Early trial results of SARS-CoV-2 vaccines: a review

Cheng En Xi[1]; Peter Anto Johnson[2]; John Christy Johnson[2]; Austin Mardon[2]

[1] Faculty of Health Sciences, McMaster University
[2]Faculty of Medicine & Dentistry, University of Alberta

Abstract

Introduction: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) initially emerged in Wuhan, China in December 2019. The virus causes the disease that is termed COVID-19 and has led to a global pandemic. As of October 16, 2020, it has led to more than 39 million cases worldwide and has killed more than 1 million people. Since the posting of the SARS-CoV-2 genome, vaccine development has begun around the world, with Canada placing orders for millions of vaccine doses through advanced purchasing agreements (APA) with major developers. As of July 2020, early human clinical trial results of three vaccine candidates, namely ChAdOx1, Ad5-nCoV, and mRNA-1273, have been published, two of which are included in Canada's APAs.

Objective: The aim of this review is to examine and summarize early clinical trial results of the three aforementioned COVID-19 vaccine candidates as of July 20th, 2020. The primary focus of this review will be the methods, procedures, results, and discussions of each published study.

Methods: All vaccine candidates undergoing human trials were searched and identified using PubMed through a combination of search terms. Only the most recent human trial report published in peer-reviewed journals between May 15th and July 20th, 2020, was selected for each vaccine candidate.

Results and Conclusion: The review concludes that all three vaccine candidates have demonstrated a strong safety profile, as well as a robust immune response in the participants of their respective trials. All three vaccine candidates have shown strong immunogenicity, in terms of receptor-binding domain-specific antibody response and neutralizing antibody response. No serious adverse effects were observed in the three trials and all local or systemic reactions were self-limiting. Both ChAdOx1 and Ad5-nCoV will be moving on to phase 3 clinical trials, with mRNA-1273 moving on to phase 2 trials, before the end of 2020.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a coronavirus that belongs to the β-coronavirus cluster and emerged initially in Wuhan, China in December 2019.[1] The virus causes the disease that is termed COVID-19, which is the third known zoonotic coronavirus disease, with the two previous disease types being severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS).[2] The virus was found to be a positive-sense single-stranded ribonucleic acid (RNA) virus, with 88-89% similarity to two SARS-like coronaviruses derived from bats, namely bat-SL-CoVZC45 and bat-SL-CoVZXC21.[1] It also shares a 79% similarity to the SARS virus and 50% similarity to the MERS virus.1 A study by Li et al. analyzed the first 425 confirmed cases in Wuhan, and found evidence of human to human transmission, as well as estimating that the virus has a R0 value of 2.2.[3] The World Health Organization (WHO) declared the COVID-19 outbreak to be a global pandemic on March 11, 2020.[4] As of October 16, 2020, it has spread to almost every country in the world, leading to more than 39 million cases and over 1,000,000 deaths worldwide.[5]

Antibodies are proteins produced by the immune system in response to foreign microbes or cancer cells.[6] They attach to these foreign substances in order for the immune system to sense and eliminate them.[6] The main five types of antibodies include: IgA, IgG, IgM, IgD, and IgE.[6] However, only a small subset of antibodies that bind a virus are neutralizing antibodies.[7] Neutralizing antibodies bind to a virus in a way that inhibits infection.[7] This can be achieved through blocking virus interaction with the receptor of the target cell or through binding a viral capsid to inhibit the uncoating of the genome.[7] A titre is a laboratory measurement that determines the amount or concentration of antibodies, in the blood.[8] In clinical evaluation of vaccines, geometric mean titre (GMT) is typically the standard to determine the average antibody response in a group of subjects.[9] Another measure of antibody response is seroconversion, which is the period during which antibodies become detectable in the blood.[10] Individuals who have detectable antibodies are seropositive, and those who have do not are seronegative. T cells,

Corresponding Author:
Cheng En Xi
xichengen99@163.com

in addition to antibodies, are part of the adaptive immune system and are crucial to the immune response against viral infections.[11] T cells are produced in the bone marrow and develop their own T cell receptors that are specific to one type of antigen.[11] The antigen marks a virus-infected cell and prompts the T cell to eliminate that target.[11] Due to their importance in fighting viral infections, antibody and T cell responses make them important measures in vaccine development.

