COVID-19 Vaccine Safety Considerations

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Disclaimer

- Kathryn Edwards MD is the Principal Investigator of the CDC-funded Clinical Immunization Safety Assessment (CISA) Project
- The findings and conclusions in this presentation are those of the author and do not represent the official position of CDC

Previous vaccine enhanced disease

- Respiratory syncytial virus
- Dengue

Animal vaccines for SARS

Animal models for SARS 2

- Challenge/Rechallenge Studies
- Chimp adenovirus vaccine

Vaccine Studies in Humans

- Chimp adenovirus vaccine
- mRNA vaccines

Outline of the Presentation

AMERICAN JOURNAL OF EPIDEMIOLOGY
Vol. 89, No. 4

RESPIRATORY SYNCYTIAL VIRUS DISEASE IN INFANTS DESPITE PRIOR ADMINISTRATION OF ANTIGENIC INACTIVATED VACCINE[1, 2]

HYUN WHA KIM, JOSE G. CANCHOLA[3], CARL D. BRANDT, GLORIA PYLES, ROBERT M. CHANOCK, KEITH JENSEN, AND ROBERT H. PARROTT[4]

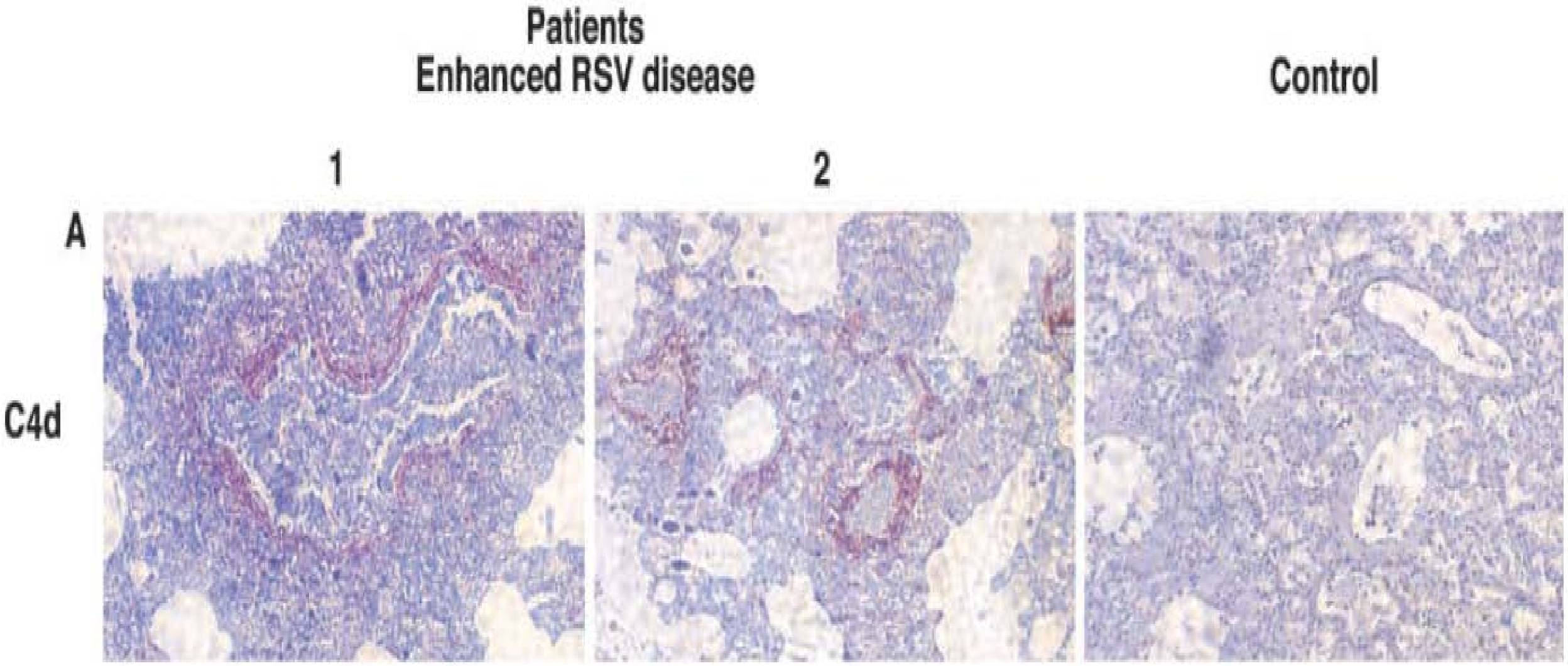
(Received for publication August 8, 1968)

RS complement fixing (CF) and neutralizing antibody (NA) status of infants who received inactivated RS virus vaccine (lot 100) or inactivated parainfluenza virus vaccines (lot 23 and lot 6279)

Vaccine	Time of antibody determination	No. in group	4-fold or greater rise in antibody			
			CF antibody		Neutralizing antibody	
			No. infants	Mean fold rise	No. infants	Mean fold rise
Respiratory syncytial vaccine (lot 100)	After 1 injection	31	4 (13%)	2.7	1 (3%)	0.8
	After 2 injections	29	18 (62%)	21	5 (17%)	1.6
	After 3 injections	23	21 (91%)	30	10 (43%)	2.6
	Natural RS virus infection with recovery of virus	16	15 (94%)	165	12 (75%)	21

RS virus infection and serious illness in comparable groups of infants receiving one or more injections of inactivated RS and parainfluenza vaccines

Vaccine	Category of infants	No. and age of infants during designated time period of RS virus prevalence				
		1965–1966		1966–1967		Total No. infants
		No. infants	Age§ (mo.)	No. infants	Age§ (mo.)	
RS lot 100	At risk*	20	5.1	25‡	12.7	31
	RS infection†	5		15		20 (65%)‖
	Hospitalized	4		12		16 (80%)¶
Para 1 lot 23	At risk*	20	5.0	17‡	15.8	20
	RS infection†	2		10		12 (60%)‖
	Hospitalized			1		1 (8%)¶



Deposition of C4d in pulmonary tissue of both patients (1 and 2) who died of ERD in 1967

Eosinophils noted in lung tissues

The Journal of Experimental Medicine • Volume 196, Number 6, September 16, 2002 859–865

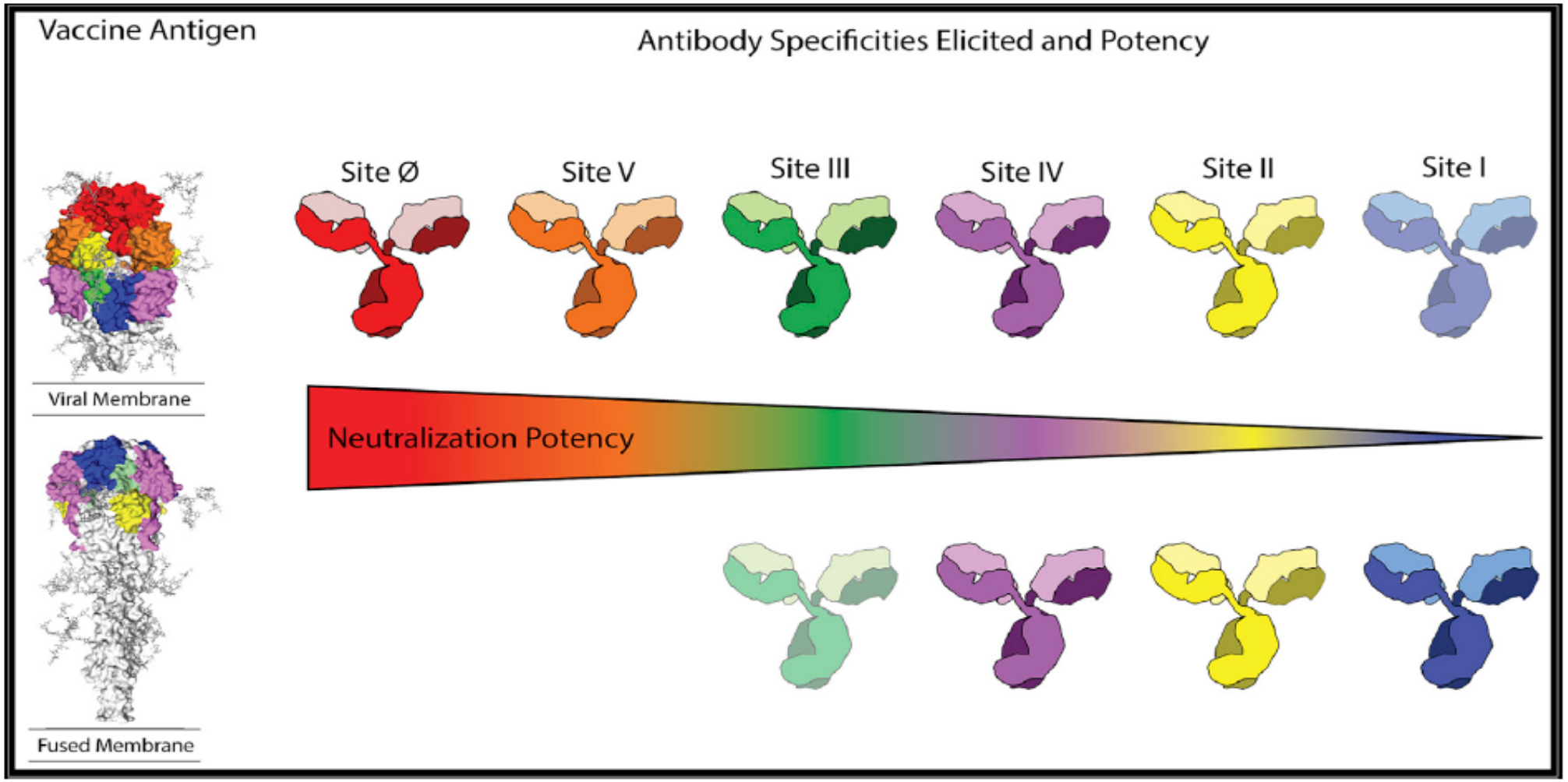


Figure 3. Antigenic Site-Specific Antibodies Elicited by Pre-F or Post-F Antigens

Pre-F elicits antibodies to all the antigenic sites that have been identified on the F protein. While post-F elicits antibodies to antigenic sites I, II, III, and IV, which can sometimes recognize shared surfaces on the pre-F structure, it does not display sites Ø and V, which have been shown to elicit antibodies with high neutralizing activity. Antibodies targeting site I show preference for post-F and tend to have low neutralizing activity, while those that target site III show preference for pre-F and have relatively potent neutralizing activity.

