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Reports

COVID-19 vaccine therapeutic trials review: published results and registered protocols

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Background

Since the emerging of Coronavirus disease 2019 (COVID-19) in late 2019 and the World Health Organization (WHO) declaring it as a pandemic, a race to develop a vaccine against COVID-19 has started worldwide and therefore huge efforts and resources have been put into achieving it. This review summarizes COVID-19 vaccines in phase III and IV.

Methods

A review of the scientific literature was conducted using the medical subject heading (MeSH) word "COVID-19 vaccines" on PubMed and the words "COVID-19", "SARS-CoV-2" and "vaccine" on ClinicalTrials.gov as of January 24, 2021. The published WHO reports on candidate COVID-19 vaccines were reviewed. For clinical trials, only phase III and IV COVID-19 vaccines were included.

Results

Of the 1300 citations identified on January 24, 2021, 81 were eligible and included in this review. According to WHO report of January 22, 2021, there were 237 candidates vaccines in development and among them 64 vaccines were in advanced stages of development. On the same date, on ClinicalTrials.gov, there were 66 registered COVID-19 vaccines clinical trials on phase III and IV. Thirty seven were new candidates vaccines on phase III, 23 were BCG vaccines including five on phase VI, three were measles vaccines on phase III and three were polio vaccines (one on phase VI and one on phase III).

Conclusions

Despite safe and effective vaccines are available many challenges remain including logistic difficulties concerning mass production, supply, storage, cold chain, administration at community level and equitable distribution to the most vulnerable populations. Hence the need to continue preventive measures including, hand wash, wearing mask, cough and sneeze etiquette and social distancing.

Coronavirus disease 2019 (COVID-19), an infection caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in December 2019, in Wuhan, province of Hubei in China. Since then, it has become one of the world's toughest health problems. The World Health Organization (WHO) announced on January 30, 2020 that the COVID-19 epidemic was a public health emergency of international concern and on March 20, 2020, that it was a pandemic.[1] As of January 24, 2021, more than 97 million cases of COVID-19 have been reported worldwide, causing more than 2 million deaths.[2] In just a few months, huge efforts have been made and several vaccines are in development.

This review summarizes COVID-19 vaccines clinical trials in phase III and IV and all published clinical trials' results.

METHODS

A review of the scientific literature was conducted with the aim to study the therapeutic trials of vaccines against the coronavirus disease 2019 (COVID-19). To this end, as of January 24, 2021 a search for articles published on PubMed

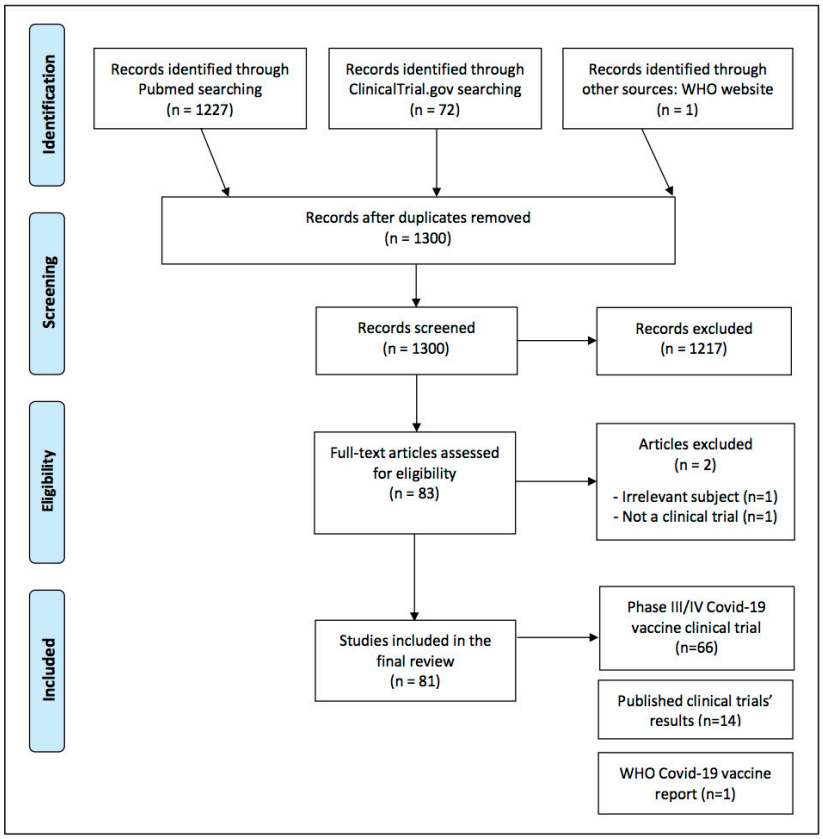

Figure 1: PRISMA flow chart.

using the Mesh word "COVID-19 Vaccine", as well as a search for protocols registered on ClinicalTrials.gov by combining the words "COVID-19", "SARS-CoV-2" and "Vaccine" was made. The published WHO reports on candidate COVID-19 vaccines were reviewed. At first, citations that were not in French or in English and not a clinical trial or randomized controlled trial were excluded. Then, those with irrelevant information or subject and studies with focus other than COVID-19 vaccine development or clinical trial were excluded. For registered protocols, those in relation with drugs were excluded.

RESULTS

INCLUDED CITATIONS IN THE COVID-19 VACCINE THERAPEUTIC TRIALS REVIEW

On PubMed, 1227 articles were initially found, out of which 16 articles were selected. In the end, 14 articles were selected. On ClinicalTrials.gov, as of January 24, 2021, 72 phase III or IV, clinical trial protocols, encompassing vaccines and treatments have been identified initially, of which 66 for COVID-19 vaccines have been selected (**Figure 1**).

WHO COVID-19 VACCINE REPORT AS OF JANUARY 24, 2021

According to the WHO COVID-19 vaccine report of January 22, 2021, there were 237 vaccines. More specifically, 64 vaccines were in clinical evaluation (16 in phase III, 6 in phase II / III, 5 in phase II, 19 in phase I / II and 18 in phase I) and 173 vaccines were in preclinical evaluation.[3]

PHASE III AND IV CLINICAL TRIALS

NEW COVID-19 VACCINES

Vaccine development, determined by clinical trials, is divided into three phases between preclinical exploratory work and vaccine approval (**Box 1**).[4]

Most of the candidate COVID-19 vaccines are based on the S antigen in the form of inactivated vaccines, subunit vaccines, viral vector vaccines, and DNA or mRNA 3 nucleic acid vaccines.[5]

In this review, the focus will be on clinical trials for vaccines in phase III and above.

