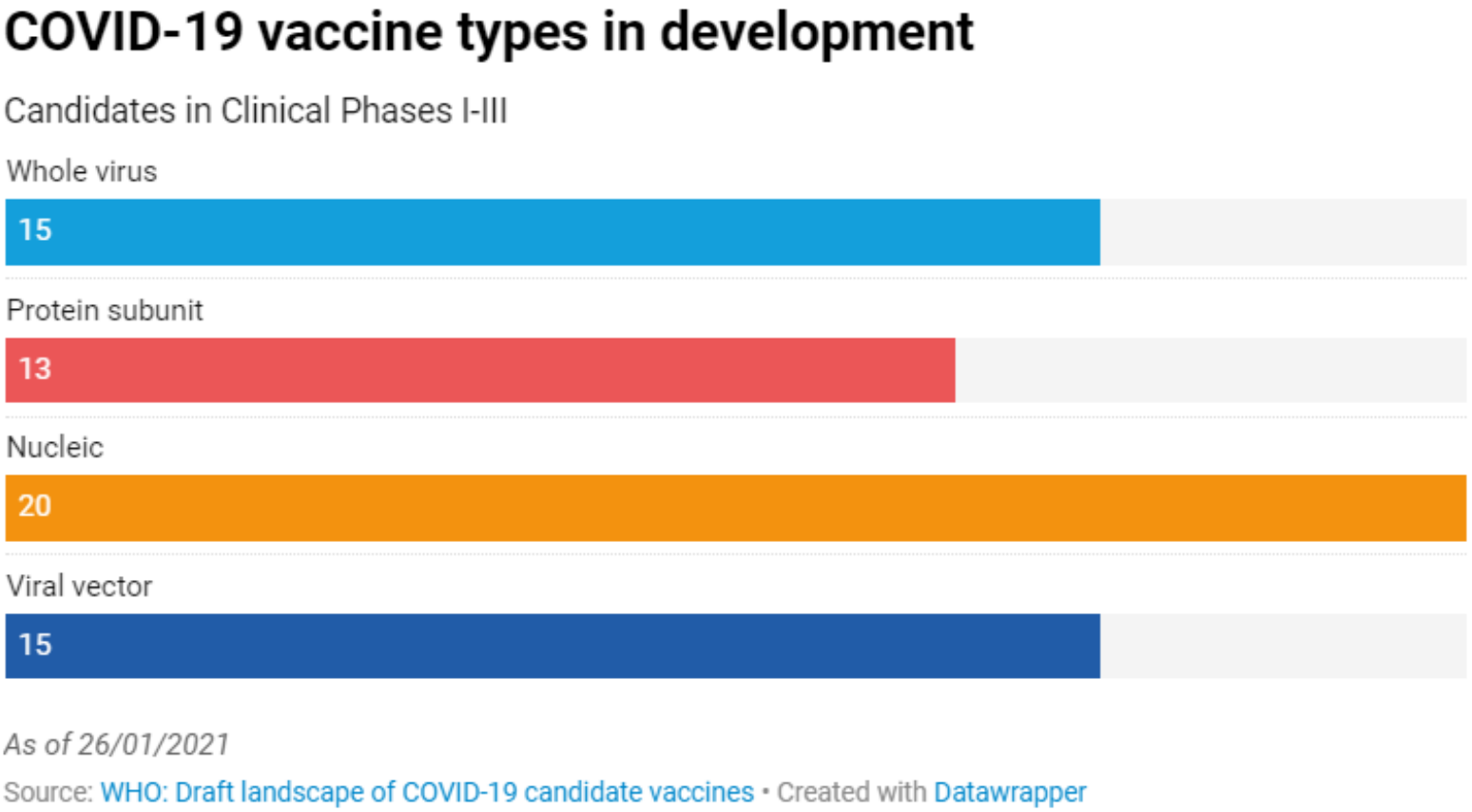
Human papillomavirus recombinant (quadrivalent) (2006)
Human papillomavirus recombinant (bivalent) (2009)
Meningococcal group B proteins (2013)

Advantages and Disadvantages of Inactivated Vaccines

- Technology is well established
- Relatively simple to manufacture
- Easily stored and shipped
- Can be given to most people, no chance of the dead virus causing disease.
- Cheap

- Batch to batch variations
- Reactogenicity and side effects
- Using large amounts of antigen to elicit an adequate antibody response is a major disadvantage.
- Multiple doses and/or booster shots to achieve the same level of protection as live attenuated vaccines.

Covid-19 vaccine strategies



COVID-19 Current Vaccines (Approved and EUA)

Leading vaccines

Developer	How It Works	Phase	Status
Pfizer-BioNTech	mRNA	2 3	Approved in several countries. Emergency use in U.S., E.U., other countries.
Moderna	mRNA	3	Approved in Switzerland. Emergency use in U.S., U.K., E.U., others.
Gamaleya	Ad26, Ad5	3	Early use in Russia. Emergency use in other countries.
Oxford-AstraZeneca	ChAdOx1	2 3	Emergency use in U.K., E.U., other countries.
CanSino	Ad5	3	Limited use in China.
Johnson & Johnson	Ad26	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, other coutries.
Sinovac	Inactivated	3	Approved in China. Emergency use in Brazil, other countries.
Sinopharm-Wuhan	Inactivated	3	Limited use in China, U.A.E.
Bharat Biotech	Inactivated	3	Emergency use in India.

SinoPharm-BBIBP-CorV

SinoPharm-BBIBP-CorV

- In early 2020, the Beijing Institute of Biological Products created an inactivated coronavirus vaccine called **BBIBP-CorV**.

PHASE 3

APPROVED IN CHINA, BAHRAIN, U.A.E.

EMERGENCY USE IN OTHER COUNTRIES

VACCINE NAME: BBIBP-CorV

EFFICACY: 79.34%

DOSE: 2 doses, 3 weeks apart

TYPE: Muscle injection

Pre-clinical studies

Cell

Article

Development of an Inactivated Vaccine Candidate, BBIBP-CorV, with Potent Protection against SARS-CoV-2

Highlights

- An inactivated SARS-CoV-2 vaccine candidate, BBIBP-CorV, is developed
- BBIBP-CorV induces high levels of neutralizing antibodies titers in animal models
- Two-dose immunization with 2 μg/dose BBIBP-CorV efficiently protects rhesus macaques
- BBIBP-CorV is efficiently produced, genetically stable, and seems to be safe in animals

August 2020

Phase I, II clinical trials

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial

Shengli Xia, Yuntao Zhang*, Yanxia Wang*, Hui Wang*, Yunkai Yang*, George Fu Gao*, Wenjie Tan*, Guizhen Wu*, Miao Xu*, Zhiyong Lou*, Weijin Huang*, Wenbo Xu*, Baoying Huang*, Huijuan Wang*, Wei Wang, Wei Zhang, Na Li, Zhiqiang Xie, Ling Ding, Wangyang You, Yuxiu Zhao, Xuqin Yang, Yang Liu, Qian Wang, Lili Huang, Yongli Yang, Guangxue Xu, Bojian Luo, Wenling Wang, Peipei Liu, Wanshen Guo, Xiaoming Yang*

Summary

Background The ongoing COVID-19 pandemic warrants accelerated efforts to test vaccine candidates. We aimed to assess the safety and immunogenicity of an inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine candidate, BBIBP-CorV, in humans.

