Biotech companies, pharma firms, universities, and government agencies are all rushing to start clinical trials of newly created gene-based vaccines for COVID-19.

Developer	Technology	Phase I clinical trial
Moderna and National Institutes of Health	mRNA vaccine	Began in March 2020
CanSino Biologics	Adenoviral vector vaccine	Began in March 2020
BioNTech, Shanghai Fosun Pharmaceutical, and Pfizer	mRNA vaccine	April 2020
Inovio Pharmaceuticals and Wistar Institute	DNA vaccine	April 2020
University of Oxford	Adenoviral vector vaccine	April 2020
CureVac	mRNA vaccine	By early summer
Imperial College London	mRNA vaccine	Early summer
Arcturus Therapeutics and Duke-NUS Medical School	mRNA vaccine	Second half of 2020
Johnson & Johnson and Biomedical Advanced Research and Development Authority	Adenoviral vector vaccine	By September
Altimmune	Adenoviral vector vaccine	Q3 2020

Translate Bio and Sanofi Pasteur

mRNA vaccine | By end of 2020

eTheRNA Immunotherapies

mRNA vaccine | 2021

Karolinska Institute

DNA vaccine | 2021

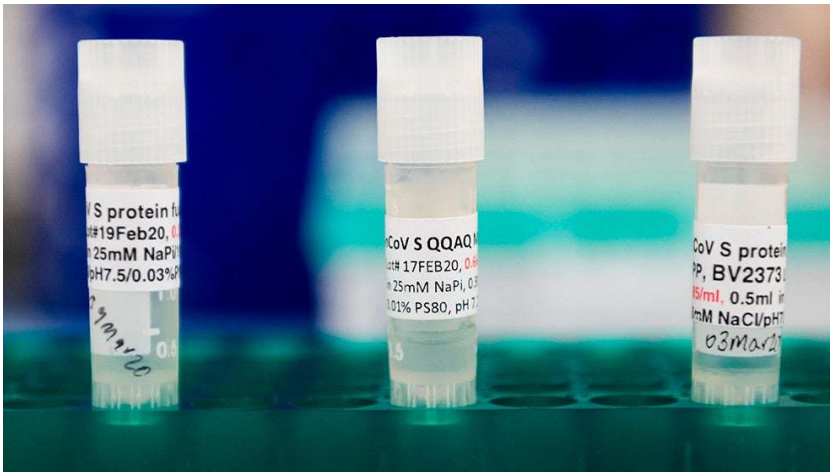
University of Pennsylvania and Duke Human Vaccine Institute

mRNA vaccine | Unknown

First Phase 3 test of coronavirus vaccine candidate begins in US

Zack Budryk 2 hrs ago

An investigational vaccine developed by drugmaker Moderna and the National Institute of Allergy and Infectious Diseases began Phase 3 trials on Monday, becoming the first candidate to reach that step in testing.



© Getty Images First Phase 3 test of coronavirus vaccine candidate begins in US

About 30,000 adult volunteers are set to be enrolled in the trial, according to CNN, which added that the first patient was dosed at a site in Savannah, Ga. A trial group will receive two 100 microgram injections of the candidate while a control group receiving a placebo, both about four weeks apart, the network noted.

"We are pleased to have started the Phase 3 COVE study," Moderna CEO Stephane Bancel said in a statement. "We are grateful to the efforts of so many inside and outside the company to get us to this important milestone. We are indebted to the participants and investigators who now begin the work of the COVE study itself. We look forward to this trial demonstrating the potential of our vaccine to prevent COVID-19, so that we can defeat this pandemic."

According to data published in the New England Journal of Medicine, earlier testing induced immune responses in all volunteers. Mild side effects included chills, headaches, muscle pain and fatigue but the vaccine was generally safe.

Several drug manufacturers, including Moderna, are receiving support from the federal government through its Operation Warp Speed program, with the company announcing Sunday that the Biomedical Advanced Research and Development Authority has provided $472 million more for the Phase 3

study and later development, for a total of $955 million thus far.

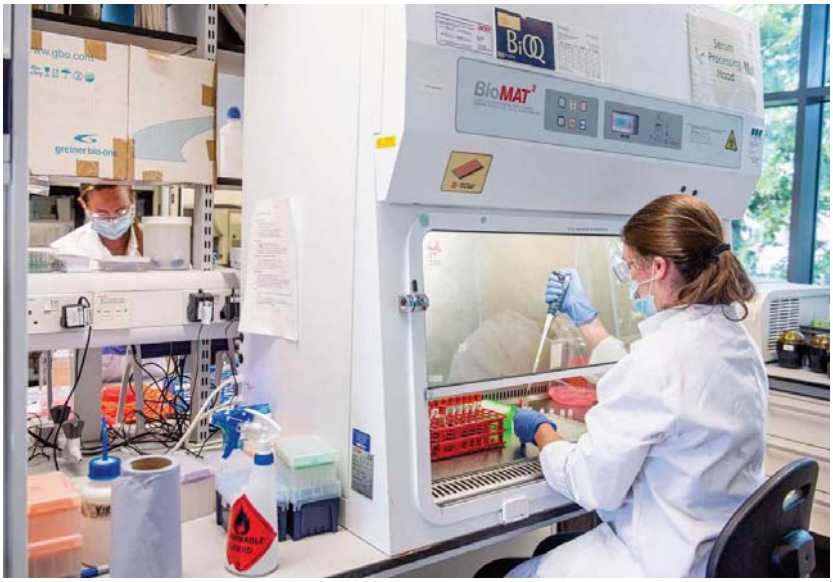
The World Health Organization lists about 25 potential vaccines in clinical trials worldwide. Phase 1 of trials usually analyzes whether a drug induces an immune response in a small number of people, while a Phase 2 trial expands the study to people with characteristics similar to those of the intended vaccine recipients. Phase 3 trials typically involve thousands of subjects and tests for safety and efficacy.

The Washington Post

Oxford coronavirus vaccine safe and promising, according to early human trial results published in the Lancet

William Booth, Carolyn Y. Johnson 2 hrs ago

LONDON —An Oxford University group and the British-Swedish pharmaceutical company AstraZeneca, which together are developing a leading vaccine candidate against the novel coronavirus, reported Monday that their early-stage human trial showed their vaccine to be safe and that it stimulates the body to produce both antibodies and white blood cells to fight off infection.



