Beth Israel Deaconess Medical Center

HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

SARS-CoV-2 Vaccine

Noe Mercado

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March 25th 2021

Noe Mercado, a scientist at the Center for Virology and Vaccine Research in Boston, which is developing a coronavirus vaccine with Johnson & Johnson. Tony Luong for The New York Times

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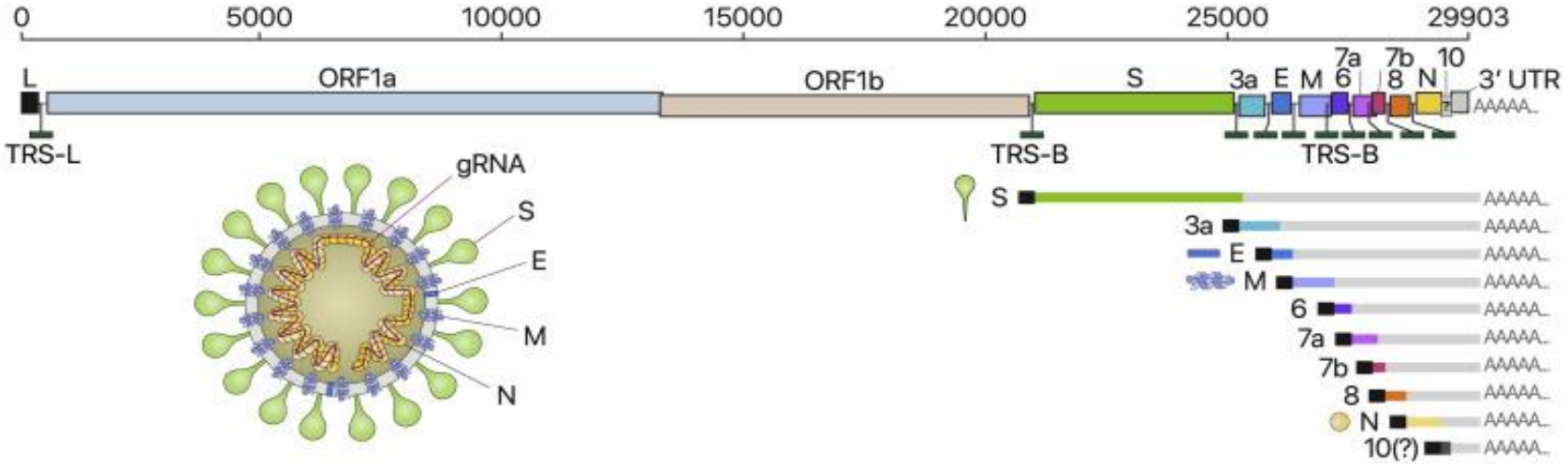
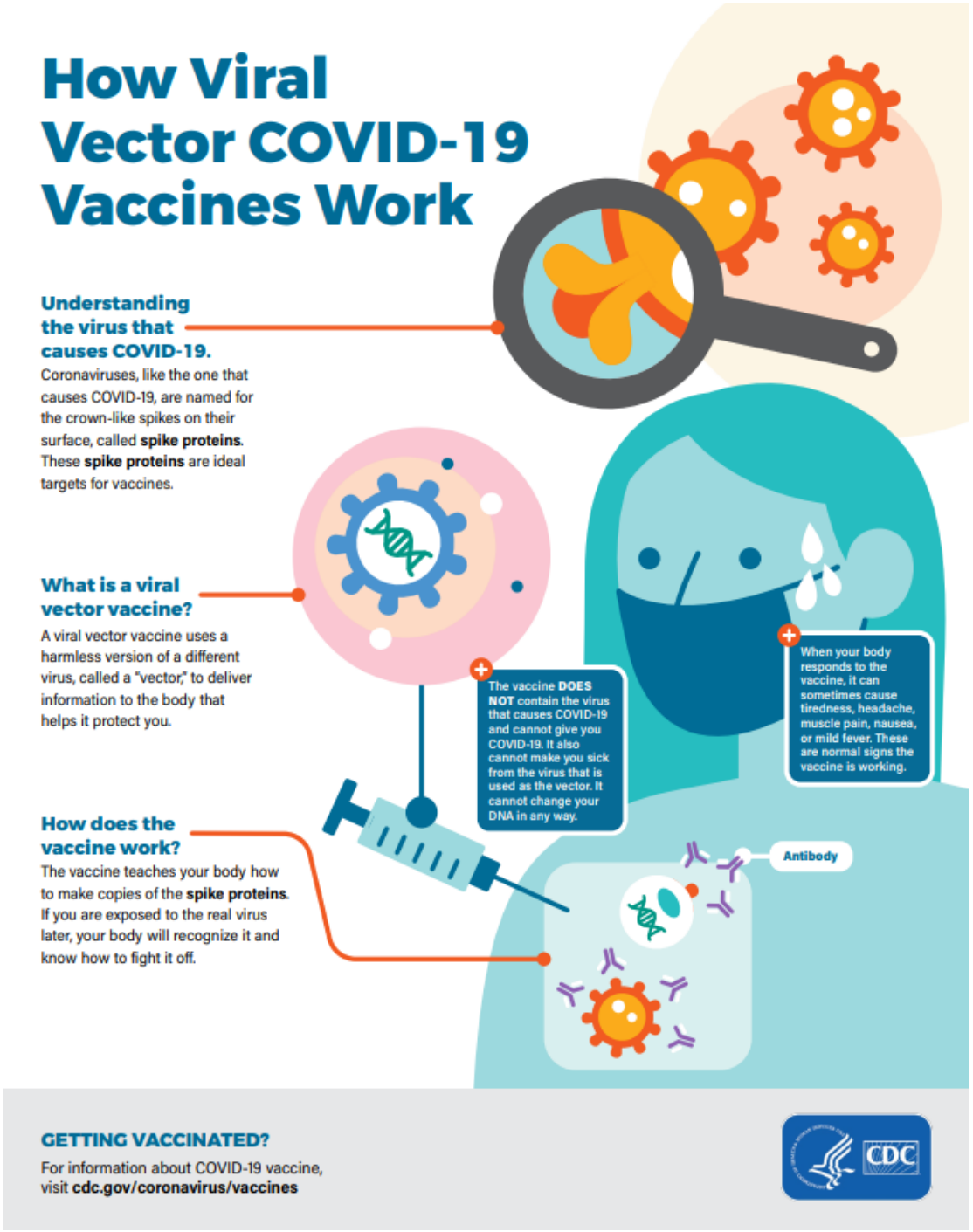
- Mosaic HIV-1 Vaccine in large scale phase 2b trial in Africa and Phase 3 efficacy trial in the Americas and Europe
- (Ad26.ZIKV.001) Zika virus vaccine completed phase 1 clinical trial
- SARS-CoV-2 vaccine FDA approved

Severe Acute Respiratory Syndrome 2 (SARS-CoV-2)

- Positive sense single stranded RNA virus with a single linear RNA segment
- Genome size ~30kb
- Main focus for vaccination strategies is spike protein
- SARS-CoV-2 utilizes ACE2 receptors distributed predominantly in epithelial cells of lung and small intestines



Kim et al. *Cell.* 2020



- Vector based vaccines have been used since the 1970s
- Replication-incompetent, safe and immunogenic
- Vector technology has been applied to develop vaccine candidates against ZIKA, HIV, Flu, and Ebola

