GBL-VAC-0340

INVENTING FOR LIFE

COVID-19
Vaccine Candidate Landscape

SCIENTIFIC DIGEST

COVID-19 Vaccine Candidate Landscape

CONTENTS

The content in this document is current as of August 24, 2020.

It is subject to rapid change and will be updated routinely. Some data presented here are derived from non-peer reviewed preprints and press releases, and must be interpreted with extreme caution until peer-reviewed reports become available.

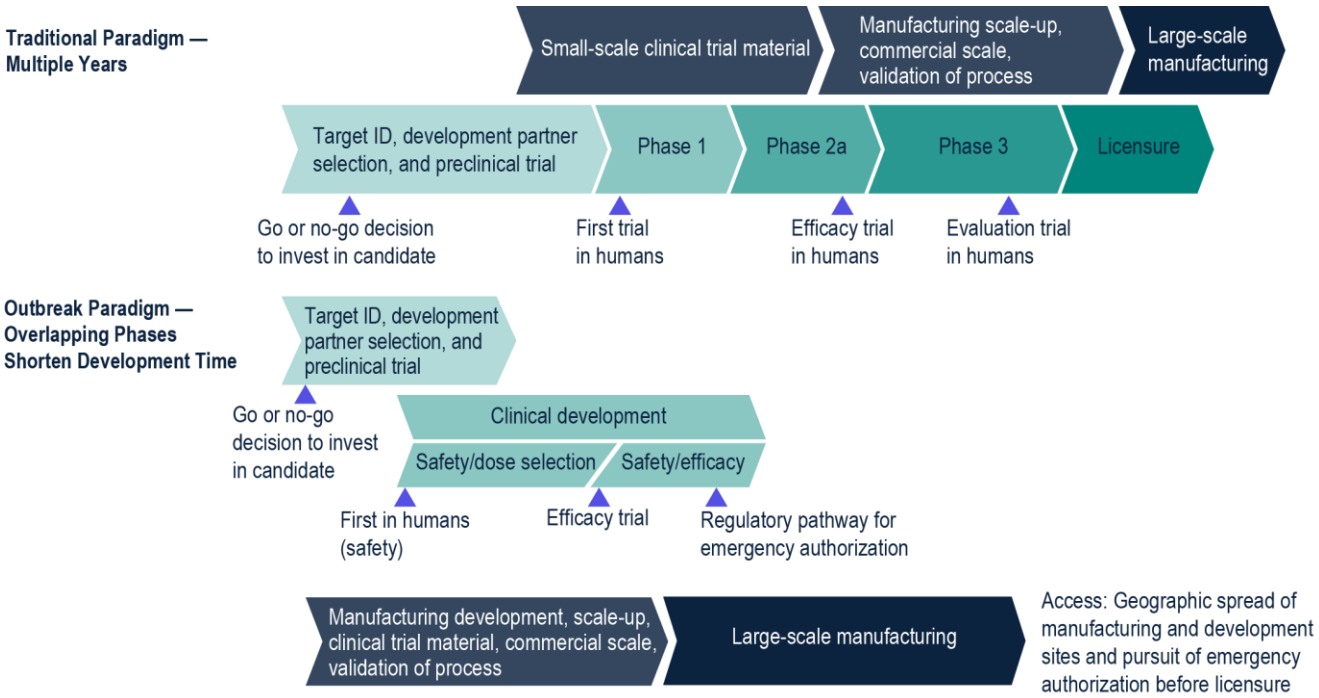
INTRODUCTION

The COVID-19 pandemic has resulted in a vast effort focused on identifying, evaluating, and manufacturing vaccine candidates against COVID-19. As of August 10, 2020, the World Health Organization COVID-19 Candidate Vaccine Landscape lists a total of 167 vaccines candidates being developed worldwide, of which 28 are in clinical evaluation and 139 are in preclinical evaluation (World Health Organization 2020b).

The "Outbreak Paradigm" for Vaccine Development

Conventional vaccine development is typically a lengthy, expensive process. Attrition is high, and multiple candidates can be evaluated over many years to identify and produce a licensed vaccine. The urgent need for an effective vaccine against SARS-CoV-2 has introduced a new paradigm in the vaccine development process, the "outbreak paradigm," in which overlapping phases reduce development time and dramatically shorten clinical development pathways, with manufacturing scale-up and validation occurring at the same time (Figure 1). Large-scale manufacturing closely follows the clinical study data suggesting the vaccine is immunogenic and has an acceptable safety profile. (Lurie et al. 2020).

Figure 1. Difference between conventional vaccine development and development using a "pandemic paradigm" (Lurie et al. 2020)



Vaccine Development Initiatives

At present, multiple government initiatives are ongoing worldwide to invest in and accelerate development of coronavirus vaccine candidates under aggressive timelines. Operation Warp Speed and the European Union Strategy for COVID-19 Vaccines are examples of 2 such initiatives.

Operation Warp Speed (United States)

In the United States, Operation Warp Speed (OWS) was developed to "deliver 300 million doses of a safe, effective vaccine for COVID-19 by January 2021, as part of a broader strategy to accelerate the development, manufacturing, and distribution of COVID-19 vaccines, therapeutics, and diagnostics." (US Department of Health and Human Services 2020) The OWS engages with private firms and coordinates work on therapeutics and vaccines across US agencies (US Department of Health and Human Services 2020). As of August 10, 2020, OWS has provided proactive funding ranging from US $450 million to US $2 billion for vaccine candidates or treatments from Johnson & Johnson, Moderna Inc, AstraZeneca, Regeneron, Novavax, Pfizer Inc, and Sanofi/GlaxoSmithKline (US Department of Health and Human Services 2020). The vaccine candidates represent a selection from multiple strategies.

COVAX

COVAX is the vaccines pillar of the Access to COVID-19 Tools (ACT) Accelerator, a global collaboration to accelerate the development, production, and equitable access to COVID-19 tests, treatments, and vaccines. COVAX is led by the Global Alliance for Vaccines and Immunization (Gavi), the Coalition for Epidemic Preparedness Initiatives (CEPI), and the World Health Organization. COVAX aims to provide doses for at least 20% of countries' populations (Gavi 2020).

European Union Strategy for COVID-19 Vaccines (European Union)

The European Commission has proposed a strategy to secure sufficient production of vaccines in the European Union, and adequate supplies for member states. Through advance purchase agreements it has also proposed that additional financing, as well as other forms of support, can be made available on top of such agreements. The European Commission is working towards adapting the European Union's regulatory framework to accelerate development, authorization, and availability of vaccines while maintaining standards for vaccine quality, safety, and efficacy (European Commission 2020).

Coronavirus Vaccine Candidates in Development

The document is organized by the underlying strategy used for each vaccine candidate. While vaccines can be categorized in various ways, broadly, the primary strategies that are in development for SARS-CoV-2—vaccination include (Table 1) (Lurie et al. 2020):

- Nucleic acid vaccines: Those that deliver coronavirus nucleic acid into cells, which codes for the antigen(s). These can be further categorized into DNA-based and RNA-based vaccines
- Viral vector vaccines: Those that use a virus to deliver coronavirus genes into cells, which codes for the antigen(s)
- Protein-based vaccines: Those that use a protein or protein fragment to induce an immune response
- Whole-virus vaccines: Those that use inactivated or live-attenuated viruses to elicit an immune response Each of these strategies will be described in greater detail in their respective sections.

Table 1. Vaccine platforms and key attributes (Lurie et al. 2020)

Technology		Attributes			
		Single Dose	Licensed Platform	Speed	Current Scale
Nucleic Acid	DNA	No	No	Fast	Medium
	RNA	No	No	Fast	Low to medium
Viral Vector	Nonreplicating	Yes	No	Medium	High
	Replicating	Yes	Yes	Medium	High
Protein Subunit		No	Yes	Medium to Fast	Medium to High
Whole Virus	Inactivated	No	Yes	Medium	Medium to High
	Live attenuated	Yes	Yes	Slow	High

LINKS TO RESOURCES

World Health Organization COVID-19 Candidate Vaccine Landscape

United States Department of Health and Human Services Operation Warp Speed

The New York Times Vaccine Tracker

OVERVIEW

The selection of vaccine candidates in this document is based on the August 10, 2020 version of the **WHO COVID-19 Candidate Vaccine Landscape**. As of that time, a total of 28 vaccine candidates, representing a variety of strategies, had entered clinical trials (Figure 2).

Table 2 summarizes vaccine candidates that had reached at least phase 1/2 of development (World Health Organization 2020b). Detailed information on additional candidates will be added as data are published. Merck's vaccine candidates are also included in this table for context; please note that additional information on these candidates will be provided in separate training.

Figure 2. Distribution of strategies among all vaccine candidates that have entered clinical trials as of August 10, 2020

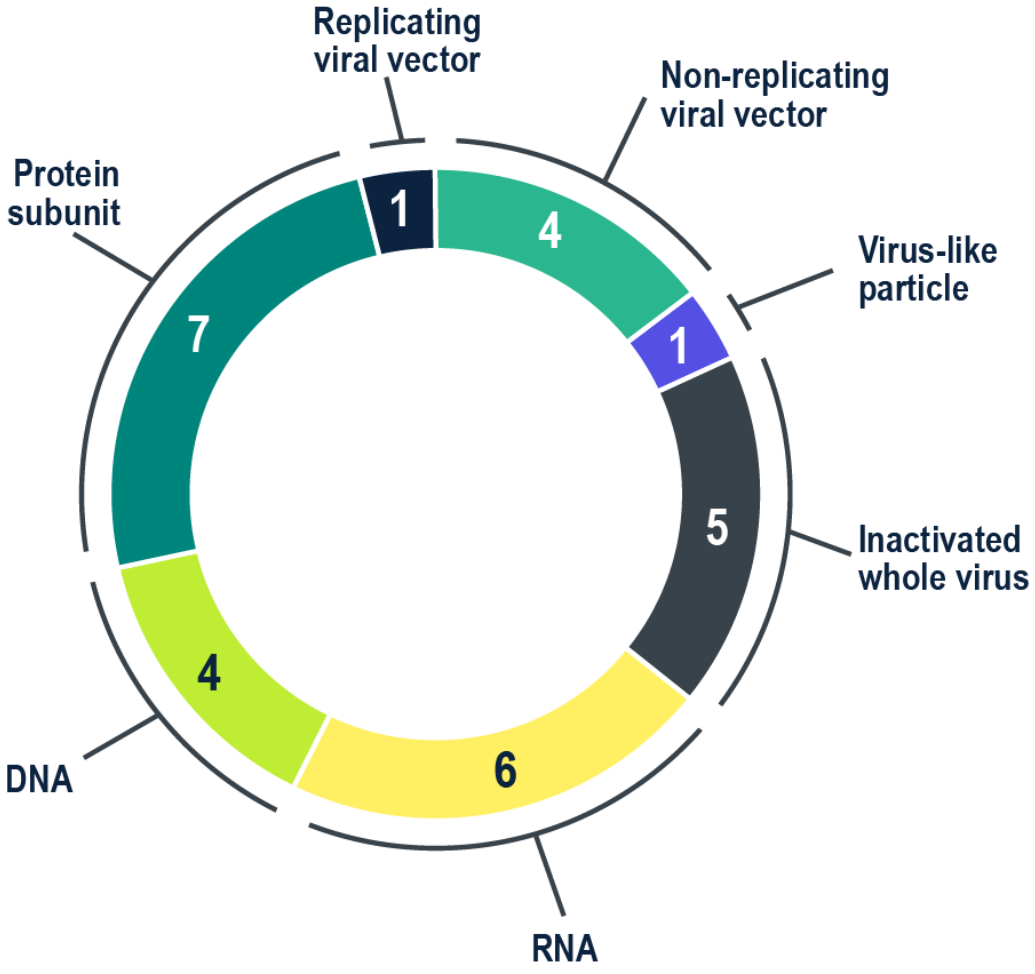


Table 2. COVID-19 Candidate Vaccine Landscape (entering phase 1/2 or later as of August 10, 2020). Highlighted rows indicate vaccine candidates that are covered in detail in the following sections (World Health Organization 2020b)

Developer / Manufacturer	Type of Candidate Vaccine	Number of Doses	Timing of Doses	Route of Administration	Phase
Nucleic Acid Vaccine Candidates					
Moderna/NIAID	LNP-encapsulated pseudouridine-modified mRNA	2	0, 28 days	IM	3
BioNTech/Pfizer/ Fosun Pharma	LNP-encapsulated nucleoside-modified mRNA	2	0, 21 days	IM	3
Inovio Pharmaceuticals/ International Vaccine Institute	DNA plasmid vaccine with electroporation	2	0, 28 days	ID	1/2
Arcturus/Duke-NUS	mRNA	2		IM	1/2
Osaka University/ AnGes/Takara Bio	DNA plasmid vaccine + adjuvant	2	0, 14 days	IM	1/2
Cadilla Healthcare	DNA plasmid vaccine	3	0, 28, 56 days	ID	1/2
Genexine Consortium	DNA vaccine	2	0, 28 days	IM	1/2
Viral Vector Vaccine Candidates					
University of Oxford/AstraZeneca	Chimpanzee adenovirus-based vector	2	0, 28	IM	3
CanSino Biological Inc/ Beijing Institute of Biotechnology	Adenovirus type 5 vector	1		IM	2
Janssen Pharmaceutical	Adenovirus type 26-based vector	2	0, 56 days	IM	1/2
Merck (V590)	Chimeric vesicular stomatitis virus vector	1/2	TBD	IM, OM	P
Merck (V591)	Modified recombinant measles virus	1/2	TBD	IM	1/2

ID = intradermal; IM = intramuscular; LNP = lipid nanoparticle; OM = oral mucosa; P = preclinical; TBD = to be determined.