As a response to the COVID-19 pandemic caused by this novel coronavirus, Canada has announced purchasing agreements (APA) with several vaccine developers (shown in Table 1).[12–18]

The objective of this review was to examine and summarize the most recent published clinical trial results COVID-19 vaccines as of July 20th, 2020. The summary will focus primarily on the methods and procedures, results, and discussions of each published study.

Methods

A list of all COVID-19 vaccine candidates currently in development was obtained through the Government of Canada website.19All vaccine candidates undergoing human trials were searched and identified using PubMed to obtain any published data from their studies. Additional vaccine candidates were identified in PubMed through combinations of search terms "SARS-CoV-2", "COVID-19", "vaccine", "trial", and "safety". The time range for the search was set between May 15th and July 20th, 2020, and only the most recent human trial report was selected for each vaccine candidate. Only peer-reviewed published literature was included. Their respective methods and results were subsequently reviewed and summarized. The aspects of methods reviewed included vaccination schedule and adverse event report. The aspects of results reviewed included reports of adverse effects and immunogenicity of the vaccine candidates, with all numeric results included in this review having a p-value < 0.05, if significant.

Results

The search resulted in the finding of published clinical trial data for three vaccine candidates: ChAdOx1, Ad5-nCov, and mRNA-1273. Only two of these vaccine candidates, namely ChAdOx1 and mRNA-1273, have an APA with the Canadian government.[12]

ChAdOx1

ChAdOx1 nCoV-19 is a vaccine candidate developed by the University of Oxford and pharmaceutical company AstraZeneca. They published their first human trial results on July 20th, 2020. The vaccine candidate consists of the chimpanzee adenovirus vector, ChAdOx1, without the ability to replicate while containing the full-length structural surface glycoprotein (spike protein) of SARS-CoV-2.[20] In a previous study using rhesus macaques, the vaccine candidate was able to protect the lungs from damage and produce a robust immune response when the rhesus macaques were exposed to high doses of SARS-CoV-2.[21] The vaccine candidate was administered through an intramuscular injection to the deltoid muscle, at a dose of 5×10^{10} viral particles.[10,20]

The study published was a phase 1 and 2 single-blinded randomized controlled trial, performed at five different testing centres in the United Kingdom. Participants were between the ages of 18 and 55 and underwent a screening visit, where a full medical history and examination was completed, along with blood and urine tests. Exclusion criteria included: individuals with a history of confirmed SARS-CoV-2 infection, front-line health workers and other individuals who are at higher risk for SARS-CoV-2 exposure pre-enrolment, and those who had a new onset of COVID-like symptoms since Feb 1, 2020.[20] Participants were randomly assigned to receive either the ChAdOx1 nCoV-19 vaccine or the MenACWY vaccine. MenACWY was utilized as a comparator placebo vaccine, as opposed to saline, in an effort to blind the participants. Since viral vector vaccinations are known to elicit local or systemic reactions, a lack of reactions from saline would unblind the participants who had notable reactions, thus MenACWY was chosen as placebo.[20] MenACWY vaccine is routinely given to teenagers in the United Kingdom to prevent meningococcal disease, and would typically produce mild reactions such as redness at injection site, nausea, fatigue, headache, and fever.[22] Thus, the presence of these reactions would sufficiently blind the participants.

Table 1. Summary of the Canadian advanced purchasing agreement of COVID-19 vaccines as of September 25, 2020[12–18]

Developer	Astra-Zeneca/ Oxford	Janssen Pharma Co.	Moderna	Novavax	Pfizer/ BioNTech	Sanofi/ GSK
Type	Non-replicating viral vector	Non-replicating viral vector	mRNA	Protein subunit	mRNA	Protein subunit
Dose requirements	2 doses	1/2 doses	2 doses	2 doses	2 doses	1/2 doses
Dose reserved	~ 20 million	Max 38 million	Min 20 million	~ 76 million	Min 20 million	Max 72 million
Storage temperature	2-8 °C	2-8 °C	-24 °C	2-8 °C	-70 °C	2-8 °C