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RESEARCH ARTICLE

SARS-CoV-2 infection protects against rechallenge in rhesus macaques

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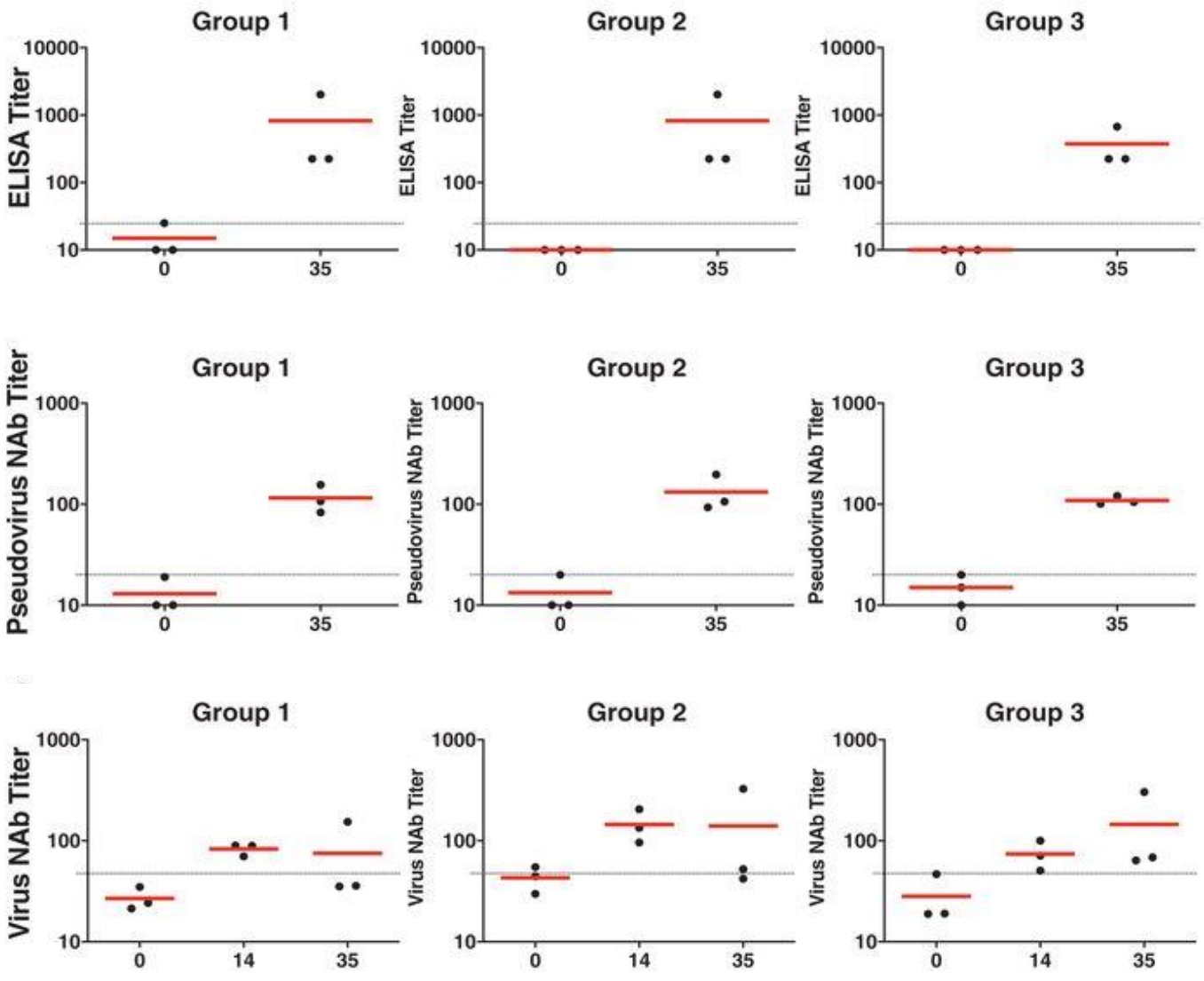
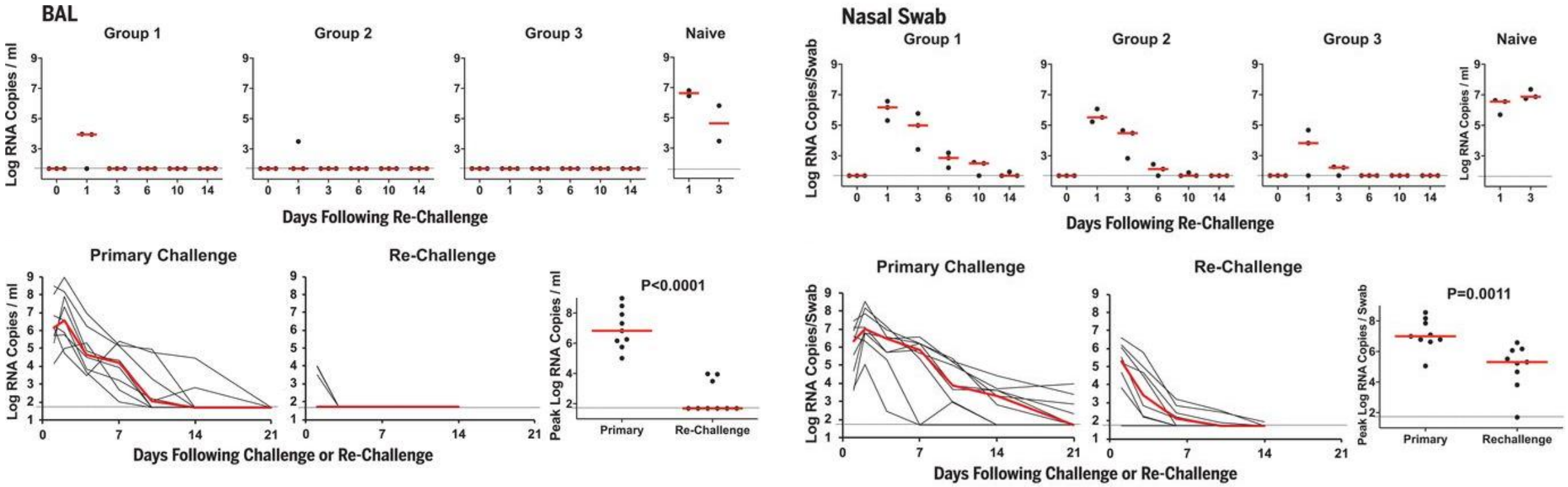
Rhesus macaques were inoculated by the IN and IT routes
1.1×10^6 PFU (Group 1; N = 3)
1.1×10^5 PFU (Group 2; N = 3)
1.1×10^4 PFU (Group 3; N = 3)



- High antibody titers are elicited post initial challenge

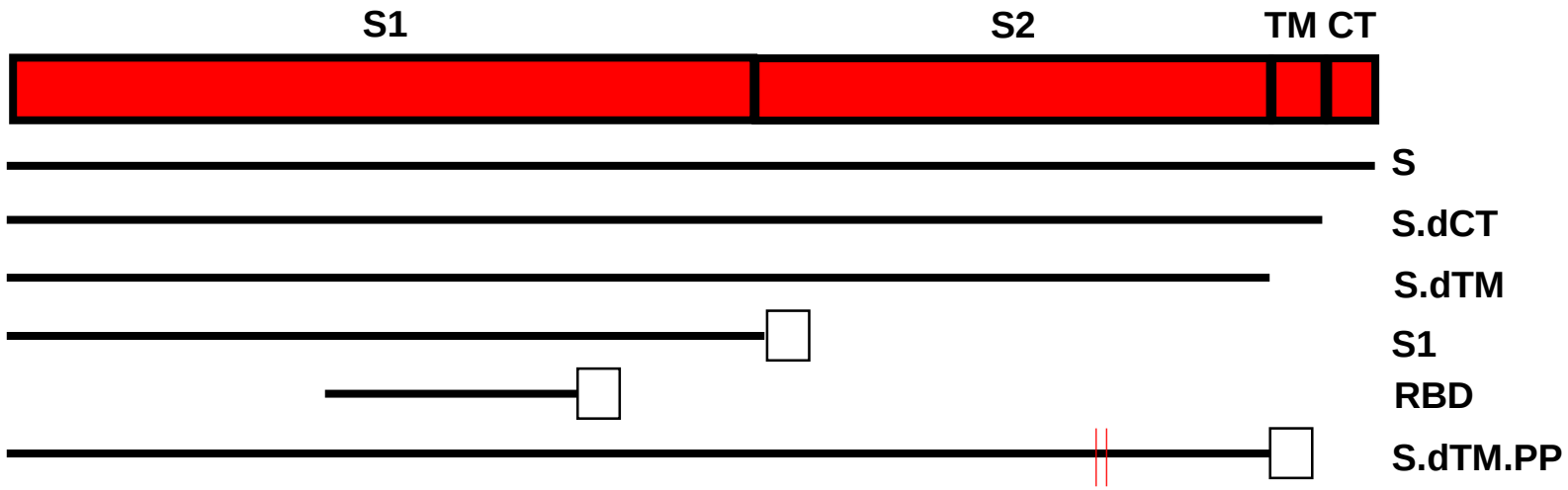
Chandrashekar et al. *Science* (2020)