Table 2. COVID-19 Candidate Vaccine Landscape (entering phase 1/2 or later as of August 10, 2020) (Continued). Highlighted rows indicate vaccine candidates that are covered in detail in the following sections (World Health Organization 2020b)

Developer / Manufacturer	Type of Candidate Vaccine	Number of Doses	Timing of Doses	Route of Administration	Phase
Protein Subunit Vaccine Candidates					
Anhui Zhifei Longcom Biopharmaceutical/ Institute of Microbiology, Chinese Academy of Sciences	Adjuvanted recombinant receptor binding domain dimer	2 or 3	0, 28 or 0, 28, 56 days	IM	2
Novavax	Adjuvanted recombinant SARS CoV-2 glycoprotein nanoparticle	2	0, 21 days	IM	1/2
Kentucky Bioprocessing	Receptor binding domain-based	2	0, 21 days	IM	1/2
Whole Virus Vaccine Candidates					
Wuhan Institute of Biological Sciences/ Sinopharm	Inactivated	2	0, 14 or 0, 21 days	IM	3
Beijing Institute of Biological Sciences/ Sinopharm	Inactivated	2	0, 14 or 0, 21 days	IM	3
Sinovac	Inactivated	2	0, 14 days	IM	3
Institute of Medical Biology, Chinese Academy of Medical Sciences	Inactivated	2	0, 28 days	IM	2
Baharat Biotech	Inactivated	2	0, 14 days	IM	1/2

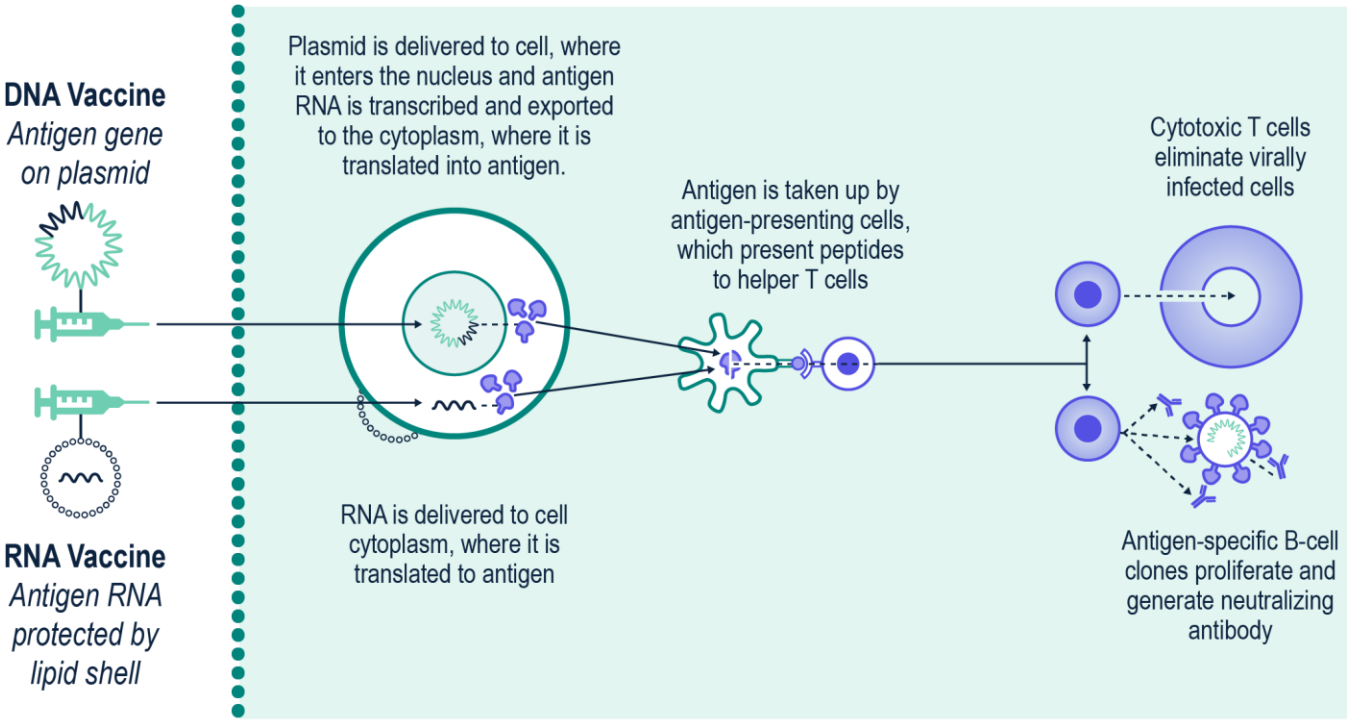
ID = intradermal; IM = intramuscular; LNP = lipid nanoparticle; OM = oral mucosa; P = preclinical; TBD = to be determined.

NUCLEIC ACID VACCINE CANDIDATES

MECHANISM

Both RNA-based and DNA-based nucleic acid vaccine platforms are under investigation for SARS-CoV-2 vaccination (Figure 3).

Figure 3. Mechanism of action for nucleic acid vaccines (Callaway 2020)



RNA Vaccines

Two approaches to RNA vaccines are being explored for SARS-CoV-2 vaccination (University of Cambridge 2020):

- Nonreplicating mRNA: mRNA (sometimes modified) coding for antigen is packaged and delivered to cells, which translate the mRNA into antigen
- Self-replicating mRNA vaccines: Antigen mRNA is packaged in with additional mRNAs coding for replicative enzymes resulting in more robust production of antigen mRNA and quantities of the antigen

At present, the most common way to package mRNAs for vaccines is in lipid nanoparticles. These nanoparticles protect the mRNA from degradation and may stimulate an immune response (Reichmuth 2016)

Table 3. Potential advantages and disadvantages of mRNA vaccines

Advantages (University of Cambridge 2020)	Disadvantages (University of Cambridge 2020)
• RNA vaccines are not made with whole pathogens and are not pathogenic, nor do they have the potential to become infectious • RNA does not integrate into host genomes and is quickly degraded by the host cell • RNA vaccines can be produced and scaled up rapidly	• Not a proven platform: No RNA vaccines have been licensed for use • The potential for the vaccine mRNA itself to elicit an immune reaction against the vaccine. This immune reaction can be dampened by incorporated non-natural nucleosides such as 1-methyl-pseudouridine • Free RNA is quickly degraded; various delivery technologies have been developed to deliver intact RNA to target cells, such as encapsulation in lipid nanoparticles • Like most vaccines, RNA vaccines must be frozen or refrigerated

DNA Vaccines

The mechanism of action of DNA vaccines is similar, but not identical, to that of RNA vaccines. DNA encoding the antigen of interest is inserted into a plasmid that is introduced into appropriate tissues (World Health Organization 2020a). The plasmid must enter the nucleus, where it is used as a template to produce mRNA transcripts that are exported from the nucleus and subsequently translated into the antigen of interest (Hobernik et al. 2018).

Several DNA vaccine candidates have been developed for human use, but none have been licensed. DNA-based vaccines have been approved in the United States and elsewhere for West Nile virus in horses and canine melanoma (Hobernik et al. 2018).

Table 4. Potential advantages and disadvantages of DNA vaccines

Advantages (Hobernik et al. 2018, Smith et al. 2020)	Disadvantages (Hobernik et al. 2018, Smith et al. 2020)
• Platform has been used for the development of animal vaccines • DNA vaccines are not made with whole pathogens and are not pathogenic, nor do they have the potential to become infectious • DNA vaccines can be developed and scaled up rapidly • Temperature stability (cold-chain free)	• Potential for integration of transferred DNA into the genome of recipient cells • Variable mucosal immunity and other immune responses • Some require special tools for delivery to the sub-dermal layer

MODERNA: mRNA-1273

Manufacturer	Moderna
Platform	LNP-encapsulated pseudouridine-modified mRNA
Number of Doses	2
Timing of Doses	0, 28 days
Route of Administration	Intramuscular
Current Phase*	3

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

mRNA-1273 is a lipid nanoparticle-encapsulated, nucleoside-modified mRNA-based vaccine candidate that encodes the SARS-CoV-2 spike (S) glycoprotein, stabilized in its prefusion conformation (S-2P) (Jackson et al. 2020).

KEY CLINICAL EVIDENCE

The results of a phase 1, dose-escalation, open-label trial were published in the *New England Journal of Medicine* in July 2020 (Jackson et al. 2020).

Design

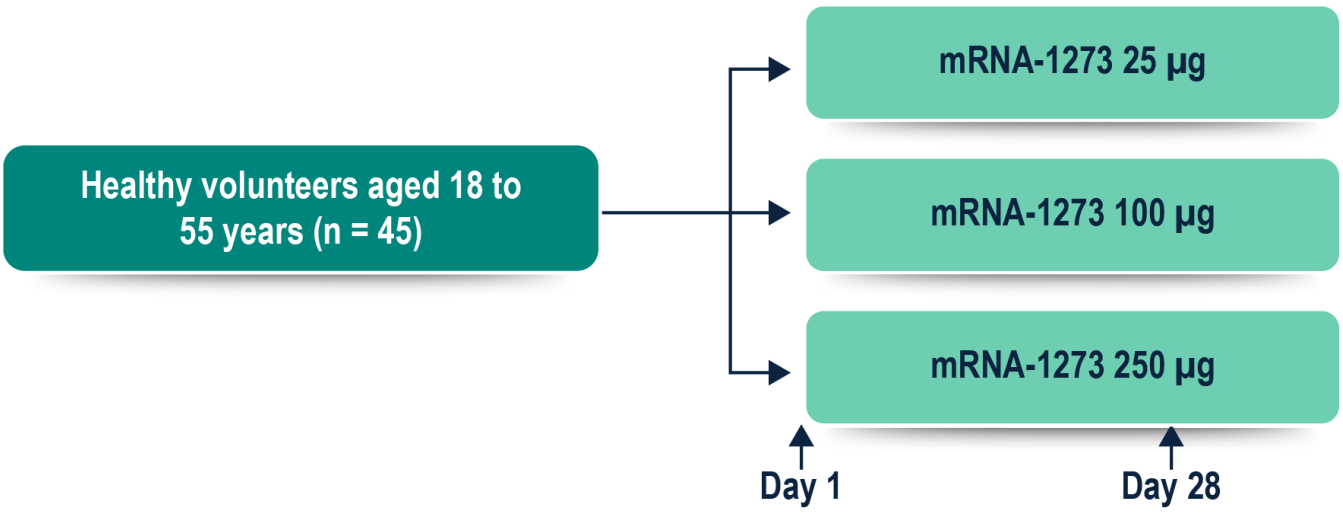
Subjects

- The trial enrolled 45 healthy adults aged 18 to 55 years at 2 centers in the United States. Subjects were not screened for SARS-CoV-2 infection prior to enrollment (Jackson et al. 2020).

Treatments

- All subjects were administered 2 injections of the trial vaccine 28 days apart at a dose of 25, 100, or 250 µg (Figure 4). On the basis of the results obtained in subjects at these dose levels, additional groups were added to the protocol, the results for which are expected to be reported in subsequent publications (Jackson et al. 2020).

Figure 4. Trial design



Outcomes

- Subjects recorded local and systemic reactions for 7 days after each vaccination (Jackson et al. 2020).
- Binding antibody responses were assessed by enzyme-linked immunosorbent assay (ELISA).
- Vaccine-induced neutralizing activity was assessed in a pseudotyped lentivirus reporter single-round-of-infection neutralization assay (PsVNA) and by live wild-type SARS-CoV-2 plaque reduction neutralizing testing assay ($PRNT_{80}$). Both assays were performed on specimens collected on days 1, 15, 29, 36, 43, and 57. For comparison, serum specimens from convalescent subjects were also tested (Jackson et al. 2020).
- T-cell responses were assessed on samples collected on days 1, 29, and 43 by an intracellular cytokine-staining assay (Jackson et al. 2020). No ELISpot data were reported in the publication.

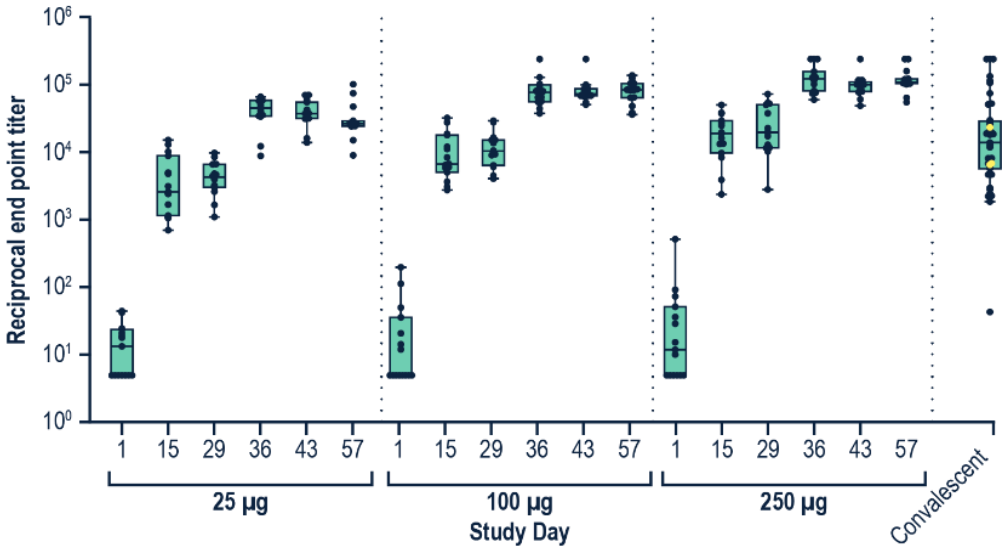
Results—Safety

- No serious adverse events occurred.
- Local adverse events, when present, were nearly all mild or moderate; pain at the injection site was common (Jackson et al. 2020).
- After the first vaccination, solicited systemic adverse events were reported in 33% to 67% of subjects, depending on group. All adverse events were mild or moderate in severity. Solicited systemic adverse events were more common after the second vaccination, occurring in 54% to 100% of subjects, depending on group. No events of fever were reported after the first vaccination; after the second, no participants in the 25-µg group, 40% in the 100-µg group, and 57% of subjects in the 250-µg group reported fever; one of the events was graded severe (Jackson et al. 2020).
- Note that the phase 3 study of this vaccine candidate, initiated in July 2020, is evaluating the 100-µg dose exclusively, likely due to the high rate of fever in the 250-µg group.

Results—Immunogenicity

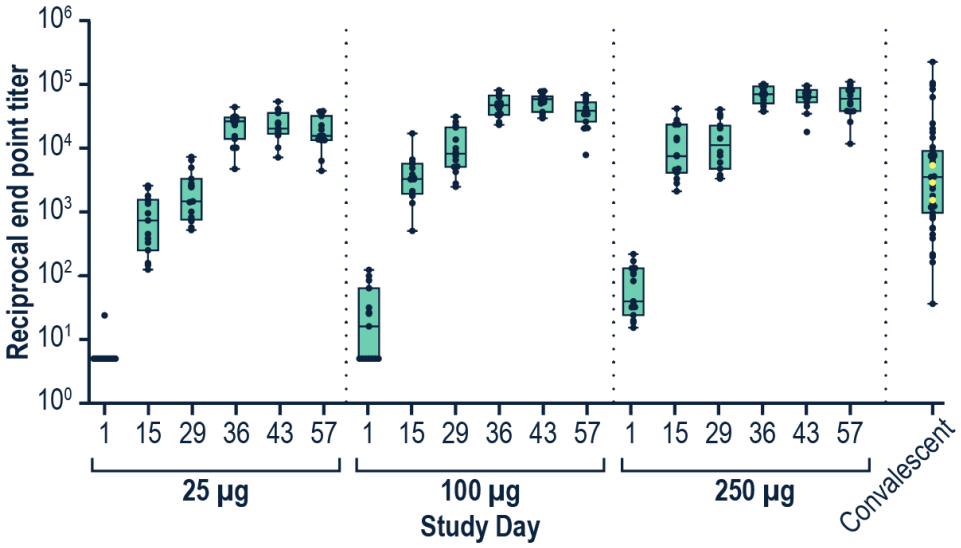
- Binding antibody responses increased with dose after the first vaccination. Binding antibody IgG geometric mean titers (GMTs) to the S-2P subunit of the spike protein increased rapidly after the first vaccination, with seroconversion in all participants by day 15 (Figure 5). The GMTs at day 57 exceeded that seen in convalescent specimens that were used for comparison. (Jackson et al. 2020).