For the new candidates COVID-19 vaccines, there were 37 clinical trials on Phase III, of which one clinical trial was simultaneously in phase I/II/III and eight in phase II/III. Eleven (30%) clinical trials concerned inactivated vaccines and 30 (81%) clinical trials used two doses. Six clinical trials were active and not recruiting while 23 were still recruiting participants. The number of participants to be recruited varied from 100 to 60,000 (**Table 1**).

Table 1: Candidate vaccines against COVID-19 in phase III as of January 24, 2021

COVID-19 vaccine developer / Manufacturer	Type of vaccine	Number of doses	Timing of doses	Route of administration	Country	Recruitment status	Estimated number of participants	Description of the clinical trial
BioNTech SE/Pfizer [6]	RNA (3 LNP-mRNA)	2	Day 0 and Day 21	IM	Argentina, Brazil, Germany, South Africa, Turkey, United States	Active, not Recruiting	43 998	Phase I/II/III, randomized, triple-blind (participant, care provider, investigator), placebo-controlled clinical trial with participants randomly assigned to placebo and experimental vaccine cohorts (BNT162b1 and BNT162b2) in healthy individuals aged 12 years and over The study consists of 2 parts: • Phase I: to identify the preferred candidate vaccine (s) and dose levels • Phase II/III: an enlarged cohort and an efficiency part The candidate vaccine selected for Phase II/III evaluation was BNT162b2 in medium dose **ClinicalTrials.gov Identifier :** NCT04368728 **Estimated Study Completion Date :** January 31, 2023
Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation [7]	Combined viral vector (Adenovirus (rAd26-S + rAd5-S))	2	Day 0 and Day 21	IM	Russian Federation	Active, not recruiting	33 758	Multicenter, randomized, double-blind, placebo-controlled clinical trial in healthy adults aged 18 to 111 years. After screening, they will be randomized (3:1) into two groups, a reference group of 10,000 volunteers receiving placebo and a study group of 30,000 volunteers receiving the Gam-COVID-Vac combined vector vaccine. The trial subjects will be randomized into five age strata: 18-30, 31-40, 41-50, 51-60, and 60+ years. **ClinicalTrials.gov Identifier :** NCT04530396 **Estimated Study Completion Date :** May 1, 2021
ModernaTX/NIAD [8]	RNA (Encapsulated LNP-mRNA)	2	Day 0 and Day 28	IM	United States	Active, not recruiting	30 000	Quadruple-blind (participant, caregiver, investigator, outcome assessor), placebo-controlled randomized clinical trial with participants randomly assigned to placebo and experimental vaccine cohorts (mRNA-1273) in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04470427 **Estimated Study Completion Date :** October 27, 2022
Laboratory Elea Phoenix S.A [9]	Inactivated	2	Day 0 and Day 21	IM	Argentina	Active not recruiting	3000	Double-blind, placebo-controlled clinical trial with randomly (1:1) participants assigned to placebo and experimental (Vero cell) vaccine cohorts in healthy adults aged 18 to 85 years. **ClinicalTrials.gov Identifier :** NCT04560881 **Estimated Study Completion Date :** December 1, 2021
NPO Petrovax [10]	Adenovirus type 5 Vector	1	Day 0	IM	Russian Federation	Active, not recruiting	500	Randomized, multicenter, quadruple-blind (participant, care provider, investigator, outcome assessor), placebo-controlled clinical trial with randomized (3:1) participants assigned in placebo (n=125) and experimental vaccine (n=375) cohorts in adults in good health aged 18 to 85 years. **ClinicalTrials.gov Identifier :** NCT04540419 **Estimated Study Completion Date :** July 31, 2021
Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation [11]	Combined viral vector (Adenovirus (rAd26-S + rAd5-S))	2	Day 0 and Day 21	IM	Belarus	Active, not Recruiting	100	Double-blind, placebo-controlled clinical trial with participants randomly assigned (3:1) to placebo (n=25) and experimental (GAM-COVID-Vac; n=75) vaccine cohorts in healthy adults aged from 18 to 60 years old. **ClinicalTrials.gov Identifier :** NCT04564716 **Estimated Study Completion Date :** April 10, 2021
Janssen Vaccines & Prevention B.V [12]	Non-replicating viral vector	1	Day 0	IM	Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, United States	Recruiting	60 000	A randomized, quadruple-blind (participant, caregiver, investigator, outcome assessor), placebo-controlled clinical trial with participants randomly assigned to placebo and experimental vaccine (Ad26.COV2.S) cohorts in healthy adults aged 18 and older. **ClinicalTrials.gov Identifier:** NCT04505722 **Estimated Study Completion Date**: March 10, 2023
China National	Inactivated	2	Day 0	IM	Bahrain,	Recruiting	45 000	Double-blind, placebo-controlled clinical trial with participants randomly assigned (1:1:1) to