© John Cairns/AP Samples from coronavirus vaccine trials are handled inside the Oxford Vaccine Group laboratory in Oxford, England.

The study of 1,077 volunteers was described as promising. The report in the British medical journal the Lancet suggested that the vaccine appeared safe and was able to conjure a promising immune response. A second report in the same medical journal on a Chinese vaccine said it also showed positive results.

At this early stage, neither vaccine has proven itself to protect people from infection or illness.

But with hopes soaring that a number of vaccines will soon emerge to quiet the global pandemic, Britain and the United States have already ordered millions of doses of the Oxford vaccine, while the Chinese military is preparing to deploy its candidate if it proves effective in larger studies.

The Oxford vaccine is named ChAdOx1 nCoV-19 and was made from a weakened and nonreplicating version of a common cold virus, an adenovirus. The vaccine has been engineered to express a bit of the coronavirus that produces the spike protein

that the virus uses to enter and infect human cells.

An editorial in the Lancet warned, “The race for a vaccine moves fast, as the need for a solution is evident, but we cannot forget that safety is of the highest importance.”

Infectious-disease experts caution that vaccines must be widely administered to protect the general population, and in an era of widespread skepticism, and even overt hostility toward research and scientists, any vaccine that underperforms or causes serious side effects will set back the effort.

The Oxford candidate is one of 23 vaccines now being tested in human trials, according to a running tally kept by the World Health Organization. More than 130 others are in preclinical trials.

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DNA vaccine protection against SARS-CoV-2 in rhesus macaques

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The global COVID-19 pandemic caused by the SARS-CoV-2 virus has made the development of a vaccine a top biomedical priority. In this study, we developed a series of DNA vaccine candidates expressing different forms of the SARS-CoV-2 Spike (S) protein and evaluated them in 35 rhesus macaques. Vaccinated animals developed humoral and cellular immune responses, including neutralizing antibody titers comparable to those found in convalescent humans and macaques infected with SARS-CoV-2. Following vaccination, all animals were challenged with SARS-CoV-2, and the vaccine encoding the full-length S protein resulted in >3.1 and >3.7 $\log_{10}$ reductions in median viral loads in bronchoalveolar lavage and nasal mucosa, respectively, as compared with sham controls. Vaccine-elicited neutralizing antibody titers correlated with protective efficacy, suggesting an immune correlate of protection. These data demonstrate vaccine protection against SARS-CoV-2 in nonhuman primates.

The COVID-19 pandemic has made the development of a safe, effective, and deployable vaccine a critical global priority (*1*–*8*). However, our understanding of immune correlates of protection to SARS-CoV-2 is currently very limited but is essential for the development of SARS-CoV-2 vaccines and other immunotherapeutic interventions. To facilitate the preclinical evaluation of vaccine candidates, we recently developed a rhesus macaque model of SARS-CoV-2 infection (*9*). In the present study, we constructed a set of prototype DNA vaccines expressing various forms of the SARS-CoV-2 Spike (S) protein and assessed their immunogenicity and protective efficacy against SARS-CoV-2 viral challenge in rhesus macaques.

Construction and immunogenicity of DNA vaccine candidates

We produced a series of prototype DNA vaccines expressing six variants of the SARS-CoV-2 S protein: 1) full-length (S), 2) deletion of the cytoplasmic tail (S.dCT) (*10*), 3) deletion of the transmembrane domain and cytoplasmic tail reflecting the soluble ectodomain (S.dTM) (*10*), 4) S1 domain with a foldon trimerization tag (S1), 5) receptor-binding domain with a foldon trimerization tag (RBD), and 6) a prefusion stabilized soluble ectodomain with deletion of the furin cleavage site, two proline mutations, and a foldon trimerization tag (S.dTM.PP) (*11*–*13*) (Fig. 1A). Western blot analyses confirmed expression in cell lysates for all the constructs and in culture supernatants for the soluble S.dTM and S.dTM.PP constructs (Fig. 1, B and C). Proteolytic cleavage of the secreted protein was noted for S.dTM but not S.dTM.PP, presumably due to mutation of the furin cleavage site in S.dTM.PP.

We immunized 35 adult rhesus macaques (6-12 years old) with DNA vaccines in the following groups: S (N = 4), S.dCT (N = 4), S.dTM (N = 4), S1 (N = 4), RBD (N = 4), S.dTM.PP (N = 5), and sham controls (N = 10). Animals received 5 mg DNA vaccines by the intramuscular route without adjuvant at week 0 and week 3. After the boost immunization at week 5, we observed S-specific binding antibodies by ELISA (Fig. 2A)

and neutralizing antibodies (NAbs) using both a pseudovirus neutralization assay (*10*) (Fig. 2B) and a live virus neutralization assay (*14*, *15*) (Fig. 2C). Two animals had binding antibodies at baseline by ELISA, which we speculate might reflect cross-reactivity of other natural primate coronaviruses. NAb titers measured by the pseudovirus neutralization assay correlated with NAb titers measured by the live virus neutralization assay ($P < 0.0001$, $R = 0.8052$, two-sided Spearman rank-correlation test; fig. S1). Moreover, NAb titers in the vaccinated macaques (median titer 74; median titer in the S and S.dCT groups 170) were comparable in magnitude to NAb titers in a cohort of 9 convalescent macaques (median titer 106) and a cohort of 27 convalescent humans (median titer 93) who had recovered from SARS-CoV-2 infection (Fig. 2D).

S-specific and RBD-specific antibodies in the vaccinated macaques included diverse subclasses and effector functions, including antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement deposition (ADCD), antibody-dependent monocyte cellular phagocytosis (ADCP), and antibody-dependent NK cell activation (IFN-γ secretion, CD107a degranulation, and MIP-1β expression) (*16*) (Fig. 2E). A trend toward higher ADCD responses was observed in the S and S.dCT groups, whereas higher NK cell activation was observed in the RBD and S.dTM.PP groups. A principal component analysis of the functional and biophysical antibody features showed overlap of the different vaccine groups, with more distinct profiles in the S and RBD groups (Fig. 2E).