Figure 5. Binding antibodies titers to S-2P subunit of spike protein (Jackson et al. 2020)



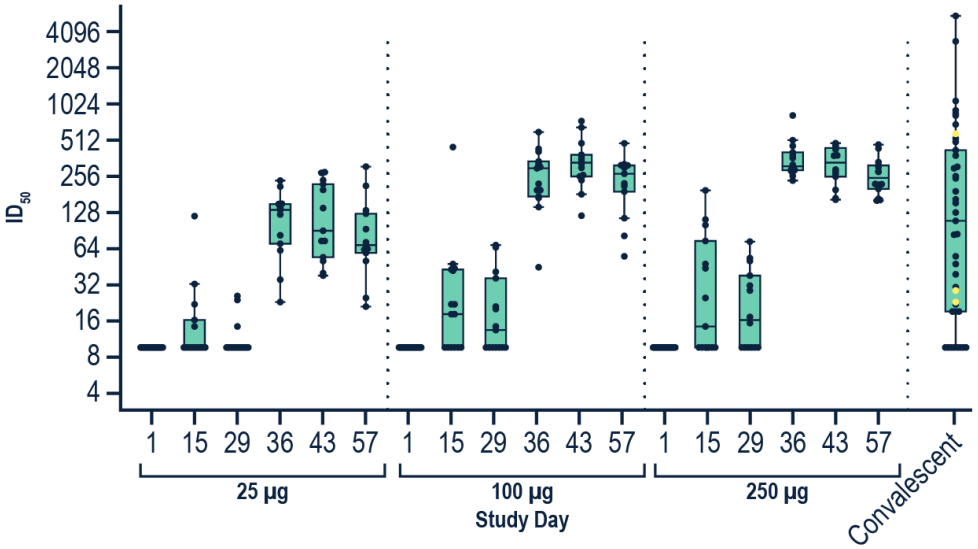
- Receptor-binding domain-specific antibody responses were similar in pattern and magnitude across doses, and met or exceeded the response seen with human convalescent serum (Figure 6) (Jackson et al. 2020).

Figure 6. Receptor-binding domain-specific titers (Jackson et al. 2020)



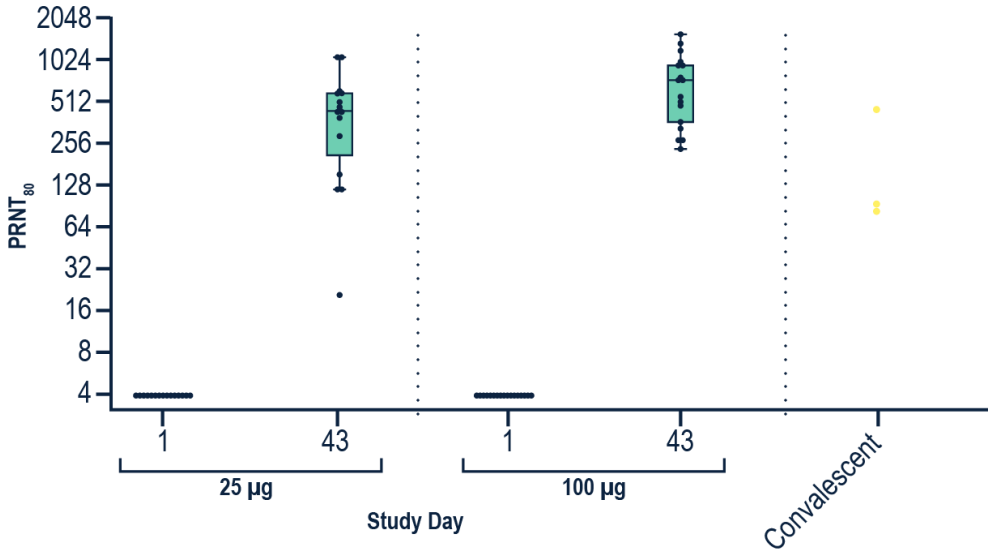
- Neutralization responses (as assessed by PsVNA) were detected in <50% of participants after the first vaccination; however, after the second vaccination, PsVNA responses were identified in serum samples from all participants, with lower responses in the 25-µg group at day 43 and comparable responses in the 100- and-250 µg groups (Figure 7) (Jackson et al. 2020).
- The responses in these groups were comparable to those seen in the upper half of the distribution of values for convalescent specimens (Jackson et al. 2020).

Figure 7. Pseudovirion Neutralization Assay (PsVNA) (Jackson et al. 2020)



- Wild-type virus-neutralizing activity capable of reducing SARS-CoV-2 infectivity by ≥80% ($PRNT_{80}$) was detected in all participants at day 43 and was generally at or above the value of the 3 convalescent serum specimens tested, with geometric mean $PRNT_{80}$ responses of 339.7 (95% CI, 184.0 to 627.1) in the 25-µg group and 654.3 (95% CI, 460.1 to 930.5) in the 100-µg group, as compared with 158.3 (95% CI 15.1-1663.0) with convalescent serum. (Figure 8) (Jackson et al. 2020).

Figure 8. Wild-type virus neutralizing activity capable of reducing SARS-CoV-2 infectivity by ≥80% ($PRNT_{80}$) (Jackson et al. 2020)



- Evaluation of T-cell responses was conducted on specimens 2 weeks after the last vaccination (in contrast, the Pfizer study, summarized below, reported data from 1 week after vaccination). Only flow cytometry data are reported in this publication. The 25-µg and 100-µg doses of the vaccine candidate elicited CD4 (helper) T-cell responses in approximately 0.1% of CD4 T cells, with a cytokine profile strongly biased toward Th1 cytokines, such as interferon-γ, interleukin (IL-2), and tumor necrosis factor (TNF), which is associated with less severe disease, with minimal Th2 cytokine (IL-4, IL-13) expression. Moderna demonstrated about 0.04% of CD8+ T cell responses on additional flow cytometry. (Jackson et al. 2020).

BIONTECH, PFIZER, FOSUN PHARMA: BNT162B1

Manufacturer	BioNTech, Pfizer, Fosun Pharma
Platform	LNP-encapsulated nucleoside-modified mRNA
Number of Doses	2
Timing of Doses	0, 21 days
Route of Administration	Intramuscular
Current Phase*	3

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

BNT162b1, which is being evaluated in a collaboration between Pfizer Inc, the German biotech company BioNTech, and the Chinese pharmaceutical company Fosun Pharma, is a nucleoside-modified RNA that encodes the receptor binding domain of the SARS-CoV-2 spike protein that is modified by the addition of a "foldon" trimerization domain that increases its immunogenicity. Like the Moderna vaccine candidate, it is formulated in lipid nanoparticles for efficient delivery into cells after intramuscular injection (Mulligan et al. 2020). A second candidate, BNT162b2, codes for the full-length spike protein. Pfizer and collaborators have made the decision to advance only this candidate into phase 3. Data related to BNT162b2 will be included in future updates.

KEY CLINICAL EVIDENCE

Early phase 1/2 data through day 14 after a second dose of BNT162b1 from a US-based study have been published as a preprint (Mulligan et al. 2020).

Design

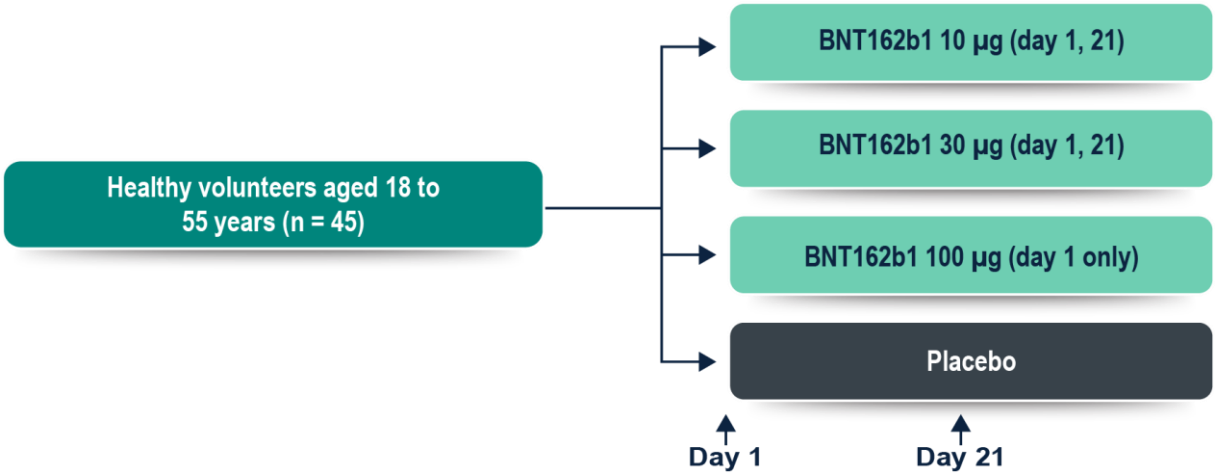
Subjects

- The trial enrolled 45 participants aged 18-55 years (Mulligan et al. 2020).

Treatments

- Twelve participants per dose level (10 µg and 30 µg) were vaccinated on days 1 and 21 and 12 received a 100-µg dose on day 1 (Figure 9). Nine participants received placebo (Mulligan et al. 2020).

Figure 9. Trial design



Outcomes

- Safety assessments included 30-minute to 4-hour observation after vaccination and self-reporting of prompted local reactions for 7 days after vaccination (Mulligan et al. 2020).
- Immunogenicity
  - RBD binding was assessed by ELISA (Mulligan et al. 2020).
  - SARS-CoV-2 neutralization was assessed using a strain of SARS-CoV-2 engineered with the insertion of a fluorescent reporter gene which aided in the detection and quantification of foci of infection in cell culture (Mulligan et al. 2020).

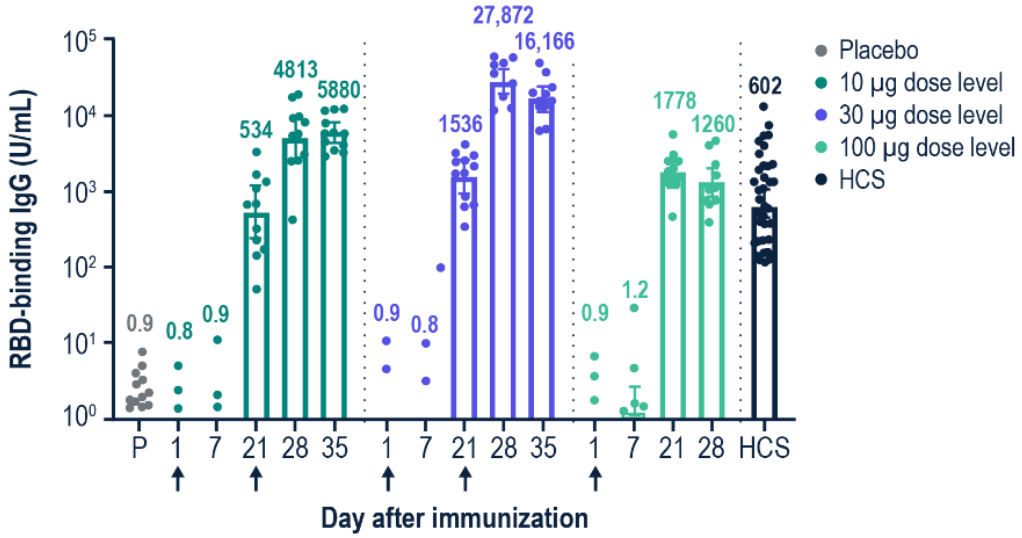
Results—Safety

- Local reactions (Mulligan et al. 2020):
  - In the 7 days following either dose 1 or 2, pain at the injection site was the most frequent solicited local adverse event, reported after dose 1 by 58.3% in the 10-µg, 100.0% in the 30-µg and 100-µg groups, and by 22.2% of placebo recipients.
  - After dose 2, pain was reported by 83.3% and 100.0% of BNT162b1 recipients at the 10-µg and 30-µg dose levels, respectively, and by 16.7 % of placebo recipients.
  - All local reactions were mild or moderate in severity except for one report of severe pain following dose 1 of 100 µg.
- Systemic reactions (Mulligan et al. 2020):
  - The most common systemic adverse events were mild to moderate fatigue and headache, which were more common in the vaccinated groups than the placebo group.
  - The rate of systemic adverse events increased with dose level.

Results—Immunogenicity

- Receptor binding domain (RBD)-binding IgG concentrations and SARS-CoV-2 neutralizing titers were assessed at baseline and at 7 and 21 days after the first dose and 7 (day 28) and 14 days (day 35) after the second dose of BNT162b1 and compared with RBD binding concentrations in convalescent serum. For all 3 dose levels, by 21 days after the first dose, geometric mean concentrations (GMCs) of RBD-binding IgG were 534-1778 U/mL (Figure 10) (Mulligan et al. 2020).
- At 14 days after the second dose, RBD-binding antibody concentrations were substantially greater among samples from vaccinated subjects (5880-16,166 U/mL) compared to those in convalescent serum (602 U/mL) (Figure 10) (Mulligan et al. 2020).

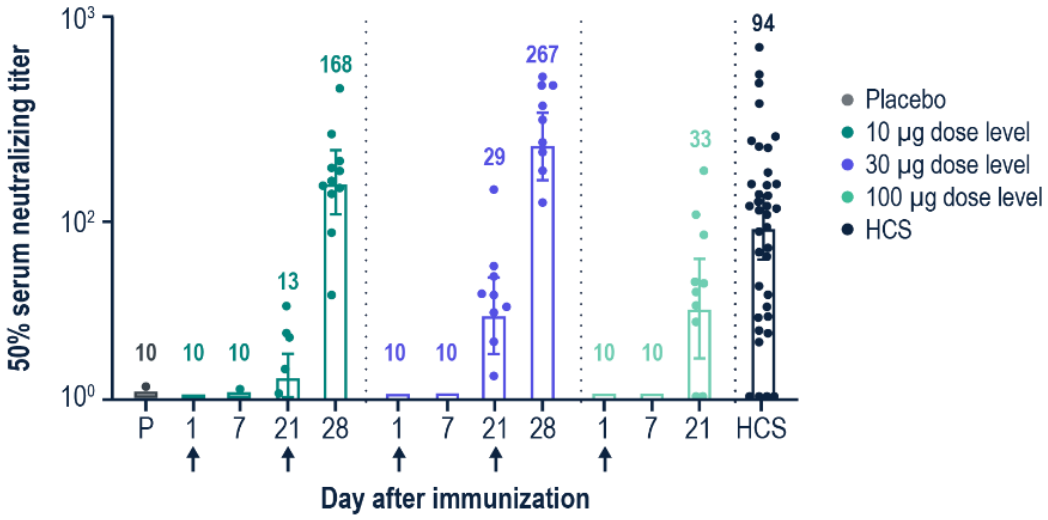
Figure 10. Receptor-binding domain (RBD) IgG through day 35 post-immunization (Mulligan et al. 2020)



HCS = human convalescent serum; RBD = receptor binding domain.

- Modest increases in neutralizing GMTs were observed 21 days after dose 1. Compared with the convalescent serum panel, significantly greater neutralizing GMTs were seen 7 days after the second 10 or 30 µg dose (Figure 11) (Mulligan et al. 2020).