Immunity 51, September 17, 2019 Published by Elsevier Inc.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

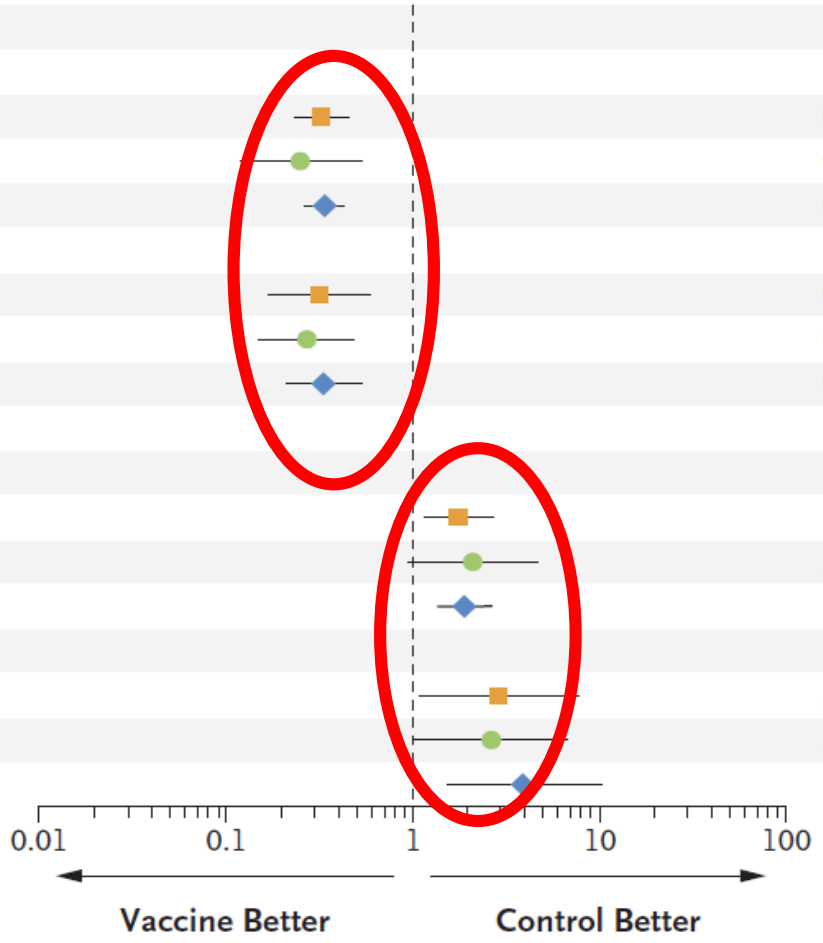
Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy

S. Sridhar, A. Luedtke, E. Langevin, M. Zhu, M. Bonaparte, T. Machabert, S. Savarino, B. Zambrano, A. Moureau, A. Khromava, Z. Moodie, T. Westling, C. Mascareñas, C. Frago, M. Cortés, D. Chansinghakul, F. Noriega, A. Bouckenooghe, J. Chen, S.-P. Ng, P.B. Gilbert, S. Gurunathan, and C.A. DiazGranados

Risk of Hospitalization for Virologically Confirmed Dengue (VCD) and of Severe VCD

B 2–16 Yr of Age

Serostatus, End Point, and Method	Vaccine Group	Control Group	Relative Risk or Hazard Ratio (95% CI)
	no./total no.		
Seropositive			
Hospitalization for VCD			
MI, month 0 onward	152.4/1816.1	227.5/886.2	0.32 (0.23–0.45)
TMLE, month 0 onward	99.2/1742.3	199.5/846.7	0.25 (0.12–0.53)
NS1, T9, month 13 onward	124/1750	175/822	0.34 (0.26–0.43)
Severe VCD			
MI, month 0 onward	35.1/1816.1	53.4/886.2	0.31 (0.17–0.58)
TMLE, month 0 onward	28.2/1742.3	49.9/846.7	0.27 (0.15–0.48)
NS1, T9, month 13 onward	31/1750	44/822	0.33 (0.21–0.53)
Seronegative			
Hospitalization for VCD			
MI, month 0 onward	201.6/567.9	62.5/307.8	1.75 (1.14–2.70)
TMLE, month 0 onward	244.0/547.2	65.5/296.8	2.10 (0.94–4.70)
NS1, T9, month 13 onward	187/512	53/272	1.89 (1.35–2.65)
Severe VCD			
MI, month 0 onward	44.9/567.9	8.6/307.8	2.87 (1.09–7.61)
TMLE, month 0 onward	44.6/547.2	9.3/296.8	2.62 (1.03–6.70)
NS1, T9, month 13 onward	37/512	5/272	3.93 (1.53–10.10)



Mechanisms of Vaccine-Enhanced Disease

Immune response	Antibody		T cell
Syndrome	Antibody-dependent enhancement (ADE)	Vaccine-associated enhanced respiratory disease (VAERD)	
Mechanism	Fc-mediated increase in viral entry	Immune complex formation Complement deposition	T_H2-biased immune response
Effectors	Macrophage activation Inflammatory cytokines	Complement activation Inflammatory cytokines	Allergic inflammation T_H2 cytokines
Mitigation	Conformationally correct antigens High quality neutralizing antibody		T_H1-biasing immunization $CD8^+$ T cells

Rapid COVID-19 Vaccine Development: Finding the fastest pathway to vaccine availability includes the avoidance of safety pitfalls . Science 2020

Vaccine 38 (2020) 4783–4791

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Conference report

Consensus summary report for CEPI/BC March 12–13, 2020 meeting: Assessment of risk of disease enhancement with COVID-19 vaccines

Paul-Henri Lambert [a], Donna M. Ambrosino [b], Svein R. Andersen [c], Ralph S. Baric [d], Steven B. Black [e], Robert T. Chen [e], Cornelia L. Dekker [e,*], Arnaud M. Didierlaurent [a], Barney S. Graham [g], Samantha D. Martin [h], Deborah C. Molrine [i], Stanley Perlman [j], Philip A. Picard-Fraser [k], Andrew J. Pollard [l], Chuan Qin [f], Kanta Subbarao [m], Jakob P. Cramer [n]

Enhanced Disease in Animal Models after SARS-Cov1 Vaccines

Table 1
Evidence of enhanced disease in SARS-CoV-1 vaccine candidates.

Animal Model	Vaccine	Adjuvant	Immunopathology	Reference
Murine[1]	VEE Replicon Particles expressing N protein	–	YES	Deming 2006
Murine[2]	Recombinant Vaccinia virus expressing N protein	–	YES	Yasui 2008
Murine[3]	Inactivated Whole Virus	Alum	YES	Bolles 2011
		–	YES	
Murine[4]	Replicon Particles expressing S protein	–	YES	Sheahan 2011
Murine[5]	Inactivated Whole Virus and S protein vaccines	Alum	YES	Tseng 2012
		–	YES	
Ferret[6]	Recombinant Modified Vaccinia Virus Ankara (rMVA) expressing S protein	–	YES[†]	Weingartl 2004
NHP[7]	Modified Vaccinia Ankara (MVA) virus encoding full-length S protein	–	YES	Liu 2019
	Passive anti-S sera	N/A	YES	
NHP[7]	Inactivated Whole Virus	–	YES	Wang 2016/2020
	Passive Human SARS Antiserum	N/A	YES	

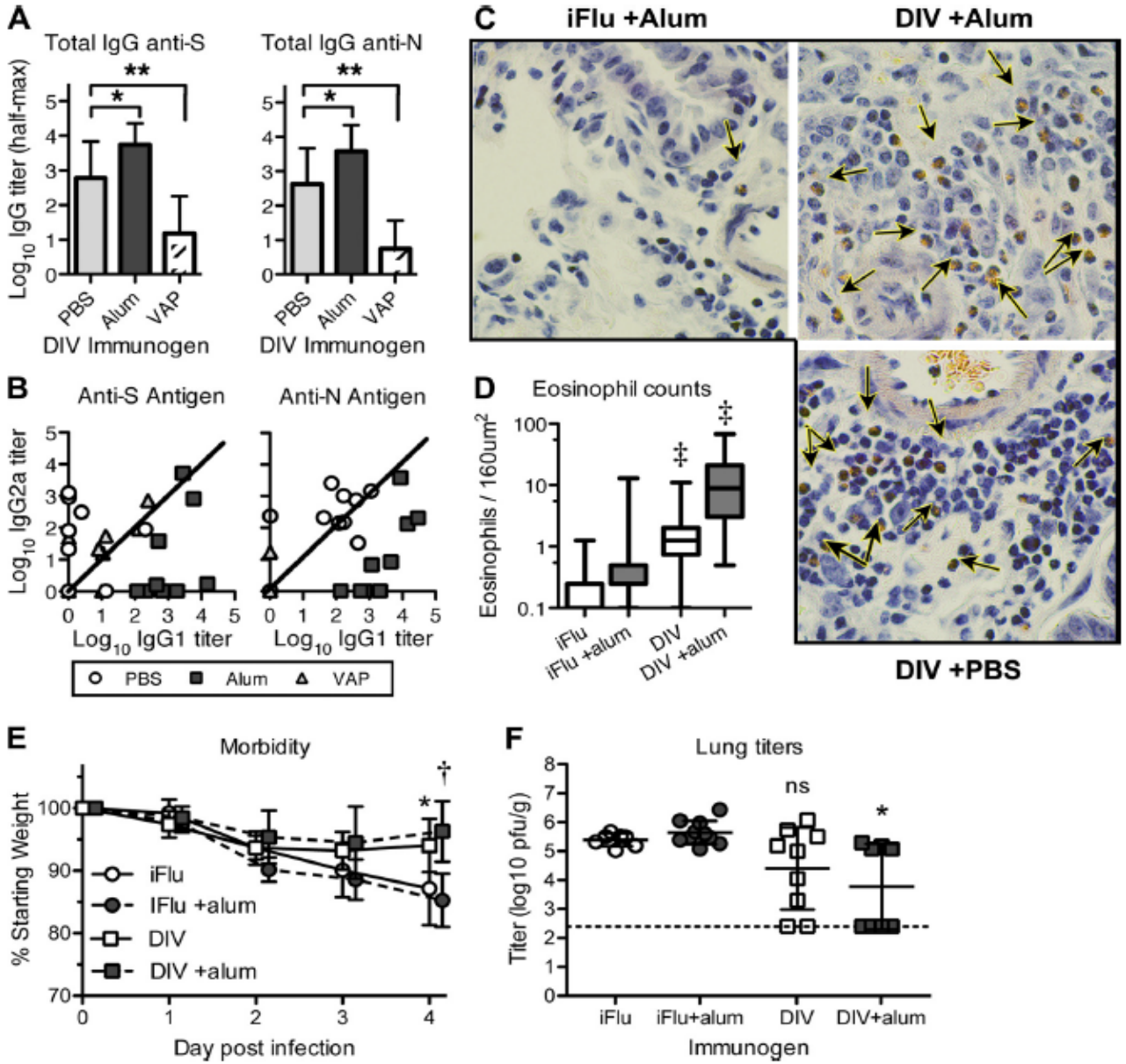
[1] Young and senescent female BALB/c mice.
[2] BALB/c mice.
[3] Aged BALB/c mice.
[4] Young and aged BALB/c mice.
[5] Female BALB/c mice.
[6] *Mustela putorius furo*, castrated males.
[7] Chinese rhesus macaque.
[†] Acute hepatitis.