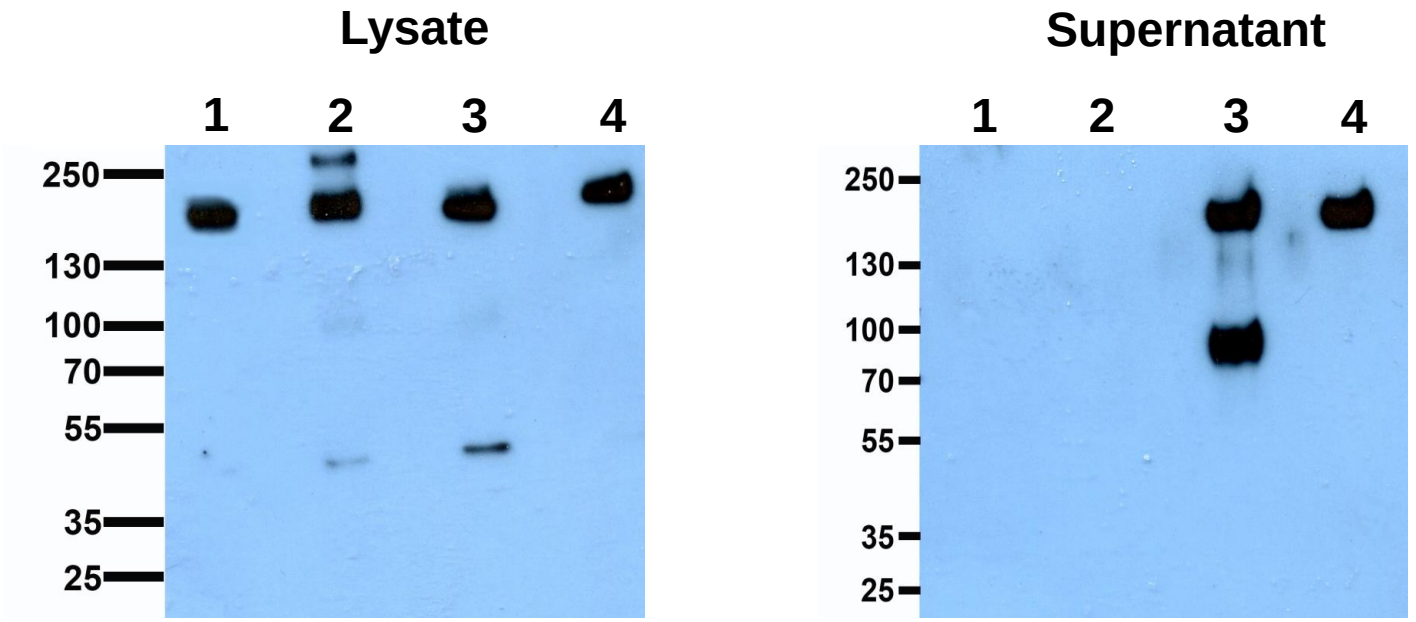


- Immunity acquired through initial infection protects against future challenge in rhesus macaques

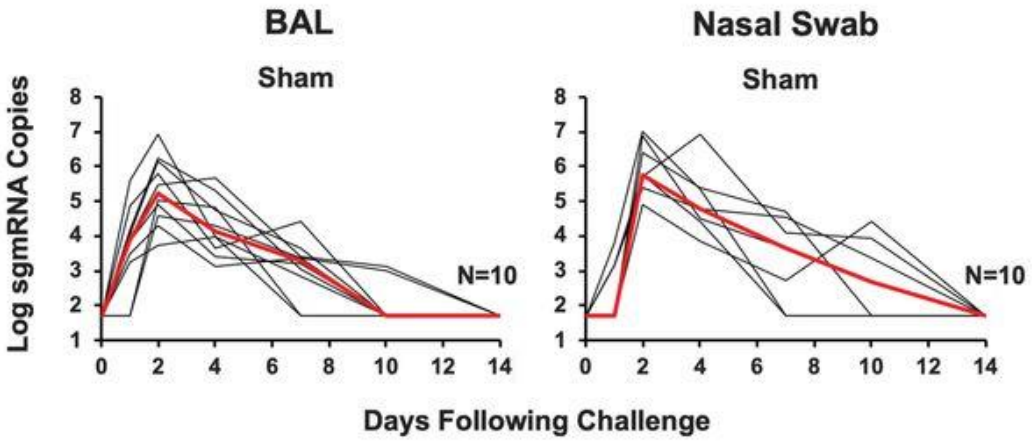
Chandrashekar et al. *Science* (2020)

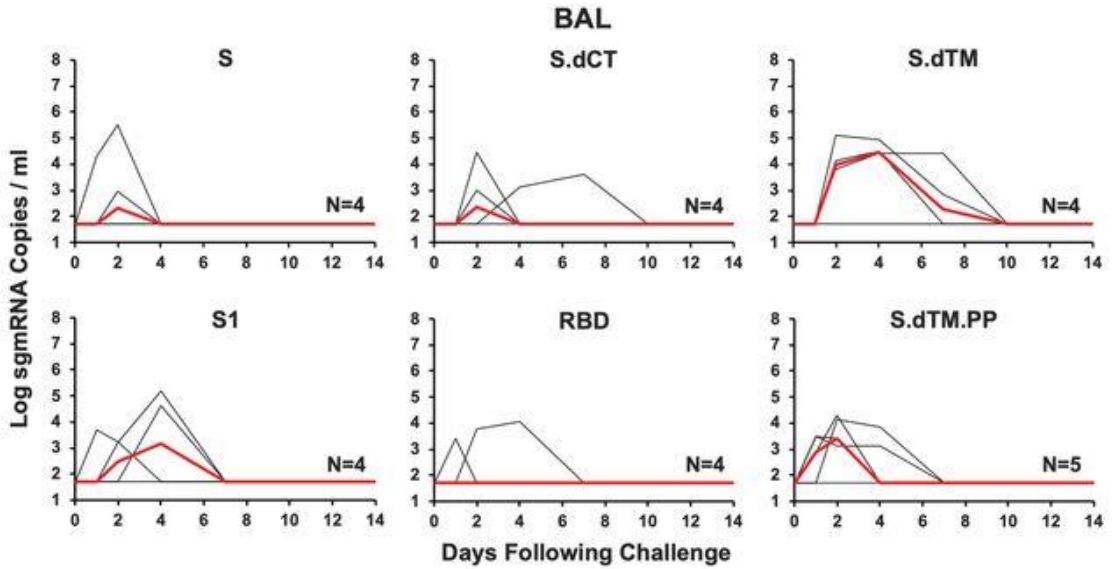
- Generate DNA vaccines expressing different versions of spike protein