Figure 11. 50% serum neutralizing titer through day 28 post-vaccination (Mulligan et al. 2020)



HCS = human convalescent serum.

KEY CLINICAL EVIDENCE —GERMAN STUDY

Selected results of a study of BNT162b1 conducted in Germany have been made available as a press release and a preprint focused on T-cell responses. The phase 1/2 study was conducted in 60 adults aged 18 to 55 years who received 1 µg (n = 12), 10 µg (n = 12), 30 µg (n = 12), or 50 µg (n = 12) doses of the vaccine candidate. Forty-eight subjects were vaccinated on day 1 and day 22 and 12 received a single injection of 60 µg (Pfizer Inc [press release] 2020; Sahin 2020).

- High, dose-dependent SARS-CoV-2 neutralizing titers and RBD-binding IgG concentrations were observed after the second dose. At day 43, neutralizing antibody titers ranged from 0.7-fold (1 µg) to 3.2-fold (50 µg) compared with human convalescent sera After the 30-µg dose, the serum neutralizing GMT was 308 (note that, in the US study, summarized above, it was 267) and 578 for the 50-µg dose. Notably, the 50-µg dose was considered too reactogenic, and the BNT162b2 candidate will be advanced into phase 3 at the 30-µg dose only.
- The vaccine had broad neutralizing activity across a panel of 16 SARS-CoV-2 RBD variants representing publicly available SARS-CoV-2 sequences, including against the newly dominant D614G strain
- High-level CD4+ and CD8+ T-cell responses against the SARS-CoV-2 RBD were observed. All subjects in the prime-boost cohorts, except for 2 at the lowest dose level, had CD4+ T cell responses
- The T-cell cytokine profile suggests a Th1 phenotype (which is associated with less severe disease) ELISpot data demonstrated <0.1% T-cells stimulated (note that in this evaluation, the investigators evaluated only the CD3+ subset of PBMCs, which constitute approximately 30% to 60% of PBMCs). On flow cytometry, the Pfizer candidate stimulated approximately 0.1% of CD4+ cells (IFN-γ and IL-2) but did not stimulate a Th2 response (IL-4). CD8+ T-cell responses were 0.07% (IL-2) to 1.0% (IFN-γ) one week after vaccination (which is likely when the peak response would be observed).
- Local and systemic events after immunization were dose-dependent, generally mild to moderate and transient, with occasional severe adverse events (grade 3; flu-like symptoms or injection-site reactions) that resolved spontaneously or could be managed with simple measures

INOVIO: INO-4800

Manufacturer	BioNTech, Pfizer, Fosun Pharma
Platform	LNP-encapsulated mRNA
Number of Doses	2
Timing of Doses	0, 28 days
Route of Administration	Intramuscular
Current Phase*	3

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

INO-4800 is a DNA-based plasmid vaccine candidate that is delivered intradermally using a proprietary, hand-held electroporation device (CELLECTRA®) (Inovio Pharmaceuticals [press release] 2020). Proof-of-concept for this strategy came from a phase 1, open-label, single-arm, dose-escalation study of an anti-Middle East respiratory syndrome coronavirus DNA vaccine candidate that demonstrated the development of durable (up to 1 year) immune responses in >85% of subjects (Modjarrad et al. 2019).

The company claims that the vaccine candidate is stable at room temperature for >1 year and does not require freezing for transport or storage (Inovio Pharmaceuticals [press release] 2020).

KEY CLINICAL EVIDENCE

Limited data from a press release are currently available for this vaccine candidate and must be interpreted with extreme caution.

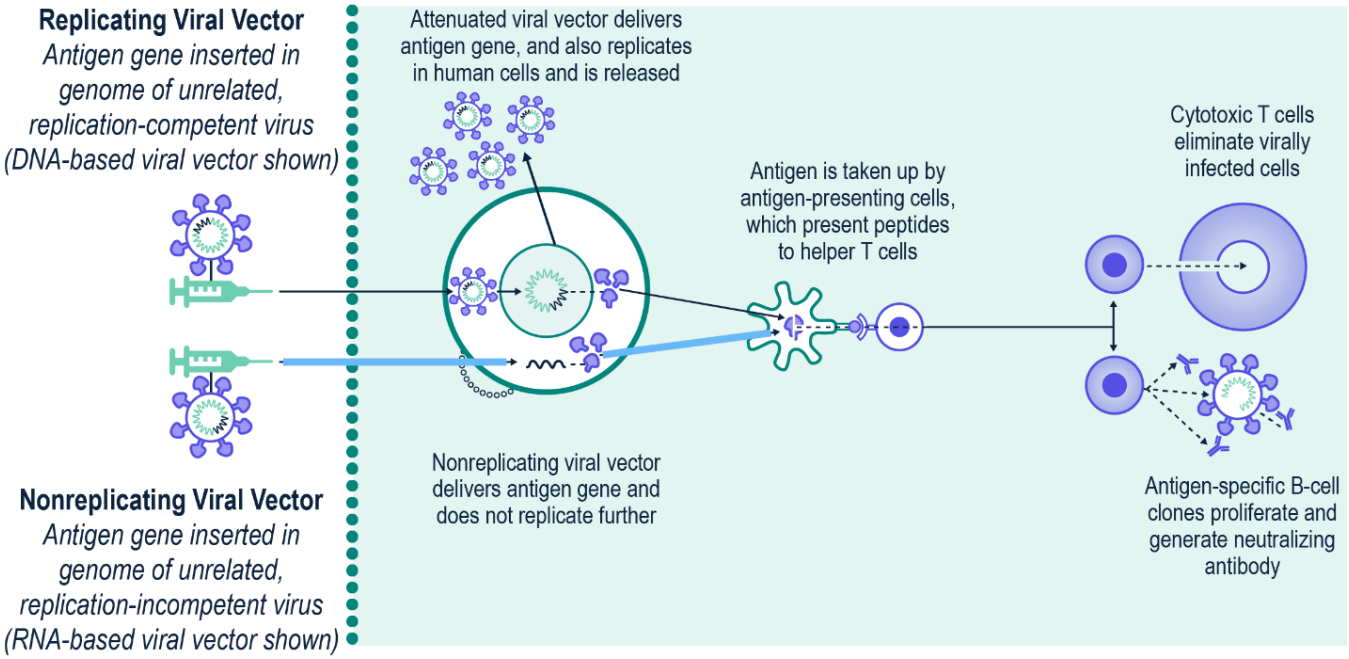
A phase 1 clinical trial of 40 healthy adult volunteers (age 18-50) in the United States randomized subjects to 1.0 and 2.0 mg dose cohorts who were administered 2 doses of INO-4800 4 weeks apart. According to the press release, the vaccine candidate was generally safe and well-tolerated; all 10 reported adverse events were grade 1 in severity, and most were local injection site redness (Inovio Pharmaceuticals [press release] 2020).

At the time the study was reported via press release, 94% of subjects "demonstrated overall immunological response rates based on preliminary data assessing humoral (binding and neutralizing) and T-cell immune responses" (Inovio Pharmaceuticals [press release] 2020). A phase 2/3 study has been initiated.

VIRAL VECTOR VACCINE CANDIDATES

Viral vector vaccines leverage a virus to deliver the gene for an antigen to target cells, which produce the antigen. These vaccines can be based on either replicating or nonreplicating viral vectors (Figure 12) (Callaway 2020).

Figure 12. Viral vector vaccines (Callaway 2020)



The most commonly used viral vectors for these vaccines include (Rauch et al. 2018):

- Adenovirus has a DNA genome. Adenovirus-based vaccines can be constructed as replication-competent or replication-defective vectors. Adenoviral vectors can induce potent antibody and T cell responses. Widespread pre-existing immunity to adenovirus is a major barrier to their use and has been addressed in some vaccines by using non-human-origin adenoviral vectors.
- Measles virus vaccines, which have an RNA genome, have been generated by serial passaging of infectious virus through different cell lines, resulting in a live attenuated virus that is replication deficient in humans. Because this process generates numerous mutations, reversion to pathogenicity has not been observed. The genome of this virus can accept inserts coding for antigens of up to 6000 bases. Recombinant measles viruses can produce high levels of both humoral and cellular immune responses against the transgene. Previous vaccination against measles does not appear to inhibit subsequent immune responses to measles-vectored viruses (Frantz 2018).
- Vesicular stomatitis virus has a single-stranded RNA genome. It naturally infects livestock, with only sporadic infections in humans, resulting in low risk for pre-existing immunity. Vesicular stomatitis virus is usually employed as an attenuated vector. The virus induces a robust neutralizing antibody response to antigens coded by inserted transgenes. Previous vaccination with vesicular stomatitis virus-vectored vaccines does not appear to inhibit subsequent immune responses to subsequent vesicular stomatitis virus-vectored vaccines (Marzi 2015)

Table 5. Potential advantages and disadvantages of viral vector vaccines (Funk et al. 2020)

Advantages (Funk et al. 2020)	Disadvantages (Funk et al. 2020)
• Some platforms have been extensively evaluated in the setting of gene therapy • Elicits a strong antibody and cellular response	• Risk for chromosomal integration and oncogenesis (DNA viruses) • Often contraindicated in immunocompromised patients, depending on degree and type of immunosuppression • Pre-existing antibodies to some vectors have been detected • Potential for inflammatory adverse reactions • Variable immunogenicity • Must be refrigerated or frozen

Relative to nucleic acid vaccines, the production of viral vector vaccines is complex. As viruses can undergo recombination during production, caution must be taken to keep cell cultures free of material that can lead to recombined virus. The presence of microorganisms or other contaminants that may be unintentionally introduced must be carefully assessed throughout the manufacturing process. The impact of pre-existing immunity to vectors based on viruses that naturally infect humans must also be considered (Rauch et al. 2018).

Both of Merck's vaccine candidates against SARS-CoV-2 rely on viral vector platforms.

- V590 is based on the chimeric vesicular stomatitis virus vaccine platform with some modifications, a proven methodology that was previously used to develop the Ebola virus vaccine, ERVEBO®.
- V591 is based on the modified Schwarz Measles genetic sequence and on the technique of creating recombinant viruses in cell culture originally developed by scientists at the Institut Pasteur and licensed to Themis, a company that was recently acquired by Merck.

Merck's COVID-19 vaccine candidates are currently in preclinical and early clinical (Phase 1/2) development. Additional information on these vaccine candidates will be provided in separate training.

AstraZeneca/University of Oxford: AZD1222 (Previously Known as ChAdOx1)

Manufacturer	AstraZeneca/University of Oxford
Platform	Nonreplicating adenovirus vector
Number of Doses	2
Timing of Doses	0, 28
Route of Administration	Intramuscular
Current Phase*	3

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

AZD1222 (previously known as ChAdOx1) consists of a replication-deficient simian adenovirus vector, ChAdOx1, containing the transgene coding for the full-length Spike protein of SARS-CoV-2 with a tissue plasminogen activator leader sequence. The transgene is codon optimized, a process in which the DNA sequence of the transgene is modified to improve translation of transgene RNA into protein in humans (Folegatti et al. 2020). This platform was previously developed to support vaccines against certain cancers and less acute viruses; by design it is intended to induce strong cellular immunity.

KEY CLINICAL EVIDENCE

The results of a phase 1/2, single-blind, randomized controlled trial were published in the *Lancet* in July 2020 (Folegatti et al. 2020).

Design

Subjects

The trial enrolled 1077 healthy adults aged 18 to 55 years with no history of laboratory-confirmed SARS-CoV-2 infection or of COVID-19-like symptoms (Folegatti et al. 2020).

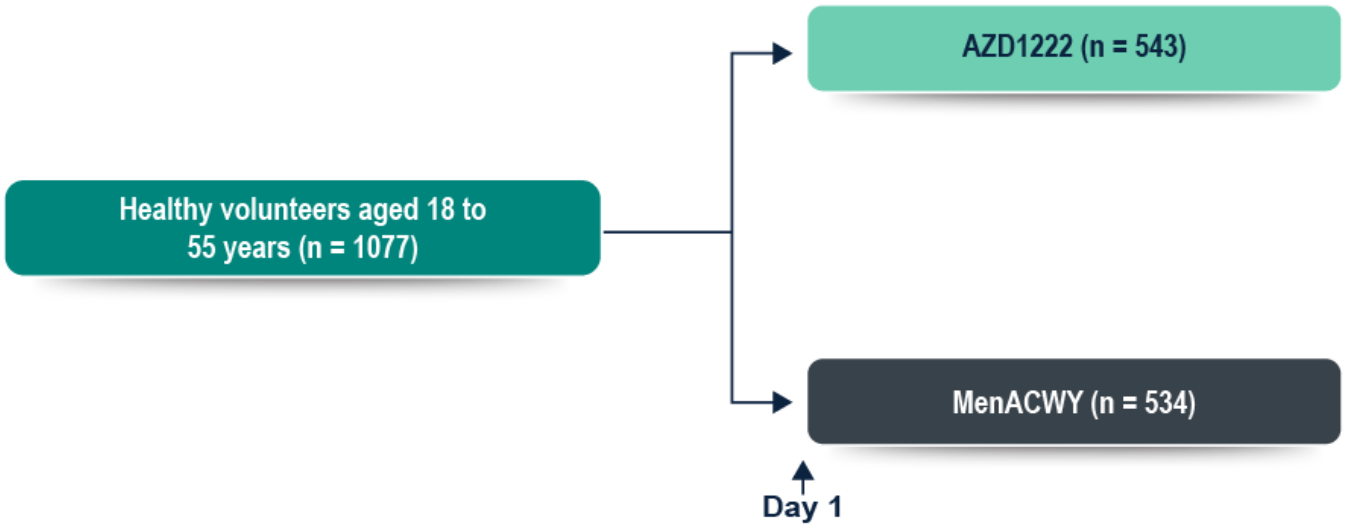
Treatments

Subjects were randomly assigned (1:1) to receive (Figure 13) (Folegatti et al. 2020):

- AZD1222
- The meningococcal disease vaccine MenACWY

A small (n = 10) group of subjects received a booster dose of AZD1222 28 days after the first dose (Folegatti et al. 2020).

Figure 13. Trial design (Folegatti et al. 2020)



- MenACWY was used as a comparator vaccine to maintain blinding of participants who experienced local or systemic reactions, since these reactions are a known association with viral vector vaccinations. Use of saline as a placebo would risk unblinding participants, as those who had notable reactions would know they were in the AZD1222 vaccine candidate group (Folegatti et al. 2020).

Outcomes

The coprimary outcomes were:

- Assess efficacy, as measured by cases of symptomatic confirmed COVID-19 (Folegatti et al. 2020).
- Assess safety as measured by the occurrence of serious adverse events.

Secondary outcomes included safety, reactogenicity, and immunogenicity profiles and efficacy against hospital-attended COVID-19, death, and seroconversion against non-spike proteins (Folegatti et al. 2020).