Methods We did a randomised, double-blind, placebo-controlled, phase 1/2 trial at Shangqiu City Liangyuan District Center for Disease Control and Prevention in Henan Province, China. In phase 1, healthy people aged 18–80 years, who were negative for serum-specific IgM/IgG antibodies against SARS-CoV-2 at the time of screening, were separated into two age groups (18–59 years and ≥60 years) and randomly assigned to receive vaccine or placebo in a two-dose schedule of 2 μg, 4 μg, or 8 μg on days 0 and 28. In phase 2, healthy adults (aged 18–59 years) were randomly assigned (1:1:1:1) to receive vaccine or placebo on a single-dose schedule of 8 μg on day 0 or on a two-dose schedule of 4 μg on days 0 and 14, 0 and 21, or 0 and 28. Participants within each cohort were randomly assigned by stratified block randomisation (block size eight) and allocated (3:1) to receive vaccine or placebo. Group allocation was concealed from participants, investigators, and outcome assessors. The primary outcomes were safety and tolerability. The secondary outcome was immunogenicity, assessed as the neutralising antibody responses against infectious SARS-CoV-2. This study is registered with www.chictr.org.cn, ChiCTR2000032459.

Lancet Infect Dis 2020; 21: 39–51

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See Comment page 2

For the Chinese translation see Online for appendix 1

*Contributed equally

Henan Provincial Center for Disease Control and Prevention, Henan, China (Prof S Xia BSc, Y Wang BSc, W Zhang MSc, Z Xie MSc, W You BSc, L Huang BSc, Prof W Guo BSc); **Department of Epidemiology and**

October 2020

Phase I, II clinical trial

- The inactivated SARS-CoV-2 vaccine , BBIBP-CorV, is safe and well tolerated at all tested doses in two age groups (18–59 years and ≥60 years).

- Humoral responses against SARS-CoV-2 were induced in all vaccine recipients on day 42.

- Two-dose immunization with 4 μg vaccine on days 0 and 21 or days 0 and 28 achieved higher neutralising antibody titres than the single 8 μg dose or 4 μg dose on days 0 and 14.

October 2020

Phase III clinical trial

- On July 16, 31,000 volunteers in the **UAE**.
- On September 2, in **Casablanca and Rabat** on 600 people.
- In September**, Egypt** enrolled 6,000 people.
- In August 2020, in **Bahrain** on 6,000.
- In late August, in **Jordan** on 500 volunteers.
- In **Pakistan**, in 3,000 volunteers.
- On September 10, in **Peru** on 6,000 people.
- On September 16, **Argentina** began a Phase III trial on 3,000 volunteers.

Emergency use authorization

- **China:** Sinopharm obtained an EUA for one of its COVID-19 vaccine candidates in July.

- **Bahrain:** On November 3, granted for frontline workers.

- **UAE:** On 14 September 2020, the UAE approved Sinopharm's COVID-19 vaccine for front-line workers following successful interim Phase III trials.

- **Approved in China, U.A.E., Bahrain. Emergency use in Egypt, other coutries.**

Sinovac: CoronaVac or PiCoVacc

CoronaVac or PiCoVacc

- CoronaVac is a COVID-19 vaccine developed by the Chinese biopharmaceutical company **Sinovac**.

PHASE 3

APPROVED IN CHINA | **EMERGENCY USE IN OTHER COUNTRIES**

sinovac

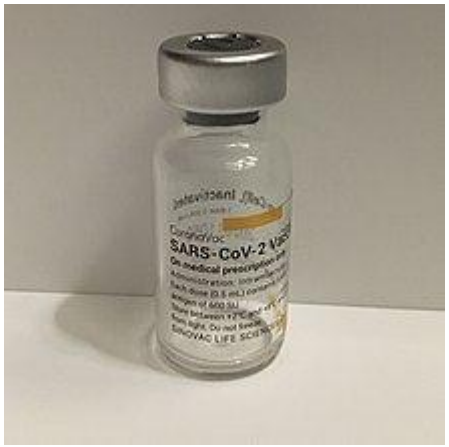
VACCINE NAME: CoronaVac (formerly PiCoVacc)

EFFICACY: 50.38%

DOSE: 2 doses, 2 weeks apart

TYPE: Muscle injection

STORAGE: Refrigerated



Pre-clinical studies

Science

Development of an inactivated vaccine candidate for SARS-CoV-2

Qiang Gao, Linlin Bao, Haiyan Mao, Lin Wang, Kangwei Xu, Minnan Yang, Yajing Li, Ling Zhu, Nan Wang, Zhe Lv, Hong Gao, Xiaoqin Ge, Biao Kan, Yaling Hu, Jiangning Liu, Fang Cai, Deyu Jiang, Yanhui Yin, Chengfeng Qin, Jing Li, Xuejie Gong, Xiuyu Lou, Wen Shi, Dongdong Wu, Hengming Zhang, Lang Zhu, Wei Deng, Yurong Li, Jinxing Lu, Changgui Li, Xiangxi Wang, Weidong Yin, Yanjun Zhang and Chuan Qin

Science 369 (6499), 77-81.
DOI: 10.1126/science.abc1932originally published online May 6, 2020

- A pilot-scale production of PiCoVacc, a purified inactivated SARS-CoV-2 virus vaccine candidate, which induced SARS-CoV-2–specific neutralizing antibodies in mice, rats, and nonhuman primates.

May 2020

Phase I, II clinical trials

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18–59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial

Yanjun Zhang, Gang Zeng*, Hongxing Pan*, Changgui Li*, Yaling Hu, Kai Chu, Weixiao Han, Zhen Chen, Rong Tang, Weidong Yin, Xin Chen, Yuansheng Hu, Xiaoyong Liu, Congbing Jiang, Jingxin Li, Minnan Yang, Yan Song, Xiangxi Wang, Qiang Gao†, Fengcai Zhu†*

Summary

Background With the unprecedented morbidity and mortality associated with the COVID-19 pandemic, a vaccine against COVID-19 is urgently needed. We investigated CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated vaccine candidate against COVID-19, containing inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), for its safety, tolerability and immunogenicity.

Lancet Infect Dis 2021; 21: 181–92

Published Online November 17, 2020 https://doi.org/10.1016/S1473-3099(20)30843-4

November 2020

Phase I, II clinical trials

- In April 2020, 144 participants were enrolled in the phase 1 trial, and in May, 2020, 600 participants were enrolled in the phase 2 trial.