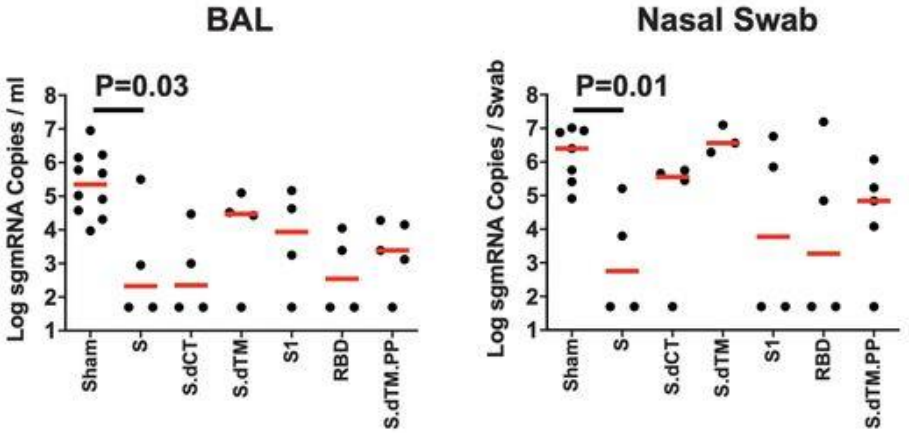


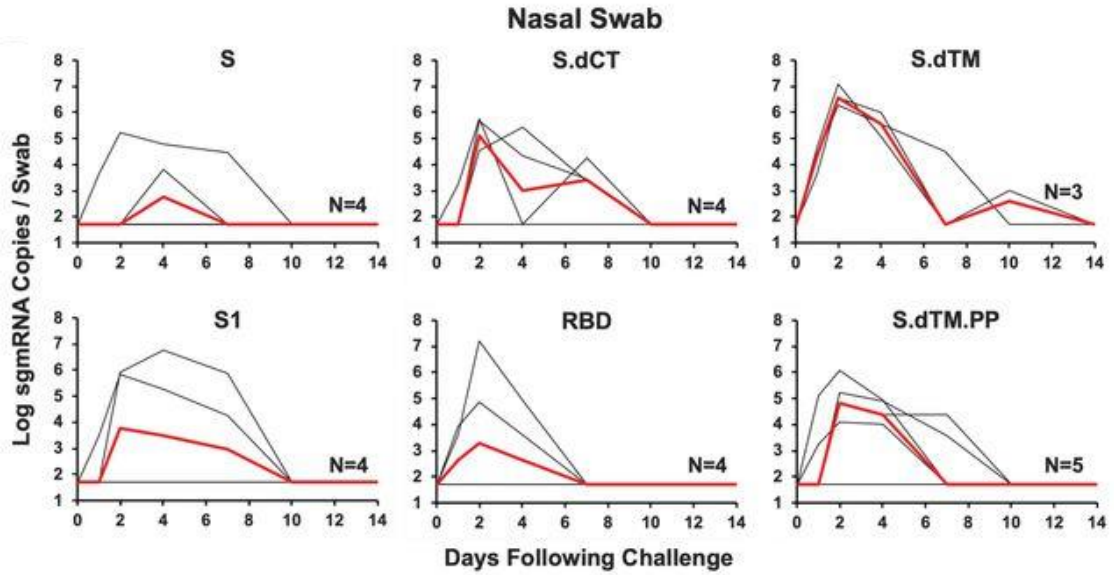


Yu et al. *Science* (2020)



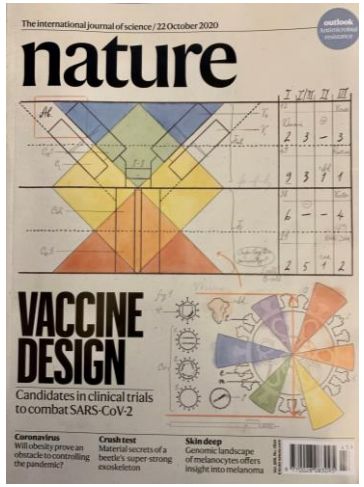






- Vaccine Dose: 5mg IM
- Challenge dose: 1.1×10^4 PFU

Yu et al. *Science* (2020)



Article

Single-shot Ad26 vaccine protects against SARS-CoV-2 in rhesus macaques

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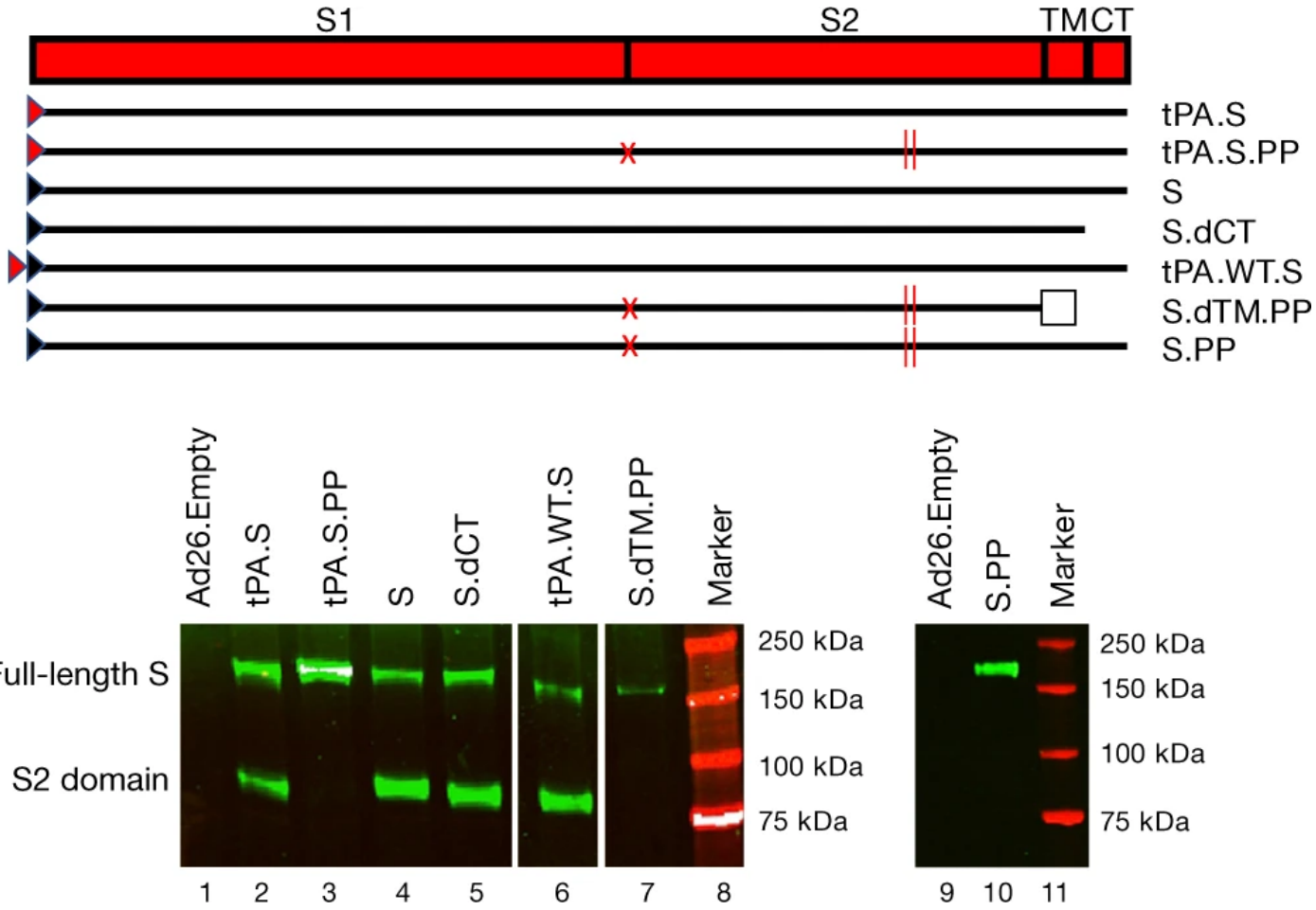
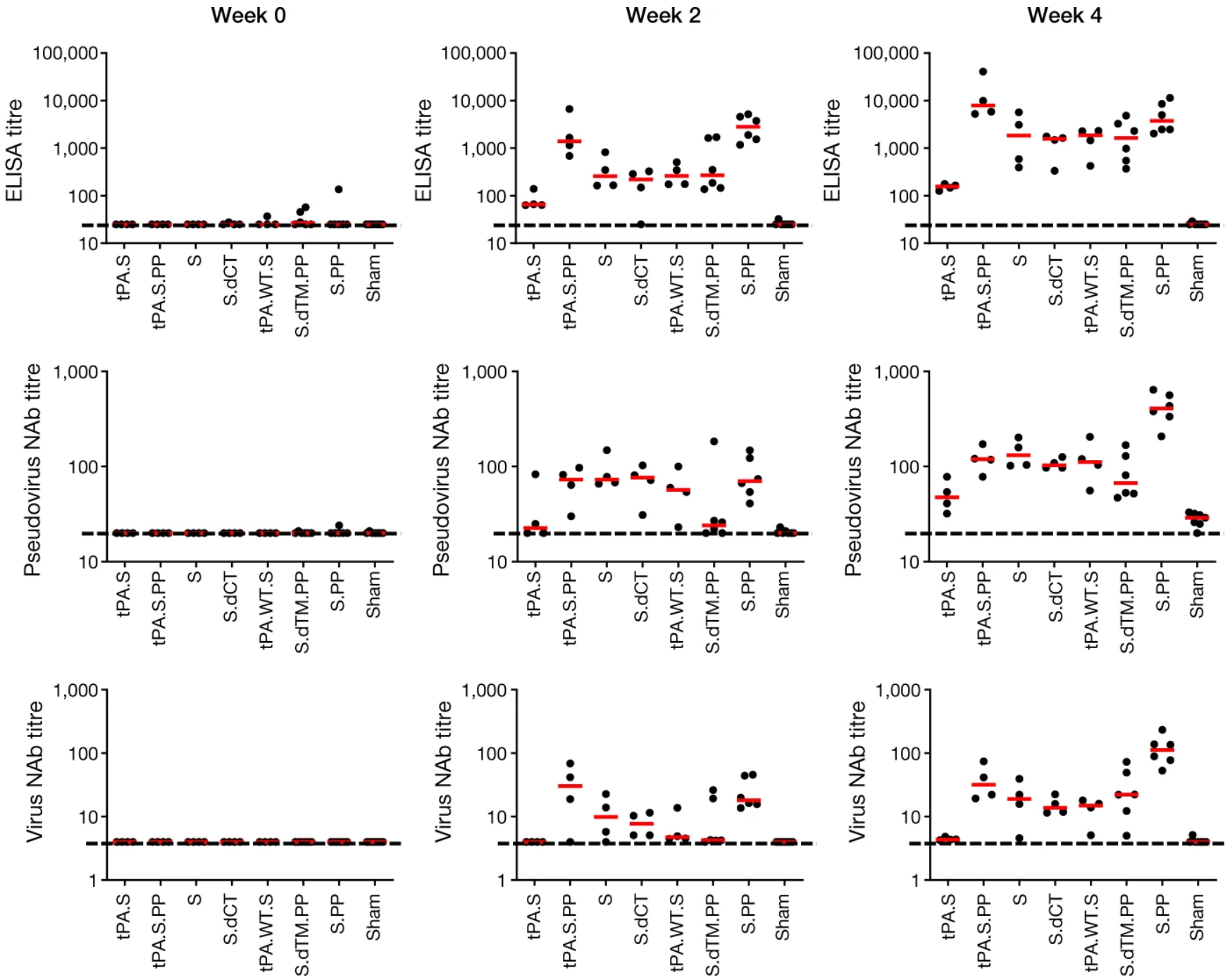
Adenovirus vector based SARS-CoV-2 Vaccine