Participants were recruited in 4 separate groups. Group 1 (the phase 1 component of the study) consisted of intensive early follow-up visits at days 3, 7, 14, 28, and 56 after vaccination to ensure safety and immunogenicity. Group 2 consisted of participants who had higher blood volumes drawn for humoral and cellular immunogenicity assessment than group 4. Group 4 consisted of participants who only had a serum sample drawn for humoral immunology assessments. Group 3 consisted of a non-randomized group ($n = 10$) that received a booster shot 28 days after the first dose. Group 3 participants were not blinded and had the same extensive follow-up as group 1 following each dose. All participants across the groups had blood samples taken, along with clinical assessments, at days 0 and 28 and will also be followed up at days 184 and 364. After vaccination, all participants underwent a 30-60 min observation period in the clinic and were asked to record any adverse events using electronic diaries during the 28-day follow-up period. Adverse events were graded as mild, moderate, severe, and potentially life-threatening.[20]

Cellular responses were assessed using an ex-vivo interferon-γ enzyme-linked immunospot (ELISpot) assay, as a way to enumerate antigen-specific T cells. Humoral responses were assessed using a standardized total IgG enzyme-linked immunosorbent assay (ELISA) against trimeric SARS CoV-2 spike protein, a multiplexed immunoassay (MIA), three live SARS-CoV-2 neutralization assays (PHE, MNA and Marburg), and a pseudo-virus neutralization assay (PseudoNA). Convalescent plasma samples from adults with positive SARS-CoV-2 infections were obtained from symptomatic

patients admitted to hospital or healthcare workers who did not have symptomatic infections. These samples were tested using the aforementioned assays as well.[20]

Prophylactic paracetamol was given to 56 participants in the ChAdOx1 nCoV-19 group and 57 in the MenACWY group, and was found to reduce the incidence of adverse events. Common adverse events in both groups included pain, tenderness, fatigue, headache, fever, muscle ache, malaise, chills, and feeling feverish. The prevalence of these events among these groups are displayed in Table 1.[20]

In dose groups 1, 2, and 4, where no subsequent booster shot was given, as well as the ChAdOx1 nCoV-19 group where only one dose was administered, antibodies targeting SARS-CoV-2 spike protein peaked by day 28 (median ELISA units [EU] = 156) and remained elevated until day 56 (EU = 119). Among the 10 participants in group 3 who received a booster shot, the median antibody concentration on day 56 was increased to 639 EU. By day 28, similar increases in serum antibody levels to both the spike protein and the receptor-binding domain (RBD) were observed, regardless of booster shot. Paracetamol use did not appear to affect immunogenicity. On day 28, the PHE assay determined that 100% (35/35) of participants achieved neutralizing titres. The MNA assay also found that titres inducing 80% virus neutralization was achieved in 91% (32/35) participants after one dose, and in 100% (9/9) of participants following the booster dose. In the Marburg assay, it was found that just one dose of the vaccine candidate resulted in 62% (23/37) of participants having neutralizing antibodies that completely inhibited the cytopathic effect of SARS-CoV-2 by day 56. The same occurred in 100% (10/10) of participants after a booster dose.[20]

The preliminary findings show that the vaccine candidate ChAdOx1 nCoV-19, given as a single dose, was safe and tolerated, despite the fact that it has a higher reactogenicity profile than the control vaccine, MenACWY. No serious adverse reactions to the vaccine candidate occurred, with the majority of adverse events reported being mild or moderate in severity, and self-limiting. The use of prophylactic paracetamol also appeared to increase tolerability among the participants, while reducing potential confusion between short-lived vaccine-related symptoms and actual COVID-19 symptoms.20 Additionally, the use of prophylactic paracetamol did not impact immunogenicity.[20]

In previous clinical studies exploring DNA vaccines on rhesus macaques, neutralizing antibodies targeting the different epitopes of the spike glycoprotein were associated with protection from COVID-19.[23] In addition, there is increasing evidence to suggest that T cell responses play an important role in COVID-19 mitigation, as robust T cell immunity was found in individuals who were asymptomatic or had mild COVID-19 symptoms.[24] Older individuals also remain disproportionately affected by the more severe and fatal cases of COVID-19,[25] so it is important that any vaccines developed are safe and tolerable for older age groups.