- Taking **safety, immunogenicity, and production capacity** into account, the **3 μg dose** of CoronaVac is the suggested dose for efficacy assessment in future **phase 3 trials**.

November 2020

Phase III clinical trial

- Sinovac's vaccine is being tested in Phase III clinical trials in countries including **Brazil, Turkey and Indonesia,** where **varied efficacy readings had been released separately**, without sufficient details made available to public.

- **Approved in China**

- **Emergency use in Brazil, other countries.**

Bharat Biotech: Covaxin

Covaxin-BBV152

- India's COVID-19 vaccine by Bharat Biotech in collaboration with the Indian Council of Medical Research and and National Institute of Virology.
- Whole-Virion Inactivated Vero Cell derived platform technology.
- Formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum.

PHASE 3 **EMERGENCY USE IN INDIA**

BHARAT BIOTECH

ICMR INDIAN COUNCIL OF MEDICAL RESEARCH Serving the nation since 1911

NATIONAL INSTITUTE OF VIROLOGY PUNE

VACCINE NAME: Covaxin (also known as BBV152 A, B, C)

EFFICACY: Unknown

DOSE: 2 doses, 4 weeks apart

STORAGE: At least a week at room temperature

Pre-clinical studies, Covaxin

New Results

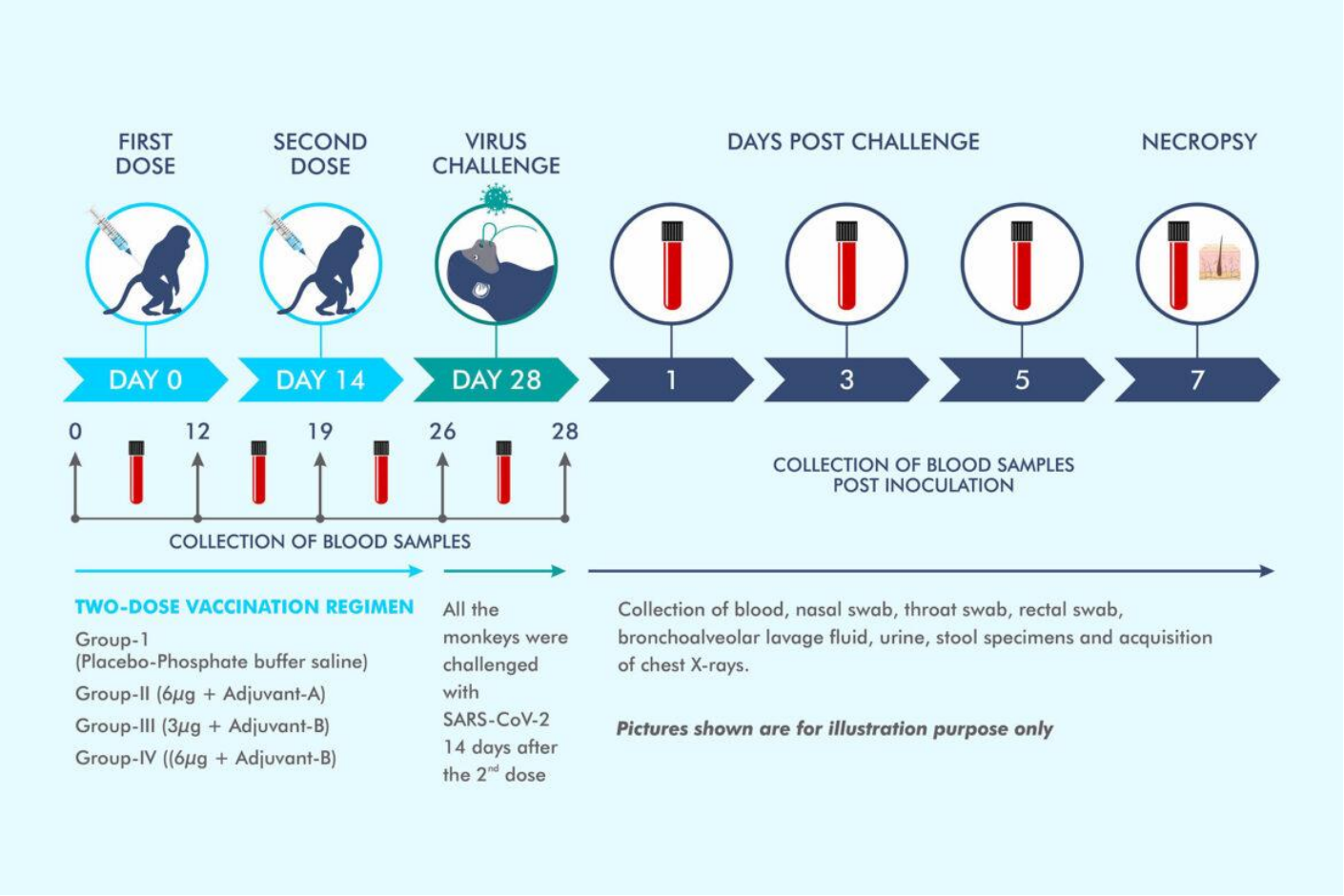
Evaluation of Safety and Immunogenicity of an Adjuvanted, TH-1 Skewed, Whole Virion Inactivated SARS-CoV-2 Vaccine - BBV152

Brunda Ganneru, Harsh Jogdand, Vijaya Kumar Dharam, Narasimha Reddy Molugu, Sai D Prasad, Srinivas Vellimudu, Krishna M Ella, Rajaram Ravikrishnan, Amit Awasthi, Jomy Jose, Panduranga Rao, Deepak Kumar, Raches Ella, Priya Abraham, Pragya Yadav, Gajanan N Sapkal, Anita Shete, Gururaj Rao Desphande, Sreelekshmy Mohandas, Ananth Basu, Nivedita Gupta, Balram Bharagava, Krishna Mohan Vadrevu

doi: https://doi.org/10.1101/2020.09.09.285445

September 2020

Pre-clinical studies, Covaxin



The vaccine received approval for Phase I & II Human Clinical Trials in July, 2020.

Phase I, II Clinical Trials, Covaxin

Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBV152: a double-blind, randomised, phase 1 trial

Raches Ella, Krishna Mohan Vadrevu, Harsh Jogdand, Sai Prasad, Siddharth Reddy, Vamshi Sarangi, Brunda Ganneru, Gajanan Sapkal, Pragya Yadav, Priya Abraham, Samiran Panda, Nivedita Gupta, Prabhakar Reddy, Savita Verma, Sanjay Kumar Rai, Chandramani Singh, Sagar Vivek Redkar, Chandra Sekhar Gillurkar, Jitendra Singh Kushwaha, Satyajit Mohapatra, Venkat Rao, Randeep Guleria, Krishna Ella, Balram Bhargava

Summary

Background To mitigate the effects of COVID-19, a vaccine is urgently needed. BBV152 is a whole-virion inactivated SARS-CoV-2 vaccine formulated with a toll-like receptor 7/8 agonist molecule adsorbed to alum (Algel-IMDG) or alum (Algel).