JOURNAL OF VIROLOGY, Dec. 2011, p. 12201–12215 Vol. 85, No.
0022-538X/11/$12.00 doi:10.1128/JVI.06048-11

A Double-Inactivated Severe Acute Respiratory Syndrome Coronavirus Vaccine Provides Incomplete Protection in Mice and Induces Increased Eosinophilic Proinflammatory Pulmonary Response upon Challenge[▽]

Meagan Bolles,[1]† Damon Deming,[1]† Kristin Long,[2] Sudhakar Agnihothram,[3] Alan Whitmore,[2] Martin Ferris,[2] William Funkhouser,[4] Lisa Gralinski,[3] Allison Totura,[1] Mark Heise,[1,2,5] and Ralph S. Baric[1,3]*

DIV vaccination and nonlethal heterologous challenge in aged animals.



CEPI/Brighton Collaboration Consensus Meeting

Concluding remarks

- The group of Experts considers that the demonstration of some disease enhancement with any candidate vaccine after viral challenge in animal models should not necessarily represent a no-go signal for deciding whether to progress into early trials in clinical development of a COVID-19 vaccine.
- Continuous monitoring of this risk during clinical trials in an epidemic context will be needed.
- Each observed effect should be discussed by the developers with their regulators who will ultimately define the actual requirements for clinical studies.

CORONAVIRUS

Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model

Barry Rockx[1]*, Thijs Kuiken[1], Sander Herfst[1], Theo Bestebroer[1], Mart M. Lamers[1], Bas B. Oude Munnink[1], Dennis de Meulder[1], Geert van Amerongen[2], Judith van den Brand[1]†, Nisreen M. A. Okba[1], Debby Schipper[1], Peter van Run[1], Lonneke Leijten[1], Reina Sikkema[1], Ernst Verschoor[3], Babs Verstrepen[3], Willy Bogers[3], Jan Langermans[4,5], Christian Drosten[6], Martje Fentener van Vlissingen[7], Ron Fouchier[1], Rik de Swart[1], Marion Koopmans[1], Bart L. Haagmans[1]*

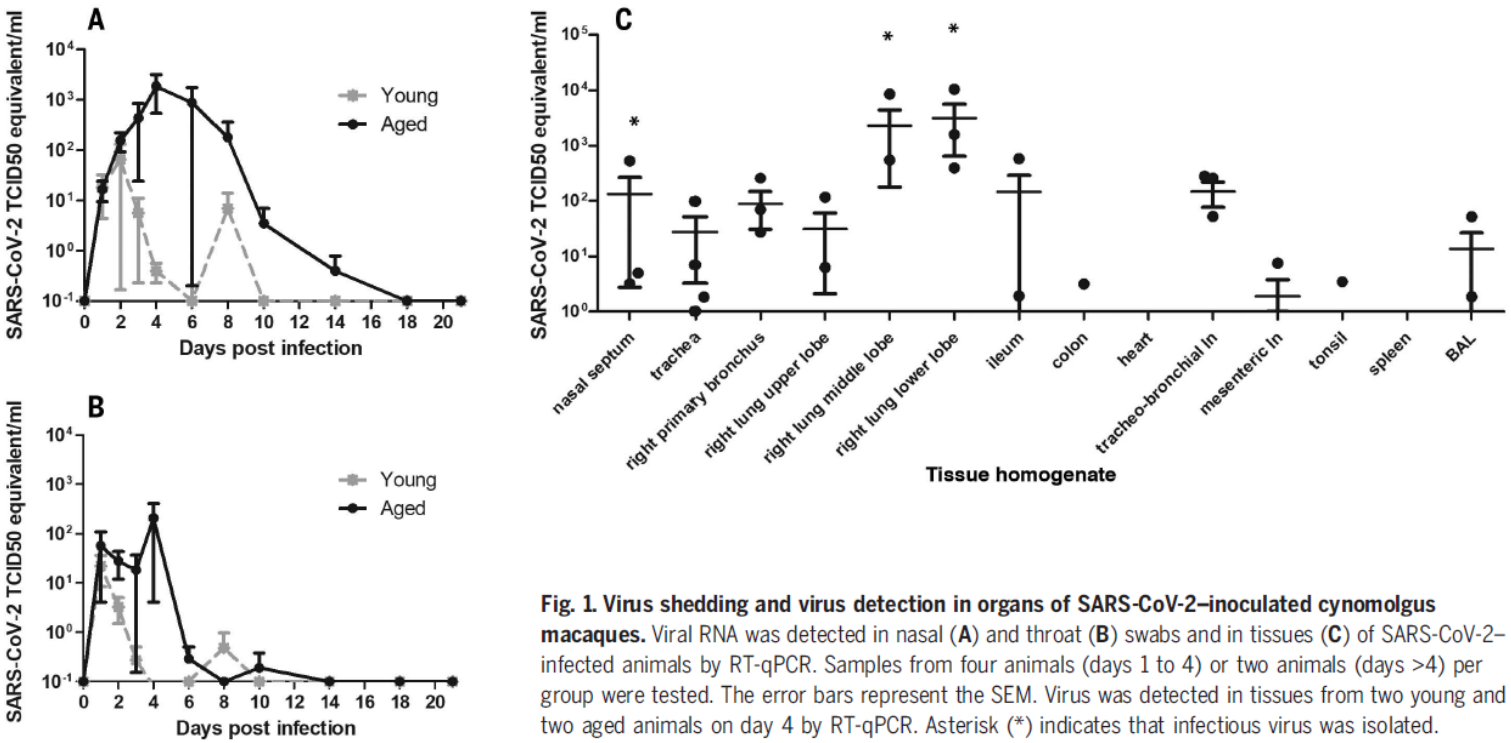
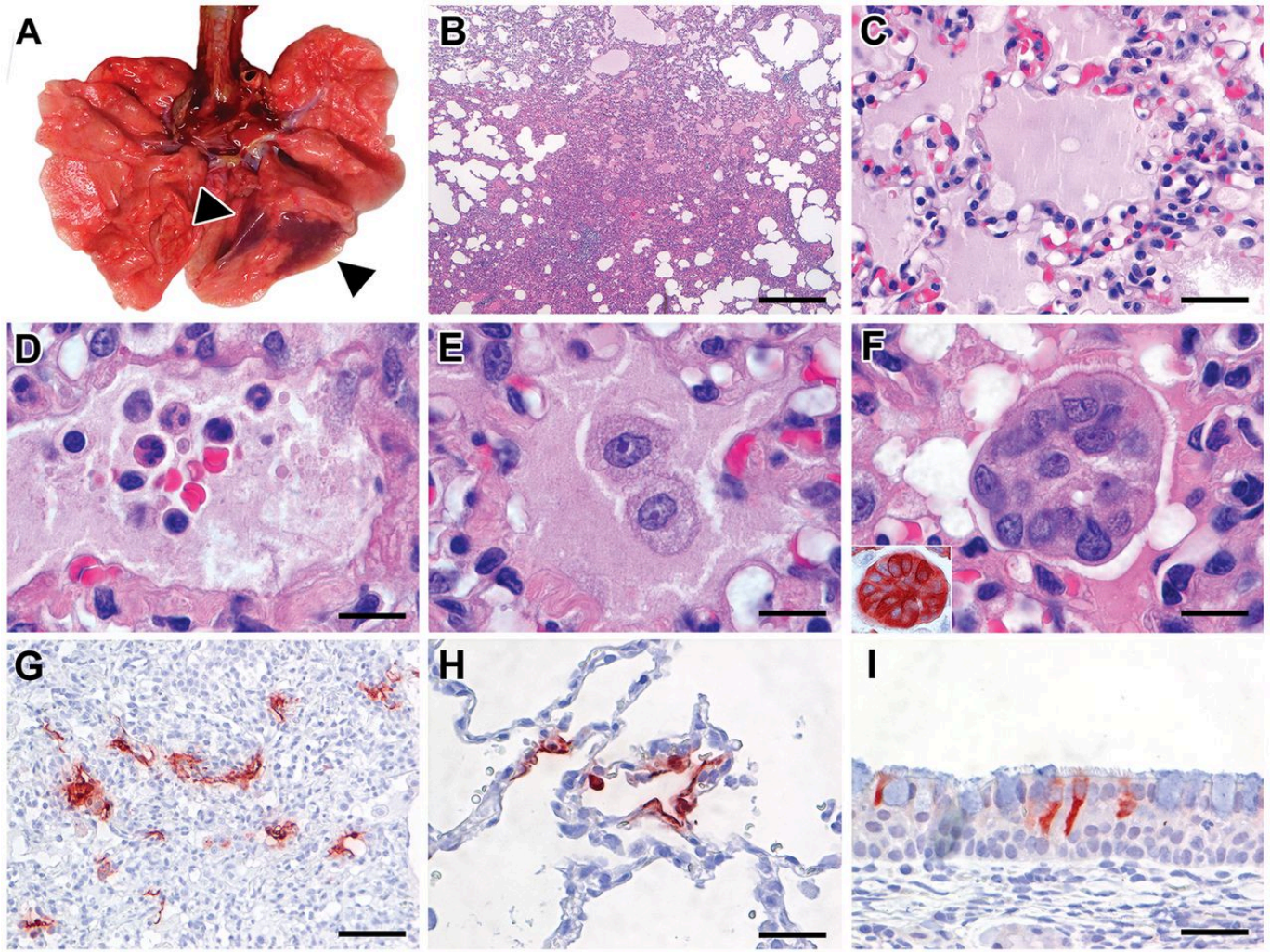


Fig. 1. Virus shedding and virus detection in organs of SARS-CoV-2–inoculated cynomolgus macaques. Viral RNA was detected in nasal (**A**) and throat (**B**) swabs and in tissues (**C**) of SARS-CoV-2–infected animals by RT-qPCR. Samples from four animals (days 1 to 4) or two animals (days >4) per group were tested. The error bars represent the SEM. Virus was detected in tissues from two young and two aged animals on day 4 by RT-qPCR. Asterisk (*) indicates that infectious virus was isolated.

Rockx *et al.*, *Science* **368**, 1012–1015 (2020) 29 May 2020

Fig. 2 Characteristic pathological changes and virus antigen expression in the lungs of SARS-CoV-2-inoculated cynomolgus macaques.