COVID-19 vaccine developer / Manufacturer	Type of vaccine	Number of doses	Timing of doses	Route of administration	Country	Recruitment status	Estimated number of participants	Description of the clinical trial
Biotec Group Company Limited [13]			and Day 21		Egypt, Jordan, United Arab Emirates,			one cohort of placebo vaccine and two cohorts of experimental vaccine (Vero Cell) in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier:** NCT04510207 **Estimated Study Completion Date :** September 16, 2021
CanSino Biologics Inc/ Beijing Institute of Biotechnology [14]	Non-replicating viral vector	1	Day 0	IM	Argentina, Chile, Mexico, Pakistan, Russian Federation	Recruiting	40 000	Double-blind, placebo-controlled clinical trial with randomly (1:1) participants assigned to placebo and experimental vaccine (Adenovirus Vector Type 5) cohorts in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04526990 **Estimated Study Completion Date:** January 30, 2022
CureVac AG [15]	mRNA	2	Day 0 and Day 28	IM	Belgium, Germany, Netherlands	Recruiting	36 500	A phase IIb/III, multicenter, randomized, double-blind, placebo-controlled clinical trial with participants randomized to placebo and experimental vaccine (CvnCoV)) cohorts in healthy adults aged 18 years and older.. **ClinicalTrials.gov Identifier :** NCT04652102 **Estimated Study Completion Date :** March 4, 2023
Chinese Academy of Medical Sciences [16]	Inactivated	2	Day 0 and Day 14	IM	Brazil, Malaysia	Recruiting	34 020	Randomized, double-blind, placebo-controlled clinical trial with participants randomized (1:1) to placebo and experimental vaccine (Vero Cell) cohorts in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04659239 **Estimated Study Completion Date :** March 2022
AstraZeneca [17]	Non-replicating viral vector	2	Day 0 and Day 28	IM	United States, Argentina, Chile, Colombia, Peru,	Recruiting	30 000	Multicenter, quadruple-blind (participant, caregiver, investigator, outcome assessor) placebo-controlled clinical trial with randomized (2:1) participants to placebo and experimental (AZD1222) vaccine cohorts in healthy adults aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04516746 **Estimated Study Completion Date :** October 5, 2022
Medicago [18]	Recombinant	2	Day 0 and Day 21	IM	United States, Canada	Recruiting	30 000	A phase II/III, randomized, double-blind, placebo-controlled clinical trial with participants randomized to placebo and experimental vaccine cohorts in healthy adults aged 18 years and older.. **ClinicalTrials.gov Identifier :** NCT04636697 **Estimated Study Completion Date :** April 30, 2022
Novavax [19]	Recombinant Spike Protein Nanoparticle Vaccine (SARS CoV 2 rS) with Matrix-M1 ™ Adjuvant	2	Day 0 and Day 21	IM	United States, Mexico, Puerto Rico	Recruiting	30 000	Quadruple-blind (participant, care provider, investigator, outcome assessor), placebo-controlled randomized clinical trial with participants randomly assigned to placebo and experimental vaccine (NVX-CoV2373) cohorts in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04611802 **Estimated Study Completion Date :** December, 2022
Janssen Vaccines & Prevention B.V [20]	Non-replicating viral vector	2	Day 0 and Day 56	IM	United States, Belgium, Colombia, France, Germany, Philippines, South Africa, Spain, United Kingdom	Recruiting	30 000	Double-blind, placebo-controlled randomized clinical trial with participants randomly assigned to placebo and experimental vaccine (Ad26.COV2.S) cohorts in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04614948 **Estimated Study Completion Date :** May 11, 2023
Anhui Zhifei Longcom Biologic Pharmacy Co.,Ltd [21]	Recombinant	3	Day 0, Day 30 and	IM	China	Recruiting	29 000	Quadruple-blind (participant, care provider, investigator, outcome assessor), placebo-controlled randomized (1:1) clinical trial with participants randomly assigned to placebo and experimental vaccine (CHO cell) cohorts in healthy adults aged 18 years and older.

COVID-19 vaccine developer / Manufacturer	Type of vaccine	Number of doses	Timing of doses	Route of administration	Country	Recruitment status	Estimated number of participants	Description of the clinical trial
			Day 60					**ClinicalTrials.gov Identifier :** NCT04646590 **Estimated Study Completion Date :** April, 2022
Baharat Biotech international Limited [22]	Whole-virion inactivated	2	-	IM	India	Recruiting	25 800	Double-blind, placebo-controlled randomized clinical trial with participants randomly (1:1) assigned to placebo and experimental vaccine (BBV152) cohorts in healthy adults aged 18 to 99 years. **ClinicalTrials.gov Identifier :** NCT04641481 **Estimated Study Completion Date :** March 1, 2022
Novavax [23]	Recombinant Spike Protein Nanoparticle Vaccine (SARS CoV 2 rS) with Matrix-M1 ™ Adjuvant	2	Day 0 and Day 21	IM	United Kingdom	Recruiting	15 000	Quadruple-blind (participant, care provider, investigator, outcome assessor), placebo-controlled randomized clinical trial with participants randomly assigned to placebo and experimental vaccine (NVX-CoV2373) cohorts in healthy adults aged 18 to 84 years. **ClinicalTrials.gov Identifier :** NCT04583995 **Estimated Study Completion Date :** January, 2022
Health Institutes of Turkey [24]	Inactivated	2	Day 0 and Day 14	IM	Turkey	Recruiting	13 000	Double-blind, placebo-controlled clinical trial with randomized participants assigned to placebo and experimental vaccine cohorts (Vero-Cell) in healthy adults aged 18 to 59 years old. **ClinicalTrials.gov Identifier :** NCT04582344 **Estimated Study Completion Date :** April 15, 2021
University of Oxford [25]	Non-replicating viral vector	1 or 2	If 2 doses, 4-6 weeks apart	IM	United Kingdom	Recruiting	12 390	Phase II /III, single-blind, controlled clinical trial, having 11 study groups with participants aged 18 years and older. Groups will receive the experimental vaccine (ChAdOx1 nCoV-19) and others the meningococcal vaccine (MenACWY). **ClinicalTrials.gov Identifier :** NCT04400838 **Estimated Study Completion Date :** September 2021
Institute Butantan /Sinovac Life Sciences CO.,Ltd [26]	Inactivated	2	Day 0 and Day 14	IM	Brazil	Recruiting	13 060	Double-blind, placebo-controlled clinical trial with randomized (1:1) participants assigned to placebo and experimental vaccine cohorts in healthy adults aged 18 years and older. For safety and immunogenicity, participants are categorized in 2 age groups: adults (18-59 years) and elderly (60 years and older). **ClinicalTrials.gov Identifier :** NCT04456595 **Estimated Study Completion Date :** September 2021
University of Oxford [27]	Non-replicating viral vector	1 or 2	Day 0 or Day 0 and Day 28-90	IM	Brazil	Recruiting	10 300	Single-blind, controlled clinical trial, with 2 study groups of healthcare professionals and adults with high potential for exposure to SARS-CoV-2, aged 18 years and older. One group will receive the experimental vaccine (ChAdOx1 nCoV-19) and the other will receive the meningococcal vaccine (MenACWY). **ClinicalTrials.gov Identifier :** NCT04536051 **Estimated Study Completion Date :** September 2021
University Peruana Cayetano Heredia [28]	Inactivated	2	Day 0 and Day 14	IM	Peru	Recruiting	6000	Multicenter, double-blind, placebo-controlled clinical trial with randomized participants assigned to placebo and experimental vaccines cohorts in healthy adults aged 18 to 60 years old. **ClinicalTrials.gov Identifier :** NCT04612972 **Estimated Study Completion Date :** September 2021
Research Institute for Biological Safety Problems [29]	Inactivated	2	Day 0 and Day 21	IM	Kazakhstan	Enrolling by invitation	3000	Multicenter, double-blind, placebo-controlled clinical trial with randomized participants assigned to placebo (n=600) and experimental vaccine cohorts QazCovid-in® (n=2400) in healthy adults aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04691908 **Estimated Study Completion Date :** July 31, 2021
ModernaTX, Inc [30]	mRNA	2	Day 0 and Day	IM	United States	Recruiting	3000	A phase II/III, quadruple-blind, placebo-controlled clinical trial with randomized participants assigned to placebo and experimental vaccine (mRNA-1273) cohorts in healthy adolescents aged 12 to 17 years old **ClinicalTrials.gov Identifier :** NCT04649151 **Estimated Study**