The limitations of this study include: a short follow-up, small sample size in the prime-boost group, and the single-blinded design. However, staff undertaking clinical evaluation and laboratory staff were blinded. The findings are also not easily generalizable. While the methods of the study did not specify ethnicities and age distribution among the trial groups, the discussion of the study does state that the sample is composed of relatively young and healthy, mostly Caucasian participants. Future studies should assess the vaccine in other population groups including the elderly, those with comorbidities, and in ethnically diverse populations. The participants in this study will be followed for at least one year in order to further report on the safety, tolerability, immunogenicity, and efficacy of the vaccine candidate. The preliminary results of this study support future phase 2 and 3 trials. Phase 3 trials have begun in Brazil, South Africa, and the UK. These trials will evaluate vaccine efficacy in diverse populations such as children, healthcare workers, and older age groups.

Ad5-nCov-2

This phase 2 study, published on July 20, 2020, was a randomized, double-blinded, placebo-controlled trial of the Ad5-nCoV (Ad5) vaccine candidate.[26] This vaccine candidate is an adenovirus vector vaccine developed by CanSino Biologics Inc., and its phase 1 trial data was published on May 22, 2020.[27] The phase 1 study of this candidate was the first published human trial report of any SARS-CoV-2 vaccines.[27] It was a recombinant adenovirus type-5 vectored vaccine candidate that expresses the spike glycoprotein of the SARS-CoV-2 virus strain; however, it did not have replicating abilities.[27] The aim of the phase 2 study was to determine an appropriate dose for a phase 3 efficacy study.[26]

This study was randomized, double-blind, and placebo controlled. It was conducted at a single testing centre in Wuhan, China, involving healthy adult participants with no upper age limit. Exclusion criteria included: HIV positivity, previous SARS-CoV-2 infections, and the presence of mental disease, history of allergies, or serious cardiovascular disease. The placebo shot contained no viral particles but shared identical packaging as the vaccine candidate. Three treatment groups (1×10^{11} viral particles/mL [medium],[27] 5×10^{10} viral particles/mL [low],[27] and placebo) were randomized using software at a 2:1:1 ratio. In total, 603 participants were recruited and screened, with 95 individuals excluded, leaving 508 eligible participants in the trial. Of these, 253 were randomly assigned to the medium dose group, 129 to the low dose group, and 126 to the placebo group. A single injection of the vaccine candidate or placebo was administered intramuscularly in the arms of the participants, and they were monitored for 30 minutes afterwards for immediate adverse reactions. All participants were followed up for any local or systemic adverse reactions within 14 days and adverse events within 28 days after the injection. Participants also self-reported any serious adverse events throughout the study.[26]

Blood samples were collected from participants immediately before vaccination, as well as at days 14 and 28 post-vaccination. The measurement of specific antibody responses against the RBD were done using ELISA kits. The neutralizing antibody responses to live SARS-CoV-2 virus or a pseudo virus, made of a vesicular stomatitis virus pseudo virus system expressing the SARS-CoV-2 spike glycoproteins, were also measured. Additionally, cellular immune responses before and 28 days after the vaccination were also measured. The cellular immune responses of the expression of interferon (IFN) γ, which demonstrates positive T cell responses, were detected by ELISpot assay, and serum neutralization assay was used to assess neutralizing antibody titers. Follow-up appointments were scheduled on days 14 and 28, and 6 months post-vaccination to assess safety and immunogenicity.[26]

Within 14 days post-vaccination, at least one adverse reaction

was reported by 72% (183/253) of the participants in the medium dose group and 74% (96/129) of the participants in the low dose group; this was significantly higher than the adverse reactions reported in the placebo group (37% (46/126)). The most common adverse reactions in the experimental vaccine groups were pain at the injection site, fatigue, fever, and headache. The incidence rate is outlined in Table 2.[26]

Table 2. Prevalence of local or systemic adverse events among the participants receiving the ChAdOx1 nCoV-19 experimental vaccine or the MenACWY control vaccine[20]

	Incidence in the ChAdOx1 nCoV-19 group		Incidence in the MenACWY group	
	Without paracetamol	With paracetamol	Without paracetamol	With paracetamol
Pain	67%	50%	38%	32%
Tenderness	83%	77%	58%	46%
Fatigue	70%	71%	48%	46%
Headache	68%	61%	41%	37%
Fever (min 38°C)	18%	16%	< 1%	0%
Fever (min 39°C)	2%	0%	0%	0%
Muscle ache	60%	48%	Not specified	Not specified
Malaise	61%	48%	Not specified	Not specified
Chills	56%	27%	Not specified	Not specified
Feeling feverish	51%	36%	Not specified	Not specified