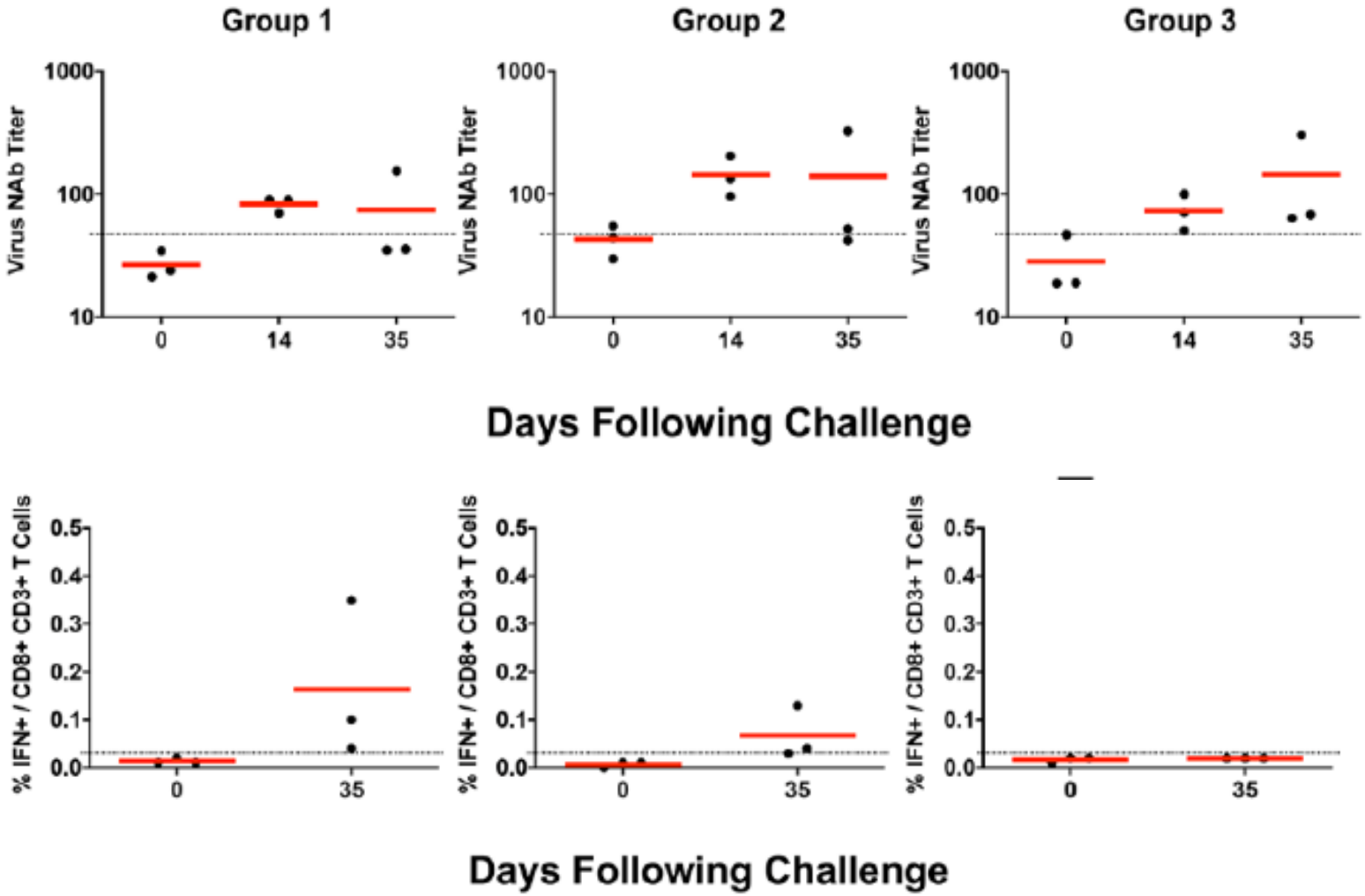
Barry Rockx et al. Science 2020;science.abb7314

Cite as: A. Chandrashekar *et al.*, *Science*
10.1126/science.abc4776 (2020).

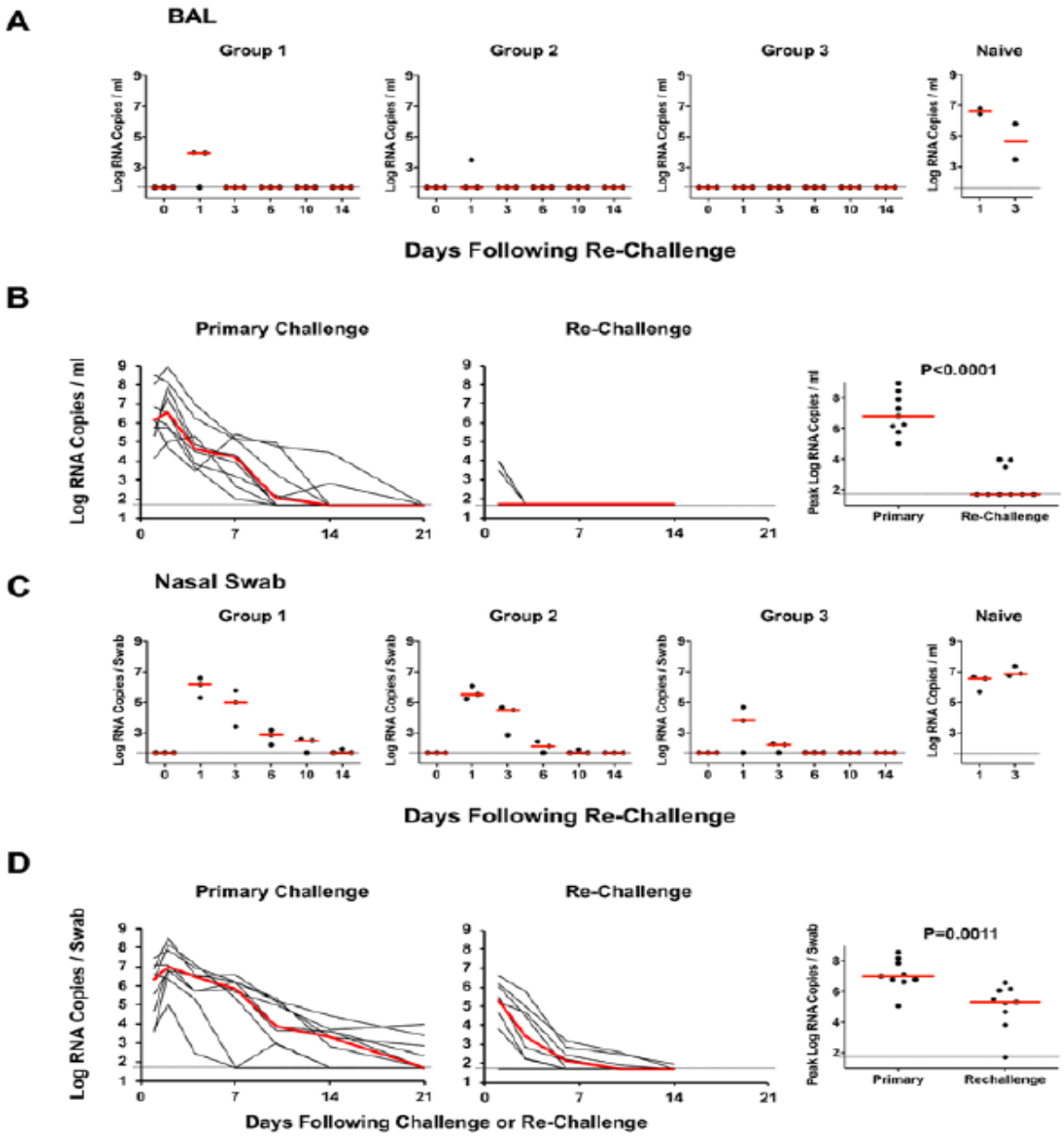
SARS-CoV-2 infection protects against rechallenge in rhesus macaques

Neutralizing Antibody

Th1 response



Viral loads following SARS-CoV-2 rechallenge in rhesus macaques



Cite as: A. Chandrashekar *et al.*, *Science* 10.1126/science.abc4776 (2020).

Vaccine Studies in Nonhuman Primates

ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques

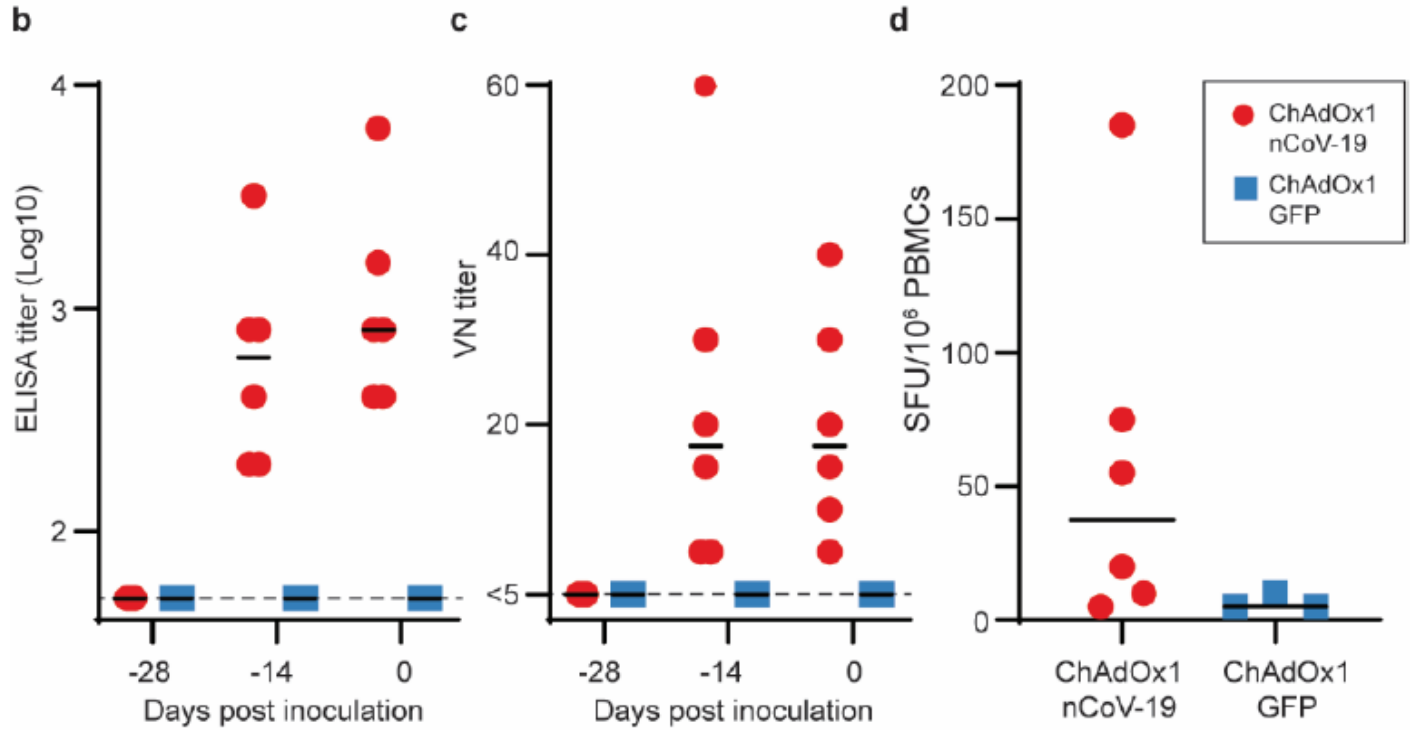
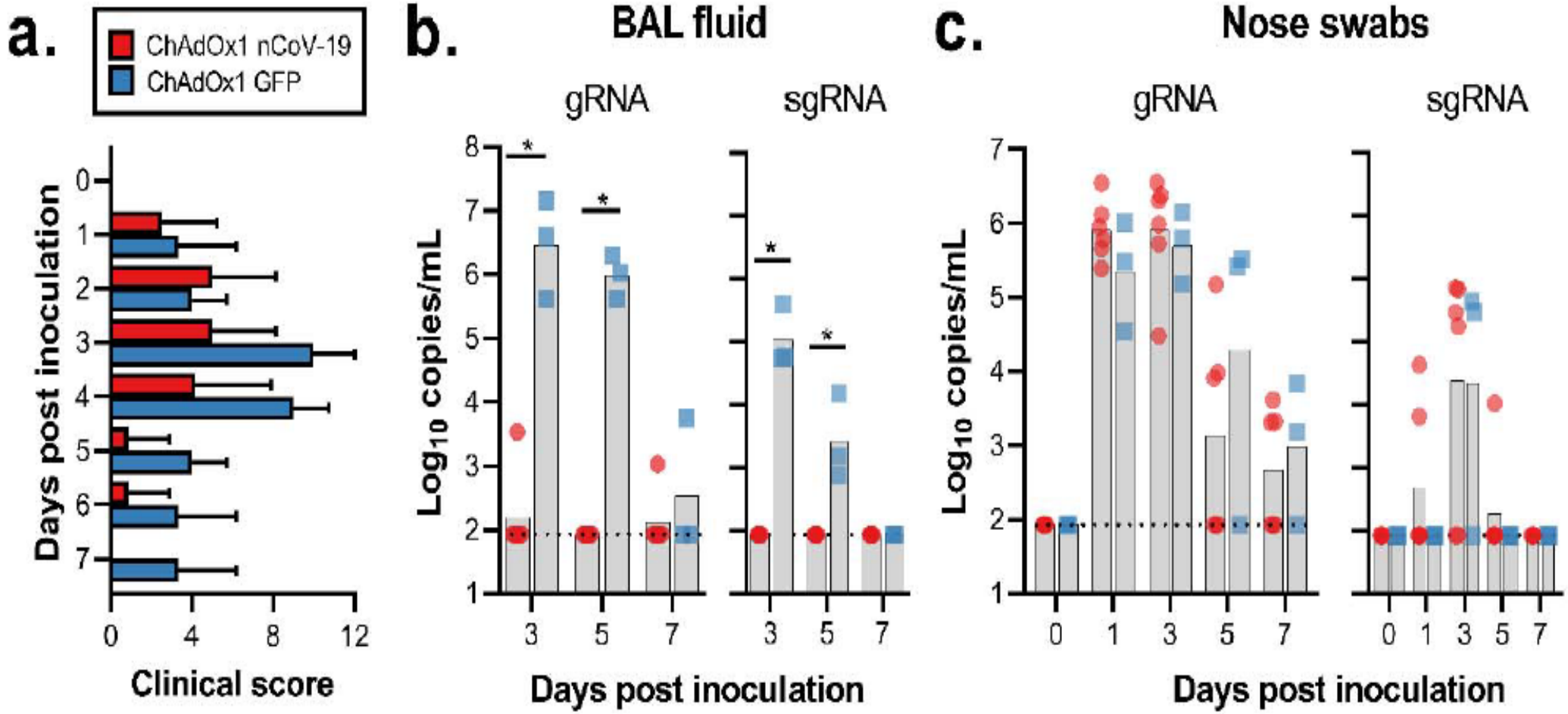