Methods We did a double-blind, multicentre, randomised, controlled phase 1 trial to assess the safety and immunogenicity of BBV152 at 11 hospitals across India. Healthy adults aged 18–55 years who were deemed healthy by the investigator were eligible. Individuals with positive SARS-CoV-2 nucleic acid and/or serology tests were excluded. Participants were randomly assigned to receive either one of three vaccine formulations (3 µg with Algel-IMDG, 6 µg with Algel-IMDG, or 6 µg with Algel) or an Algel only control vaccine group. Block randomisation was done with a web response platform. Participants and investigators were masked to treatment group allocation. Two intramuscular doses of vaccines were administered on day 0 (the day of randomisation) and day 14. Primary outcomes were solicited local and systemic reactogenicity events at 2 h and 7 days after vaccination and throughout the full study duration, including serious adverse events. Secondary outcome was seroconversion (at least four-fold increase from baseline) based on wild-type virus neutralisation. Cell-mediated responses were evaluated by intracellular staining and ELISpot. The trial is registered at ClinicalTrials.gov (NCT04471519).

Lancet Infect Dis 2021

Published Online
January 21, 2021
https://doi.org/10.1016/S1473-3099(20)30942-7

See Online/Comment
https://doi.org/10.1016/S1473-3099(20)30988-9

Bharat Biotech, Hyderabad, India (R Ella MBBS, K M Vadrevu PhD, H Jogdand DVM, S Prasad MSc, S Reddy MSc, V Sarangi BSc, B Ganneru PhD, K Ella PhD); **Indian Council of Medical Research-National Institute c Virology, Pune, India** (G Sapkal PhD, P Yadav PhD,

January 2020

Phase I, II Clinical Trials, COVAXIN

- A total of 375 subjects generated excellent safety data without any reactogenicity.

- Vaccine-induced neutralizing antibody titers were observed with two divergent SARS-CoV-2 strains. Percentage of all the side-effects combined was only 15% in vaccine recipients.

- In Phase 2 study, 380 participants of 12-65 years were enrolled. COVAXIN led to tolerable safety outcomes and enhanced humoral and cell-mediated immune responses.

January 2020

Phase III multi-center trial, Covaxin

- The first dose of vaccination has been given to all the participants and presently, second dose of either vaccine/placebo is being administered.

- Efficacy will commence two weeks after the second dose. The interim efficacy estimate will be generated by the end of Feb, 2021.

- **COVAXIN has been granted approval for emergency restricted use in India on Jan 03, 2021.**

COVIran Barakat

PHASE 1

Shafa Pharmed Pars

COVIran Barakat

- Is a COVID-19 vaccine candidate developed by **Iranian** Shifa-Pharmed Industrial Group.
- Inactivated platform. 2 doses at days 0 and 14.
- On 29 December, human trials of Iran's first domestic COVID-19 vaccine candidate was started.
- 56 selected people take apart in the first phase of human trials which last 45 to 60 days (mid Esfand).

Protein-based Recombinant Vaccines

Definition

Recombinant vaccines:

- A recombinant vaccine is a vaccine produced through **recombinant DNA technology.** This involves inserting the DNA encoding an antigen that stimulates an immune response.

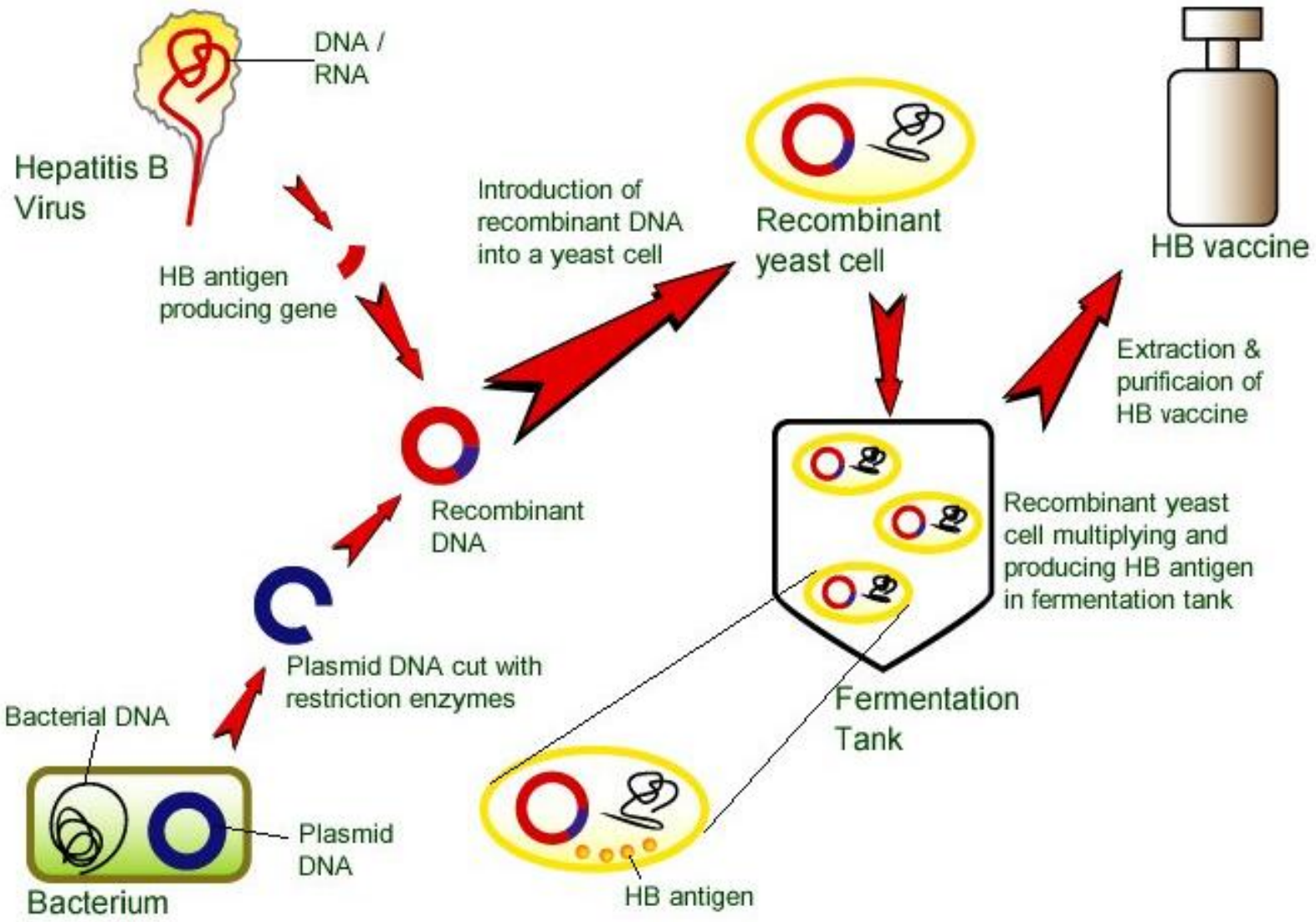
Protein-based recombinant vaccine:

- The **immunogenic protein** associated with a recombinant DNA vaccine **is made in the laboratory** and injected into the vaccine recipient.