Table 3. The prevalence of local or systemic adverse events among the participants receiving 1×10^{11} (medium dose) or 5×10^{10} (low dose) experimental Ad5-nCoV vaccine[26]

	Incidence in the 1×10^{11} viral particles (medium) dose group	Incidence in the 5×10^{10} viral particles (low) dose group
Fatigue	42%	34%
Fever	32%	16%
Headache	29%	28%
Pain at injection site	57%	56%

While most adverse reactions were reported as either mild or moderate, 9% (24/253) of the participants in the medium viral particles group had severe adverse reactions; this was significantly higher than those in the low viral particles or placebo groups. The most common severe adverse reaction was fever, which was reported in 8% (20/253) of the participants in the medium particles dose group and 1% (1/129) of the participants in the low dose group. These reactions were self-limited and were resolved within 72-96 hours without need for medication. Overall, within 28 days of the injection, 77% (196/253) of the participants in the medium dose group, 76% (98/129) of those in the low dose group, and 48% (61/126) of those in the placebo group experienced at least one adverse event.[26]

RBD-specific ELISA antibody responses induced by Ad5 were detected since day 14, with a higher response in the medium dose group. On day 28, these antibodies peaked at 656.5 in the medium dose group and 571.0 in the low viral particles dose group; 244 of the 253 participants in the medium dose group and 125 of the 129 participants in the low dose group showed seroconversion of the aforementioned antibodies on the same day. No antibody increases from baseline occurred in the placebo group. Neutralizing antibody responses to live SARS-CoV-2 was induced by both doses on day 28, with GMTs of 19.5 and 18.3 in medium and low dose groups, respectively. At 28 days post-injection, seroconversion of neutralizing antibody responses also occurred in 148 of the 253 participants receiving the medium dose and in 61 of the 129 participants receiving the low dose. In terms of neutralizing antibody responses to the pseudo-virus, the GMTs were 61.4 in the medium dose group and 55.3 in the low dose group, with seroconversion also occurring in both groups. Older age (>55) was found to have a negative impact on the RBD-specific ELISA antibody and neutralizing antibody responses to both the live virus and pseudo-virus. Nonetheless, antibodies in both groups remained significantly higher on day 28 when compared to the placebo group, despite old age. Significant SARS-CoV-2 spike glycoprotein-specific IFNγ-ELISpot responses were induced in 227 of the 253 participants in the medium dose group and 113 of the 129 participants in the low dose group. Both groups increased by a factor of 10 in this metric when compared to baseline. No such increase was observed in the placebo group. In terms of immune response, no gender differences were observed.[26]

This study is the first randomized, double-blind, placebo-controlled trial for the Ad5-nCoV vaccine candidate. A single injection of the vaccine candidate at 1×10^{11} viral particles (medium) and 5×10^{10} viral particles (low) was able to induce specific immune responses to the SARS-CoV-2 spike glycoprotein on day 28, with no significant differences observed between the two dose groups. The two doses induced seroconversion of neutralizing antibodies in 59% and 47% of participants and seroconversion of binding antibody in 96% and 97% of participants in the medium and low dose groups, respectively. Positive specific T-cell responses were found in 90% and 88% of participants in the medium and low dose groups, respectively.[26] A dose of 1.5×10^{11} was explored in a previous phase 1 study, but it was not selected for further study.[27]

The most common reactions reported in this study were mild or moderate, though the incidence rate of adverse events such as fever, fatigue, and injection site pain were significantly higher in vaccine recipients than those in placebo recipients. These events are generally resolved within 48 hours. All severe reactions reported were in the medium dose group, except for one adverse reaction that occurred in the low dose group. Overall, the results indicate that Ad5-nCoV has demonstrated a good safety profile in healthy adults.[26]