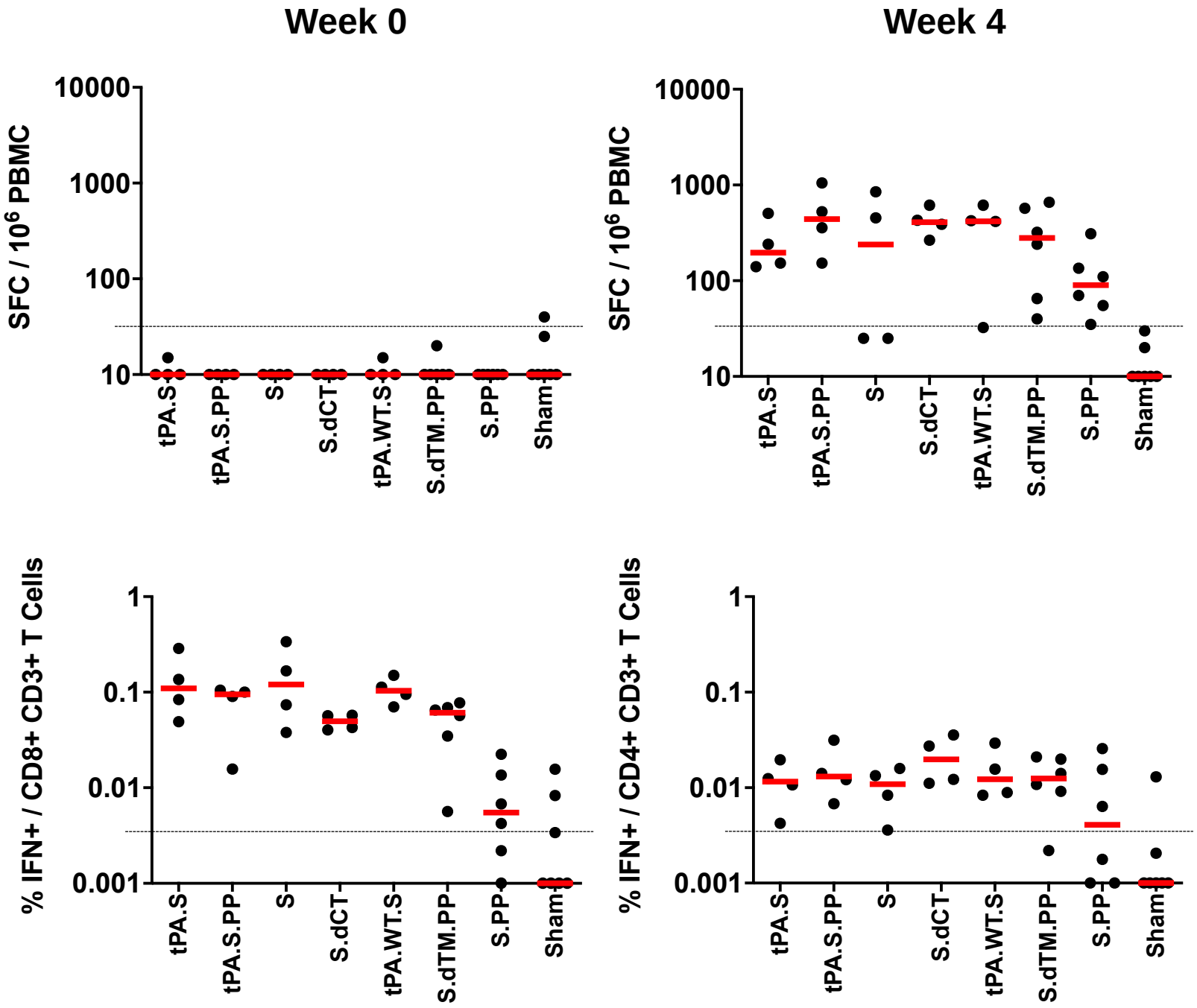
- Seven vaccines were designed in collaboration with Janssen (Johnson & Johnson)
- Recombinant Adenovirus Serotype 26 as delivery platform
- Immunized rhesus monkeys, then challenge with SARS-CoV-2

Mercado et al. *Nature* (2020)