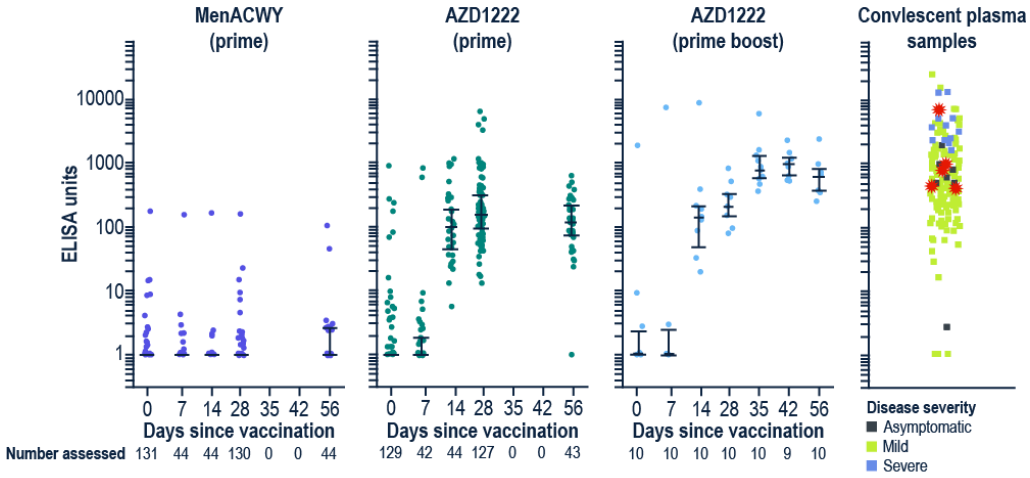
Results—Safety

- Among subjects who did not receive prophylactic acetaminophen, pain after vaccination (mostly mild or moderate in intensity) and tenderness (mostly mild in intensity) was reported by 67% and 83% of subjects who received AZD1222, respectively, and 38% and 58% of those who received MenACWY, respectively (Folegatti et al. 2020).
- Fatigue (70% vs 48% with control) and headache (68% vs 41% with control) were the most commonly reported systemic reactions (Folegatti et al. 2020). Other systemic adverse reactions that were common in the AZD1222 group included muscle ache (60%), malaise (61%), chills (56%), and feeling feverish (51%). Eighteen percent of subjects reported a temperature of ≥38° C (Folegatti et al. 2020).
- Rates of adverse events were generally lower when prophylactic acetaminophen was administered, with significant reductions in pain, feeling feverish, chills, muscle ache, headache, and malaise (Folegatti et al. 2020).

Results—Immunogenicity

- In the AZD1222 group, antibodies against the spike protein, as detected with ELISA, peaked by day 28 and remained elevated to day 56 in participants who received 1 dose; among the 10 subjects who received a booster dose, there was a further increase in antibodies at day 56 (Figure 14) (Folegatti et al. 2020).

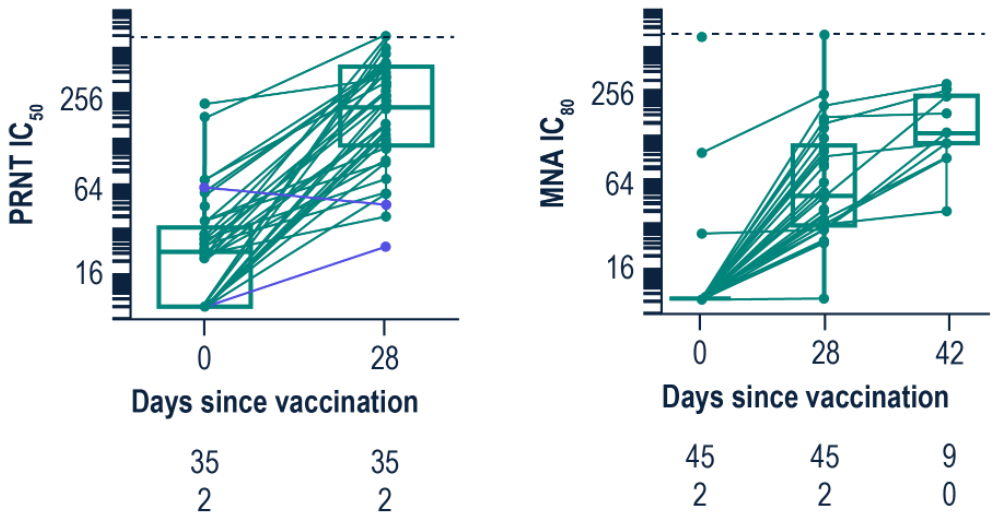
Figure 14. SARS-CoV-2 IgG response by ELISA to spike protein (Folegatti et al. 2020)



ELISA = enzyme-linked immunosorbent assay

- By $PRNT_{50}$ assay, 100% of the 35 subjects in whom neutralizing antibodies were evaluated achieved 50% neutralizing titers (median titer, 218 [IQR 122-395]) at day 28 after a single dose (Figure 15, left). Note that only $PRNT_{50}$ data at day 28 after the first dose was published; no data are available for subjects who received the booster.
- The PHE microneutralization $(MNA)_{80}$ assay evaluated only RBD neutralization (not to the full spike protein). In this assay, titers inducing 80% virus neutralization were achieved at day 28 in 91% of 35 subjects who received 1 dose (median titer, 51 [IQR 32-103]). Titers inducing 80% virus neutralization were achieved at day 42 in 100% of 9 subjects who received the booster dose (median titer, 136 [IQR 115-241]) (Figure 15, right). (Folegatti et al. 2020).

Figure 15. Development of SARS-CoV-2 neutralizing antibodies by (left) PRNT (IC_{50}) (after a single dose) and (right) MNA (IC_{80}) (after the first dose and booster) (Folegatti et al. 2020)

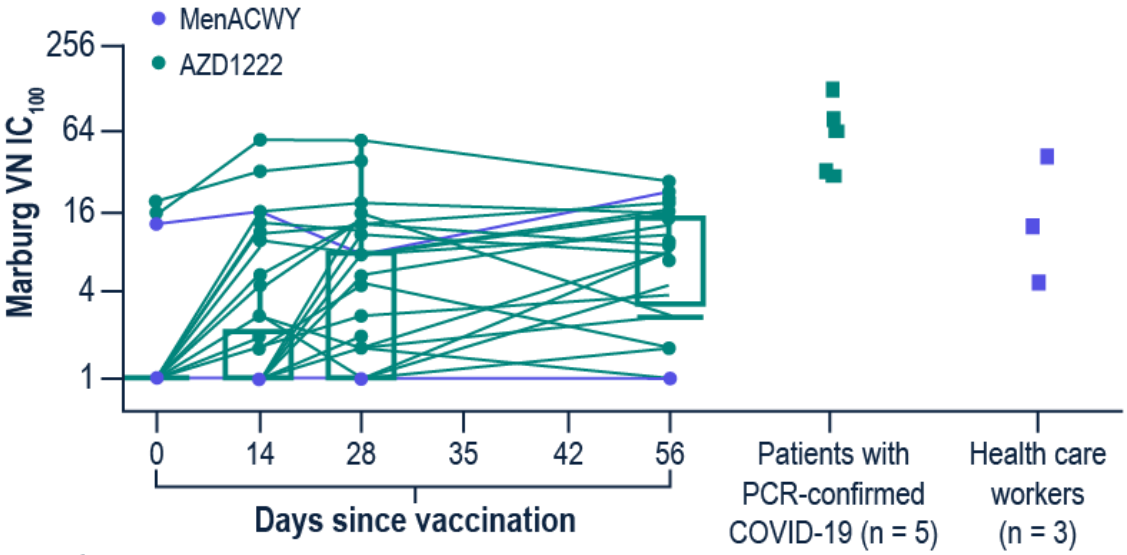


PRNT = plaque reduction neutralization test; MNA = microneutralization assay.

- The Marburg VN assay is a cytopathic effect assay, which measures <u>any</u> observable effect and is thus different from a traditional PRNT assay. In this assay, 62% of 37 subjects had neutralizing antibodies that induced complete inhibition of the cytopathic effect of SARS- CoV-2 by day 56 after 1 dose, as did 100% of the 10 subjects who received a booster dose (Figure 16) (Folegatti et al. 2020).

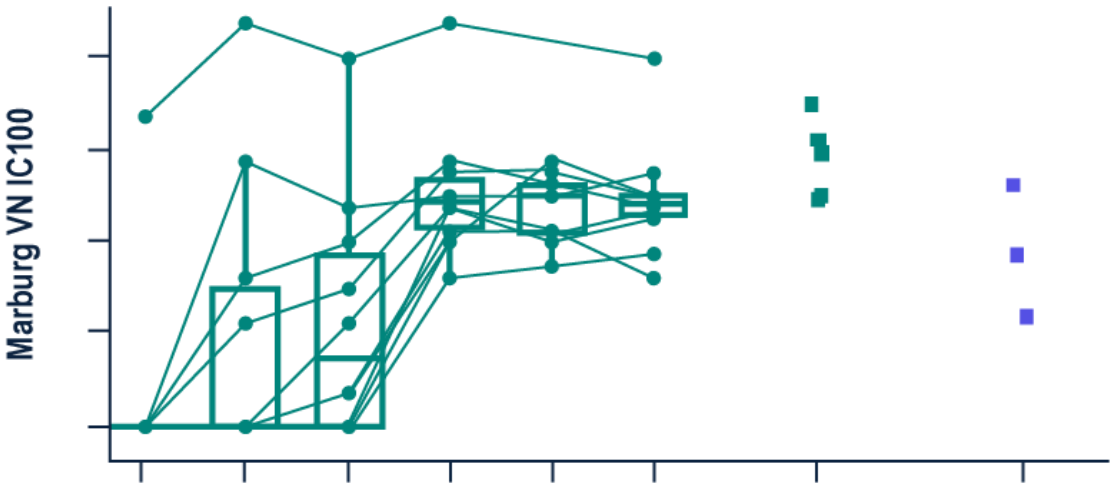
Figure 16. SARS-CoV-2 100% neutralization after initial dose (Marburg VN assay) (Folegatti et al. 2020)

Prime



Number assessed								
AZD1222	44	44	44	0	0	37	..	..
MenACWY	44	44	43	0	0	25	..	..

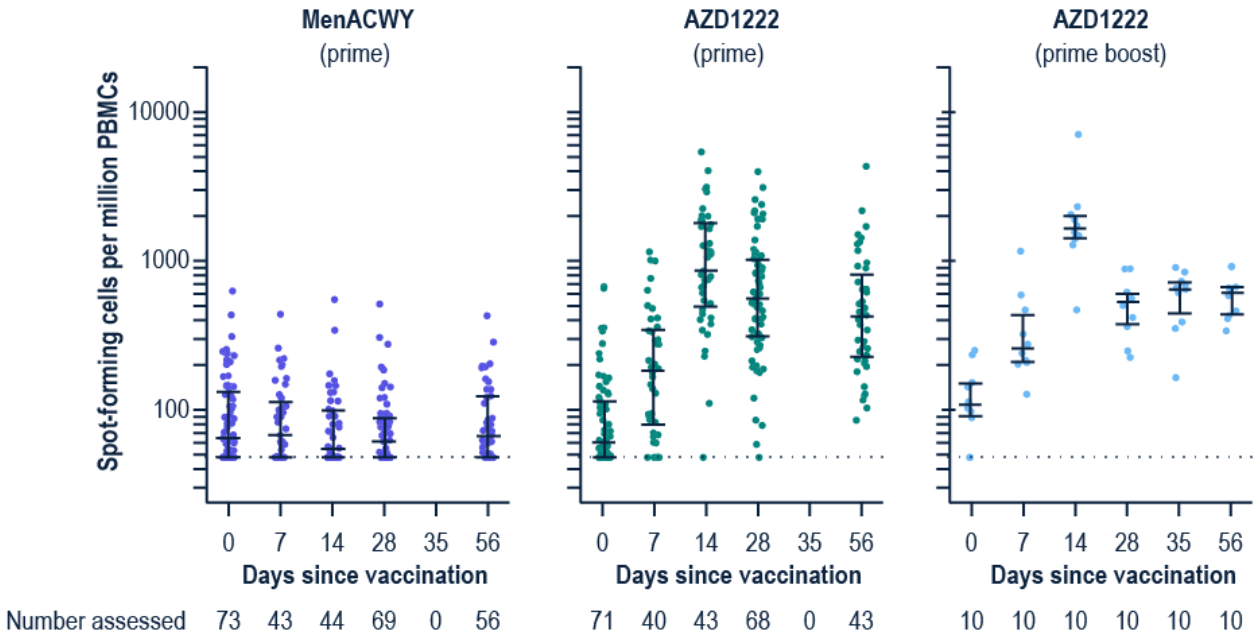
Prime Boost



	10	10	10	10	9	10	..	..
	..	..	..	..	..	..	..	..

- AZD1222 resulted in marked increases in SARS-CoV-2 spike-specific effector T-cell responses as early as day 7 that peaked at day 14 at 856 spot-forming cells/million PBMCs (0.09%) and subsequently declined to 424 spot-forming cells/million PBMCs (0.04%) by day 56 after vaccination (Figure 17) (Folegatti et al. 2020). A boost in cellular responses was not observed following the second dose of the vaccine candidate, consistent with previous data on viral vector vaccines that showed no effect with a homologous prime-boost regimen. Note that, in contrast to the assays conducted by Pfizer (discussed above), this assay was conducted on total PBMCs, instead of the CD3+ subset of PBMCs. Thus, the result is artificially low compared to the assay used in the Pfizer study. The authors did not report data for CD4+ and CD8+ cells separately.

Figure 17. Interferon-gamma ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine candidate insert (Folegatti et al. 2020)



PBMC = peripheral blood mononuclear cells.

Prevalence and Impact of Preexisting Antibodies to AZD1222

- Before vaccination, only 1 patient of the 98 who were tested had high-titer neutralizing antibodies against AZD1222. Antibodies were detectable at a lower level in 18 subjects. There was no relationship between anti-AZD1222 neutralizing antibodies and ELISA titer to SARS-CoV-2 spike protein (Folegatti et al. 2020).

CanSino Biological Inc

Manufacturer	CanSino Biological, Inc
Platform	Nonreplicating adenovirus vector
Number of Doses	1
Timing of Doses	Day 0
Route of Administration	Intramuscular
Current Phase*	2

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

The vaccine candidate is a replication-defective adenovirus 5 (Ad5) vector expressing the full-length spike gene (Zhu et al. 2020).

KEY CLINICAL EVIDENCE

A randomized, double-blind, single-center placebo-controlled phase 2 trial was published in the *Lancet* in July 2020 (Zhu et al. 2020).