We also observed cellular immune responses to pooled S peptides in the majority of vaccinated animals by IFN-γ ELISPOT assays at week 5 (Fig. 3A). Intracellular cytokine staining assays at week 5 demonstrated induction of S-specific IFN-γ+ CD4+ and CD8+ T cell responses, with lower responses induced by the shorter S1 and RBD immunogens (Fig. 3B). S-specific IL-4+ CD4+ and CD8+ T cell responses were marginal (Fig. 3C), suggesting induction of Th1-biased cellular immune responses.

Protective efficacy against SARS-CoV-2 challenge

At week 6, which was 3 weeks after the boost immunization, all animals were challenged with 1.2×10^8 VP (1.1×10^4 PFU) SARS-CoV-2, administered as 1 ml by the intranasal (IN) route and 1 ml by the intratracheal (IT) route. Following challenge, we assessed viral RNA levels by RT-PCR (*17*) in bronchoalveolar lavage (BAL) and nasal swabs (NS). Viral RNA was negative in plasma, and animals exhibited only mild clinical symptoms. High levels of viral RNA were observed in the sham controls with a median peak of 6.46 (range 4.81-7.99) $\log_{10}$ RNA copies/ml in BAL and a median peak of 6.82 (range 5.96-7.96) $\log_{10}$ RNA copies/swab in NS (fig. S2). Lower levels of viral RNA were observed in the vaccine groups (figs. S3 and S4), including 1.92 and 2.16 $\log_{10}$ reductions of median peak viral RNA in BAL and NS, respectively, in S vaccinated animals compared with sham controls ($P = 0.02$ and $P = 0.04$, two-sided Mann-Whitney tests) (fig. S5). Viral RNA assays were confirmed by PFU assays, which similarly showed lower infectious virus titers in S vaccinated animals compared with sham controls ($P = 0.04$, two-sided Mann-Whitney test) (fig. S5).

We speculated that a substantial fraction of viral RNA in BAL and NS following challenge represented input challenge virus, and thus we also assessed levels of subgenomic mRNA (sgmRNA), which is believed to reflect viral replication cellular intermediates that are not packaged into virions and thus putative replicating virus in cells (*18*). High levels of sgmRNA were observed in the sham controls (Fig. 4A) with a median peak of 5.35 (range 3.97-6.95) $\log_{10}$ sgmRNA copies/ml in BAL and a median peak of 6.40 (range 4.91-7.01) $\log_{10}$ sgmRNA copies/swab in NS. Peak viral loads occurred variably on day 1-4 following challenge. Markedly lower levels of sgmRNA were observed in the vaccine groups (Fig. 4, B and C), including >3.1 and >3.7 $\log_{10}$ decreases of median peak sgmRNA in BAL and NS, respectively, in S vaccinated animals compared with sham controls ($P = 0.03$ and $P = 0.01$, two-sided Mann-Whitney tests) (Fig. 4D). Reduced levels of sgmRNA were also observed in other vaccine groups, including S.dCT, S1, RBD, and S.dTM.PP, although minimal to no protection was seen in the S.dTM group, confirming the importance of prefusion ectodomain stabilization, as reported previously (*13*). Protection was generally more robust in BAL compared with NS, particularly for the less immunogenic constructs. A total of 8 of 25 vaccinated animals exhibited no detectable sgmRNA in BAL and NS at any timepoint following challenge.

Immune correlates of vaccine-induced protection

The variability in protective efficacy in this study facilitated an analysis of immune correlates of protection. The $\log_{10}$ pseudovirus NAb titer at week 5 inversely correlated with peak $\log_{10}$ sgmRNA in both BAL ($P < 0.0001$, $R = -0.6877$, two-sided Spearman rank-correlation test) and NS ($P = 0.0199$, $R = -0.4162$) (Fig. 5A). Similarly, the $\log_{10}$ live virus NAb titer at week 5 inversely correlated with peak $\log_{10}$ sgmRNA levels in both BAL ($P < 0.0001$, $R = -0.7702$) and NS ($P = 0.1006$, $R = -0.3360$) (Fig. 5B). These data suggest that vaccine-elicited serum NAb titers may be immune correlates of protection against SARS-CoV-2 challenge. We speculate that correlations were more robust with viral loads in BAL compared with viral loads in NS due to intrinsic variability of collecting swabs. The $\log_{10}$ ELISA titer at week 5 also inversely correlated with peak $\log_{10}$ sgmRNA levels in BAL ($P = 0.0041$, $R = -0.4733$) (fig. S6). Vaccine-elicited ELISPOT responses (fig. S7), CD4+ ICS responses (fig. S8), and CD8+ ICS responses (fig. S9) did not correlate with protection.

We next explored the potential contribution of other antibody effector functions to immune correlates of protection.

In addition to NAb titers, S- and RBD-specific ADCD responses inversely correlated with peak $\log_{10}$ sgmRNA levels in BAL (Fig. 5C, top panel). Two orthogonal unbiased machine learning approaches were then utilized to define minimal combined correlates of protection. A nonlinear random forest regression analysis and a linear partial least squares regression analysis showed that utilizing two features improved the correlations with protection, such as RBD-specific $Fc\gamma R2a$-1 binding with ADCD responses, or NAb titers with RBD-specific IgG2 responses (Fig. 5C, bottom left panel). Moreover, NAb titers correlated with most antibody effector functions, except for antibody-mediated NK cell activation (Fig. 5C, bottom right panel). Taken together, these data suggest a primary role of NAbs in protecting against SARS-CoV-2, supported by certain innate immune effector functions such as ADCD.

Finally, we compared antibody parameters in the vaccinated animals that were completely protected (defined as no detectable sgmRNA following challenge) with the vaccinated animals that were partially protected (defined as detectable sgmRNA following challenge). Completely protected animals showed higher $\log_{10}$ NAb titers ($P = 0.0004$, two-sided Mann-Whitney test), RBD-specific ADCD responses ($P = 0.0001$), S-specific RBD responses ($P = 0.0010$), and RBD-specific ADCP responses ($P = 0.0005$) compared with partially protected animals (Fig. 5D).

Anamnestic immune responses following challenge

All animals exhibited anamnestic humoral and cellular immune responses following challenge, including increased ELISA titers (fig. S10), pseudovirus NAb titers (fig. S11), live virus NAb titers (fig. S12), and IFN-γ ELISPOT responses (fig. S13) on day 14 after challenge. These data suggest that vaccine protection was probably not sterilizing, including in the 8 of 25 animals that had no detectable sgmRNA in BAL and NS at any timepoint following challenge, but rather was likely mediated by rapid virologic control following challenge.