Figure 2. Humoral and cellular immune responses to ChAdOx1 nCoV-19 vaccination in rhesus macaques.

bioRxiv preprint doi: https://doi.org/10.1101/2020.05.13.093195.



bioRxiv preprint doi: https://doi.org/10.1101/2020.05.13.093195.

Control Animals

Immunized Animals

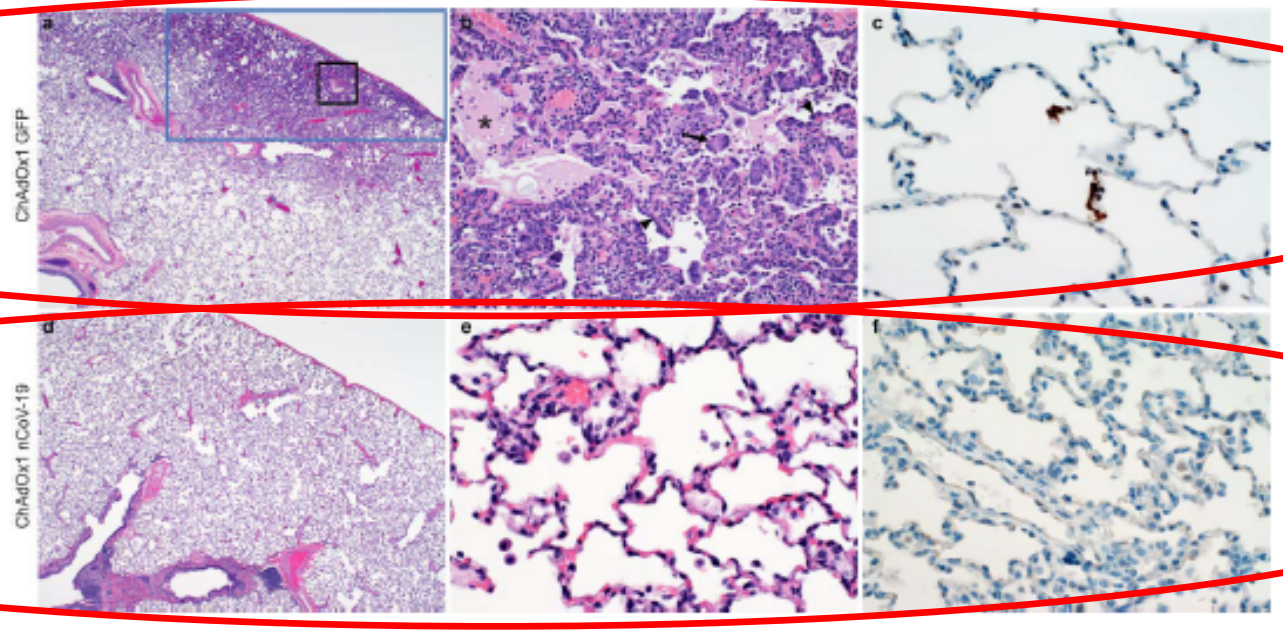


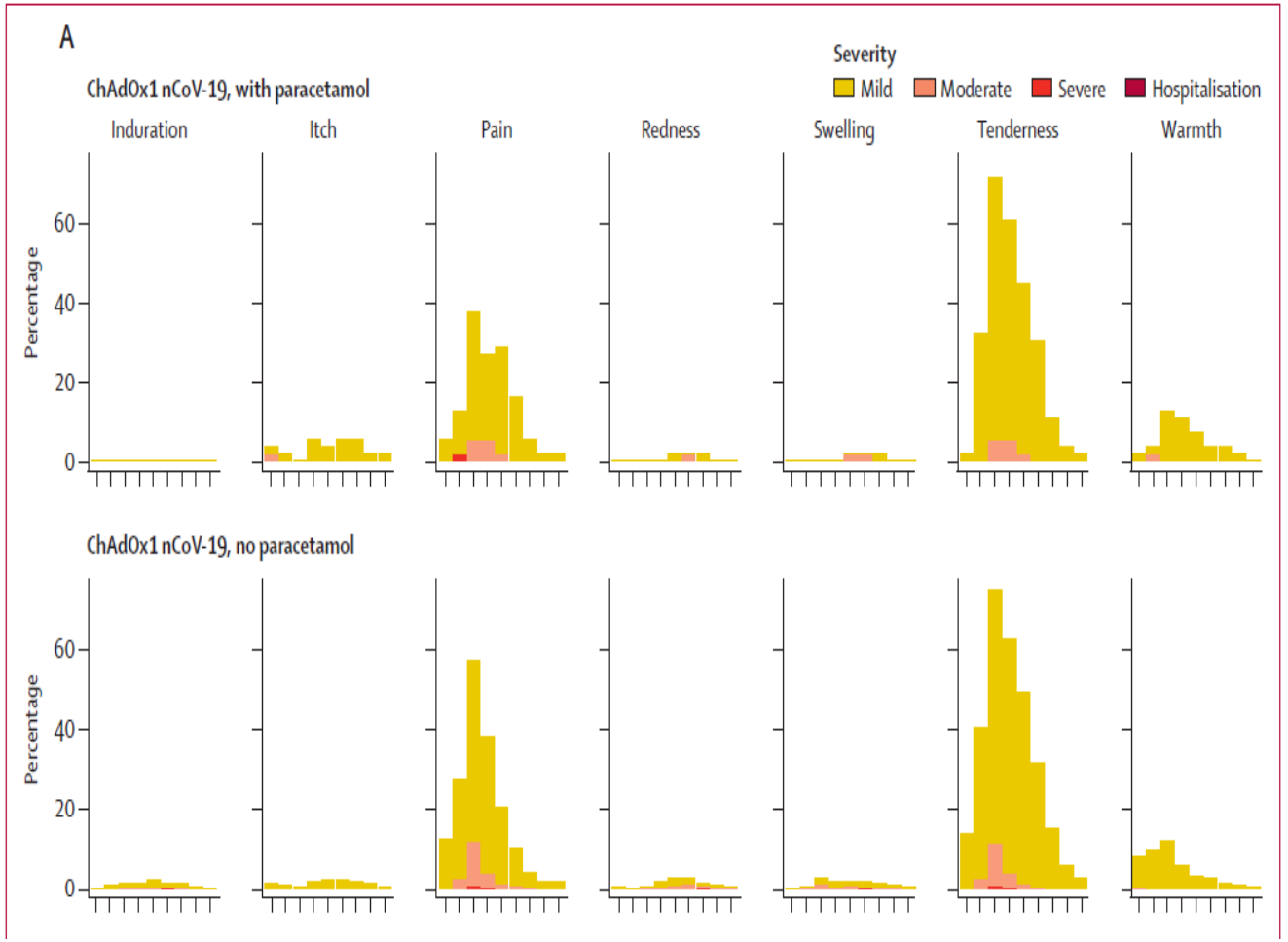
Figure 4. Histological changes in lungs of rhesus macaques on 7 dpi. a) Focal interstitial pneumonia in lungs of a control animal (blue box). The area in the black box is magnified in panel b. b) Interstitial pneumonia with edema (asterisk), type II pneumocyte hyperplasia (arrowhead) and syncytial cells (arrow) in control animals. c) SARS-CoV-2 antigen (visible as red-brown staining) was detected by immunohistochemistry in type I and type II pneumocytes in the lungs of control animals. d) No histological changes were observed in the lungs of ChadOx1 nCoV-19-vaccinated animals. e) Higher magnification of lung tissue in panel d. No evidence of pneumonia or immune-enhanced inflammation is observed. f) No SARS-CoV-2 antigen was detected by immunohistochemistry in the lungs of vaccinated animals. Magnification: panels a, d 40x; panels b, c, e, f 400x.

bioRxiv preprint doi: https://doi.org/10.1101/2020.05.13.093195.