COVID-19 vaccine developer / Manufacturer	Type of vaccine	Number of doses	Timing of doses	Route of administration	Country	Recruitment status	Estimated number of participants	Description of the clinical trial
			28					**Completion Date :** June 30, 2022
CureVac AG [31]	mRNA	2	Day 0 and Day 28	IM	Germany	Recruiting	2520	Double-blind, placebo-controlled clinical trial with randomized participants (1:1) assigned to placebo and experimental vaccine (CvnCoV) cohorts in healthy adults aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04674189 **Estimated Study Completion Date :** April 30, 2022
Pontifica Unversidad Catolica de Chile [32]	Inactivated	2	Day 0 and Day 14	IM	Chile	Recruiting	2300	Multicenter, double-blind, placebo-controlled clinical trial with randomized participants (1:1) assigned to placebo and experimental vaccine cohorts in healthy adults aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04651790 **Estimated Study Completion Date :** March 2022
PT Bio Farma [33]	Inactivated	2	Day 0 and Day 14	IM	Indonesia	Recruiting	1620	Randomized, double-blind, placebo-controlled clinical trial with participants randomized (1:1) to placebo and experimental vaccine cohorts in healthy adults aged 18 to 59 years. **ClinicalTrials.gov Identifier :** NCT04508075 **Estimated Study Completion Date :** September 2021
Sinovac Biotech Co., Ltd [34]	Inactivated	2	Day 0 and Day 14	IM	China	Recruiting	1040	Randomized, double-blind, placebo-controlled clinical trial to evaluate the non-inferiority of the commercial scale Inactivated SARS-CoV-2 vaccine against that of the pilot scale among healthy adults aged 26-45 years, and the open-labelled, bridging non-inferiority of the vaccine induced immunogenicity in healthy elderly (aged 60 years and older) against that in healthy adults (18-59 years old). **ClinicalTrials.gov Identifier :** NCT04617483 **Estimated Study Completion Date :** May 31, 2021
AnGes, INC [35]	DNA	2	Day 0 and Day 14 or Day 0 and Day 28	IM	Japan	Recruiting	500	A phase II/III, randomized, double-blind, placebo-controlled clinical to assess safety, immunogenicity, and efficacy of twice dosing of IM AG0302-Covid-19 (2mg) in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04655625 **Estimated Study Completion Date :** March 31, 2022
Clover Biopharmaceuticals AUS Pty Ltd [36]	Adjuvanted recombinant Subunit vaccine	2	Day 0 and Day 21	IM	Belgium, Brazil, Colombia, Dominican Republic, Germany, Nepal, Panama, Philippines, Poland, South Africa	Not yet recruiting	34 000	A Phase II/III, double-blind, placebo-controlled clinical trial with randomized participants to placebo and experimental vaccine (AS03-adjuvanted SCB-2019) cohorts in healthy adults aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04672395 **Estimated Study Completion Date :** March, 2022
COVAXX [37]	Protein subunit	2	Day 0 and Day 28	IM	-	Not yet Recruiting	7320	A phase II/III, multicenter, double-blind, placebo-controlled, dose-response study to evaluate the safety, immunogenicity and efficacity of UB-612 in age groups, adults aged 18 to 59 years and elderly aged more than 60 years with or without comorbidities. **ClinicalTrials.gov Identifier :** NCT04683224 **Estimated Study Completion Date :** March 22, 2023
Gamaleya Research Institute of	Combined viral vector	2	Day 0 and	IM	Venezuela	Not yet Recruiting	2000	Double-blind, placebo-controlled clinical trial with participants randomly assigned (3:1) to placebo (n=500) and experimental (GAM-COVID-Vac; n=1500) vaccine cohorts in healthy

COVID-19 vaccine developer / Manufacturer	Type of vaccine	Number of doses	Timing of doses	Route of administration	Country	Recruitment status	Estimated number of participants	Description of the clinical trial
Epidemiology and Microbiology, Health Ministry of the Russian Federation [38]	(Adenovirus (rAd26-S + rAd5-S))		Day 21					adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04642339 **Estimated Study Completion Date :** December, 2021
Dr Reddy's Laboratories Limited / Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation [39]	Combined viral vector	2	Day 0 and Day 21	IM	India	Not yet Recruiting	1600	A phase II/III, double-blind, placebo-controlled clinical trial with participants randomly assigned (3:1) to experimental (GAM-COVID-Vac) vaccine and placebo cohorts in healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04640233 **Estimated Study Completion Date :** September, 2021
Pfizer/ BioNTech SE [40]	RNA	2	Day 0 and Day 21	IM	-	Not yet Recruiting	1280	Double-blind, placebo-controlled clinical trial with participants randomly assigned to placebo and experimental vaccine (BNT162B2) cohorts in healthy adults aged 18 to 55 years. **ClinicalTrials.gov Identifier :** NCT04713553 **Estimated Study Completion Date :** April 9, 2021
Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation [41]	Combined viral vector	1	Day 0	IM	United Arab Emirates	Not yet Recruiting	1000	Double-blind, placebo-controlled clinical trial with participants randomly assigned (3:1) to placebo (n=250) and experimental (GAM-COVID-Vac; n=750) vaccine cohorts in healthy adults aged 18 years and older. The trial subjects will be randomized into five age strata: 18-30, 31-40, 41- 50, 51-60, and 60+ years **ClinicalTrials.gov Identifier :** NCT04656613 **Estimated Study Completion Date :** December, 2021
AstraZeneca [42]	Non-replicating viral vector	2	Day 0 and Day 28	IM	Russian Federation	Suspended	100	Multicenter, unblinded, uncontrolled clinical trial in which all participants receive the experimental vaccine (AZD1222). Included are healthy adults aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04540393 **Estimated Study Completion Date :** Mach 12, 2021

*IM : Intramuscular

OTHER VACCINES TO FIGHT COVID-19

MEASLES VACCINE

With the hypothesis that the measles vaccine could reduce the incidence of COVID-19, as of January 24, 2021, there were three clinical trials, in phase III, using this vaccine in the fight against infection with SARS-CoV-2:

- An international clinical trial (NCT04333732), randomized, double-blind, placebo-controlled, in healthcare workers at risk of contracting COVID-19 (N = 30 000) and aged 18 years and older. These are randomly assigned to cohorts of placebo vaccine and MMR or MR vaccine. The estimated end of study date is August 2021.[43]
- A randomized, single-blinded, placebo-controlled clinical trial in New Orleans (NCT04475081), recruiting healthy healthcare workers (N=60) aged 18 to 70 years. They are randomly assigned to cohorts of placebo vaccine and MMR vaccine. The estimated end of study date is December 1st, 2021.[44]
- A randomized clinical trial in Egypt (NCT04357028), single-blind, placebo-controlled, recruiting healthy healthcare workers (N = 200) and aged between 18 and 50 years. Participants are randomly assigned to cohorts of placebo vaccine and MMR vaccine. The estimated end of study date was November 1st, 2020, but the clinical trial was suspended due to failure of subject recruitment.[45]

POLIO VACCINE

Both polio and coronavirus are positive strand RNA viruses, it is likely that they can induce common innate immune mechanisms. There were three clinical trials:

- A randomized clinical trial in Guinea-Bissau (NCT04445428), double-blind and in phase IV, evaluating the effect of the administration of the oral polio vaccine (OPV) compared to the absence of vaccine in 3400 people, aged over 50 years and recruited by invitation. The objective of the trial is to test the hypothesis that OPV reduces the combined risk of admission or death from morbidity by at least 28% over the next six months. The estimated end of this study date is December 2021.[46]
- A Phase IV clinical trial in United States (NCT04639375), evaluating whether an immune response to SARS-CoV 2 RdRp is induced in adults after receiving a booster inoculation of IPV. The number of participants is estimated at 25 healthy volunteers aged between 18 and 80 years old. All participants will receive one IPV by injection. The estimated end of this study date is January 15, 2021.[47]
- A randomized, multi-center, phase III, clinical trial in the United States and New Zealand (NCT04540185), evaluating the safety and efficacy of OPV with and without NA-831 versus to placebo. The number of participants is estimated at 3600, aged over 18 years, in good health and recruited by invitation.[48]

BCG VACCINE

Hypotheses have been made that the tuberculosis vaccine (BCG) may induce partial protection against the severity of infection with SARS-CoV-2. In this context, as of January 24, 2021, there were 23 clinical trials using the BCG vaccine, including six in phase IV.[49-54] Four (17%) clinical trials were active and not recruiting,[49,55-57] while the Colombian clinical trial was withdrawn due to the lack of sponsorship.[58] The number of recruits ranged from 59 to 10 078 (Table 2).

PUBLISHED CLINICAL TRIALS' RESULTS

As of January 24, 2021, there was 13 clinical trials' published results in different phases, of which six were in phase I/II[59-64] and four had a number of participants less than 100.[60,64-66] Only two clinical trials had a non-randomized trial.[60,67] All studies concerned healthy adults aged 18 years and over. In general, local and systemic reactions if present, were described as mild to moderate and consisted in injection site pain, fever, myalgia, headache and fatigue (Table 3).

At this time, there is no determination as to whether a vaccine candidate will be universal or indicated for specific populations, or how many doses will be needed, or the likely presentations.[68]

DISCUSSION

Since the emergence of SARS-CoV-2, the scientific community has been committed to identifying a therapeutic approach as well as a vaccine that is both effective and safe to achieve the goal of reducing morbidity and mortality attributable to COVID-19.

This review is a recent synthesis of clinical trials and published protocols regarding COVID-19 vaccination.

In total, as of January 24, 2021, there were 37 phase III clinical trials involving new candidates for the COVID-19 vaccine. The number of subjects required to be included in these trials varied between 100 and 60 000. The criteria for non-inclusion and exclusion in these phase clinical trials III were mainly children and pregnant women: none of the protocols of these trials concerned pregnant women and almost all of them didn't include persons aged less than 18 years, except for the multinational BioNTech SE/Pfizer's clinical trial where they included healthy individuals aged 12 years and over for their phase II/III.[6] and ModernaTX's clinical trial including healthy adolescents aged 12 to 17 years.[30] AstraZenaca's clinical trial in Russia was suspended due the occurrence of suspected unexpected serious adverse reaction at University of Oxford sponsored study, and will continue to be on hold until the approval on the Russian Ministry of health.[42]

Under the hypothesis that certain other vaccines can strengthen innate immunity, thus making it possible to induce a decrease in infection by SARS CoV2, several other phase III and IV clinical trials have been launched such as BCG vaccine (n=23), measles vaccines (n=3) and polio vac-

Table 2: Phase III and IV clinical trials using the tuberculosis vaccine for the fight against COVID-19 as of January 24, 2021