Discussion

A safe and effective SARS-CoV-2 vaccine may be required to end the global COVID-19 pandemic. Several vaccine candidates have initiated clinical testing, and many others are in preclinical development (*19*, *20*). However, very little is currently known about immune correlates of protection and protective efficacy of candidate SARS-CoV-2 vaccines in animal models. In this study, we generated a series of prototype DNA vaccines expressing various S immunogens and assessed protective efficacy against intranasal and intratracheal SARS-CoV-2 challenge in rhesus macaques. We demonstrate vaccine protection with substantial >3.1 and >3.7 $\log_{10}$ reductions in median viral loads in BAL and NS, respectively, in S immunized animals compared with sham controls. Protection was likely not sterilizing but instead appeared to be mediated by rapid immunologic control following challenge.

Our data extend previous studies on SARS and MERS vaccine protection in mice, ferrets, and macaques (*10*, *21–24*). Phase 1 clinical studies for SARS and MERS vaccine candidates have also been conducted (*25*), but these vaccines have not been tested for efficacy in humans. Our data suggest that vaccine protection against SARS-CoV-2 in macaques is feasible. We observed a dramatic reduction of viral replication in both the upper respiratory tract and the lower respiratory tract with the optimal vaccines. In contrast, the less immunogenic vaccines, such as S.dTM, showed partial protection in BAL but essentially no protection in NS. These data suggest that it may be easier to protect against lower respiratory tract disease compared with upper respiratory tract disease. In the present study, optimal protection was achieved with the full-length S immunogen in both the upper and lower respiratory tracts, and reduced protection was observed with soluble constructs and smaller fragments. Our study did not address the question of whether emerging mutations in the SARS-CoV-2 S sequence may mediate escape from NAb responses induced by immunogens designed from the Wuhan/WIV04/2019 sequence.

Further research will need to address the important questions of the durability of protective immunity and the optimal vaccine platforms for a SARS-CoV-2 vaccine for humans (*26*). Although our data are restricted to DNA vaccines, we believe that our findings should be generalizable to other gene-based vaccines as well, including RNA vaccines and recombinant vector-based vaccines. Additional research should also evaluate vaccine immunogenicity and protective efficacy in older animals. Further studies will also need to address the question of enhanced respiratory disease, which may result from antibody-dependent enhancement (*27–29*). Although our study was not designed to address safety issues, it is worth noting that the DNA vaccines induced Th1 rather than Th2 responses, and we did not observe enhanced clinical disease even with the suboptimal vaccine constructs that failed to protect.

We identified serum NAb titers, as measured by two independent assays (pseudovirus neutralization and live virus neutralization), as a significant correlate of protection in this study against both lower respiratory tract disease as well as upper respiratory tract disease. It is likely that protection in both anatomic compartments will be necessary for pandemic control, although protection in the upper respiratory tract may be more difficult to achieve. If this NAb correlate proves generalizable across multiple vaccine studies in both NHPs and humans, then this parameter would be a simple and useful benchmark for clinical development of SARS-CoV-2 vaccines. Innate immune effector functions such as ADCD may also contribute to protective efficacy. In summary, we

demonstrate effective vaccine protection against SARS-CoV-2 in rhesus macaques and define NAb titers as an immune correlate of protection, which will accelerate the development of SARS-CoV-2 vaccines for humans.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S13
References

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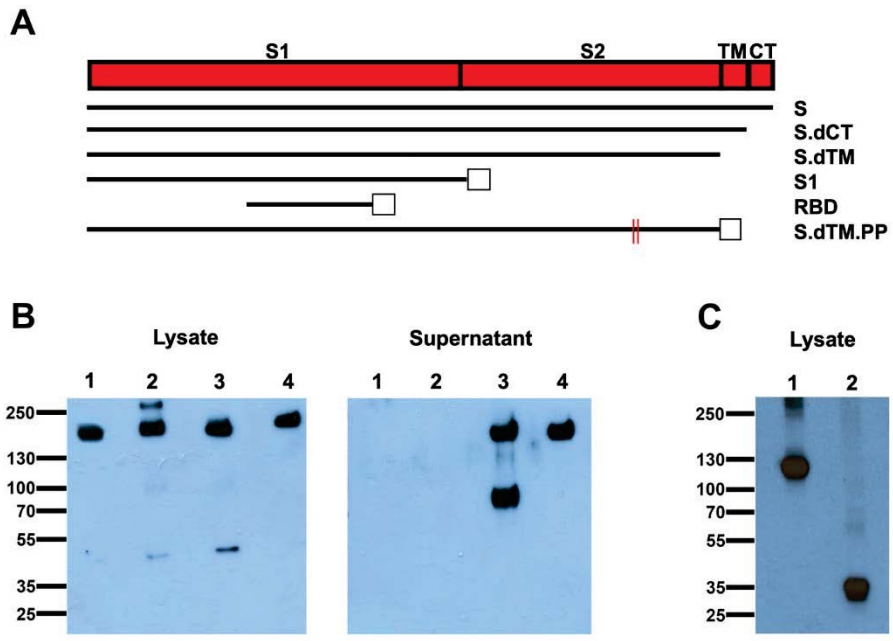

Fig. 1. Construction of candidate DNA vaccines against SARS-CoV-2. (**A**) Six DNA vaccines were produced expressing different SARS-CoV-2 Spike (S) variants: 1) full-length (S), 2) deletion of the cytoplasmic tail (S.dCT), 3) deletion of the transmembrane domain and cytoplasmic tail reflecting the soluble ectodomain (S.dTM), 4) S1 domain with a foldon trimerization tag (S1), 5) receptor-binding domain with a foldon trimerization tag (RBD), and a 6) prefusion stabilized soluble ectodomain with deletion of the furin cleavage site, two proline mutations, and a foldon trimerization tag (S.dTM.PP). Open square depicts foldon trimerization tag; red lines depict proline mutations. (**B**) Western blot analyses for expression from DNA vaccines encoding S (lane 1), S.dCT (lane 2), S.dTM (lane 3), and S.dTM.PP (lane 4) in cell lysates and culture supernatants using an anti-SARS polyclonal antibody (BEI Resources). (**C**) Western blot analyses for expression from DNA vaccines encoding S1 (lane 1) and RBD (lane 2) in cell lysates using an anti-SARS-CoV-2 RBD polyclonal antibody (Sino Biological).