Design

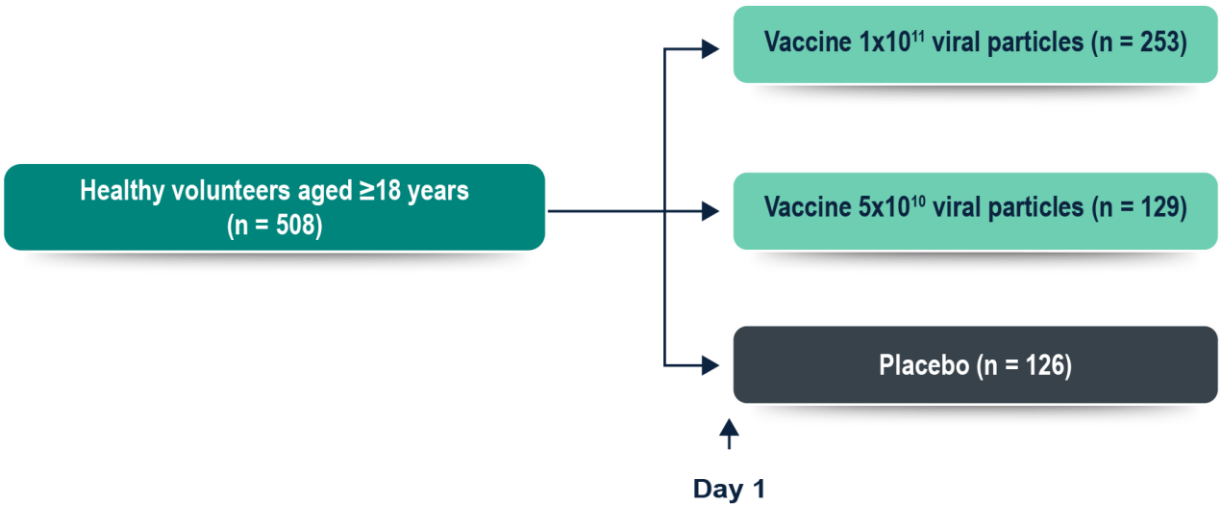
Subjects

The trial included 508 participants aged ≥18 years (Zhu et al. 2020).

Treatments

Subjects were randomized in a 2:1:1 ratio to a single dose of the vaccine candidate at 1 x 10^{11} viral particles/dose, the vaccine at 5 x 10^{10} viral particles/dose, or placebo (the type of placebo is not specified but was likely saline) (Figure 18) (Zhu et al. 2020).

Figure 18. Trial design (Zhu et al. 2020)



Outcomes

The primary objectives were to evaluate immunogenicity and safety and to determine a candidate vaccine dose for a phase 3 efficacy study (Zhu et al. 2020).

- The primary endpoint for safety evaluation was the incidence of adverse reactions within 14 days of injection.
- The primary endpoint for efficacy evaluation were the GMTs of receptor-binding domain (RBD)-specific ELISA antibody responses and neutralizing antibody responses against live virus or pseudovirus at 28 days post-vaccination

Results—Safety

- At 14 days post-vaccination, ≥1 solicited adverse reactions were reported in 72% of subjects in the 1×10^{11} viral particles dose group, 74% of the 5×10^{10} viral particles dose group, and 37% of the placebo group ($P < 0.001$) (Zhu et al. 2020).

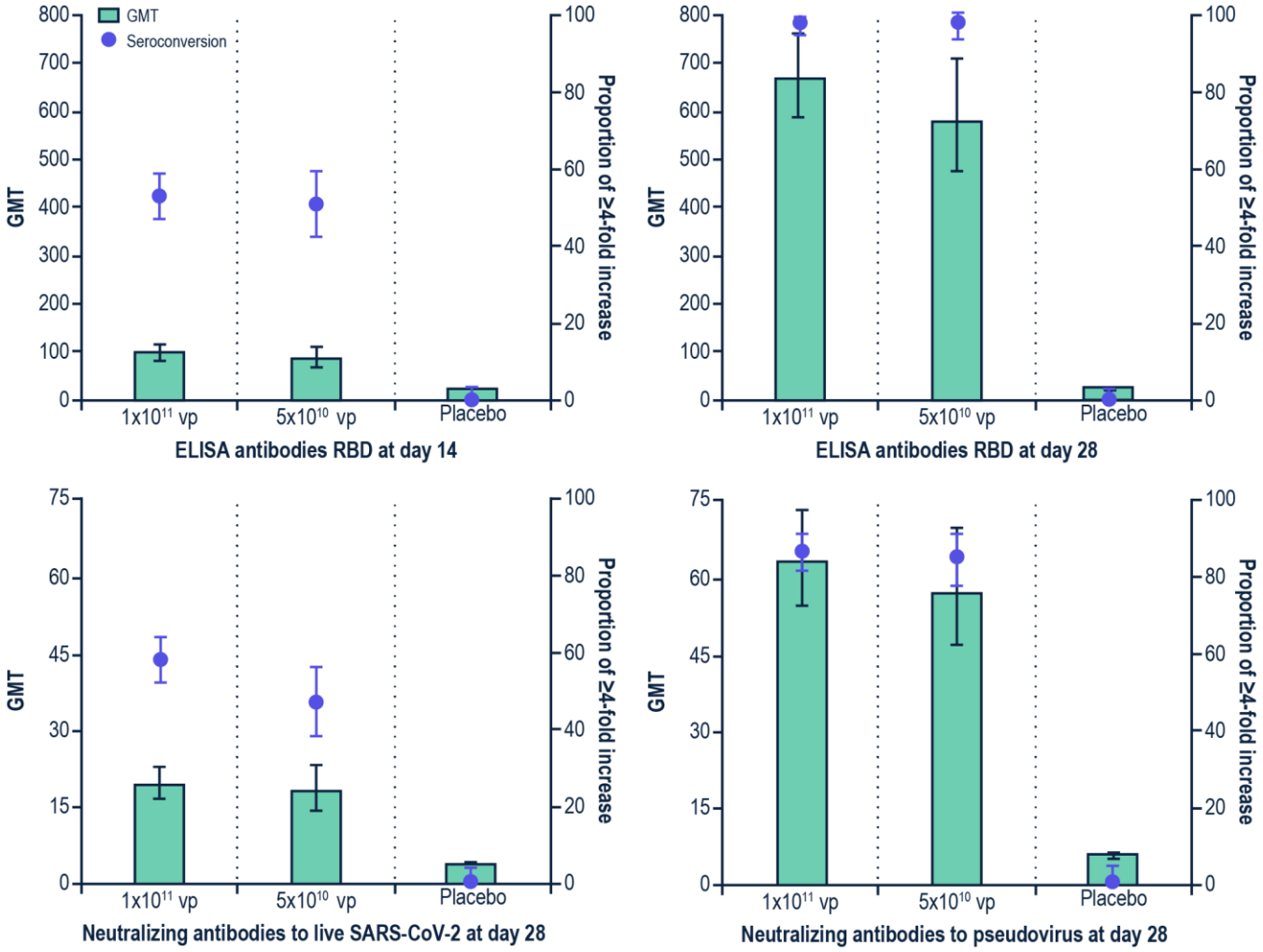
- The most common systemic solicited reactions in the 1×10^{11} and 5×10^{10} viral particles dose groups were fatigue, reported by 34% and 42%; fever, reported by 16% and 32%; and headache, reported by 28% and 29%, respectively.

- The most common injection site solicited reaction was pain, reported by 57% of the 1×10^{11} viral particles dose group and 56% of the 5×10^{10} viral particles dose group (Zhu et al. 2020).
- Grade 3 adverse reactions occurred in 9% of subjects in the 1×10^{11} viral particles group vs 1% of those in the 5×10^{10} viral particles group and 0% in the placebo group. The most commonly reported grade 3 adverse reaction was fever (in 8% and 1% of the candidate vaccine groups, respectively) (Zhu et al. 2020).

Results—Immunogenicity

- RBD-specific antibody responses, as detected by ELISA, were observed from day 14 onwards, with GMTs of 94.5 (95% CI 80.5-110.8) and 85.1 (66.0-109.7) in the $1x10^{11}$ and $5x10^{10}$ viral particles dose groups, respectively (Figure 19). At day 28, RBD-specific ELISA antibodies peaked at 656.5 (95% CI 575.2-749.2) in the $1x10^{11}$ viral particles dose group and 571.0 (95% CI 467.6-697.3) in the $5x10^{10}$ viral particles dose group (Zhu et al. 2020).
- Subjects in both dose groups showed seroconversion to RBD-specific ELISA antibodies at day 28 (97% in the 1 x 10^{11} viral particles dose group and 96% in the 5 x 10^{10} group), whereas participants in the placebo group showed no antibody response from baseline (Zhu et al. 2020).
- Seroconversion of the neutralizing antibody responses to live SARS-CoV-2 occurred in 59% of participants receiving the 1 × 10^{11} viral particles dose, and 47% of participants receiving the 5 × 10^{10} viral particles dose (Zhu et al. 2020).

Figure 19. Specific antibody responses to the receptor-binding domain and neutralizing antibodies to live SARS-CoV-2 and pseudovirus after vaccination (Zhu et al. 2020)



ELISA = enzyme-linked immunosorbent assay; GMT = geometric mean titer; vp = viral particles.

- The candidate vaccine induced significant T-cell responses in 90% of subjects receiving the 1 x 10^{11} dose and 88% of those receiving the 5 x 10^{10} viral particles dose (Zhu et al. 2020).

Results—Predictors of Immunogenicity

- Prior to vaccination, 52% of the 508 participants who were tested had high pre-existing anti-Ad5 neutralizing antibodies (Zhu et al. 2020). ELISA antibody and neutralizing antibody levels were approximately 2-fold higher in participants with low pre-existing Ad5 antibodies (Zhu et al. 2020).
- Increasing age negatively impacted RBD-specific ELISA antibody ($P = 0.0018$) and neutralizing antibody responses to live virus ($P < 0.0001$) or pseudovirus ($P = 0.046$); the relationship with age may reflect the higher probability of previous Ad5 exposure in older patients. (Zhu et al. 2020).

PROTEIN SUBUNIT VACCINE CANDIDATES

The risks associated with attenuated or killed whole-organism viruses (discussed below) can be at least partly avoided with a strategy that uses only specific, purified macromolecules, such as recombinant protein antigens, derived from the pathogen, or virus-like particles (Figure 20) (Owen et al. 2013). Protein subunit-based vaccines may require adjuvants to elicit an appropriate protective immune response (National Institutes of Health 2020).

Figure 20. Protein subunit vaccines (Callaway 2020)

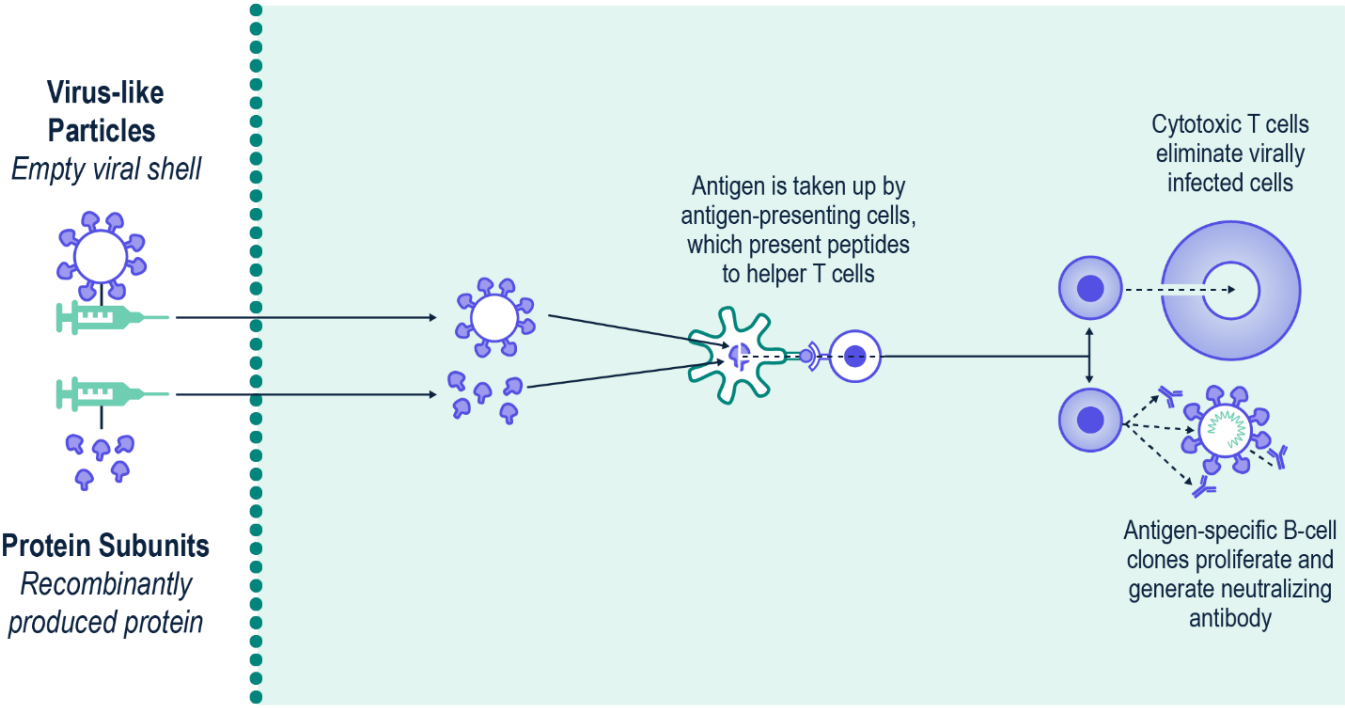


Table 6. Potential advantages and disadvantages of protein vaccines (Funk et al. 2020)

Advantages (Funk et al. 2020)	Disadvantages (Funk et al. 2020)
• Proven platform • No handling of infectious material • Strong antibody response	• May require adjuvants • Scale up of manufacturing can be challenging • Post-translational modifications of recombinant protein may not match those present on native virus

NovaVax

Manufacturer	NovaVax
Platform	Full-length recombinant SARS-CoV-2 spike glycoprotein nanoparticle candidate vaccine adjuvanted with Matrix M
Number of Doses	2
Timing of Doses	0, 21
Route of Administration	Intramuscular
Current Phase*	1/2

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

NVX-CoV2373 is a recombinant nanoparticle vaccine candidate composed of trimeric full-length SARS-CoV-2 spike glycoproteins, the sequences of which are mutated to confer protease resistance and to stabilize the construct in the prefusion conformation. It is produced in insect cells using a baculovirus Sf9 system (Coleman et al. 2014, Keech et al. 2020).

The nanoparticle is composed only of viral particles, without other potentially immunogenic viral proteins or remnants from the cell culture system (Coleman et al. 2014). The nanoparticle is mixed with a proprietary saponin-based "Matrix-M1" adjuvant, derived from the bark of the tree *Quillaja saponins* and formulated with cholesterol and phospholipids into nanoparticles, to enhance immune responsiveness (Keech et al. 2020, Magnusson et al. 2018).

KEY CLINICAL EVIDENCE

Data from a phase 1 trial are available as a preprint that has not been peer reviewed (Keech et al. 2020). Results are summarized as presented in the preprint, but these data must be interpreted with extreme caution.

Design

Subjects

The trial enrolled healthy subjects aged 18 to 59 years (Keech et al. 2020).

Treatments

Subjects were randomized to 2 injections of placebo or 2 injections of NVX-CoV2373 dosing regimens (Table 7) (Keech et al. 2020).

Table 7. Vaccine regimens in a phase 1 trial of NVX-CoV2373 (Keech et al. 2020)

	Participants		Day 0		Day 21	
	Randomized	Sentinel	Vaccine (µg)	Adjuvant (µg)	Vaccine (µg)	Adjuvant (µg)
A	25		0	0	0	0
B	25		25	0	25	0
C	25	3	5	50	5	50
D	25	3	25	50	25	50
E	25		25	50	0	0

Outcomes

Subjects were observed for ≥30 minutes after each vaccination for assessment of solicited reactogenicity and were asked to continue monitoring for events at home for 7 days (Keech et al. 2020).