The limitations of this trial include: lack of diversity in participants (all participants were Wuhan residents, which does not represent a global population), the lack of data beyond 28 days post-vaccination, and the lack of live SARS-CoV-2 exposure post-vaccination to assess efficacy. In addition, this trial began after the full data from its phase 1 study was available, so the researchers did not calculate the sample size based on study power in advance, which could lead to a lack of power to show the difference between the dose groups. These limitations emphasize the importance of an international multicentre, randomized, double-blind, placebo-controlled phase 3 efficacy trial. The immunogenicity and the feasibility of additional dose in the older population will be assessed in another phase 2B trial.[26]

mRNA-1273

The first preliminary report on the effectiveness of mRNA-1273, an mRNA vaccine developed by Moderna was published on July 15th, 2020. The mRNA-1273 vaccine candidate encodes the S-2P antigen, consisting of the SARS-CoV-2 spike protein with a transmembrane anchor and an intact S1-S2 cleavage site.[28] The mRNA-1273 vaccine was manufactured as a sterile liquid for intramuscular injection (concentration = 0.5 mg/mL), with normal saline being used to dilute the solution and prepare the doses administered.[28]

Moderna conducted a phase 1 dose-escalation clinical trial that was designed to determine the safety, reactogenicity, and immunogenicity of mRNA-1273.28 The trial consisted of 45 healthy adults between the ages of 18 to 55 years.[28] The participants received two injections of the vaccine candidate 28 days apart, at a dose of 25 μg, 100 μg, or 250 μg across three trial groups (n = 15).28 Follow-up visits were scheduled 7 and 14 days after each vaccination, as well as on days 57, 119, 209, and 394 of the clinical trial.[28] The participants were given memory aids to record local and systemic reactions for seven consecutive days after each vaccination.[28] They were also instructed to avoid routine use of acetaminophen or other analgesics and antipyretics before or after the vaccinations, but were asked to record any new medications taken.[28] Binding antibody responses to the S2P and isolated receptor-binding domains of the vaccine were assessed using ELISA.[28] To compare the immune response experienced by the participants to the individuals who had SARS-CoV-2 induced infections, 41 convalescent serum specimens from SARS-CoV-2 patients were also tested.[28] A pseudo typed lentiviral reporter single-round-of-infection neutralization assay (PsVNA) and a live wild-type SARS-CoV-2 plaque-reduction neutralization testing (PRNT) assay were used to measure vaccine-induced neutralizing activity.[28]

The vaccine candidate was found to produce no serious adverse effects.[28] Systemic adverse effects were reported by 33% (5/15) participants (33%) in the 25μg group, 67% (10/15) in the 100μg group, and 53% (8/15) in the 25 μg group after the first vaccination.28All adverse effects were reported as mild or moderate in severity.28 Such adverse events increased in occurrence after the second vaccination.[28] Adverse events occurred in 54% (7/13) in the 25μg group, and every participant in the 100μg and 250μg groups, with 3 participants reporting one or more severe events.28 No participants reported fever after the first vaccination, while 40% (6/15) in the 100μg group and 57% (8/15) in the 250μg group reported fever after the second vaccination, with one of the fever events in the 250μg group graded as severe (maximum temperature = 39.6°C).[28] Pain at the injection site was common and local adverse events were nearly all mild or moderate when they occured.[28] The most common adverse events across both vaccinations included fatigue, chills, headache, myalgia, and pain at the injection site.[28]

Binding antibody IgG GMTs to S-2P site increased rapidly after the first vaccination and seroconversion occurred in all participants by day 15. It was also evident that the responses to both vaccinations were dose-dependent,28 with the 25, 100, and 250μg dose groups reaching GMTs of 40,227, 109,209, and 213,526, on day 29, respectively.[28] Similar patterns and magnitudes were also observed in RBD-specific antibody responses.[28] For both assays, the median magnitude of antibody responses after the first vaccination in the 100μg and 250μg dose groups were similar to the median magnitude in convalescent serum specimens from SARS-CoV-2 patients.[28] Furthermore, after the second vaccination, the median magnitude across all dose groups were in the upper quartile of values in the convalescent serum specimens.[28]

Prior to vaccination, no participant had detectable PsVNA neutralization responses.[28] After the first vaccination, neutralization responses were detected in less than half of the participants, with responses being dose-dependent.[28] However, after the second vaccination, such responses were detected in serum samples from all participants.[28] The responses by all dose groups after two vaccinations were similar to the levels seen in the upper half of the distribution for convalescent serum specimens, reaching GMTs of 80.7, 231.8, and 270.2, on day 57, from the lowest to highest dose groups, respectively.[28] Moreover, at day 43, wild-type virus-neutralizing activity capable of reducing SARS-CoV-2 infectivity by 80% or more was detected in all participants using PRNT assay, with the average PRNT response being above the convalescent serum specimen tested.[28]