Vaccine Studies in Humans

Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial

Pedro M Folegatti, Katie J Ewer*, Parvinder K Aley, Brian Angus, Stephan Becker, Sandra Belij-Rammerstorfer, Duncan Bellamy, Sagida Bibi, Mustapha Bittaye, Elizabeth A Clutterbuck, Christina Dold, Saul N Faust, Adam Finn, Amy L Flaxman, Bassam Hallis, Paul Heath, Daniel Jenkin, Rajeka Lazarus, Rebecca Makinson, Angela M Minassian, Katrina M Pollock, Maheshi Ramasamy, Hannah Robinson, Matthew Snape, Richard Tarrant, Merryn Voysey, Catherine Green*, Alexander D Douglas*, Adrian V S Hill*, Teresa Lambe*, Sarah C Gilbert*, Andrew J Pollard*, on behalf of the Oxford COVID Vaccine Trial Group†*



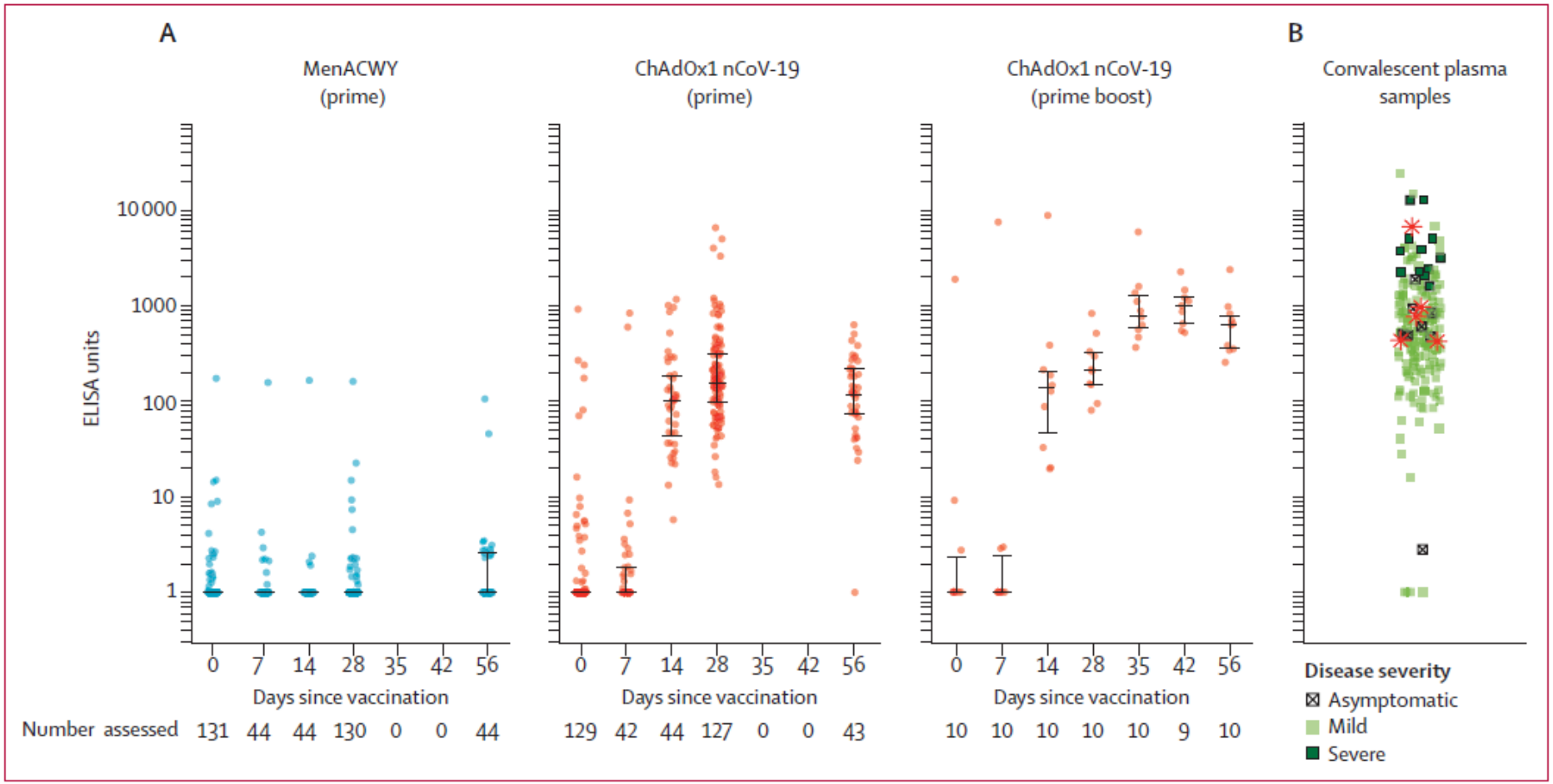


Figure 3: **SARS-CoV-2 IgG response by standardised ELISA to spike protein in trial participants (A) and in 180 convalescent plasma samples from 172 patients with PCR-confirmed COVID-19 and eight asymptomatic health-care workers (B)**

Error bars show median (IQR). Participants in the prime boost group received their second dose at day 28. Lower limit of quantification is 1 ELISA unit. Red stars in panel B show five samples also tested on the Marburg VN assay (see figure 4). MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.

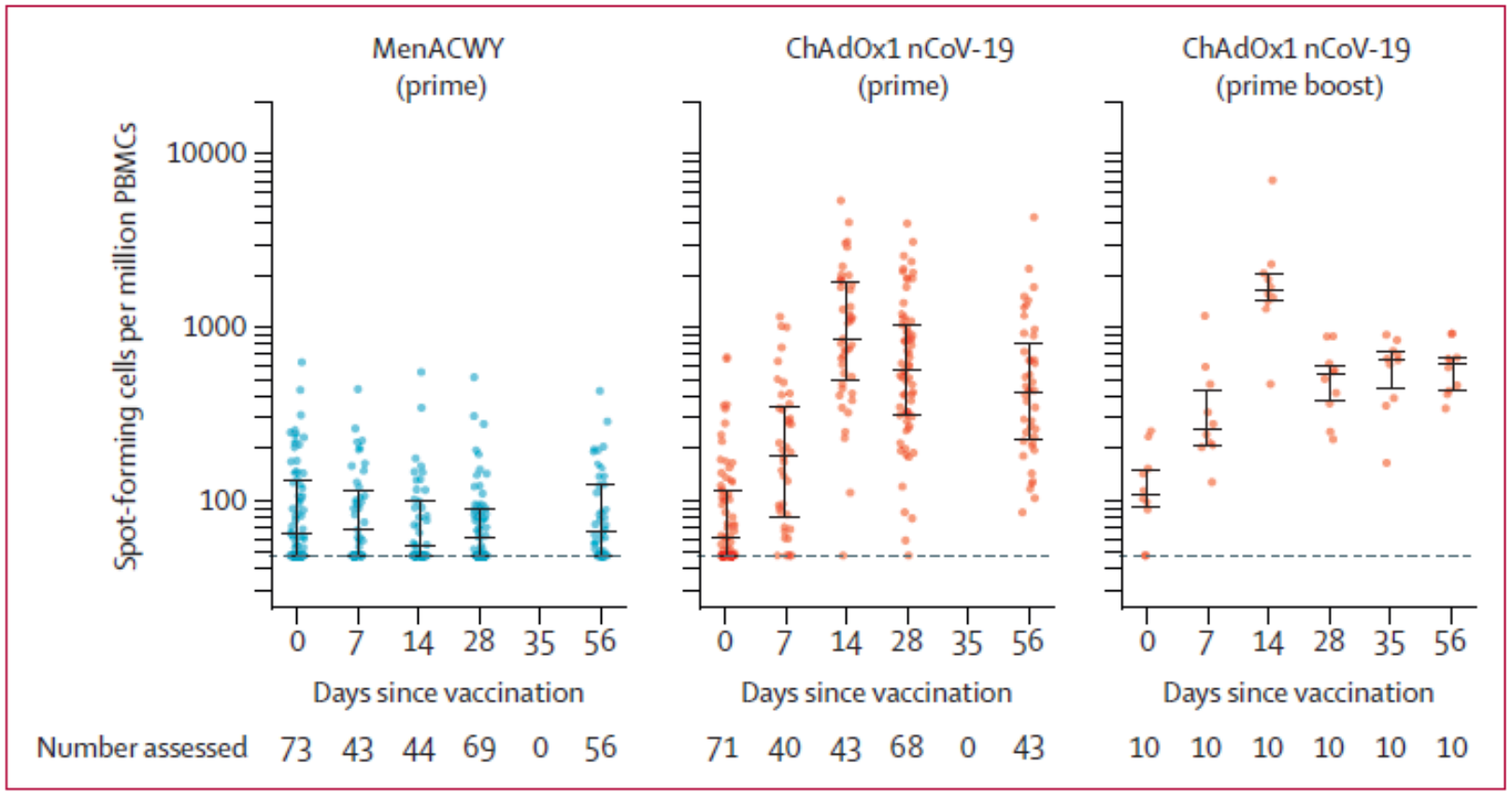


Figure 6: **Interferon-γ ELISpot response to peptides spanning the SARS-CoV-2 spike vaccine insert**
Error bars show median (IQR). The lower limit of detection, indicated with the dotted line, is 48 spot-forming cells per million PBMCs. PBMC=peripheral blood mononuclear cell. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. ELISpot=enzyme linked immunospot. MenACWY=meningococcal group A, C, W-135, and Y conjugate vaccine.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

An mRNA Vaccine against SARS-CoV-2 — Preliminary Report

L.A. Jackson, E.J. Anderson, N.G. Rouphael, P.C. Roberts, M. Makhene, R.N. Coler, M.P. McCullough, J.D. Chappell, M.R. Denison, L.J. Stevens, A.J. Pruijssers, A. McDermott, B. Flach, N.A. Doria-Rose, K.S. Corbett, K.M. Morabito, S. O'Dell, S.D. Schmidt, P.A. Swanson II, M. Padilla, J.R. Mascola, K.M. Neuzil, H. Bennett, W. Sun, E. Peters, M. Makowski, J. Albert, K. Cross, W. Buchanan, R. Pikaart-Tautges, J.E. Ledgerwood, B.S. Graham, and J.H. Beigel, for the mRNA-1273 Study Group*

This article was published on July 14, 2020, at NEJM.org.