Nucleic acid-based recombinant vaccine:

- Also known as genetic vaccines consist only of **DNA (as plasmids)** or **RNA (as mRNA)**, which is taken up by cells and translated into protein.

Production of Recombinant Vaccines



History

Maurice Hilleman watches as his granddaughter receives the recombinant hepatitis B vaccine in 1999.
Courtesy of Lorraine Hilleman

7/23/1986

Hepatitis B: Recombinant Vaccine Licensed

The FDA licensed Merck's Recombivax HB. This hepatitis B vaccine was the first human vaccine produced by recombinant DNA methods.

A challenge in creating the vaccine involved avoiding the use of human blood products, as did Maurice Hilleman's first hepatitis B vaccine. Therefore, Merck used an enzyme to remove the virus's surface protein (HBsAg, the Australia antigen). Researchers inserted the code for the antigen into yeast cells, which produced more of the surface protein. The yeast-derived surface protein produced immunity to the hepatitis B virus.

ADVANTAGES AND DISADVANTAGES OF PROTEIN SUBUNIT VACCINES

Well-established technology

Suitable for people with compromised immune systems

No live components, so no risk of the vaccine triggering disease

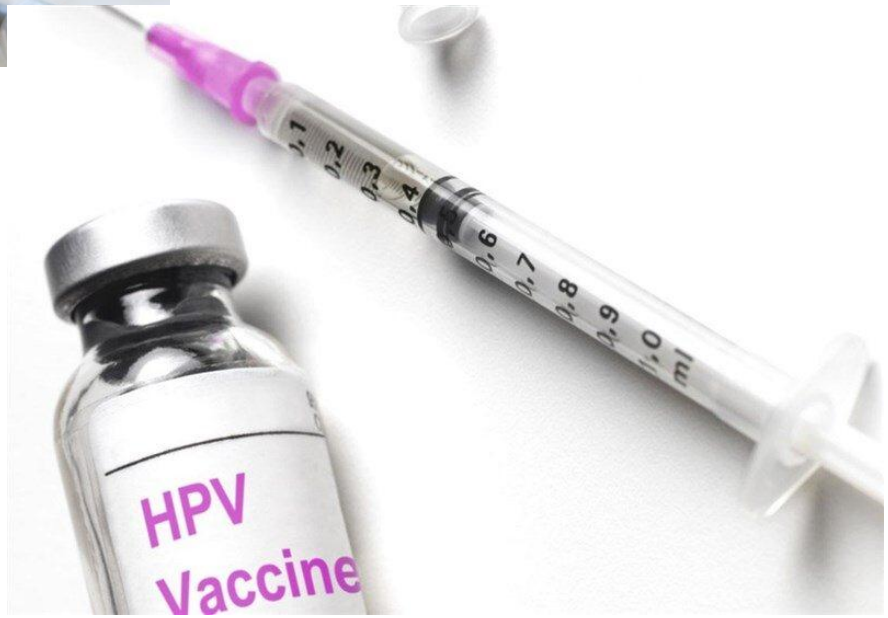
Relatively stable

Relatively complex to manufacture

Adjuvants and booster shots may be required

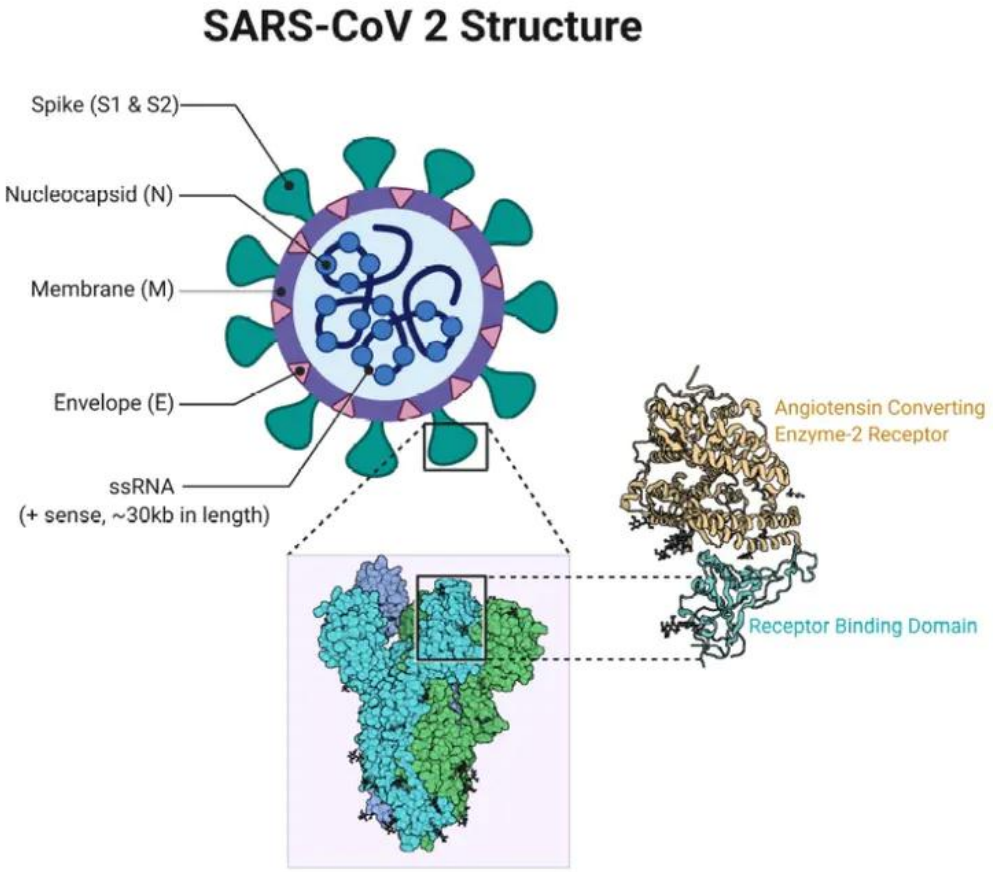
Determining the best antigen combination takes time

Some types of recombinant vaccines



COVID-19 Protein-based Recombinant Vaccines

1. **Full-length S-protein based vaccines**
2. **RBD-based vaccines**
3. **Multi-epitope vaccines**