The development of this vaccine candidate began after the SARS-CoV-2 genome was posted on January 10, 2020, and the manufacture and delivery of clinical trial material was completed within 45 days.[28] The first trial participants were vaccinated on March 16, 2020, just 66 days after the genomic sequence of the virus was posted.[28]

The mRNA-1273 vaccine candidate was able to induce a strong immune response in all 45 participants after two doses of the vaccine, with median immune responses similar to the higher end distribution of patients who were infected with SARS-CoV-2.[28] Both immunogenicity and reactogenicity appear to be dose-dependent.[28] Systemic adverse events were all reported to be mild after the first vaccination, with more severe and frequent adverse events occurring after the second vaccination, particularly in the 250μg group.[28]

Seroconversion also occurred rapidly for binding antibodies, as it occurred within 2 weeks of the first vaccination.[28] Serum neutralization also occurred in all participants after the second vaccination. Previous studies have shown that there is a correlation between serum neutralization activity and the protection for other respiratory viruses.[29] This was further supported by the pre-clinical trial of a DNA vaccine against SARS-CoV-2 in rhesus macaques, as they found existence of a correlation between neutralizing antibody titre and protection against the challenge of SARS-CoV-2.[23]

Participants will be followed for one year after the second vaccination with scheduled blood collections to characterize the humoral and cellular immunologic responses.[28] A phase 2 trial of this vaccine candidate (n = 600) evaluating doses of 50μg and 100μg is ongoing, with a large phase 3 efficacy trial expected to begin during the summer of 2020.[28]

Discussion

Overall, all three vaccine candidates explored have demonstrated a strong safety profile, as well as a capability to induce an immune response. The summary of the key safety and immunogenicity metrics of all three vaccine candidates is shown in Table 4.

The methods used in each of the three trials are similar, as they all have varying degrees of blinding, follow-up, assessment of local or systemic reactions, and measurement of immune response

Table 4. A summary of ChAdOx1, Ad5-nCoV-2, and mRNA-1273 COVID-19 vaccine candidates as of July 2020

Vaccine candidate	ChAdOx1 nCoV-19	Ad5-nCoV-2	mRNA-1273
Vaccine type	Non-replicating viral vector	Non-replicating viral vector	mRNA
Published trial phase as of July 20th, 2020	1/2	2	1
Adverse reactions	Pain, tenderness, fatigue, headache, fever; Very few fever incidents above 39°C; Paracetamol reduced incidence	Pain, fatigue, fever, headache; most events mild/moderate and self-limiting; Paracetamol NOT tested	Pain, headache, fatigue; no fevers after first dose, only one severe fever after second dose; Paracetamol NOT tested
Antibody or RBD-specific antibody responses	Median spike protein-specific antibodies: 156 EU (day 28), 119 EU (day 56), 639 EU (day 56 [booster])	Median RBD-specific antibodies (GMT) at the peak: 656.5 (medium dose), 571.0 (low dose)	Median spike protein-specific antibodies on day 29 (GMT): 40,227 (25 μg), 109,209 (100 μg), 213,526 (250 μg)
Neutralizing antibody seroconversion	100% seroconversion (day 28), 91% seroconversion of antibodies capable of 80% virus neutralization (day 28)	58% seroconversion (medium dose, day 28), 47% (low dose, day 28)	< 50% seroconversion (first dose), 100% seroconversion (second dose)

Table 5. A summary of COVID-19 vaccine candidates with published clinical trial reports (preprints excluded) as of October 19th, 2020[16,20,26-28,30-32]