COVID-19 vaccine developer / Manufacturer	Clinical Trial phase	Number of Doses	Timing of doses	Route of administration	Country	Recruitment Status	Estimated number of participants	Description of the clinical trial
Radboud University [49]	Phase IV	1	Day 0	ID	Netherlands	Active ,not recruiting	2014	A randomized, multicenter, single-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort in healthy subjects aged 60 years and older. **ClinicalTrials.gov Identifier :** NCT04417335 **Estimated Study Completion Date :** May 2021
UMC Utrecht [50]	Phase IV	1	Day 0	ID	Netherlands	Recruiting	5200	Randomized, multicenter, quadruple-blind (participant, care provider, investigator, outcome assessor) placebo-controlled clinical trial with participants randomized (1:1) to one BCG vaccine cohort and another placebo cohort in subjects aged 60 years and older, with a medical history. **ClinicalTrials.gov Identifier :** NCT04537663 **Estimated Study Completion Date :** April 2021
Texas A&M University [51]	Phase IV	1	Day 0	ID	United States	Recruiting	1800	Randomized, multicenter, double-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to a BCG vaccine cohort and an another placebo cohort in high risk healthy healthcare workers with direct COVID-19 infected patients contacts and aged between 18 and 75 years. **ClinicalTrials.gov Identifier :** NCT04348370 **Estimated Study Completion Date:** November 2021
University of Southern Denmark [52]	Phase IV	1	Day 0	ID	Cape Verde, Guinea-Bissau, Mozambique	Recruiting	1050	Randomized, multicenter, double-blind, placebo-controlled clinical trial with participants randomly (1:1) assigned to a BCG vaccine cohort and another placebo cohort in healthy healthcare workers aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04641858 **Estimated Study Completion Date :** March 2022
University of Campinas, Brazil [53]	Phase IV	1	Day 0	ID	Brazil	Recruiting	1000	Randomized, multicenter, double-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort in COVID-19 positive subjects aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04369794 **Estimated Study Completion Date :** August 2023
Hellenic Institute for the Study of Sepsis [54]</td>	Phase IV	1	Day 0	ID	Greece	Recruiting	900	Quadruple-blind randomized clinical trial (participant, care provider, investigator, outcome assessor) placebo-controlled with healthy participants aged 50 years and older and randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort. **ClinicalTrials.gov Identifier:** NCT04414267 **Estimated Study Completion Date :** May 25, 2021
UMC Utrecht/ Radboud University [55]	Phase III	1	Day 0	ID	Netherlands	Active , not recruiting	1500	Placebo-controlled, randomized, quadruple-blind (participant, provider, investigator, outcome assessor) clinical trial with participants randomly (1:1) assigned to a BCG vaccine cohort and a placebo cohort among healthy healthcare workers in hospitals, aged 18 years and older, and caring for COVID-19 positive patients. **ClinicalTrials.gov Identifier :** NCT04328441 **Estimated Study Completion Date :** April 30, 2021
Hospital University Dr. Jose E. Gonzalez [56]	Phase III	1	Day 0	ID	Mexico	Active ,not recruiting	908	Multicenter, randomized, triple-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort in healthcare workers aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04461379 **Estimated Study Completion Date :** January 1, 2021
Vakzine Projekt Management GmbH [57]	Phase III	1	Day 0	ID	Germany	Active not recruiting	59	Randomized, triple-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine (VPM1002) cohort and an another placebo cohort in hospital workers with high exposure to SARS-CoV-2, healthy and aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04387409 **Estimated Study Completion Date :** May 1, 2021
Murdoch Children's Research Institute [69]	Phase III	1	Day 0	ID	Australia, Netherland, Spain, United Kingdom	Recruiting	10 078	Randomized, multicenter, double-blind, placebo-controlled clinical trial with participants randomly assigned to a BCG vaccine cohort and another placebo cohort in healthy healthcare workers aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04327206 **Estimated Study Completion Date :** March 30, 2022
University Health	Phase III	1	Day 0	ID	Canada	Recruiting	3626	Randomized, double-blind, placebo-controlled clinical trial with participants randomly assigned to a BCG vaccine (VPM1002) cohort and another placebo cohort among frontline employees (municipal or provincial

COVID-19 vaccine developer / Manufacturer	Clinical Trial phase	Number of Doses	Timing of doses	Route of administration	Country	Recruitment Status	Estimated number of participants	Description of the clinical trial
Network, Toronto [70]								police, emergency medical services, fire departments, public transport service, health service, food manufacturing facility) aged 18 years and over. **ClinicalTrials.gov Identifier :** NCT04439045 **Estimated Study Completion Date :** July 1, 2021
Tuberculosis Research Center, India [71]	Phase III	1	Day 0	ID	India	Recruiting	2175	Non-randomized, unblinded clinical trial with healthy participants aged between 60 and 80 years, assigned (2:1) to one BCG vaccine cohort and one without vaccination. **ClinicalTrials.gov Identifier :** NCT04475302 **Estimated Study Completion Date :** May 2021
Vakzine Projekt Management GmbH [72]	Phase III	1	Day 0	ID	Germany	Recruiting	2038	Randomized, multicenter, triple-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort (VPM1002) and another placebo cohort in healthy adults aged 60 years and older. **ClinicalTrials.gov Identifier :** NCT04435379 **Estimated Study Completion Date :** September 30, 2021
Bandim Health Project [73]	Phase III	1	Day 0	ID	Denmark	Recruiting	1900	Randomized, double-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and an another placebo cohort in healthy adults aged 65 years and older. **ClinicalTrials.gov Identifier :** NCT04542330 **Estimated Study Completion Date :** March 2022
Bandim Health Project [74]	Phase III	1	Day 0	ID	Denmark	Recruiting	1500	Randomized, double-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to a BCG vaccine cohort and a placebo cohort in healthy healthcare workers with direct contact with patients with COVID-19 and aged 18 years to 100 years. **ClinicalTrials.gov Identifier :** NCT04373291 **Estimated Study Completion Date :** August, 2021
Assistance Publique-Hôpitaux de Paris [75]	Phase III	1	Day 0	ID	France	Recruiting	1120	Randomized, single-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort in healthy healthcare workers treating patients with COVID-19 and aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04384549 **Estimated Study Completion Date :** February 20, 2021
Hanna Czajka, University of Rzeszow [76]	Phase III	1	Day 0	ID	Poland	Recruiting	1000	Multicenter, placebo-controlled, randomized, Partially double blinded clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort among healthy health care workers aged 25 years and older. **ClinicalTrials.gov Identifier :** NCT04648800 **Estimated Study Completion Date :** April , 2021
Henry M. Jackson Foundation for the advancement of Military Medicine [77]	Phase III	1	Day 0	ID	United States	Recruiting	550	Multicenter, placebo-controlled, randomized, triple-blind (participant, care provider, investigator) clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort (Tice® BCG) and another placebo cohort among healthy healthcare workers who are likely to care for Covid-19 patients and aged 18 to 64 years old. **ClinicalTrials.gov Identifier :** NCT04632537 **Estimated Study Completion Date :** April , 2023
TASK Applied Science [78]	Phase III	1	Day 0	ID	South Africa	Recruiting	500	Placebo-controlled, randomized, quadruple-blind (participant, provider, investigator, outcome assessor) clinical trial with participants randomly assigned (1:1) to one BCG vaccine cohort and another placebo cohort among healthy healthcare workers aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04379336 **Estimated Study Completion Date :**April 28, 2021
Fundació Institute Germans Trias i Pujol [79]	Phase III	2	Day 0 and Day 14	ID	Spain	Not yet recruiting	315	Quadruple-blind randomized clinical trial (participant, provider, investigator, outcome assessor) placebo-controlled trial with participants randomly assigned to cohorts of placebo vaccine and RUTI® vaccine in healthy healthcare workers aged 18 years old and older. **ClinicalTrials.gov Identifier :** NCT04453488 **Estimated Study Completion Date :** December 2020
Harvard	Phase	1	Day 0	ID	-	Not yet	2100	Randomized, triple-blind, placebo-controlled clinical trial with participants randomly assigned (1:1) to BCG