COVID-19 Protein-based Recombinant Vaccines

Select recombinant protein vaccine candidates in clinical trials for COVID-19 as of December 8, 2020 [5]

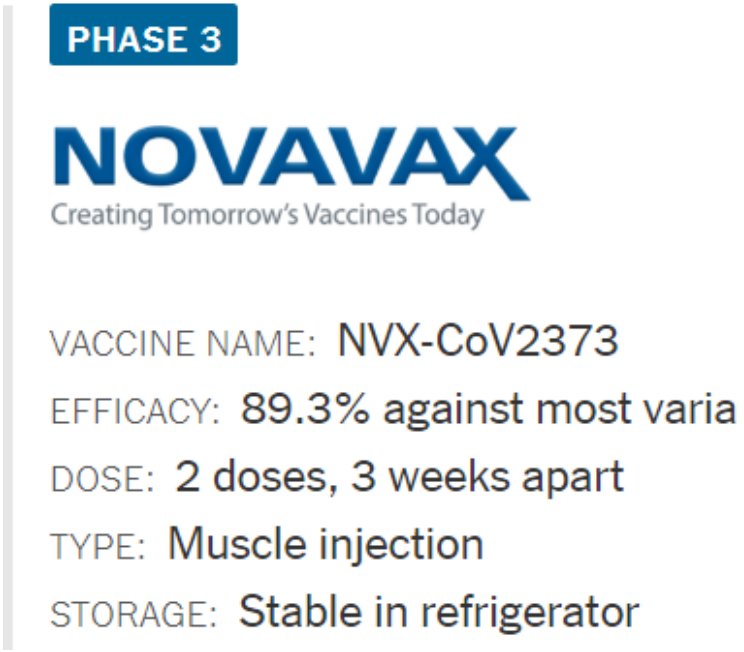
Antigen	Vaccine developer	Platform/technology	Adjuvants	Most advanced clinical stage
Full-length S-protein based vaccines				
Trimer	Novavax	Insect cells	Matrix M	Phase 3
S-protein	Sanofi Pasteur/GSK	Insect cells	2 different adjuvants (likely variants of AS03)	Phase 1 (to be repeated)
SCB-2019 trimer	Clover Biopharmaceuticals Inc./GSK/Dynavax	CHO cells	Alum+CpG 1018 or AS03	Phase 1
S-2P (MVC-COV1901)	Medigen Vaccine Biologics Corporation/NIAID/Dynavax	CHO cells	Alum+CpG1018	Phase 1
Covax-19	Vaxine Pty Ltd/Medytox	Insect cells	AdvaxCpG55.2	Phase 1
RBD-based vaccines				
AdimrSC-2f	Adimmune	Baculovirus/Sf9	Alum	Phase 1
SARS-CoV-2-RBDN1C1	Biological E/BCM	Yeast	Alum+CpG	Phase 1-2
FINLAY-FR-1/2	Instituto Finlay de Vacunas, Cuba			Phase 1
KBP-201	Kentucky Bioprocessing, Inc	Plants		Phase 1-2
RBD Dimer	Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences	CHO Cells	Aluminum preparation	Phase 3
RBD	West China Hospital, Sichuan University P	Insect Cells	Alum	Phase 2
Multi-epitope vaccines				
Multitope Peptide-based Vaccine (MPV)	COVAXX	Peptides	CpG and alum (AdjuPhos®)	Phase 1
EpiVacCoron	Vektor Laboratories, Russia	Chemical synthesis	Alum	Phase 1
CoVac-1	University Hospital Tübingen	Peptides	Montanide ISA51	Phase 1

NVX-CoV2373

NVX-CoV2373

- NVX-CoV2373 is a recombinant (rSARS-CoV-2) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant.

- Two intramuscular injections, 21 days apart.



Preclinical studies, NVX-CoV2373

ARTICLE

https://doi.org/10.1038/s41467-020-20653-8 OPEN

Check for updates

SARS-CoV-2 spike glycoprotein vaccine candidate NVX-CoV2373 immunogenicity in baboons and protection in mice

SARS-CoV-2 protein subunit vaccination elicits potent neutralizing antibody responses

Marco Mandolesi[1,*], Daniel J. Sheward[1,2,*✉], Leo Hanke[1], Junjie Ma[1], Pradeepa Pushparaj[1], Laura Perez Vidakovics[1], Changil Kim[1], Karin Loré[3], Xaquin Castro Dopico[1], Jonathan M. Coquet[1], Gerald McInerney[1], Gunilla B. Karlsson Hedestam[1,†✉], and Ben Murrell[1,†✉]

June & July 2020

Phase I, II Clinical Trial, NVX-CoV2373

Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine

C. Keech, G. Albert, I. Cho, A. Robertson, P. Reed, S. Neal, J.S. Plested, M. Zhu, S. Cloney-Clark, H. Zhou, G. Smith, N. Patel, M.B. Frieman, R.E. Haupt, J. Logue, M. McGrath, S. Weston, P.A. Piedra, C. Desai, K. Callahan, M. Lewis, P. Price-Abbott, N. Formica, V. Shinde, L. Fries, J.D. Lickliter, P. Griffin, B. Wilkinson, and G.M. Glenn

ABSTRACT

BACKGROUND

NVX-CoV2373 is a recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant.

METHODS

We initiated a randomized, placebo-controlled, phase 1–2 trial to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine (in 5-μg and 25-μg doses, with or without Matrix-M1 adjuvant, and with observers unaware of trial-group assign-

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Keech at Novavax, 21 Firstfield Rd., Gaithersburg, MD, 20878, or at Ckeech@novavax.com.

This article was published on September 2, 2020, at NEJM.org.

September 2020

Phase I, II Clinical Trial, NVX-CoV2373

- No serious adverse events were noted. Reactogenicity was absent.
- At 35 days, NVX-CoV2373 appeared to be safe
- Elicited immune responses that exceeded levels in Covid-19 convalescent serum.
- The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype.