Vaccine candidate	ChAdOx1-nCov-19	Ad5-nCoV-2	mRNA-1273	rAd26 and rAd5	BNT162b1 and BNT162b2	Unnamed Sinopharm Vaccine
Publication date(s)	July 20th, 2020	May 22nd, 2020 (phase 1); July 20th, 2020 (phase 2)	July 14th, 2020 (phase 1); September 29th, 2020 (expanded phase 1)	September 26th, 2020	October 14th, 2020	August 14th, 2020
Published trial phase(s)	Phase 1/2	Phase 1 and phase 2	Phase 1 and expanded phase 1	Phase 1/2	Phase 1	Phase 1
APA status with Canada	Yes	No	Yes	No	Yes	No
DOI	10.1016/S0140-6736(20)31604-4	10.1016/S0140-6736(20)31208-3	10.1056/NEJMoa2022483 (phase 1)	10.1016/S0140-6736(20)31866-3	10.1056/NEJMoa2027906	10.1001/jama.2020.15543
		10.1016/S0140-6736(20)31605-6 (phase 2)	10.1056/NEJMoa2028436 (expanded phase 1)			

via standard laboratory techniques. However, there are a few differences in their results worth looking at. The trial exploring ChAdOx1 explicitly included Paracetamol use as a part of the study, evaluating its impacts on immunogenicity and effects in reducing the adverse reactions.[20] The same was not done in the other two studies, and its inclusion can be considered a strong point in the ChAdOx1 study, as they did find the Paracetamol to be helpful in reducing adverse effects while not impacting immunogenicity.20 Since this was not explicitly done for the other two vaccine candidates, it should not be assumed that they share this quality. In addition, the ChAdOx1 study also opted to measure antibody responses in ELISA units, while the other two studies used GMT, which makes it difficult to compare the antibody responses across the three studies.[28] However, all three studies indicate baseline antibody levels, which enables one to evaluate the effectiveness of the vaccines based on the immune response compared to baseline.[28] Convalescent serum samples from real-life patients infected with SARS-CoV-2 were also used as a comparator in the ChAdOx1 and mRNA-1273 studies, providing another method to judge vaccine effectiveness.[20,27]

The three studies also share similar limitations. All three studies have limitations when it comes to the sample population, either in terms of size or diversity.[28] Both the ChAdOx1 and Ad5-nCoV studies had a sample size that lacked diversity, with the former being mainly Caucasian, and then latter being only Wuhan residents.20,[26] While the study exploring mRNA-1273 did not explicitly mention such issues, it has a sample size smaller than both ChAdOx1 and Ad5-nCoV, due to its nature as a phase 1 trial.[28] However, many of these issues are expected to be resolved to varying degrees as these vaccine candidates enter larger scale clinical trials.

Since the review of the three studies as of July 20th, much has changed in the landscape of COVID-19 vaccine development. Other vaccine candidates have also had published clinical trial reports since then, making the three vaccine candidates reviewed no longer the only ones with clinical trial data. A list of all published COVID-19 vaccine clinical trial reports as of October 19th, 2020 is shown in Table 5.

Another notable development of COVID-19 vaccine development since the publication of the three studies is the pausing of phase 3 clinical trials of ChAdOx1, and another vaccine candidate by Janssen Pharmaceutical Company, named Ad.26.COV2.S.[33,34] In early September 2020, it was reported that AstraZeneca is pausing its ChAdOx1 vaccine phase 3 trials in Britain after the incidence of transverse myelitis, a spinal inflammation disorder, in a female subject.[35] The trials resumed soon after in Britain, while remaining paused in some other countries.[36] This is not the first pause for this vaccine candidate, as there was another incidence of multiple sclerosis during its trial in July, which was later determined to be unrelated to vaccines. Similarly, in October 2020, Janssen Pharmaceutical Company announced that it is halting further dosing in their COVID-19 vaccine trials, due to safety concerns arising from an incidence of unexplained illness.[34] However, the company has announced it is preparing to resume recruitment for its COVID-19 vaccine trials since no evidence of the vaccine causing the illness was found.[34] The incidence of unexplained illnesses and subsequent pauses of these trials highlights the importance of large-scale phase 3 trials in determining the safety of vaccines in the general population.

Conclusion

In summary, all three experimental vaccine candidates reviewed, ChAdOx1 nCoV-19, Ad5-nCoV, and mRNA-1273, have shown strong immunogenicity and safety profile in their respective phase 1 or 2 human clinical trials. All three vaccine candidates are expected to conduct their respective phase 2 or 3 clinical trials as soon as possible, as well as following up with the participants involved in their published trials.

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