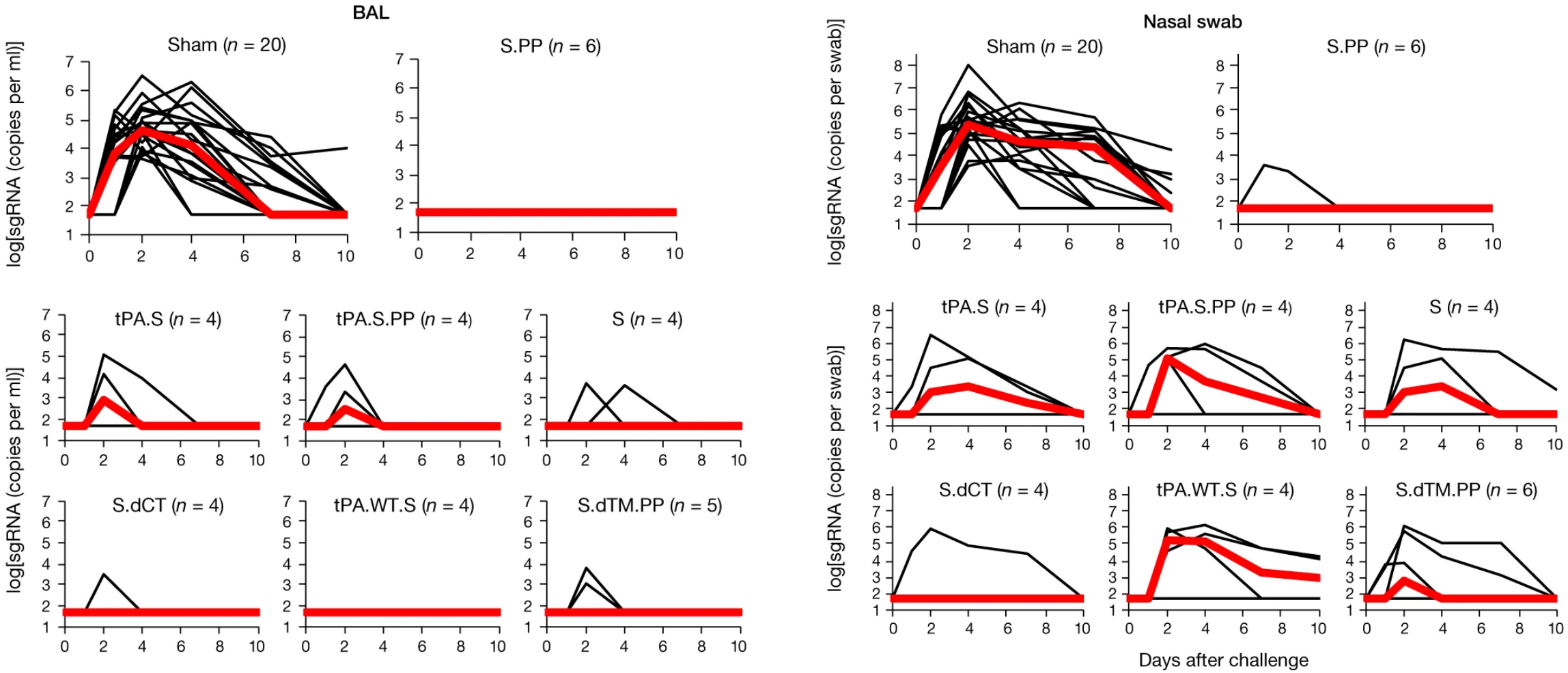


- Vaccine candidates elicited high levels of binding and neutralizing antibody titers

Mercado et al. *Nature* (2020)



Mercado et al. *Nature* (2020)



- Full protection in the lower respiratory tract and near full protection in the upper respiratory tract

Mercado et al. *Nature* (2020)

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Vaccines and Antiviral Agents

Comparison of Subgenomic and Total RNA in SARS-CoV-2 Challenged Rhesus Macaques

Gabriel Dagotto, Noe B. Mercado, David R. Martinez, Yixuan J. Hou, Joseph P. Nkolola, Robert H. Carnahan, James E. Crowe Jr, Ralph S. Baric, Dan H. Barouch

DOI: 10.1128/JVI.02370-20

Article | Info & Metrics | PDF

ABSTRACT

Respiratory virus challenge studies involve administration of the challenge virus and sampling to assess for protection from the same anatomical locations. It can therefore be difficult to differentiate actively replicating virus from input challenge virus. For SARS-CoV-2, specific monitoring of actively replicating virus is critical to investigate the protective and therapeutic efficacy of vaccines, monoclonal antibodies, and antiviral drugs. We developed a SARS-CoV-2 subgenomic RNA (sgRNA) RT-PCR assay to differentiate productive infection from inactivated or neutralized virus. Subgenomic RNAs are generated after cell entry and are poorly incorporate into mature virions, and thus may provide a marker for actively replicating virus. We show envelope (E) sgRNA was degraded by RNase in infected cell lysates, while genomic RNA (gRNA) was protected, presumably due to packaging into virions. To investigate the capacity of the sgRNA assay to distinguish input challenge virus from actively replicating virus *in vivo*, we compared the E sgRNA assay to a standard nucleoprotein (N) or E total RNA assay in convalescent rhesus macaques and in antibody-treated rhesus macaques after experimental

Abdominal Radiology
https://doi.org/10.1007/s00261-020-02753-7

INTERVENTIONAL RADIOLOGY

Feasibility and safety of ultrasound-guided minimally invasive autopsy in COVID-19 patients

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Abstract

Objectives To determine the feasibility and safety of ultrasound-guided minimally invasive autopsy in COVID-19 patients.

Methods 60 patients who expired between 04/22/2020–05/06/2020 due to COVID-19 were considered for inclusion in the study, based on availability of study staff. Minimally invasive ultrasound-guided autopsy was performed with 14G core biopsies through a 13G coaxial needle. The protocol required 20 cores of the liver, 30 of lung, 12 of spleen, 20 of heart, 20 of kidney, 4 of breast, 4 of testis, 2 of skeletal muscle, and 4 of fat with total of 112 cores per patient. Quality of the samples was evaluated by number, size, histology, immunohistochemistry, and in situ hybridization for COVID-19 and PCR-measured viral loads for SARS-CoV-2.

Results Five (5/60, 8%) patients were included. All approached families gave their consent for the minimally invasive autopsy. All organs for biopsy were successfully targeted with ultrasound guidance obtaining all required samples, apart from 2 patients where renal samples were not obtained due to atrophic kidneys. The number, size, and weight of the tissue cores met expectation of the research group and tissue histology quality was excellent. Pathology findings were concordant

LETTERS
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nature medicine

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Ad26 vaccine protects against SARS-CoV-2 severe clinical disease in hamsters

Lisa H. Tostanoski[1,10], Frank Wegmann[2,10], Amanda J. Martinot[1,3,10], Carolin Loos[4,5,10], Katherine McMahan[1,10], Noe B. Mercado[1,10], Jingyou Yu[1,10], Chi N. Chan[6], Stephen Bondoc[6], Carly E. Starke[6], Michael Nekorchuk[6], Kathleen Busman-Sahay[6], Cesar Piedra-Mora[1,3], Linda M. Wrijil[3], Sarah Ducat[3], Jerome Custers[2], Caroline Atyeo[4,7], Stephanie Fischinger[4,7], John S. Burke[4], Jared Feldman[4,7], Blake M. Hauser[4,7], Timothy M. Caradonna[4,7], Esther A. Bondzie[1], Gabriel Dagotto[1,7], Makda S. Gebre[1,7], Catherine Jacob-Dolan[1,7], Zijin Lin[1], Shant H. Mahrokhian[1], Felix Nampanya[1], Ramya Nityanandam[1], Laurent Pessaint[8], Maciel Porto[8], Vaneesha Ali[8], Dalia Benetiene[8], Komlan Tevi[8], Hanne Andersen[8], Mark G. Lewis[8], Aaron G. Schmidt[4,7,9], Douglas A. Lauffenburger[5], Galit Alter[4,9], Jacob D. Estes[6], Hanneke Schuitemaker[2], [illegible]nd Zahn[2] and Dan H. Barouch[1,4,7,9] ✉

Article

Correlates of protection against SARS-CoV-2 in rhesus macaques

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Recent studies have reported the protective efficacy of both natural[1] and vaccine-induced[2–7] immunity against challenge with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in rhesus macaques. However, the importance of humoral and cellular immunity for protection against infection with SARS-CoV-2 remains to be determined. Here we show that the adoptive transfer of purified IgG from convalescent rhesus macaques (*Macaca mulatta*) protects naive recipient macaques against challenge with SARS-CoV-2 in a dose-dependent fashion. Depletion of $CD8^+$ T cells in convalescent macaques partially abrogated the protective efficacy of natural immunity against rechallenge with SARS-CoV-2, which suggests a role for cellular immunity in the context of waning or subprotective antibody titres. These data demonstrate that relatively low antibody titres are sufficient for protection against SARS-CoV-2 in rhesus macaques, and that cellular immune responses may contribute to protection if antibody responses are suboptimal. We also show that higher antibody titres are required for treatment of SARS-CoV-2 infection in macaques. These findings have implications for the development of SARS-CoV-2 vaccines and immune-based therapeutic agents.