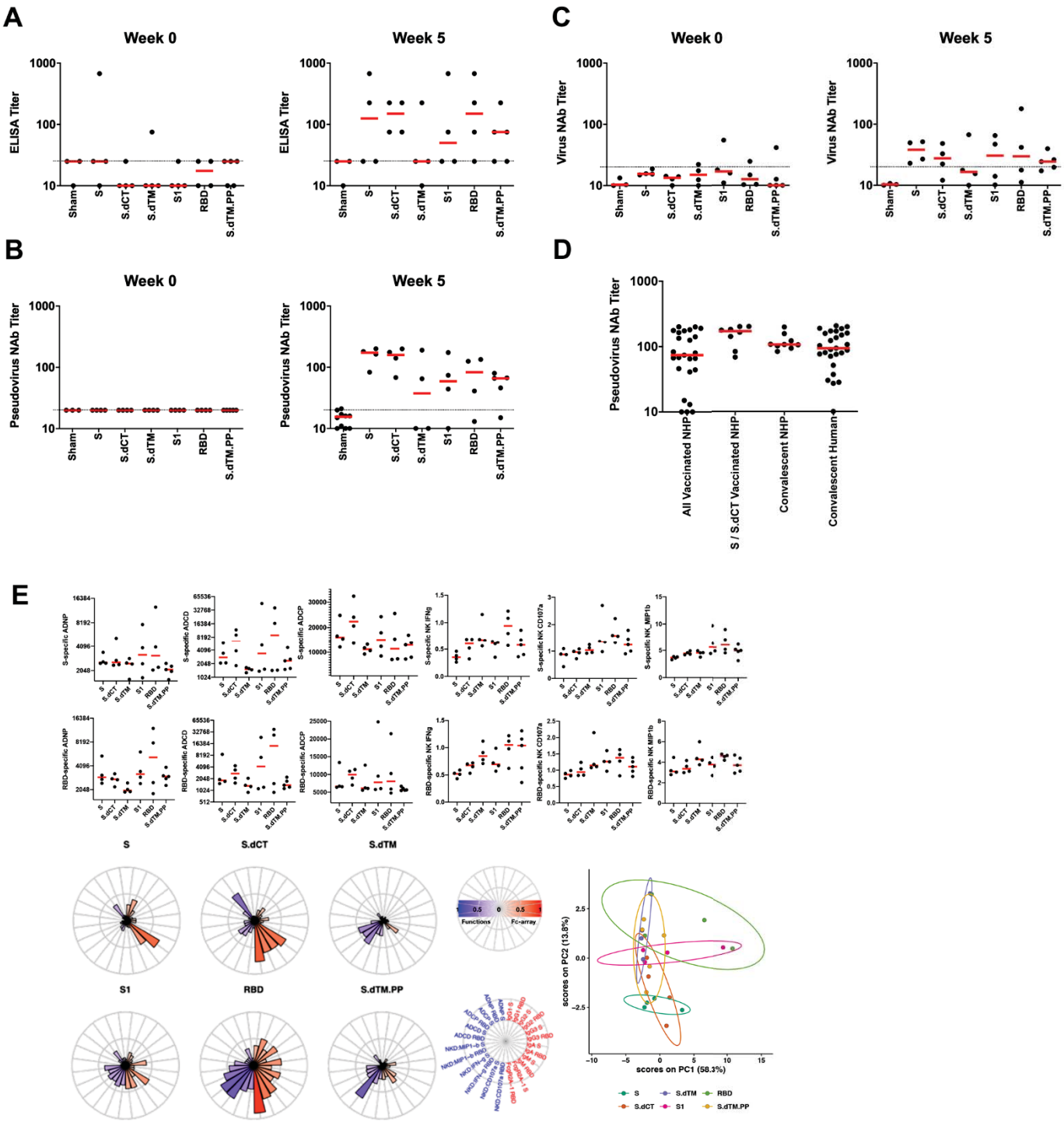

Fig. 2. Humoral immune responses in vaccinated rhesus macaques. Humoral immune responses were assessed following immunization by (**A**) binding antibody ELISA, (**B**) pseudovirus neutralization assays, and (**C**) live virus neutralization assays. (**D**) Comparison of pseudovirus neutralization titers in vaccinated macaques (all animals and S / S.dCT groups), a cohort of 9 convalescent macaques, and a cohort of 27 convalescent humans from Boston, United States who had recovered from SARS-CoV-2 infection. (**E**) S- and RBD-specific antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement deposition (ADCD), antibody-dependent monocyte cellular phagocytosis (ADCP), and antibody-dependent NK cell activation (IFN-γ secretion, CD107a degranulation, and MIP-1β expression) are shown. Radar plots show the distribution of antibody features across the vaccine groups. The size and color intensity of the wedges indicate the median of the feature for the corresponding group (blue depicts antibody functions, red depicts antibody isotype/subclass/FcγR binding). The principal component analysis (PCA) plot shows the multivariate antibody profiles across groups. Each dot represents an animal, the color of the dot denotes the group, and the ellipses shows the distribution of the groups as 70% confidence levels assuming a multivariate normal distribution. Red bars reflect median responses. Dotted lines reflect assay limit of detection.