Table 1. Characteristics of the Participants in the mRNA-1273 Trial at Enrollment.*

Characteristic	25-μg Group (N=15)	100-μg Group (N=15)	250-μg Group (N=15)	Overall (N=45)
Sex — no. (%)				
Male	9 (60)	7 (47)	6 (40)	22 (49)
Female	6 (40)	8 (53)	9 (60)	23 (51)
Age — yr	36.7±7.9	31.3±8.7	31.0±8.0	33.0±8.5
Race or ethnic group — no. (%)†				
American Indian or Alaska Native	0	1 (7)	0	1 (2)
Asian	0	0	1 (7)	1 (2)
Black	0	2 (13)	0	2 (4)
White	15 (100)	11 (73)	14 (93)	40 (89)
Unknown	0	1 (7)	0	1 (2)
Hispanic or Latino — no. (%)	1 (7)	3 (20)	2 (13)‡	6 (13)
Body-mass index§	24.6±3.4	26.7±2.6	24.7±3.1	25.3±3.2

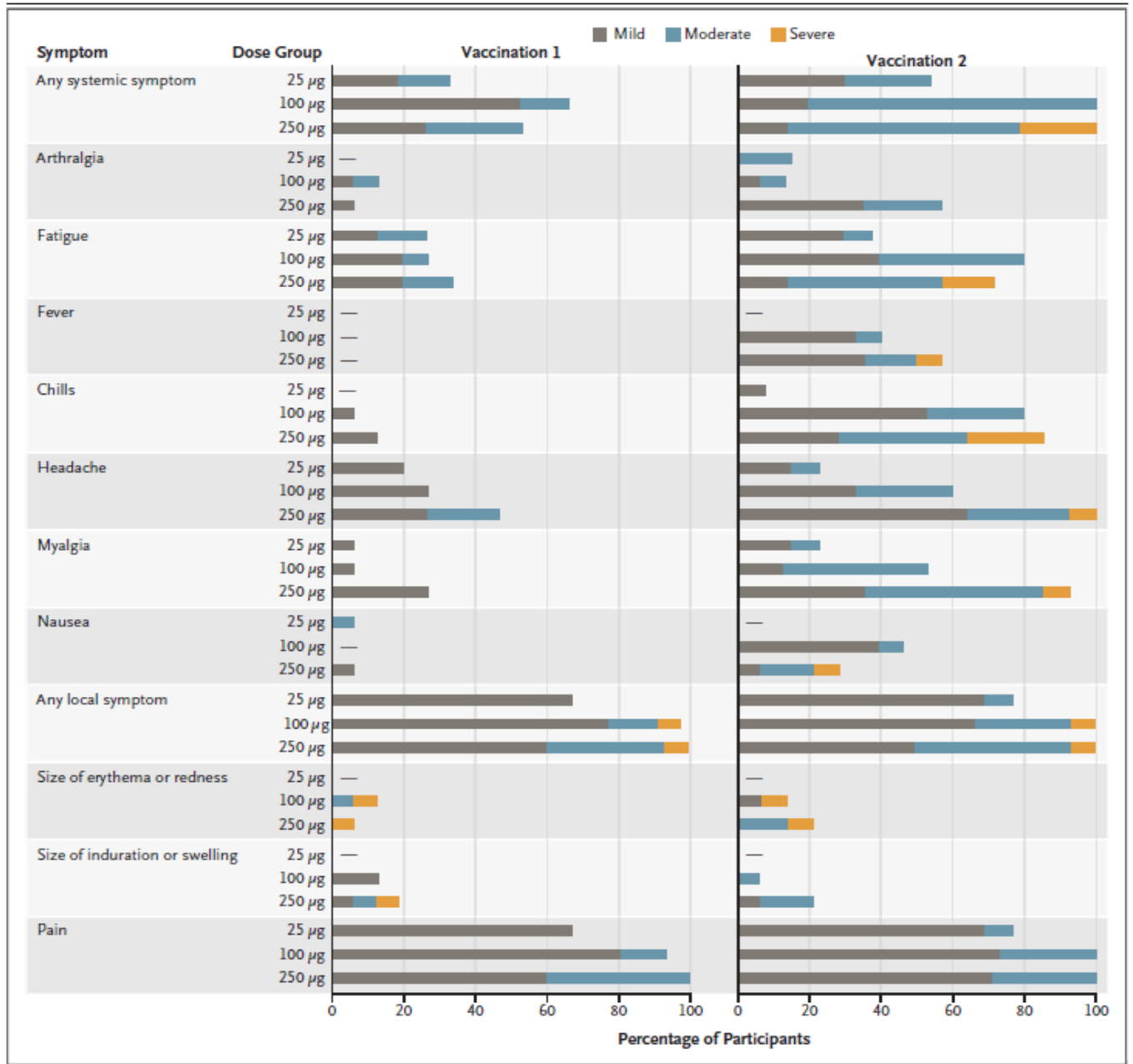
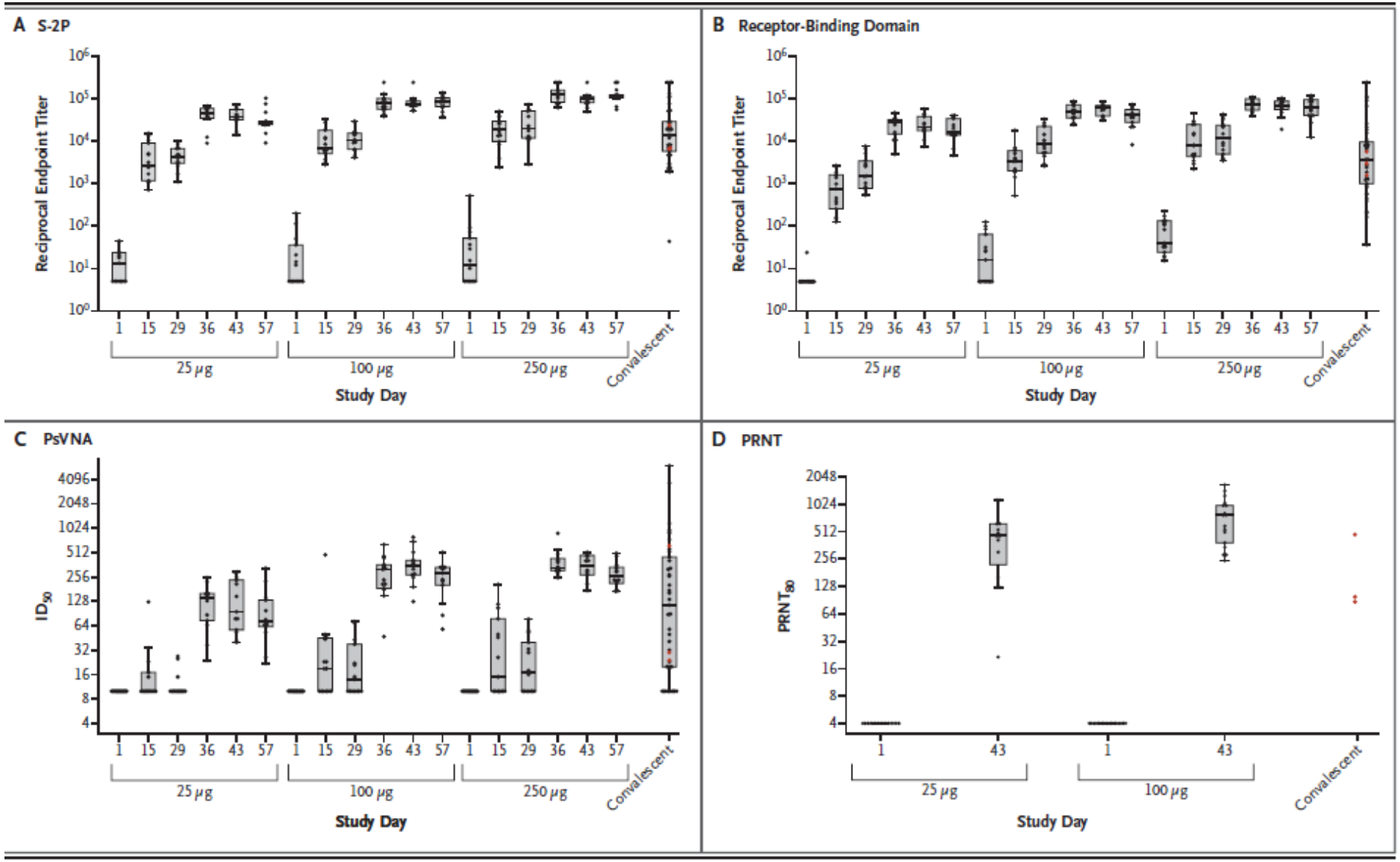


Figure 1. Systemic and Local Adverse Events.

The severity of solicited adverse events was graded as mild, moderate, or severe (see Table S1).



This article was published on July 14, 2020,
at NEJM.org.

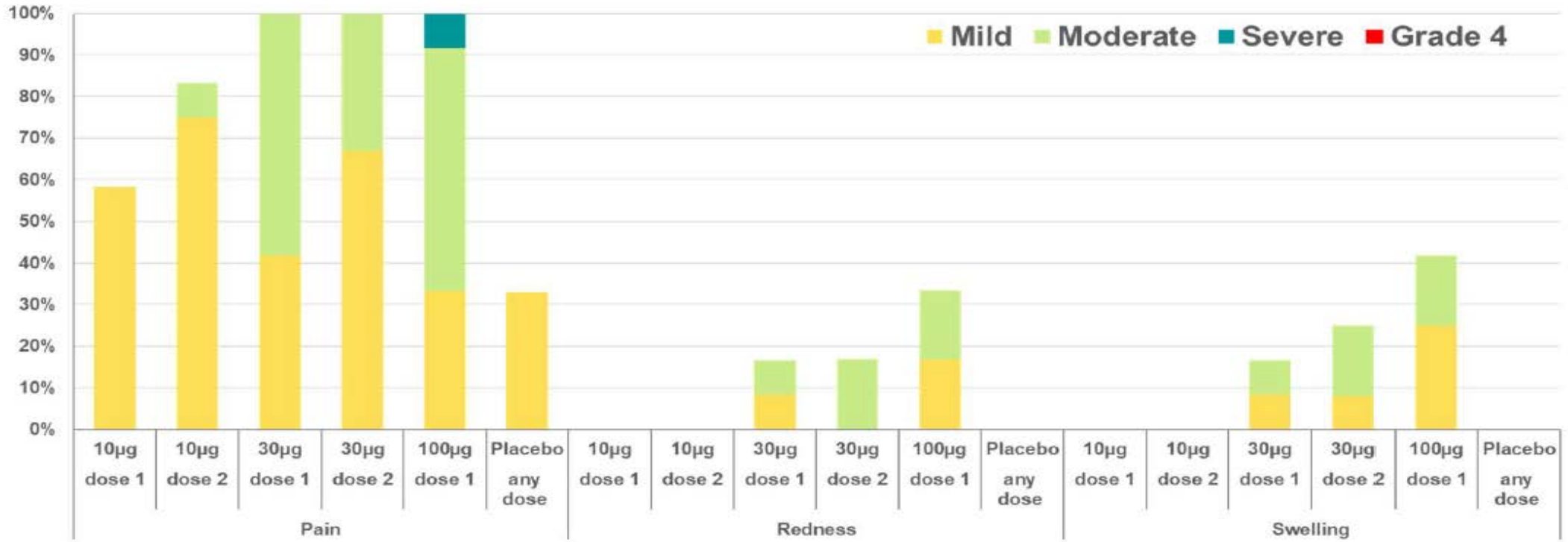
Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report