Article

Potently neutralizing and protective human antibodies against SARS-CoV-2

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Seth J. Zost[1,15], Pavlo Gilchuk[1,15], James Brett Case[2], Elad Binshtein[1], Rita E. Chen[2,3], Joseph P. Nkolola[4], Alexandra Schäfer[2], Joseph X. Reidy[1], Andrew Trivette[1], Rachel S. Nargi[1], Rachel E. Sutton[1], Naveenchandra Suryadevara[1], David R. Martinez[2], Lauren E. Williamson[2], Elaine C. Chen[2], Taylor Jones[1], Samuel Day[1], Luke Myers[1], Ahmed O. Hassan[2], Natasha M. Kafai[2,3], Emma S. Winkler[2,3], Julie M. Fox[2], Swathi Shrihari[2], Benjamin K. Mueller[2], Jens Meiler[7,8], Abishek Chandrashekar[4], Noe B. Mercado[4], James J. Steinhardt[9], Kuishu Ren[10], Yueh-Ming Loo[10], Nicole L. Kallewaard[10], Broc T. McCune[2], Shamus P. Keeler[2,11], Michael J. Holtzman[2,11], Dan H. Barouch[4], Lisa E. Gralinski[5], Ralph S. Baric[5], Larissa B. Thackray[2], Michael S. Diamond[2,3,12,13], Robert H. Carnahan[1,14] ✉ & James E. Crowe Jr[1,6,14] ✉

The ongoing pandemic of coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major threat to global health[1] and the medical countermeasures available so far are limited[2,3]. Moreover, we currently lack a thorough understanding of the mechanisms of humoral immunity to SARS-CoV-2[4]. Here we analyse a large panel of human monoclonal antibodies that target the spike (S) glycoprotein[5], and identify several that exhibit potent neutralizing activity and fully block the receptor-binding domain of the S protein (S_{RBD}) from interacting with human angiotensin-converting enzyme 2 (ACE2). Using competition-binding, structural and functional studies, we show that the monoclonal antibodies can be clustered into classes that recognize distinct epitopes on the S_{RBD}, as well as distinct conformational states of the S trimer. Two potently neutralizing monoclonal antibodies, COV2-2196 and COV2-2130, which recognize non-overlapping sites, bound simultaneously to the S protein and neutralized wild-type SARS-CoV-2 virus in a synergistic manner. In two mouse models of SARS-CoV-2 infection, passive transfer of COV2-2196, COV2-2130 or a combination of both of these antibodies protected mice from weight loss and reduced the viral burden and levels of inflammation in the lungs. In addition, passive transfer of either of two of the most potent ACE2-blocking monoclonal antibodies (COV2-2196 or COV2-2381) as monotherapy protected rhesus macaques from SARS-CoV-2 infection. These results identify protective epitopes on the S_{RBD} and provide a structure-based framework for rational vaccine design and the selection of robust immunotherapeutic agents.

navirus disease 2019 (COVID-19) in humans is often a ally mild illness, but some individuals develop severe monia, respiratory failure and death[1–4]. Studies of severe respiratory syndrome coronavirus 2 (SARS-CoV-2) tion in hamsters[5–7] and nonhuman primates[8–10] have rally reported mild clinical disease, and preclinical -CoV-2 vaccine studies have demonstrated reduction of replication in the upper and lower respiratory tracts in uman primates[11–13]. Here we show that high-dose intranaRS-CoV-2 infection in hamsters results in severe clinical se, including high levels of virus replication in tissues, sive pneumonia, weight loss and mortality in a subset of als. A single immunization with an adenovirus serotype ctor-based vaccine expressing a stabilized SARS-CoV-2 protein elicited binding and neutralizing antibody nses and protected against SARS-CoV-2-induced t loss, pneumonia and mortality. These data demone vaccine protection against SARS-CoV-2 clinical dis. This model should prove useful for preclinical studies of -CoV-2 vaccines, therapeutics and pathogenesis.

RS-CoV-2 can infect nonhuman primates[8–10], hamsters[5–7], fer-[16], hACE2 transgenic mice[17,18] and other species[16], but clinical e in these models has generally been mild. A severe pneumodel would be useful for preclinical evaluation of SARS-CoV-2 es and other countermeasures, because SARS-CoV-2 infecn humans can lead to severe clinical disease, respiratory failure ortality[1–4]. We assessed the clinical and virologic characterof high-dose SARS-CoV-2 infection in hamsters and evalue protective efficacy of an adenovirus serotype 26 (Ad26) vector-based vaccine[19] encoding a stabilized SARS-CoV-2 spike (S) in this stringent model.

We inoculated 20 Syrian golden hamsters (10–12 weeks old) with 5×10^4 50% tissue culture infective dose ($TCID_{50}$) ($n=4$; low-dose) or 5×10^5 $TCID_{50}$ ($n=16$; high-dose) SARS-CoV-2 by the intranasal route. In the high-dose group, four animals were necropsied on day 2, four animals were necropsied on day 4 for tissue viral loads and histopathology and the remaining eight animals were followed longitudinally. All remaining animals were necropsied on day 14. In the low-dose group, hamsters lost a median of 14.7% of body weight by day 6 but fully recovered by day 14 (Fig. 1a,b), consistent with previous studies[5–7]. In the high-dose group, hamsters lost a median of 19.9% of body weight by day 6. Of the eight animals in this group that were followed longitudinally, four met Institutional Animal Care and Use Committee humane euthanasia criteria of more than 20% weight loss and respiratory distress on day 6, and two additional animals met these criteria on day 7. The remaining two animals recovered by day 14. These data demonstrate that high-dose SARS-CoV-2 infection in hamsters led to severe weight loss and partial mortality.

Tissue viral loads were assessed in the four animals that received high-dose SARS-CoV-2 and were necropsied on day 2, the four animals that were necropsied on day 4 and five of six of the animals that met euthanasia criteria on days 6–7 (Fig. 1c). High median tissue viral loads on day 2 of 10^{12} RNA copies per gram in lung tissue and 10^8–10^9 RNA copies per gram in nares and trachea were observed, with a median of 10^5–10^8 RNA copies per gram in heart, gastrointestinal tract, brain, spleen, liver and kidney, indicative of disseminated infection. By days 6–7, tissue viral loads were approximately 2 logs lower, despite continued weight loss.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Interim Results of a Phase 1–2a Trial of Ad26.COV2.S Covid-19 Vaccine

J. Sadoff, M. Le Gars, G. Shukarev, D. Heerwegh, C. Truyers, A.M. de Groot, J. Stoop, S. Tete, W. Van Damme, I. Leroux-Roels, P.-J. Berghmans, M. Kimmel, P. Van Damme, J. de Hoon, W. Smith, K.E. Stephenson, S.C. De Rosa, K.W. Cohen, M.J. McElrath, E. Cormier, G. Scheper, D.H. Barouch, J. Hendriks, F. Struyf, M. Douoguih, J. Van Hoof, and H. Schuitemaker

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Low-Dose Vaccine Group	High-Dose Vaccine Group	Placebo Group	All Participants
Cohort 1 (ages 18–55 yr)†				
No. of participants	162	158	82	402
Sex — no. (%)				
Male	78 (48)	72 (46)	40 (49)	190 (47)
Female	84 (52)	85 (54)	42 (51)	211 (52)
Nonbinary	0	1 (1)	0	1 (<1)
Age — yr				
Mean	36.1±10.1	34.8±10.3	35.4±10.0	35.4±10.2
Range	18–55	19–55	19–55	18–55
Race or ethnic group — no. (%)‡				
White	149 (92)	145 (92)	70 (85)	364 (91)
Black	4 (2)	7 (4)	9 (11)	20 (5)
Asian	5 (3)	5 (3)	0	10 (2)
Native Hawaiian or other Pacific Islander	1 (1)	0	0	1 (<1)
American Indian or Alaska Native	3 (2)	0	0	3 (1)
Hispanic or Latino	8 (5)	5 (3)	4 (5)	17 (4)
Multiple	0	1 (1)	0	1 (<1)
Unknown	0	0	3 (4)	3 (1)
Body-mass index§	24.5±3.3	24.6±3.1	24.5±3.0	24.6±3.2
SARS-CoV-2 seropositive — no. (%)¶	3 (2)	2 (1)	2 (2)	7 (2)
Cohort 3 (age ≥65 yr)				
No. of participants	161	161	81	403
Sex — no. (%)				
Male	84 (52)	79 (49)	38 (47)	201 (50)
Female	77 (48)	82 (51)	43 (53)	202 (50)
Age — yr				
Mean	69.6±4.0	70.0±4.2	69.9±3.7	69.8±4.0
Range	65–83	65–88	65–79	65–88
Race or ethnic group — no. (%)				
White	158 (98)	158 (98)	81 (100)	397 (99)
Black	1 (1)	2 (1)	0	3 (1)
American Indian or Alaska Native	1 (1)	0	0	1 (<1)
Hispanic or Latino	1 (1)	2 (1)	3 (4)	6 (1)
Unknown	1 (1)	0	0	1 (<1)
Not reported	0	1 (1)	0	1 (<1)
Body-mass index§	25.3±2.8	25.5±2.7	25.2±3.1	25.4±2.8
SARS-CoV-2 seropositive — no. (%)	1 (1)	2 (1)	1 (1)	4 (1)