Immunogenicity assessments included (Keech et al. 2020):

- Anti-spike IgG ELISA (days 0, 7, 21, 28, 35)
- Wild-type virus microneutralization assay with an inhibitory concentration of >99% (MN IC>99) (days 0, 21, 35). Note that this is a cytopathic effect assay and is different from a standard PRNT assay.

Immunogenicity results were compared with a control panel of 32 convalescent serum specimens.

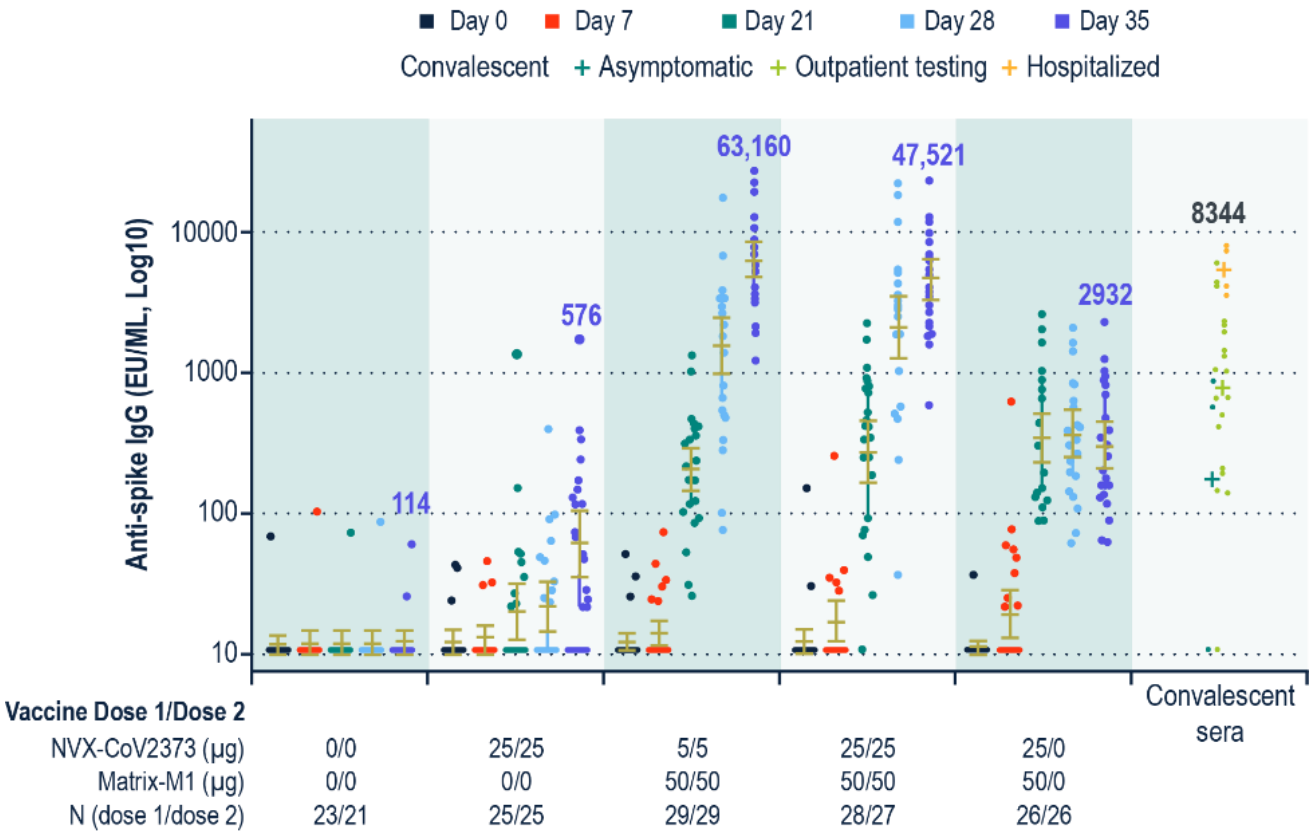
Results—Safety

- The rate of grade 1 or greater solicited local adverse events ranged from 32% for the no-adjuvant regimen to 80% for Group E (25 µg/50 µg). The majority of these were mild and none were severe; pain and tenderness were the most common local adverse reactions (Keech et al. 2020).
- Systemic adverse events most commonly included headache, fatigue, and myalgia.
- Two subjects had severe events following the first vaccination and 8 following the second vaccination, none of which required medical intervention or resulted in withdrawal from the study (Keech et al. 2020).

Results—Immunogenicity

- Robust immunologic responses by anti-spike ELISA (in geometric mean ELISA units [GMEUs]) were seen for all of the adjuvanted NVX-CoV2373 regimens relative to the unadjuvanted regimen (Figure 21). Geometric mean fold rises (GMFR) exceeded those induced by the unadjuvanted vaccine by >10-fold.
- Within 7 days of the second vaccination, GMEUs in the adjuvanted groups increased an additional 8-fold over responses seen with the first vaccination, and at 14 days, GMEUs increased another 2-fold, ultimately achieving 100-fold higher GMFRs over those seen with unadjuvanted NVX-CoV2373.
- A single injection of the adjuvanted vaccine achieved similar GMEU levels as asymptomatic COVID-19 subjects and the second injected resulted in levels similar to that of convalescent serum from hospitalized subjects (Keech et al. 2020).

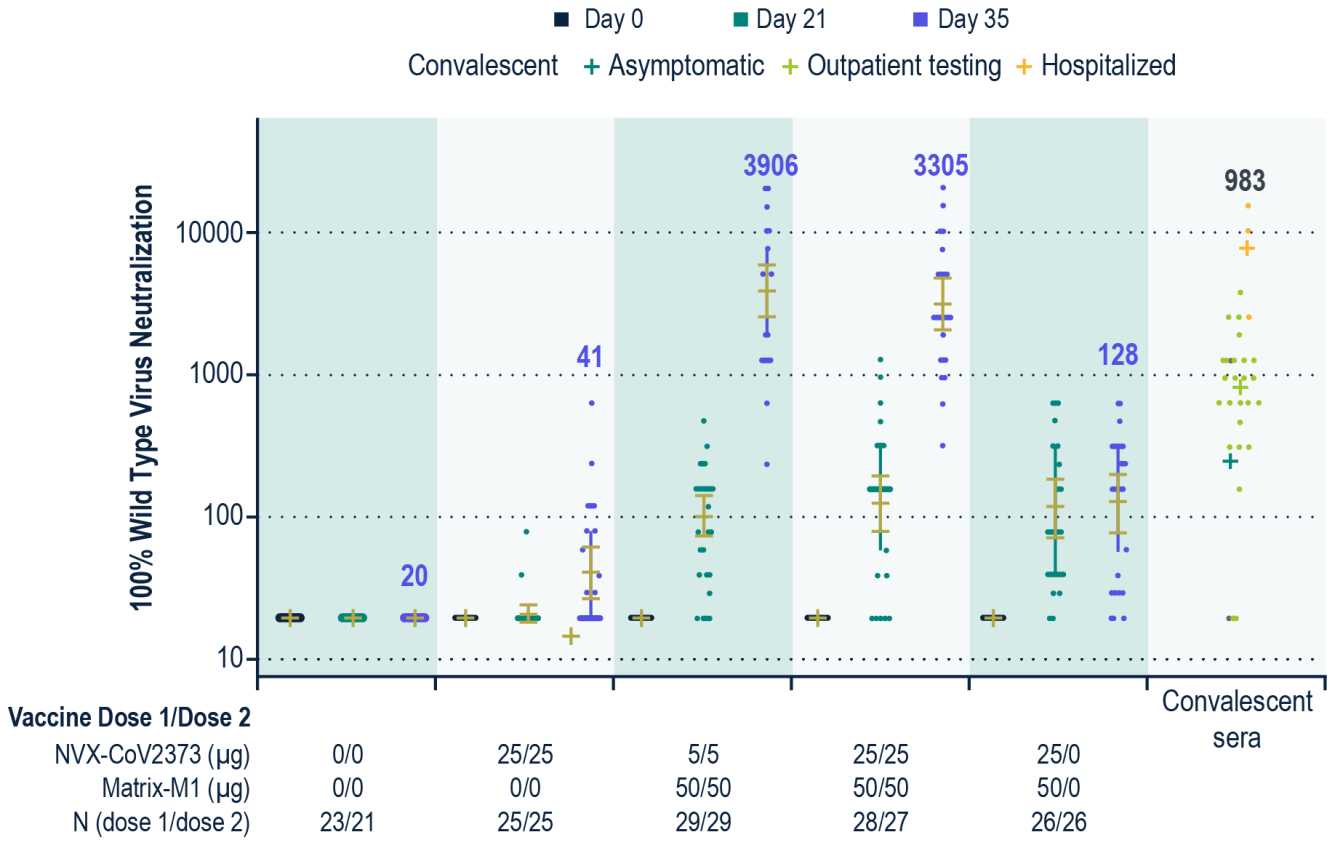
Figure 21. Geometric mean anti-spike IgG ELISA results (Keech et al. 2020)



ELISA = enzyme-linked immunosorbent assay; EU = ELISA units.

- Neutralizing antibody titers followed a similar pattern, with MN IC>99 titers most pronounced for the adjuvanted vaccine candidates (Figure 22) (Keech et al. 2020).
  - After the first vaccination, GMFRs were approximately 5-fold greater for adjuvanted candidates than nonadjuvanted candidates.
  - Second vaccinations with adjuvanted vaccine candidates resulted in a >100-fold rise over single vaccinations without adjuvant (Keech et al. 2020).
- When compared with convalescent serum, second vaccinations with the adjuvanted vaccine candidates resulted in GMT levels 4-fold greater than outpatient-treated COVID-19 subjects and levels similar to that seen in convalescent serum from subjects hospitalized with COVID-19 (Keech et al. 2020).

Figure 22. Wild-type SARS-CoV-2 microneutralization assay at inhibitory concentration >99% (MN IC>99) titer responses (Keech et al. 2020)

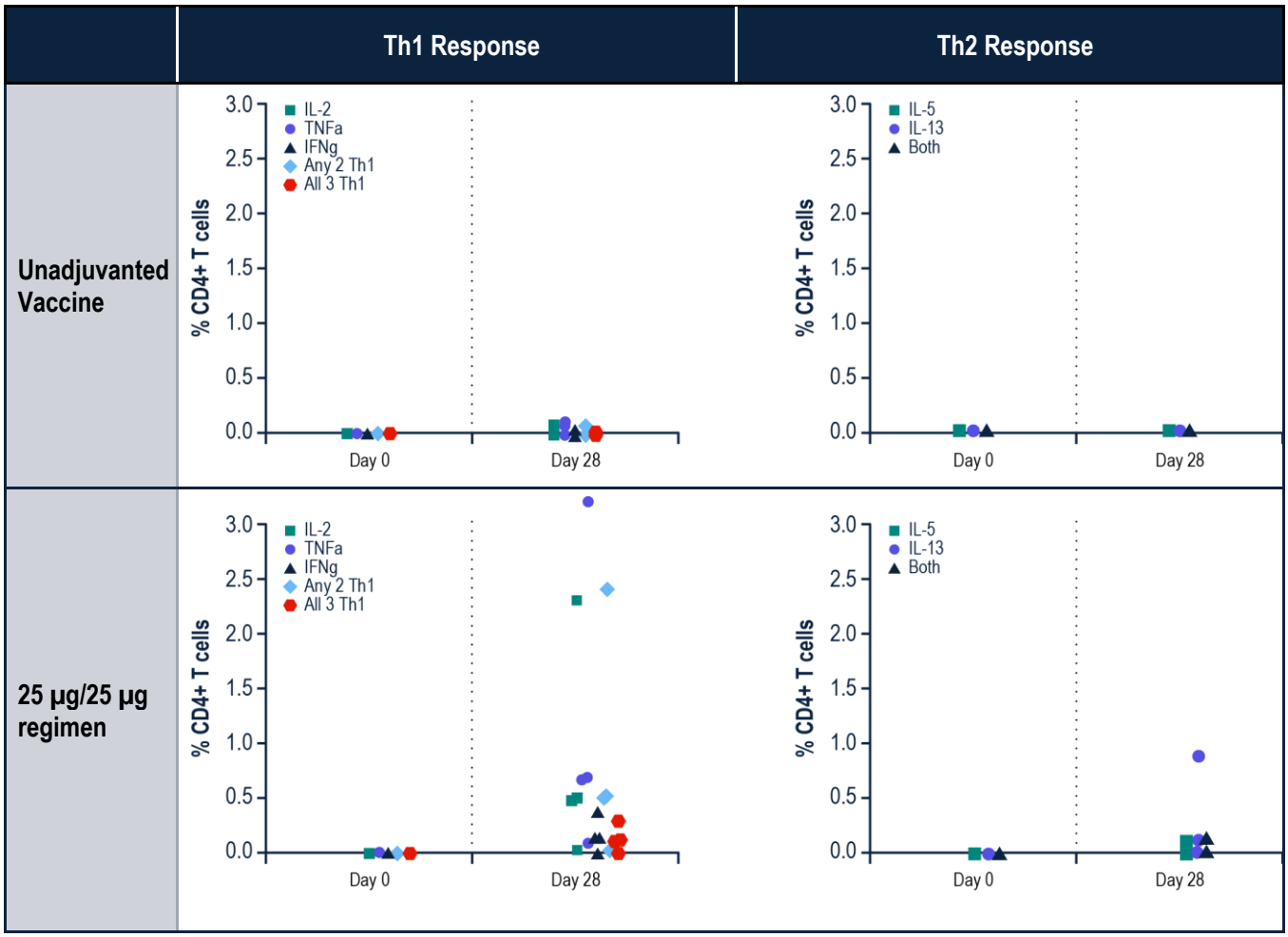


ELISA = enzyme-linked immunosorbent assay.

T-cell responses were evaluated in 16 participants randomly selected from Groups A through D (Figure 23). The assay is represented as the percentage of T cells.

- Adjuvanted vaccine induced antigen-specific polyfunctional CD4+ T-cell responses, with the Th1 cytokines IFN-γ, IL-2, and TNF-α being produced upon spike protein stimulation (Keech et al. 2020).
- Th1 responses with the unadjuvanted vaccine candidate were similar to those seen with placebo; both adjuvanted regimens tested (25 µg/25 µg [shown in the figure] and 5 µg/5 µg [not shown]) demonstrated a Th1 response (Keech et al. 2020).

Figure 23. Th1 and Th2 responses with unadjuvanted vaccine candidate and the 25 µg/25 µg adjuvanted vaccine candidate (Keech et al. 2020).


Th1 Response
Th2 Response
Unadjuvanted Vaccine
25 µg/25 µg regimen
% CD4+ T cells
3.0
2.5
2.0
1.5
1.0
0.5
0.0
IL-2
TNFa
IFNg
Any 2 Th1
All 3 Th1
IL-5
IL-13
Both
Day 0
Day 28

WHOLE-VIRUS VACCINE CANDIDATES

MECHANISM

Whole virus vaccines use the entire virus and can consist of either live, attenuated virus or inactivated virus (Figure 24). At present, there are at least 3 inactivated SARS-CoV-2 vaccines that have entered phase 3 clinical trials. To date, only data for the vaccine developed by Sinopharm, in collaboration with the Wuhan Institute, have been published in a peer-reviewed medical journal. In addition to inactivated virus vaccines, there are at least 3 live attenuated virus vaccines in preclinical development (World Health Organization 2020b).