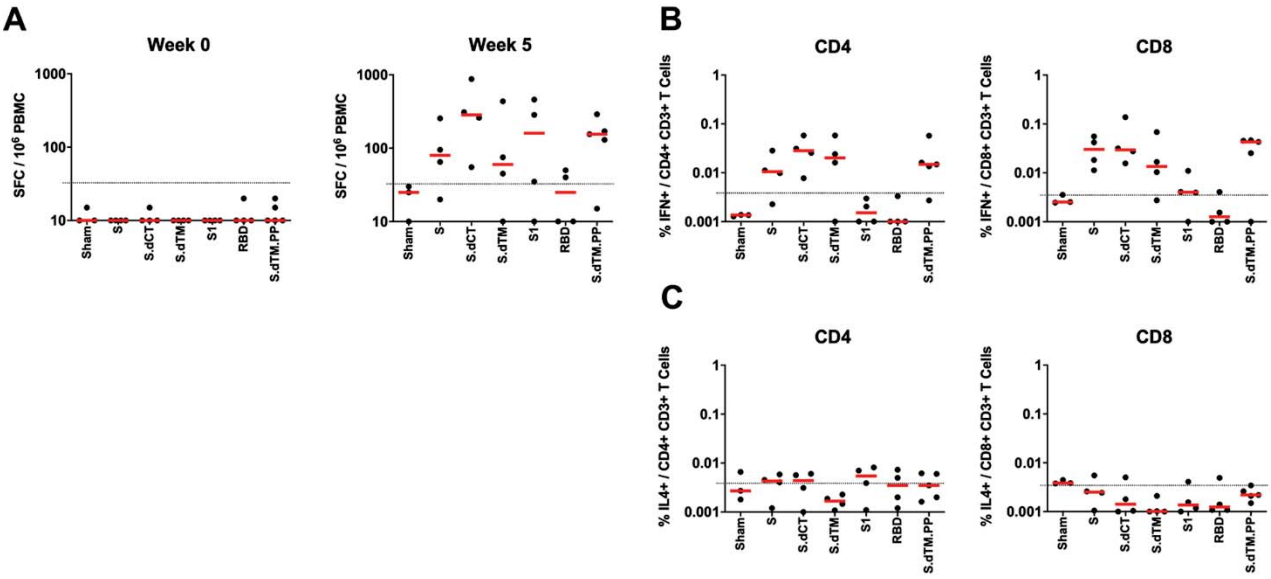

Fig. 3. Cellular immune responses in vaccinated rhesus macaques. Cellular immune responses were assessed at week 5 following immunization by (**A**) IFN-γ ELISPOT assays and (**B**) IFN-γ+ and (**C**) IL-4+ intracellular cytokine staining assays for CD4+ and CD8+ T cells in response to pooled S peptides. Red bars reflect median responses.

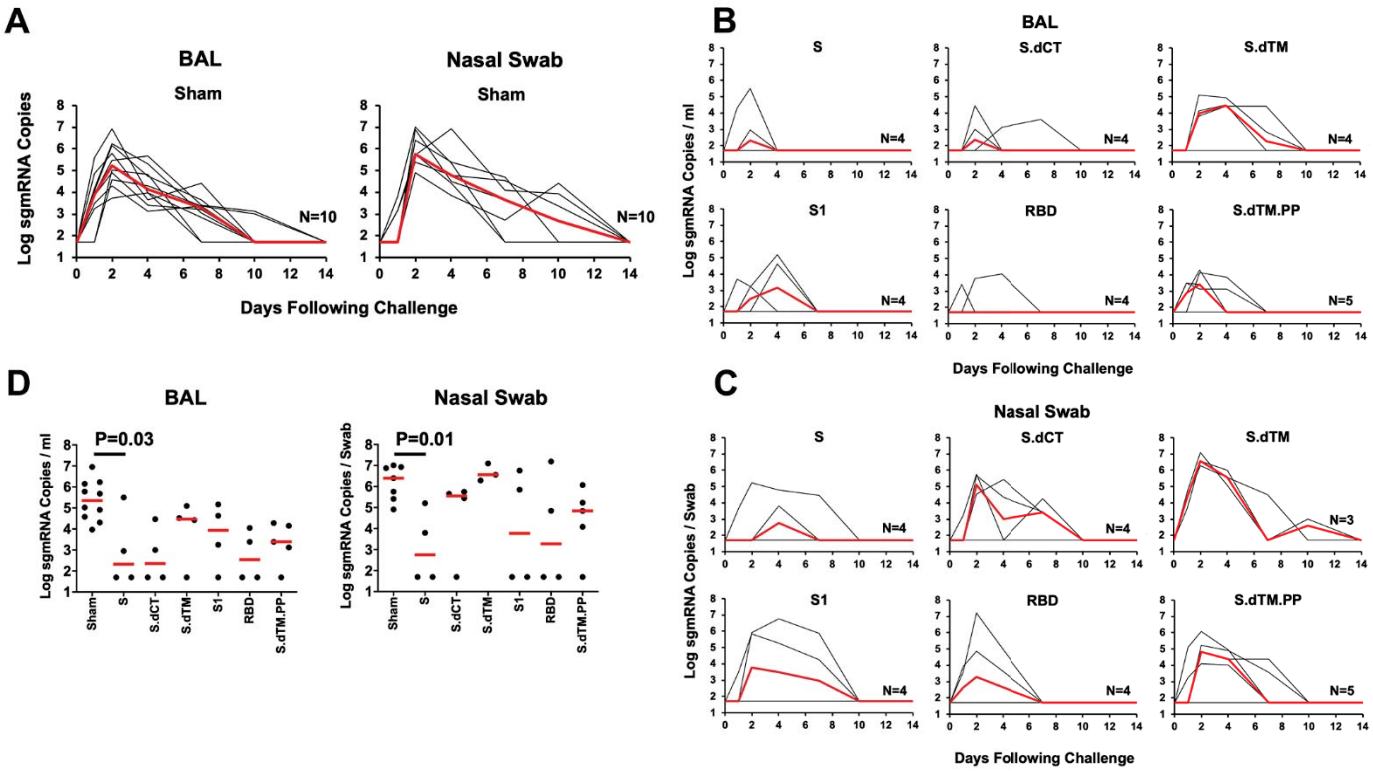

Fig. 4. Viral loads in rhesus macaques challenged with SARS-CoV-2 virus. Rhesus macaques were challenged by the intranasal and intratracheal route with 1.2×10^8 VP (1.1×10^4 PFU) SARS-CoV-2. (**A**) Log_{10} sgmRNA copies/ml or copies/swab (limit 50 copies) were assessed in bronchoalveolar lavage (BAL) and nasal swabs (NS) in sham controls at multiple timepoints following challenge. (**B**) Log_{10} sgmRNA copies/ml in BAL and (**C**) log_{10} sgmRNA copies/swab in NS in vaccinated animals at multiple timepoints following challenge. (**D**) Summary of peak viral loads in BAL and NS following challenge. Peak viral loads occurred variably on day 1-4 following challenge. Red lines reflect median viral loads. P-values indicate two-sided Mann-Whitney tests.