COVID-19 vaccine developer / Manufacturer	Clinical Trial phase	Number of Doses	Timing of doses	Route of administration	Country	Recruitment Status	Estimated number of participants	Description of the clinical trial
Medical School [80]	III					recruiting		vaccine and placebo cohorts in healthy subjects aged 70 years and older and resident in a long-term care facilities. **ClinicalTrials.gov Identifier :** NCT04534803 **Estimated Study Completion Date :** November 30, 2021
Ain Shams University [81]	Phase III	1	Day 0	ID	Egypt	Not yet recruiting	900	Multi-center, randomized, single-blind clinical trial with participants randomly assigned (2: 1) to a BCG vaccine cohort (n=600) and a placebo cohort (n=300) in healthy healthcare workers working in the isolation hospitals for COVID-19 cases and aged 18 years and older. **ClinicalTrials.gov Identifier :** NCT04350931 **Estimated Study Completion Date :** December 1, 2020
University of Antioquia [58]	Phase III	1	Day 0	ID	Colombia	Withdrawn (Principal Investigator did not obtain sponsorship to carry it out)	-	Randomized, multicenter, double-blind, placebo-controlled clinical trial with participants randomized (1:1) to BCG vaccine and placebo cohorts in healthy adults aged 18 to 65 years. **ClinicalTrials.gov Identifier :** NCT04362124 **Estimated Study Completion Date:** November 2021

* ID : Intradermal

Table 3: COVID-19 vaccine clinical trials published results, as of January 24, 2021

COVID-19 vaccine developer / Manufacturer	Identifier	Phase	Brief description	Vaccine	Country	Number of participants	Published Results	Status of the vaccine	References
CanSino Biologics Inc.	NCT04313127	I	A non-randomized clinical trial, in healthy adults (18-60 years)	Recombinant adenovirus type 5 vector	Wuhan, China	108	The vaccine was tolerable, immunogenic 28 days after vaccination and that rapid specific T lymphocytes were noted from day 14 post vaccination. Most adverse reactions were mild or moderate in severity. The most common were pain In injection side (54%), fever (46%), fatigue (44%), headache (39%) and muscle pain (17%).	Registered in phase III (NCT04526990)[14] and recruiting participants	Zhu et al [67]
Institute of Biotechnology, Academy of Military Medical Sciences, PLA of China	NCT04341389	II	Randomized, placebo controlled clinical trial in healthy adults aged 18 years and older	Recombinant adenovirus type 5 vector	Wuhan, China	508	The 5×10^{10} viral particle vaccine was safe and elicited significant immune responses in the majority of recipients after a single immunization	Registered in phase III (NCT04526990)[14] and recruiting participants	Zhu et al [82]
National Institute of Allergy and Infectious Diseases (NIAID)	NCT04283461	I	An open-label dose-ranging of the safety and immunogenicity of COVID-19 vaccine in healthy adults aged 18 years and over	mRNA-1273	United States	45 (preliminary report) 40	Its preliminary report including 45 healthy adults aged 18 to 55 years, stated that the vaccine induced an immune response in all participants and that no trial-limiting safety concerns were identified. Due to the high mortality and incidence of Covid-19 in older population, the trial was expanded to include 40 older adults aged 56 years and older. It was concluded that the mRNA-1273 had mainly mild to moderate adverse events in older adults and that the 100-µg dose induced higher binding- and neutralizing-antibody titers than the 25-µg dose.	Registered in phase III (NCT04470427) [8] and active not recruiting	Jackson et al [65] Anderson et al [83]
Beijing Institute of Biological Products Co., LTD	ChiCTR2000032459	I/II	A randomized, double-blind, placebo-controlled clinical trial in healthy adults aged 18 years and older (18-80 years in phase I and 18-59 years in phase II)	Inactivated vaccine (BBIBP-CorV)	Henan Province, China	1192 in phase I 2448 in phase II	it was reported that the vaccine was safe, well tolerated and that the two-dose immunization with 4 µg vaccine on days 0 and 21 or days 0 and 28 achieved higher neutralizing antibody titers than the single 8 µg dose or 4 µg dose on days 0 and 14. Adverse reactions were mild or moderate in severity.	-	Xia et al [59]
Gamaleya Research Institute of Epidemiology and Microbiology, Health Ministry of the Russian Federation	NCT04436471 NCT04437875	I/II	Two open-label, non-randomized clinical trial in healthy volunteers aged 18 to 60 years, aiming to assess the safety and immunogenicity of two formulations (frozen and lyophilized) of the vaccine	Recombined viral vector vaccine (rAd26 and rAd5)	Russia	76 (38 in each study)	It was reported that the vaccine was safe and induced strong humoral and cellular immune responses in participants. The most common adverse events were pain at injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), and muscle and joint pain (24%). Most adverse events were mild and no serious adverse events were detected	The vaccine is in phase III with five clinical trials (NCT04530396, NCT04564716, NCT04642339, NCT04640233 and NCT04656613) [7,11,38,39,41]	Logunov et al [60]
University of	NCT04324606	I/II	Randomized, single-	Non-	United-	1077	It was reported that the ChAdOx1 nCoV-19 vaccine had an	The vaccine is in	Folegatti et

COVID-19 vaccine developer / Manufacturer	Identifier	Phase	Brief description	Vaccine	Country	Number of participants	Published Results	Status of the vaccine	References
Oxford			blind, phase I/II clinical trial controlled by a meningococcal vaccine, in healthy adults aged 18 to 55 years.	replicating viral vector (ChAdOx1 nCoV-19)	Kingdom		acceptable safety profile and that a booster dose boosted antibody responses. Local and systemic reactions were more common in the COVID-19 vaccine group including pain, feeling feverish, chills, muscle ache, headache, and malaise.	phase II/III (NCT04400838) [25] and recruiting participants	al [61]
University of Oxford	NCT04400838 [25]	II/III	A single-blind, randomized, controlled, in healthy adults aged 18 years and older enrolled at two UK clinical research facilities, in an age-escalation manner (18–55 years, 56–69 years, and 70 years and older immunogenicity subgroups)	Non-replicating viral vector (ChAdOx1 nCoV-19)	United-Kingdom	560 (160 aged 18-55 years, 160 aged 56-69 years and 240 aged 70 years and older)	The preliminary stated that ChAdOx1 nCoV-19 appears to be better tolerated in older adults than younger adults. Local and systemic reactions (injection-site pain, feeling feverish, myalgias, headache) were less common for those aged 56 years and older. It was also reported that the vaccine had similar immunogenicity across all age groups after a booster dose.	Recruiting participants	Ramasamy et al [84]
Novavax	NCT04368988	I/II	Randomized, placebo-controlled clinical trial in healthy adults aged 18 to 59 years	Recombinant spike protein nanoparticle vaccine with Matrix-M1 adjuvant (NVX-CoV2373)	Australia	131	The primary analysis at day 35 concluded that that the vaccine appeared safe, elicited immune responses that exceeded levels in Covid-19 convalescent serum and that the adjuvant induced CD4+ T-cell responses biased toward a Th1 phenotype. Reactogenicity was absent or mild in the majority of participants, more common with adjuvant	The vaccine has two phase II clinical trials (NCT04611802 and NCT04583995) [19,23]	Keech et al [62]
BioNTch/ Pfizer's	NCT04368728	I	Placebo-controlled, observer-blinded and dose escalation clinical trial in healthy adults aged 18 to 55 years and 65 to 85 years	Two RNA vaccines (BNT162b1 and BNT162b2)	United-States	195	The trial supported the selection of BNT162b2 for advancement to a pivotal phase II/III safety and efficacy evaluation	-	Walsh et al [85]
		I/II	Ongoing placebo-controlled, observer-blinded, dose-escalation in healthy adults aged 18 to 55 years	RNA vaccines (BNT162b1)	United-States	45	It reported that the vaccine exhibited a tolerability and safety profile consistent with those previously observed for mRNA-based vaccine. Local reactions and systemic events were dose-dependent, generally mild to moderate, and transient. However, even if there was stated that there was a robust immunogenicity after vaccination with BNT162b1, the findings were not proof of vaccine efficacy	-	Mulligan et al [63]
		II/III	Ongoing multinational, placebo-controlled, observer-blinded	RNA vaccines (BNT162b2)	United-States, Argentina, Brazil,	43 548	The preliminary report stated that a two dose regimen of BNT162b2 was 95% (95% CI [90.3%-97.6%]) effective against Covid-19 in persons aged 16 years and older. Safety over two months was similar to that of other viral vaccines	-	Polack et al [86]