- Low dose= 5×10^{10} viral particles
- High dose=1×10^{11} viral particles
- Most frequent solicited adverse events were fatigue, headache, myalgia, and injection-site pain
- Systemic adverse event: fever

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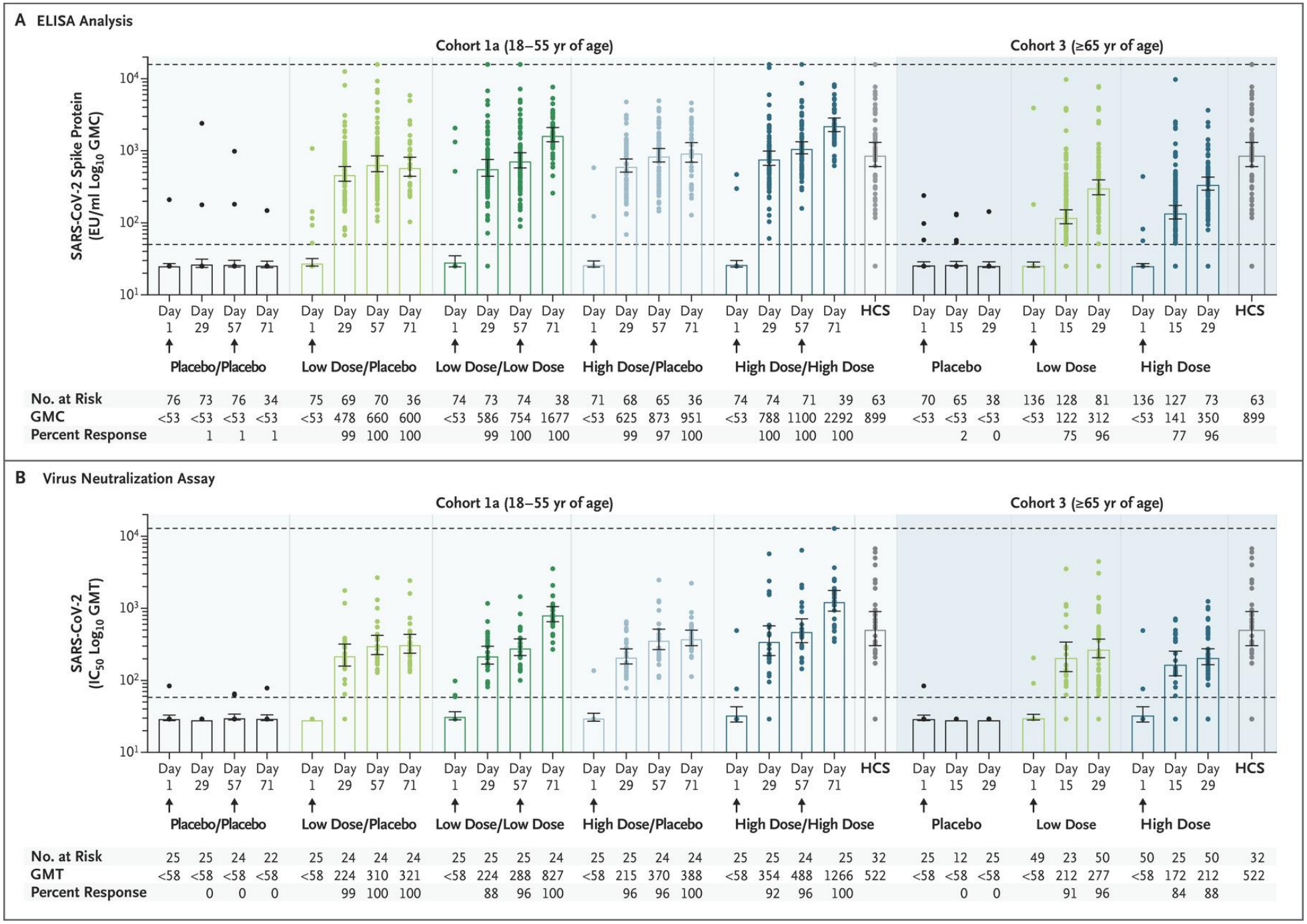

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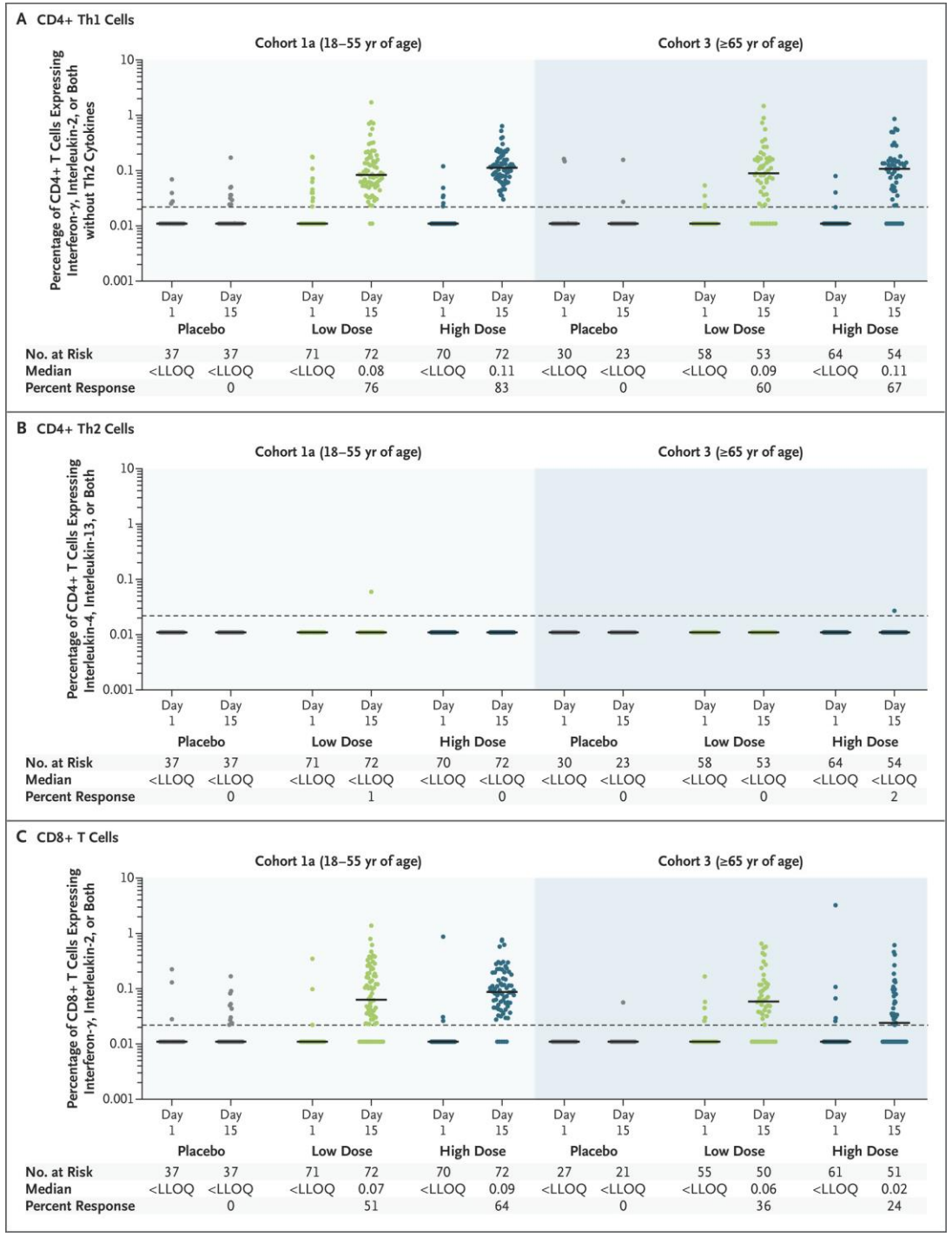

- 83% of participants had detectable CD4+ T cell responses on day 15
- 67% in cohort 3
- CD8+ T cell responses were robust overall but slightly lower in cohort 3

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BROUCH Lab

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