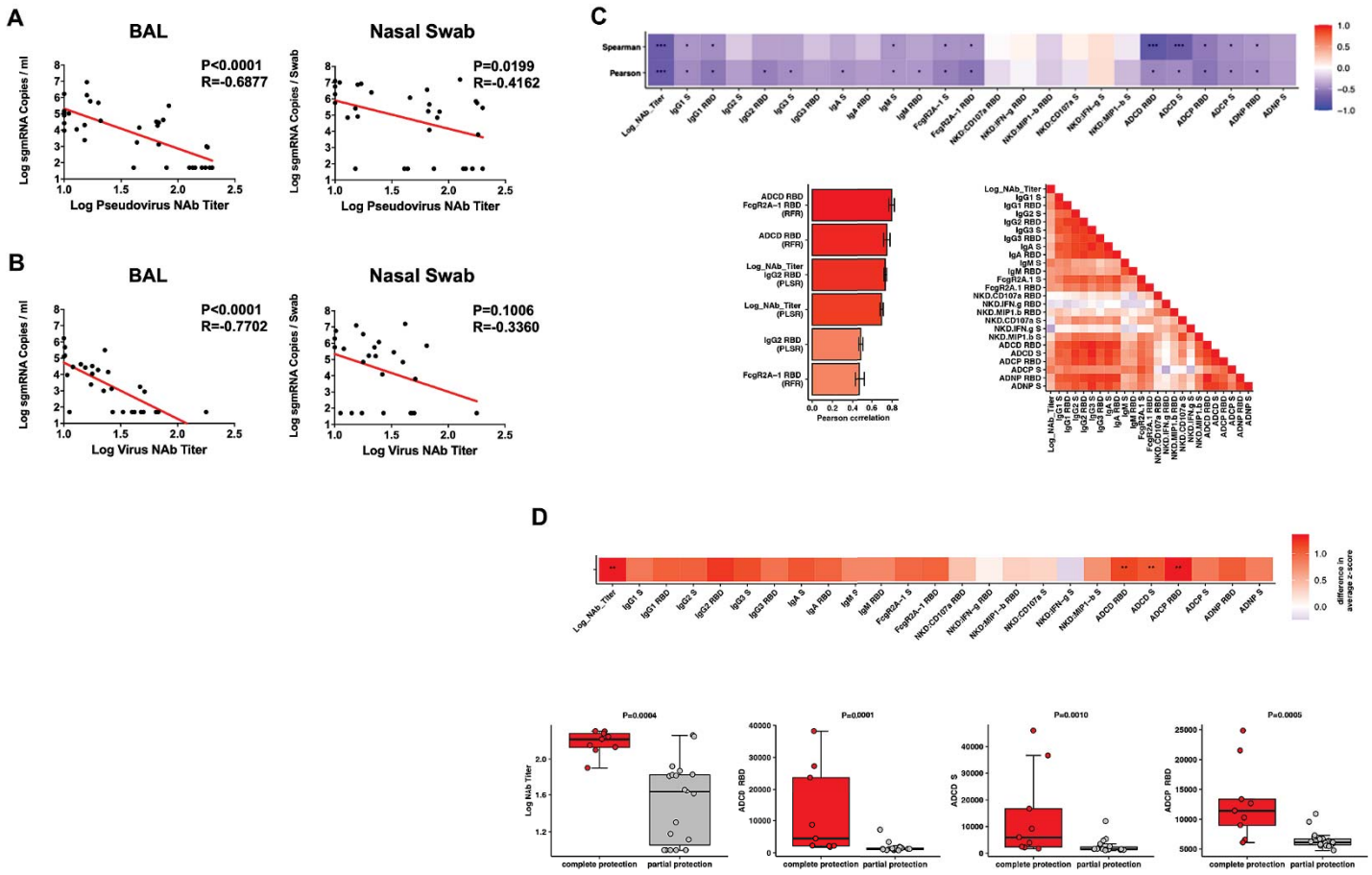

Fig. 5. Immune correlates of protection. Correlations of (**A**) pseudovirus NAb titers and (**B**) live NAb titers prior to challenge with log peak sgmRNA copies/ml in BAL or log peak sgmRNA copies/swab in nasal swabs following challenge. Red lines reflect the best-fit relationship between these variables. P and R values reflect two-sided Spearman rank-correlation tests. (**C**) The heat map (top panel) shows the Spearman and Pearson correlations between antibody features and $\log_{10}$ peak sgmRNA copies/ml in BAL (*q < 0.05, **q < 0.01, ***q < 0.001 with Benjamini-Hochberg correction for multiple testing). The bar graph (bottom left panel) shows the rank of the Pearson correlation between cross-validated model predictions and data using the most predictive combination or individual antibody features for partial least square regression (PLSR) and random forest regression (RFR). The correlation heatmap (bottom right panel) represents pairwise Pearson correlations between features across all animals. (**D**) The heat map (top panel) shows the difference in the means of the z-scored features between the completely protected and partially protected animals (**q < 0.01 with Benjamini-Hochberg correction for multiple testing). The dot plots show differences in $\log_{10}$ NAb titers, RBD-specific ADCD responses, S-specific ADCD responses, and RBD-specific ADCP responses between the completely protected and partially protected animals. P-values indicate two-sided Mann-Whitney tests.

DNA vaccine protection against SARS-CoV-2 in rhesus macaques

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SHARE

JULY 14, 2020

First COVID-19 vaccine tested in US poised for final testing

Associated Press

(AP) — The first COVID-19 vaccine tested in the U.S. revved up people's immune systems just the way scientists had hoped, researchers reported Tuesday — as the shots are poised to begin key final testing.

"No matter how you slice this, this is good news," Dr. Anthony Fauci, the U.S. government's top infectious disease expert, told The Associated Press.

The experimental vaccine, developed by Fauci's colleagues at the National Institutes of Health and Moderna Inc., will start its most important step around July 27: A 30,000-person study to prove if the shots really are strong enough to protect against the coronavirus.

But Tuesday, researchers reported anxiously awaited findings from the first 45 volunteers who rolled up their sleeves back in March. Sure enough, the vaccine provided a hoped-for immune boost.