Figure 24. Mechanism of action for whole-virus vaccines (Callaway 2020)

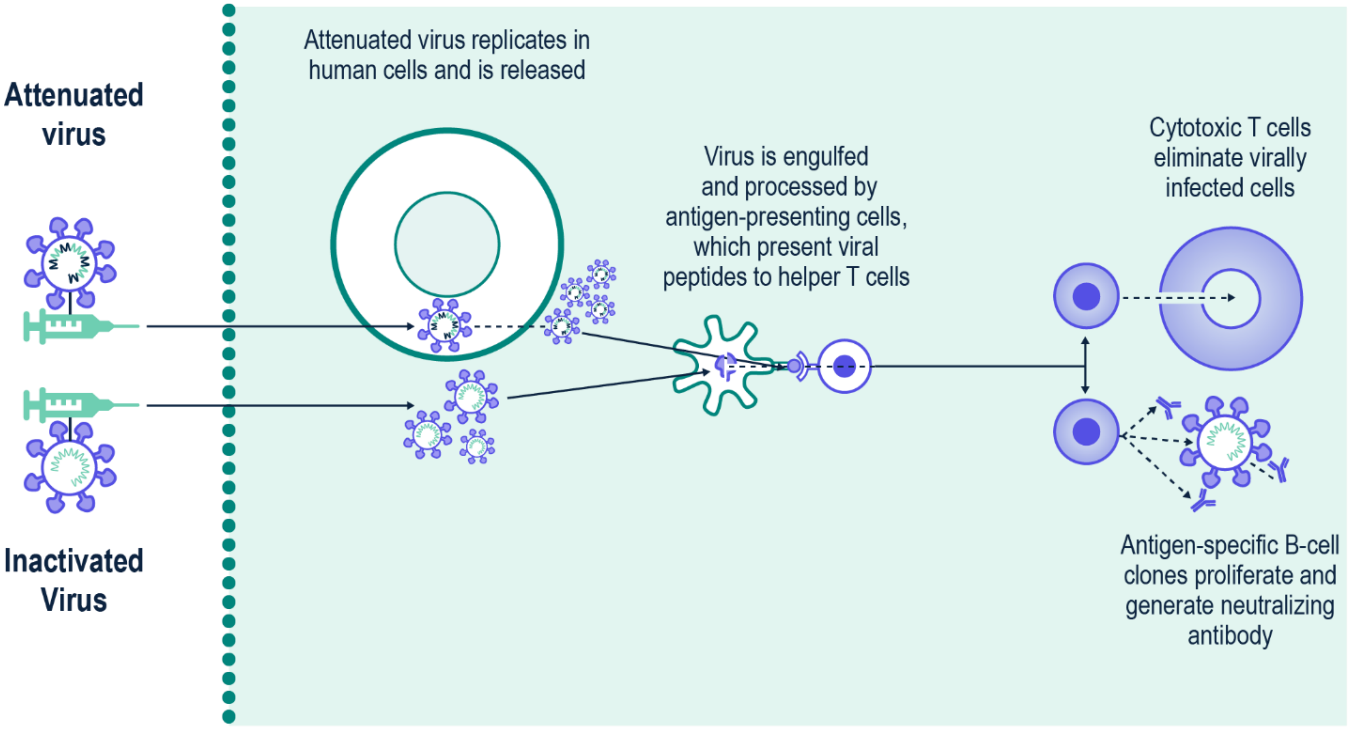


Table 8. Potential advantages and disadvantages of whole-virus vaccines (Funk et al. 2020)

Advantages (Funk et al. 2020)	Disadvantages (Funk et al. 2020)
Live Virus (attenuated) • Proven technology • Strong immune response • Multivalent • Simple formulation (no adjuvants) • Proven track record for economical large-scale manufacturing	**Live Virus (attenuated)** • Requires a higher biosafety level during manufacturing and possibly during preparation at the clinical site of vaccination • Risk for attenuated virus to regain virulence • Can be complicated to scale up manufacturing
Inactivated Virus • Proven technology • Strong immune response • Multivalent • Simple formulation (no adjuvants)	**Inactivated Virus** • Requires a lesser biosafety level during manufacturing and possibly during preparation at the clinical site of vaccination • Complicated to scale up manufacturing

SINOPHARM/WUHAN INSTITUTE OF BIOLOGICAL SCIENCES

Manufacturer	Sinopharm/Wuhan Institute of Biological Sciences
Platform	Inactivated whole virus
Number of Doses	2
Timing of Doses	0, 14 or 0, 21 days
Route of Administration	Intramuscular
Current Phase*	3

*Per World Health Organization COVID-19 Candidate Vaccine Landscape (August 10, 2020)

APPROACH

This vaccine candidate uses a beta-propiolactone-inactivated SARS-CoV-2 strain (WIV04 strain) that was isolated from a hospitalized patient in Wuhan, China (Xia et al. 2020). The vaccine candidate is adsorbed to 0.5-mg aluminum hydroxide (alum) adjuvant and packaged in prefilled syringes in 0.5-mL sterile saline without preservative (Xia et al. 2020).

KEY CLINICAL EVIDENCE

An interim analysis of a phase 1 and phase 2 trial was published in *JAMA* on August 13, 2020 (Xia et al. 2020).

Design

- In the phase 1 trial, 96 subjects were assigned to 2.5, 5.0, or 10 µg doses of the vaccine candidate or to the alum adjuvant only and received 3 intramuscular injections at days 0, 28, and 56 (Xia et al. 2020).
- In the phase 2 trial, 224 adults were randomized to the 5.0 µg dose, administered either on days 0 and 14 or days 0 and 21 or to alum only (Xia et al. 2020).

Outcomes

- The primary safety outcome was combined adverse reactions in the 7 days after each injection (Xia et al. 2020).
- The primary immunogenicity outcome was neutralizing antibody response 14 days after a completed course of vaccination, as measured by a $PRNT_{50}$ assay. (Xia et al. 2020).

Results—Safety

- Within 7 days after injection, adverse reactions were reported by 48 (15.0%) of 320 participants in the trials (Xia et al. 2020). The most common adverse reactions were injection-site pain and fever, all of which were mild (grade 1 or 2), transient, self-limiting, and did not require treatment (Xia et al. 2020).

Results—Immunogenicity

- Seroconversion was seen in all subjects receiving vaccine candidates in the low- and high-dose groups of the phase 1 trial and 95.8% of those in the medium-dose group (Xia et al. 2020). Subjects began producing antibody responses after the second injection (Xia et al. 2020). Neutralizing antibodies to live SARS-CoV-2 and specific IgG antibody responses to whole SARS-CoV-2 antigen at different time points in the phase 1 clinical trial are shown in Figures 25 and 26 (Xia et al. 2020).

Figure 25. Neutralizing antibody responses at different time points in the phase 1 trial (Xia et al. 2020)

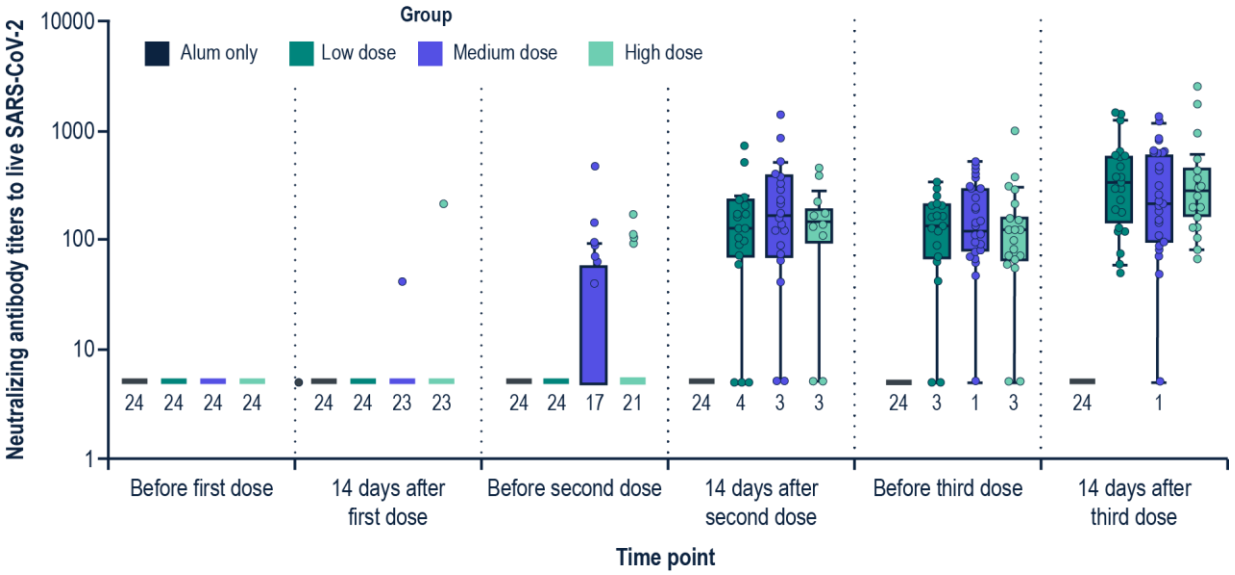
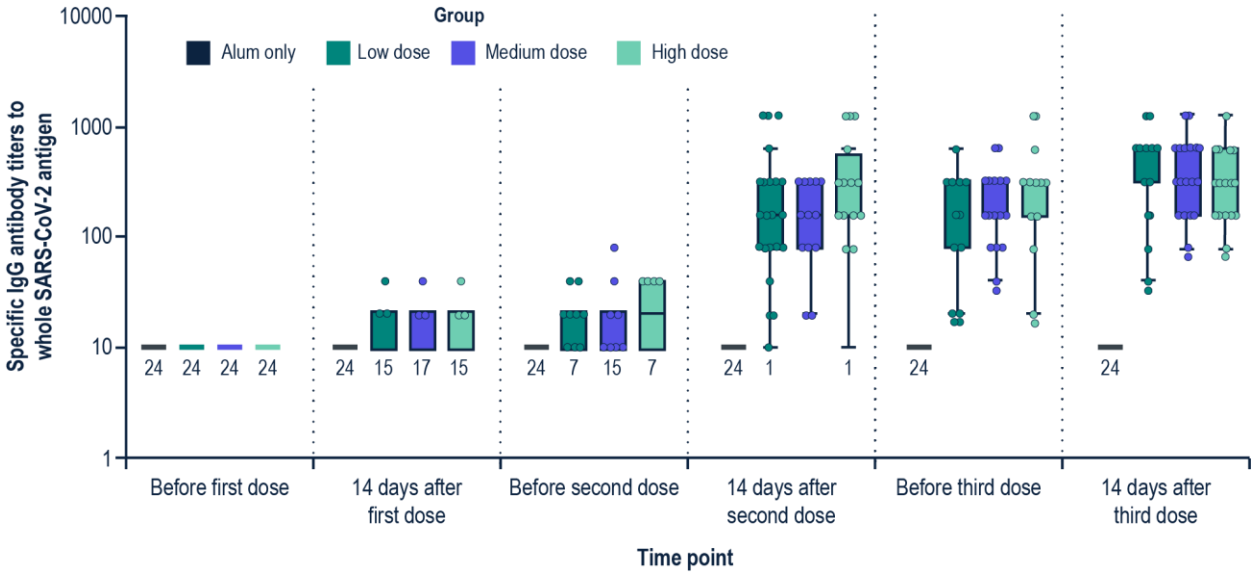
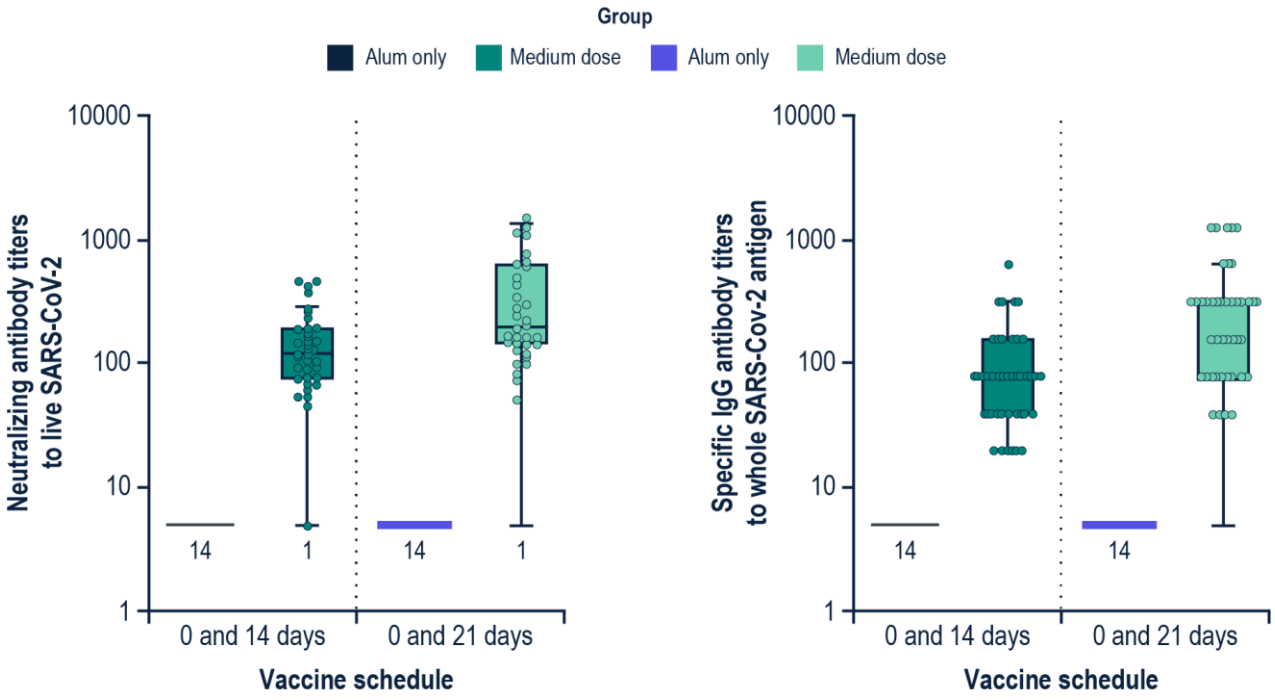


Figure 26. Specific IgG antibody responses to whole SARS-CoV-2 antigen at different time points in the phase 1 trial (Xia et al. 2020)



- Seroconversion was noted in 97.6% of subjects who received the vaccine in the phase 2 group. Neutralizing antibodies to live SARS- CoV-2 and specific IgG antibody responses to whole SARS-CoV-2 antigen at 14 days after the second dose in the phase 2 clinical trial are shown in Figure 27 (Xia et al. 2020).

Figure 27. Antibody responses 14 days after the second dose in the phase 2 trial (Xia et al. 2020)



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