September 2020

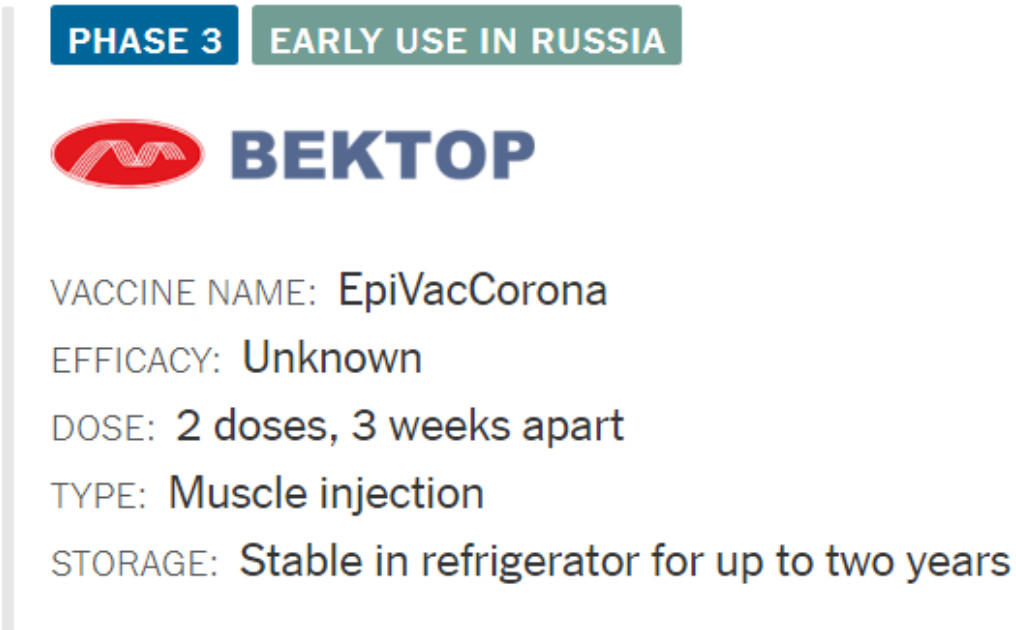
Phase III Clinical Trial, NVX-CoV2373

- In late December 2020, Novavax started the Phase III trial in the US and Mexico.
- On 28 January 2021, Novavax reported that preliminary results from the **United Kingdom trial showed 89% effective**.
- However, interim results from a trial in **South Africa** showed a lower effectiveness rate against the **501.V2 variant of the virus, at around 50-60%.**
- On 2 February 2021, **Canada** has signed a tentative agreement for Novavax to produce millions of doses of its COVID-19 vaccine in Montreal.
- On 11 February 2021, the **Europe Union** is about to close a deal to get 100 million vaccines, with the option of 100 million more.

EpiVacCorona

EpiVacCorona

- **Vector Institute**, a Russian biological research center
- The vaccine relies on chemically synthesized peptide antigens of SARS-CoV-2 proteins, conjugated to a carrier protein and adsorbed on an alum.



Cov-Pars - Razi Institute - Iran

PHASE 1

Cov-Pars

- Is a COVID-19 vaccine candidate developed by Razi Vaccine and Serum Research Institute.
- Recombinant spike protein platform.
- The vaccine will be used in three doses. The initial dose is intramuscular, the second dose is injected intramuscularly after 21 days, and the third phase will be inhaled on day 51.
- The feature making this vaccine unique is the last phase in which the vaccine should be inhaled (**nasal spray**).
- 130 selected people will take apart in the phase I clinical trial which has been started since 19 Bahman.

Current Status of COVID-19 Vaccination

Location	Source	Last observation date	Vaccines
Albania	Ministry of Health	February 9, 2021	Pfizer/BioNTech
Algeria	Ministry of Health	January 30, 2021	Sputnik V
Andorra	Government of Andorra	February 10, 2021	Pfizer/BioNTech
Anguilla	Ministry of Health	February 13, 2021	Oxford/AstraZeneca
Argentina	Ministry of Health	February 14, 2021	Sputnik V
Austria	Ministry of Health	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Azerbaijan	Government of Azerbaijan	February 6, 2021	Oxford/AstraZeneca, Sputnik V
Bahrain	Ministry of Health	February 14, 2021	Pfizer/BioNTech, Sinopharm/Beijing
Bangladesh	Directorate General of Health Services	February 14, 2021	Oxford/AstraZeneca

Belgium	Sciensano via covid-vaccinatie.be	February 13, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Bermuda	Government of Bermuda	February 9, 2021	Pfizer/BioNTech
Bolivia	Ministry of Health	February 11, 2021	Sputnik V
Brazil	Regional governments via Coronavirus Brasil	February 14, 2021	Oxford/AstraZeneca, Sinovac
Bulgaria	Ministry of Health	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Cambodia	Ministry of Health	February 10, 2021	Sinopharm/Beijing
Canada	Government of Canada	February 12, 2021	Moderna, Pfizer/BioNTech
Cayman Islands	Cayman Islands Government	February 12, 2021	Pfizer/BioNTech
Chile	Department of Statistics and Health Information	February 14, 2021	Pfizer/BioNTech, Sinovac
China	National Health Commission	February 9, 2021	Sinopharm/Beijing, Sinopharm/Wuhan, Sinovac

Costa Rica	National Health Commission	February 8, 2021	Pfizer/BioNTech
Croatia	Ministry of Health	February 11, 2021	Pfizer/BioNTech
Cyprus	Ministry of Health	February 11, 2021	Pfizer/BioNTech
Czechia	Ministry of Health	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Denmark	Statens Serum Institut	February 14, 2021	Moderna, Pfizer/BioNTech
Ecuador	Government of Ecuador	February 4, 2021	Pfizer/BioNTech
Egypt	Ministry of Health	January 30, 2021	Sinopharm/Beijing
England	Government of the United Kingdom	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Estonia	National Health Board	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Faeroe Islands	Government of the Faeroe Islands	February 10, 2021	Pfizer/BioNTech

Finland	Finnish Institute for Health and Welfare	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
France	Public Health France	February 13, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Germany	Robert Koch Institut	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Gibraltar	Government of Gibraltar	February 13, 2021	Pfizer/BioNTech
Greece	Ministry of Health	February 13, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Greenland	Government of Greenland	January 27, 2021	Pfizer/BioNTech
Guernsey	Government of Guernsey	February 6, 2021	Pfizer/BioNTech
Hungary	Government of Hungary	February 13, 2021	Pfizer/BioNTech
Iceland	Directorate of Health	February 12, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
India	Ministry of Health	February 14, 2021	Covaxin, Oxford/AstraZeneca
		February 14,	

Indonesia	Ministry of Health	February 14, 2021	Sinovac
Iran	Government of Iran	February 9, 2021	Sputnik V
Ireland	Heath Service Executive	February 11, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Isle of Man	Isle of Man Government	February 14, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Israel	Government of Israel	February 14, 2021	Moderna, Pfizer/BioNTech
Italy	Extraordinary commissioner for the Covid-19 emergency	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Jersey	Government of Jersey	February 7, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Kuwait	Ministry of Health	January 26, 2021	Pfizer/BioNTech
Latvia	National Health Service	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Liechtenstein	Federal Office of Public Health	February 10, 2021	Moderna, Pfizer/BioNTech
Lithuania	Ministry of Health	February 13, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech

Luxembourg	Government of Luxembourg	February 11, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Maldives	Presidency of the Maldives	February 14, 2021	Oxford/AstraZeneca
Malta	COVID-19 Malta Public Health Response Team	February 13, 2021	Pfizer/BioNTech
Mauritius	National Communication Committee on COVID-19	February 1, 2021	Oxford/AstraZeneca
Mexico	Secretary of Health	February 13, 2021	Pfizer/BioNTech
Monaco	National Council	January 18, 2021	Pfizer/BioNTech
Morocco	Ministry of Health	February 13, 2021	Oxford/AstraZeneca, Sinopharm/Beijing
Myanmar	Ministry of Health	February 2, 2021	Oxford/AstraZeneca
Nepal	Government of Nepal	February 4, 2021	Oxford/AstraZeneca
Netherlands	National Institute for Public Health and the Environment	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech

Northern Cyprus	Ministry of Health	January 22, 2021	Pfizer/BioNTech, Sinovac
Northern Ireland	Government of the United Kingdom	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Norway	Norwegian Institute of Public Health	February 11, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Oman	Ministry of Health	February 14, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Pakistan	National Command and Operation Centre	February 10, 2021	Oxford/AstraZeneca, Sinopharm/Beijing, Sputnik V
Panama	Ministry of Health	February 11, 2021	Pfizer/BioNTech
Peru	Ministry of Health	February 14, 2021	Sinopharm/Beijing
Poland	Ministry of Health	February 13, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Portugal	National Health Service	February 14, 2021	Moderna, Pfizer/BioNTech
Qatar	National Strategic Group on COVID-19	January 28, 2021	Pfizer/BioNTech

Romania	Government of Romania	February 14, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech
Russia	Russian Direct Investment Fund	February 10, 2021	Sputnik V
Saint Helena	Government of Saint Helena	February 3, 2021	Oxford/AstraZeneca
Saudi Arabia	Saudi Health Council	February 14, 2021	Pfizer/BioNTech
Scotland	Government of the United Kingdom	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Serbia	Government of Serbia	February 13, 2021	Pfizer/BioNTech, Sinopharm/Beijing, Sputnik V
Seychelles	Extended Programme for Immunisation	February 11, 2021	Oxford/AstraZeneca, Sinopharm/Beijing
Singapore	Ministry of Health	February 10, 2021	Pfizer/BioNTech
Slovakia	Ministry of Health	February 14, 2021	Pfizer/BioNTech
Slovenia	National Institute of Public Health, via Sledilnik	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Spain	Ministry of Health	February 11, 2021	Moderna, Oxford/AstraZeneca, Pfizer/BioNTech

Sri Lanka	Ministry of Health	February 14, 2021	Oxford/AstraZeneca
Sweden	Public Health Agency of Sweden	February 12, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
Switzerland	Federal Office of Public Health	February 10, 2021	Moderna, Pfizer/BioNTech
Turkey	COVID-19 Vaccine Information Platform	February 14, 2021	Sinovac
Turks and Caicos Islands	Ministry of Health	February 8, 2021	Pfizer/BioNTech
United Arab Emirates	National Emergency Crisis and Disaster Management Authority	February 14, 2021	Oxford/AstraZeneca, Pfizer/BioNTech, Sinopharm/Beijing, Sinopharm/Wuhan, Sputnik V
United Kingdom	Government of the United Kingdom	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech
United States	Centers for Disease Control and Prevention	February 14, 2021	Moderna, Pfizer/BioNTech
Wales	Government of the United Kingdom	February 13, 2021	Oxford/AstraZeneca, Pfizer/BioNTech


Thank you

	Name	Vaccine Type	Primary Developers	Country of Origin	Authorization/Approval
	Comirnaty (BNT162b2)	mRNA-based vaccine	Pfizer, BioNTech; Fosun Pharma	Multinational	Albania, Argentina, Australia, Bahrain, Canada, Chile, Colombia, Costa Rica, Ecuador, EU, Faroe Islands, Greenland, Iceland Iraq, Israel, Jordan, Kuwait Malaysia, Mexico, New Zealand, Norway, Oman, Panama, Philippines, Qatar Saudi Arabia, Serbia, Singapore, Switzerland, UAE, UK, US, Vatican City, WHO
	Moderna COVID-19 Vaccine (mRNA-1273)	mRNA-based vaccine	Moderna, BARDA, NIAID	US	Canada, EU, Faroe Islands, Greenland, Iceland, Israel, Norway, Qatar, Saudi Arabia, Singapore, Switzerland, United Kingdom, United States

	COVID-19 Vaccine AstraZeneca (AZD1222); also known as Covishield	Adenovirus vaccine	BARDA, OWS	UK	Argentina, Bahrain, Bangladesh, Brazil, Chile, Dominican Republic, Ecuador, El Salvador, EU, Hungary, India, Iraq, Mexico, Morocco, Myanmar, Nepal, Pakistan, Philippines, Saudi Arabia, South Africa, South Korea, Sri Lanka, Thailand, UK, Vietnam
	Sputnik V	Non-replicating viral vector	Gamaleya Research Institute, Acellena Contract Drug Research and Development	Russia	Algeria, Argentina, Armenia, Bahrain, Belarus, Bolivia, Guinea, Hungary, Iran, Kazakhstan, Laos, Lebanon, Mexico, Mongolia, Nicaragua, Pakistan, Palestine, Paraguay, Republika Srpska, Russia, Serbia, Tunisia, Turkmenistan, United Arab Emirates, Venezuela

	CoronaVac	Inactivated vaccine (formalin with alum adjuvant)	Sinovac	China	Azerbaijan, Bolivia, Brazil, China, Chile, Colombia, Indonesia, Laos, Turkey, Uruguay
	BBIBP-CorV	Inactivated vaccine	Beijing Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	Bahrain, Cambodia, China, Egypt, Hungary, Jordan, Iraq, Laos, Macau, Morocco, Pakistan, Peru, Serbia, Seychelles, UAE
	EpiVacCorona	Peptide vaccine	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology	Russia	Russia, Turkmenistan

	Convidicea (Ad5-nCoV)	Recombinant vaccine (adenovirus type 5 vector)	CanSino Biologics	China	Mexico, China (military use)
	Covaxin	Inactivated vaccine	Bharat Biotech, ICMR	India	India
	No name announced	Inactivated vaccine	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)	China	China

Factors determining the immunogenicity of genetic vaccines

Factors affecting the immunogenicity of genetic vaccines	Comments and conclusions
Structure of the plasmid backbone	Presence of immunostimulatory sequences, introns, poly-A-sequence
Amount of plasmid delivered	More is better
Expression levels of the antigen	More antigen correlates with stronger response, but not necessarily linearly
Immunization schedule	Increasing interval between immunizations can strongly enhance the response
Route of immunization	Intramuscular, intradermal (needle), epidermal (gene gun), mucosal
Target-tissue	Including what muscle is injected or what section of the skin
Number of immunizations	DNA-induced immune response can effectively be boosted with DNA
Presence or absence of introns in front of the gene	Introns increase efficacy
Strain of the particular species	Different mouse strains show qualitative and quantitative differences in DNA-induced immune responses
Age of animals	Stronger response the younger the mice
Toxicity of the antigen for transfected host cell	High expression undesirable for toxic antigens