Mark J. Mulligan[1]*, Kirsten E. Lyke[2*], Nicholas Kitchin*[3,a], Judith Absalon[3,b], Alejandra Gurtman[3,b], Stephen Lockhart[3,a], Kathleen Neuzil[2], Vanessa Raabe[1], Ruth Bailey[3,a], Kena A. Swanson[3,b], Ping Li[3,c], Kenneth Koury[3,b], Warren Kalina[3,b], David Cooper[3,b], Camila Fontes-Garfias[6],Pei-Yong Shi[6], Özlem Türeci[7], Kristin R. Tompkins[3,b], Edward E. Walsh[4], Robert Frenck[5], Ann R. Falsey[4], Philip R. Dormitzer[3,b], William C. Gruber[3,b], Uğur Şahin[7], and Kathrin U. Jansen[3,b]

	10 µg (N=12) n (%)	30 µg (N=12) n (%)	100 µg (N=12) n (%)	Placebo (N=9) n (%)	Total (N=45) n (%)
Sex					
Male	7 (58.3)	6 (50.0)	5 (41.7)	5 (55.6)	23 (51.1)
Female	5 (41.7)	6 (50.0)	7 (58.3)	4 (44.4)	22 (48.9)
Race					
White	8 (66.7)	10 (83.3)	11 (91.7)	8 (88.9)	37 (82.2)
Black or African American	1 (8.3)	0	0	0	1 (2.2)
Asian	3 (25.0)	2 (16.7)	1 (8.3)	1 (11.1)	7 (15.6)
Ethnicity					
Hispanic/Latino	1 (8.3)	1 (8.3)	0	0	2 (4.4)
Non-Hispanic/non-Latino	11 (91.7)	10 (83.3)	12 (100.0)	9 (100.0)	42 (93.3)
Not reported	0	1 (8.3)	0	0	1 (2.2)
Age at vaccination (years)					
Mean (SD)	29.4 (6.39)	35.8 (9.96)	38.3 (9.34)	39.0 (11.16)	35.4 (9.71)
Median	26.5	33.5	38.0	41.0	33.0
Min, max	(24, 42)	(23, 52)	(25, 53)	(19, 54)	(19, 54)

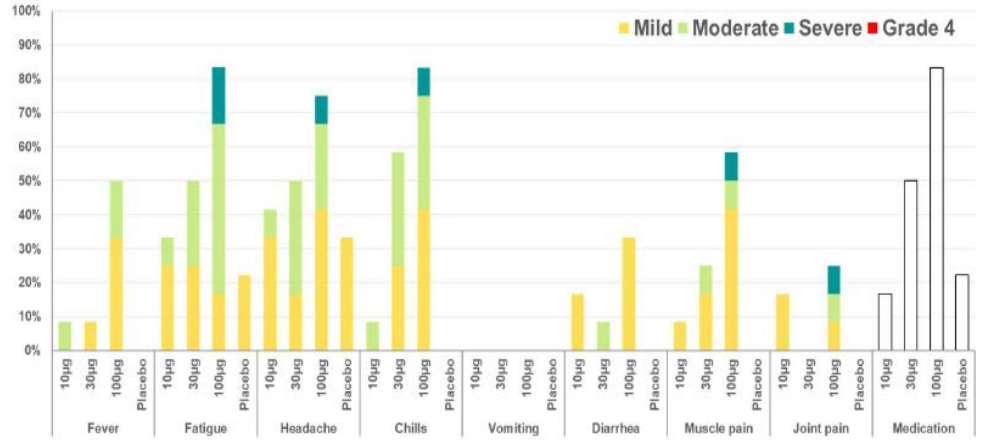
https://doi.org/10.1101/2020.06.30.20142570

Local Reactions after Vaccine

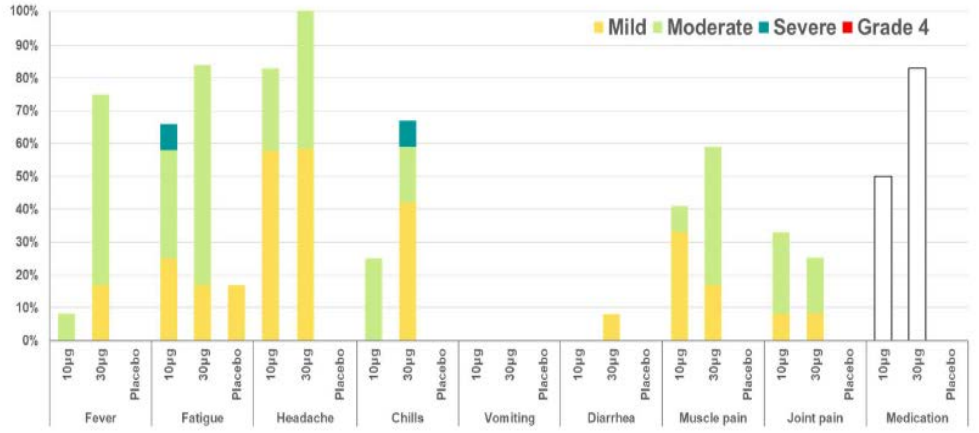


https://doi.org/10.1101/2020.06.30.20142570

Systemic Reactions after Vaccine

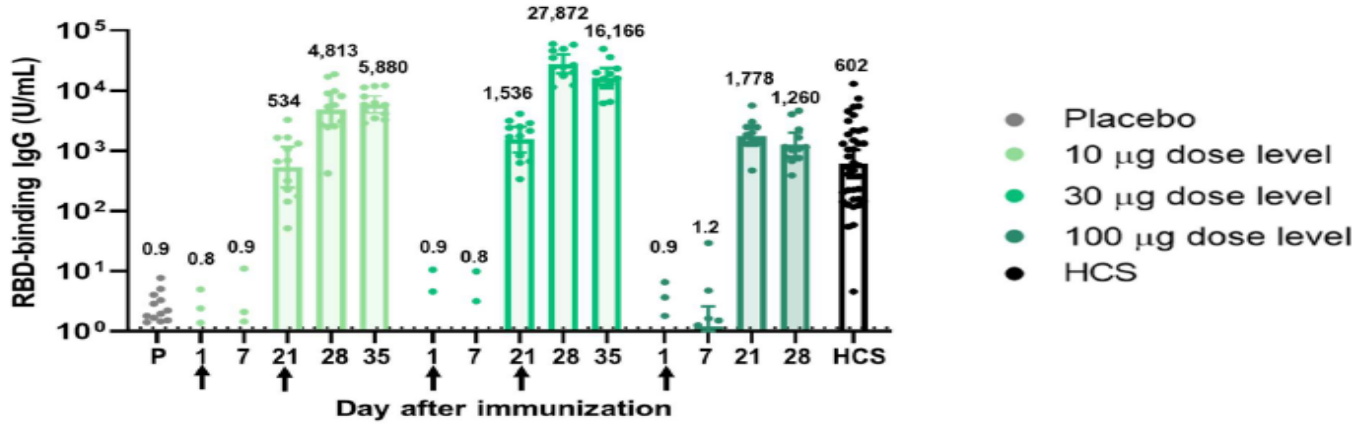


b



https://doi.org/10.1101/2020.06.30.20142570

Immune Responses to Vaccines



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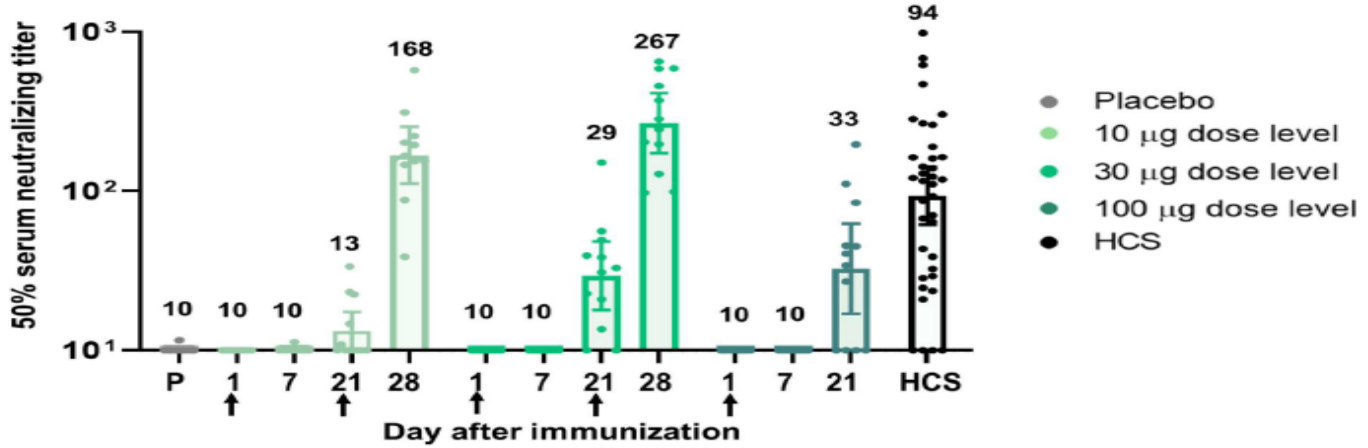

https://doi.org/10.1101/2020.06.30.20142570

Potential risks associated with vaccine development for COVID-19

Antibodies that bind virus without neutralizing infectivity can cause disease through increased viral replication or formation of immune complexes that deposit in tissue and activate complement pathways associated with inflammation. T helper 2 cell (T_H2)–biased responses have also been associated with ineffective vaccines that lead to enhanced disease after subsequent infection. Antibody-dependent enhancement (ADE) of viral replication has occurred in viruses with innate macrophage tropism. Virus-antibody immune complexes and T_H2-biased responses can both occur in vaccine-associated enhanced respiratory disease (VAERD).

	Antibody-mediated		T cell–mediated
	ADE	**VAERD**	**VAERD**
Mechanism	Fc-mediated increase in viral entry	Immune complex formation and complement deposition	T_H2-biased immune response
Effectors	Macrophage activation and inflammatory cytokines	Complement activation and inflammatory cytokines	Allergic inflammation and T_H2 cytokines
Mitigation	Conformationally correct antigens and high-quality neutralizing antibody		T_H1-biasing immunization and $CD8^+$ T cells

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Safety Assessment

- Standardized comprehensive safety assessments of local and systemic reactions.
- Recommended measuring biomarkers of vaccine-enhanced disease
  - Ratios of neutralizing and non-neutralizing antibodies
  - Antibody isotypes and affinities
  - Proinflammatory cytokine levels
  - Polarity of T cell responses

Conclusions

- An effective vaccine will likely be achieved with at least one of the vaccine approaches
- Vaccine safety will be meticulously assessed
- If enhanced disease occurs it will be carefully assessed and immune mechanisms investigated
- A safe and effective vaccine that is widely available would likely induce herd immunity
- Herd immunity to SARS 2 would allow us to resume normal activities