COVID-19 vaccine developer / Manufacturer	Identifier	Phase	Brief description	Vaccine	Country	Number of participants	Published Results	Status of the vaccine	References
			clinical trial in healthy adults aged 16 years and older		South Africa, Germany, Turkey		and was characterized, especially after the second dose, by mild to moderate local reactions (pain, erythema, swelling) and systemic reactions (fever, headache, myalgias) which resolved rapidly		
Wuhan Institute of Biological Products co., LTD.	ChiCTR2000031809	I and II	Ongoing randomized, double-blind, placebo-controlled in healthy adults aged 18 to 59 years	Inactivated vaccine	Henan Province, China	96 (phase I) 224 (phase II)	The interim analysis demonstrated immunogenicity in patients as well as a low rate of adverse reactions. The most common adverse reaction was injection site pain, followed by fever. No serious adverse reactions were noted	This vaccine is in phase III (NCT04510207) [13] and recruiting participants	Xia et al [66]
BioNTech SE	NCT04380701	I/II	An ongoing placebo controlled, observer-blinded clinical trial in healthy adults aged between 18 and 55 years	RNA vaccines (BNT162b1)	Germany	60	It was reported that the vaccine was safe, tolerable and had antibody response. Reactogenicity was dose-dependent and more pronounced after the boost dose. Side effects such as fever, chills, headache, muscle pain, joint pain, injection site pain, and tenderness, was mostly mild or moderate. The report concluded that BNT162b1 induced functional and proinflammatory $CD4^+$ and $CD8^+$ T cell responses in almost all participants, with T_H1 polarization of the helper response	-	Sahin et al [64]

cines (n=3). At the time of writing this review, there was no publication of the results of these clinical trials.

All published clinical trials' results concerning the safety and immunogenicity of the vaccine were phases I/II and II/III with promising results concerning these two criteria. Having multiples vaccines candidates could be an advantage. In fact, in case one of them fails, there is still others under development. However, the majority of the published clinical trials' results involved a small proportion of participants, in addition to the accelerated process of COVID-19 vaccines development, these could mask some side-effects. Moreover, this rush in the manufacturing process might lead to the production of a vaccine with limited effectiveness and therefore provide immunity, complete or incomplete, only to some vaccinated individuals.[87] Furthermore, published clinical trials' results involved only healthy individuals and few elderly. Even though the more vulnerable individuals, such as the elderly and those with co-morbidities would have priority for vaccines, the vaccine effectiveness and side effects are unknow in this group.[87]

Despite the progress made and the promising results of clinical trials of candidate vaccines, many obstacles and difficulties must be considered, in particular the logistical difficulties surrounding the mass production and the delivery of millions or even billions of doses to the world population, which will represent probably the biggest current challenge. Note that other constraints related to certain types of vaccines, such as mRNAs which are quite unstable at room temperature, requiring storage in freezers.[88] Indeed almost all the new COVID-19 vaccines mentioned require cold storage with different requirements. The distribution of these vaccines then assumes a need for the cooperation of government and companies for cold storage and global transport. The Pfizer vaccine should be stored at a temperature of minus 70 °C ± 10 °C,[89,90] the frozen Gam-COVID- vaccine (Sputnik V) requires a storage temperature of minus 18 °C, while its lyophilized formulation should be stored at a temperature of 2 to 8 °C.[60] Furthermore, despite the rapid development and production of vaccines, their distribution to the most vulnerable and deprived populations and in the poorest countries remains the major issue requiring to help these groups and countries in order to benefit from the necessary and efficient logistics allowing to end this pandemic.

COVID-19 vaccine development continues at unprecedented speed, but it's uncertain that there would be enough production in 2021. New waves of SARS-CoV-2 infections are likely to occur, therefore, we will have to continue preventive measures such as social distancing, mask wearing and hand hygiene.

Box 1: Vaccine development through phases of clinical trials

Phase I : These are the first experiments in humans on a small number of healthy volunteers and focusing on the safety and immunogenicity of the vaccine

Phase II : This phase covers a larger cohort and focuses more on the immunogenicity of the vaccine, allowing the immune response to be analyzed according to age, sex, ethnicity and other variables. Efficiency can also be assessed at this stage.

Parallel **phase I/II** and **phase II/III** studies can be performed, if sufficient data has been extracted from the previous phase, to achieve ethical acceleration.

Phase IV concerns post-marketing authorization trials.

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MO performed the literature search and drafted the manuscript.

MS was responsible for the redaction and revision of the manuscript, and developed the methodology with MO.

AH and HL selected the clinical trials for new candidates COVID-19 vaccines and summarized it.

SDe and HBS were responsible for the other COVID-19 vaccine part, while SDh and CH were responsible for the published clinical trials' results.

LB, SB and NBAB critically revised the manuscript.

All authors approved the final version of the manuscript.

COMPETING INTEREST

The authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available upon request from the corresponding author), and declare no conflicts of interest.

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