Those early volunteers developed what are called neutralizing antibodies in their bloodstream — molecules key to blocking infection — at levels comparable to those found in people who survived COVID-19, the research team reported in the New England Journal of Medicine.

"This is an essential building block that is needed to move forward with the trials that could actually determine whether the vaccine does protect against infection," said Dr. Lisa Jackson of the Kaiser Permanente Washington Research Institute in Seattle, who led the study.

There's no guarantee but the government hopes to have results around the end of the year — record-setting speed for developing a vaccine.

The vaccine requires two doses, a month apart.

There were no serious side effects. But more than half the study participants reported flu-like reactions to the shots that aren't uncommon with other vaccines — fatigue, headache, chills, fever and pain at the injection site. For three participants given the highest dose, those reactions were more severe; that dose isn't being pursued.

Some of those reactions are similar to coronavirus symptoms but they're temporary, lasting about a day and occur right after vaccination, researchers noted.

"Small price to pay for protection against COVID," said Dr. William Schaffner of Vanderbilt University Medical Center, a vaccine expert who wasn't involved with the study.

He called the early results "a good first step," and is optimistic that final testing could deliver answers about whether it's really safe and effective by the beginning of next year.

"It would be wonderful. But that assumes everything's working right on schedule," Schaffner cautioned.

Moderna's share price jumped nearly 15 percent in trading after U.S. markets closed. Shares of the company, based in Cambridge, Massachusetts, have nearly quadrupled this year.

Tuesday's results only included younger adults. The first-step testing later was expanded to include dozens of older adults, the age group most at risk from COVID-19. Those results aren't public yet but regulators are evaluating them. Fauci said final testing will include older adults, as well as people with chronic health conditions that make them more vulnerable to the virus — and Black and Latino populations likewise affected.

Nearly two dozen possible COVID-19 vaccines are in various stages of testing around the world. Candidates from China and Britain's Oxford University also are entering final testing stages.

The 30,000-person study will mark the world's largest study of a potential COVID-19 vaccine so far. And the NIH-developed shot isn't the only one set for such massive U.S. testing, crucial to spot rare side effects. The government plans similar large studies of the Oxford candidate and another by Johnson & Johnson; separately, Pfizer Inc. is planning its own huge study.

Already, people can start signing up to volunteer for the different studies.

People think "this is a race for one winner. Me, I'm cheering every one of them on," said Fauci, who directs NIH's National Institute of Allergy and Infectious Diseases.

"We need multiple vaccines. We need vaccines for the world, not only for our own country."

Around the world, governments are investing in stockpiles of hundreds of millions of doses of the different candidates, in hopes of speedily starting inoculations if any are proven to work.

STAT

Covid-19 vaccine from Pfizer and BioNTech shows positive results

By Matthew Herper @matthewherper

July 1, 2020

Reprints

Mark Lennihan/AP

An experimental Covid-19 vaccine being developed by the drug giant Pfizer and the biotech firm BioNTech spurred immune responses in healthy patients, but also caused fever and other side effects, especially at higher doses.

The first clinical data on the vaccine were disclosed Wednesday in a paper released on medRXiv, a preprint server, meaning it has not yet been peer-reviewed or published in a journal.

"We still have a ways to go and we're testing other candidates as well," said Philip Dormitzer, the chief scientific officer for viral vaccines at Pfizer's research laboratories. "However, what we can say at this point is there is a viable candidate based on immunogenicity and early tolerability safety data."

The study randomly assigned 45 patients to get one of three doses of the vaccine or placebo. Twelve received a 10-microgram dose, 12 a 30-microgram dose, 12 a 100-microgram dose, and nine a placebo. The 100-microgram dose caused fevers in half of patients; a second dose was not given at that level.

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Pharma giants to unveil major $1 billion venture to push novel antibiotics

Following a second injection three weeks later of the other doses, 8.3% of the participants in the 10-microgram group and 75% of those in the 30-microgram group developed fevers. More than 50% of the patients who received one of those doses reported some kind of adverse event, including fever and sleep disturbances. None of these side effects was deemed serious, meaning they did not result in hospitalization or disability and were not life-threatening.

The vaccine generated antibodies against SARS-CoV-2, the virus that causes Covid-19, and some of these antibodies were neutralizing, meaning that they appear to prevent the virus from functioning. Levels of neutralizing antibodies were 1.8 to 2.8 times the level of that in the recovered patients.

It's not certain that higher antibody levels will lead to immunity to the virus. To prove that, Pfizer will need to conduct large studies that aim to prove that people who have received the vaccine are at least 50% less likely to become infected. Those studies are expected to begin this summer, mostly in the United States. Pfizer and BioNTech are testing four different versions of the vaccine, but only one will advance to larger studies.

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Covid-19 Drugs and Vaccines Tracker

The current study did not include pregnant women, and no other information on the ethnic diversity of participants was noted, although the paper does say that future studies will need to include a more diverse group.

The second dose, a booster shot, was required for immunity. The patients who received the single 100-microgram dose had lower antibody levels than those who received two shots of the lower doses.

Fourteen Covid-19 vaccines are currently in human trials, according to the Milken Institute, including entrants from Inovio, CanSino, AstraZeneca, and Moderna. More are expected to start soon, including entrants from Merck, Johnson & Johnson, and Sanofi. In total, 178 vaccines are in various stages of development.

The Pfizer/BioNTech vaccine, like the Moderna vaccine, is based on a technology called messenger RNA, which uses a key genetic messenger found in cells to create protein that the immune system then learns to attack. Moderna has not yet published data on its vaccine but is expected to do so soon.

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BARRON'S

CORONAVIRUS

Moderna's Coronavirus Vaccine Appears to Work in Early Trials. What Comes Next.

By Josh Nathan-Kazis Updated May 18, 2020 9:16 am ET / Original May 18, 2020 7:35 am ET

The biotech firm Moderna announced what appear to be very positive results from its first human trial of its experimental Covid-19 vaccine on Monday. Not only did the vaccine lead to the creation of antibodies in eight human test subjects, but the vaccine also kept the virus that causes Covid-19 from replicating in the lungs of mice.

Moderna (ticker: MRNA) said that eight individuals treated with the vaccine at two different dose levels developed the same levels of antibodies in their blood as is found in the serum of people...