Making the Broadest, Longest-Lasting Covid-19 Vaccine

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December 6, 2023

January 11, 2020
Science

NEWS

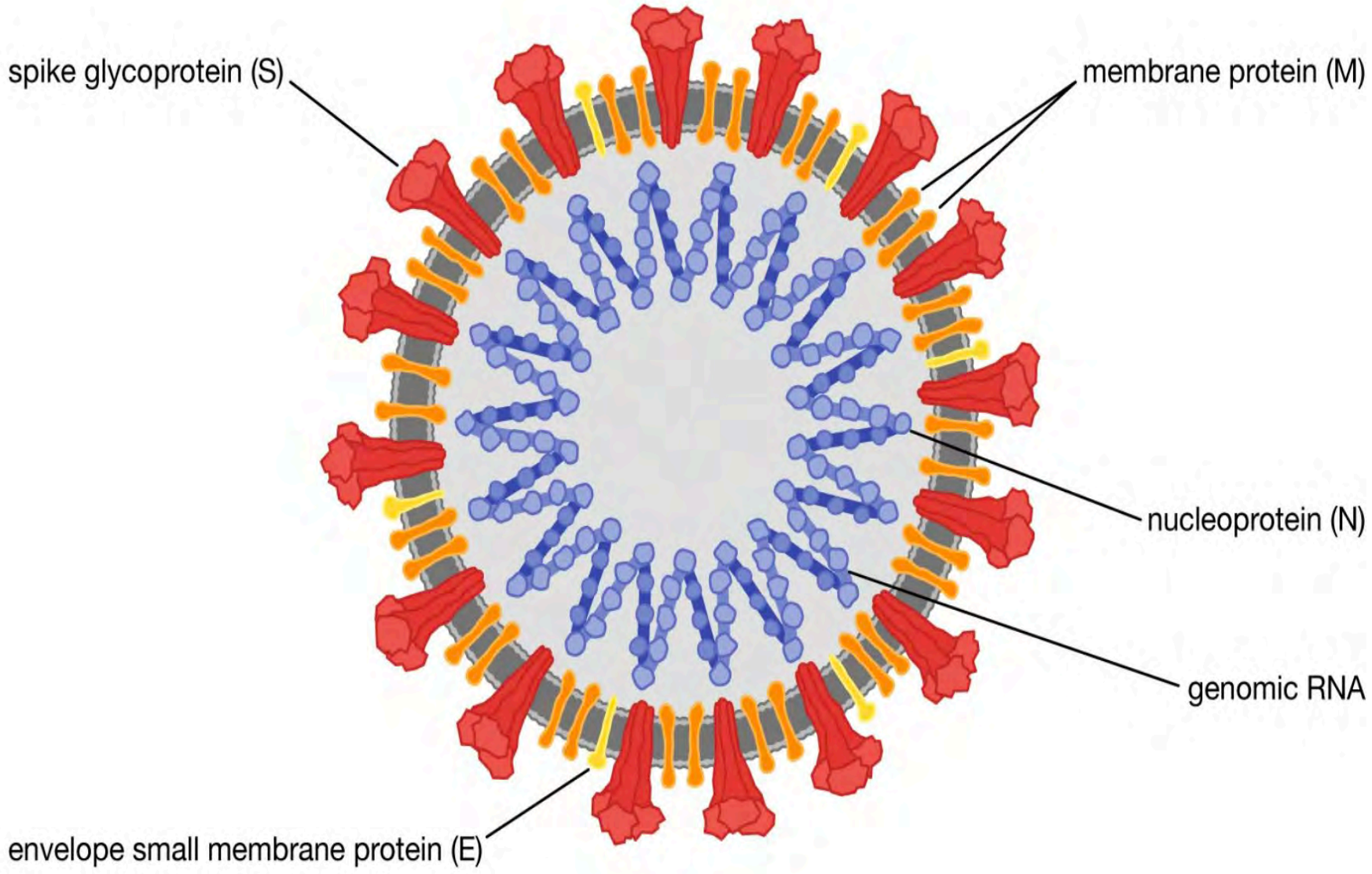
Chinese Researchers Reveal Draft Genome of Virus Implicated in Wuhan Pneumonia Outbreak

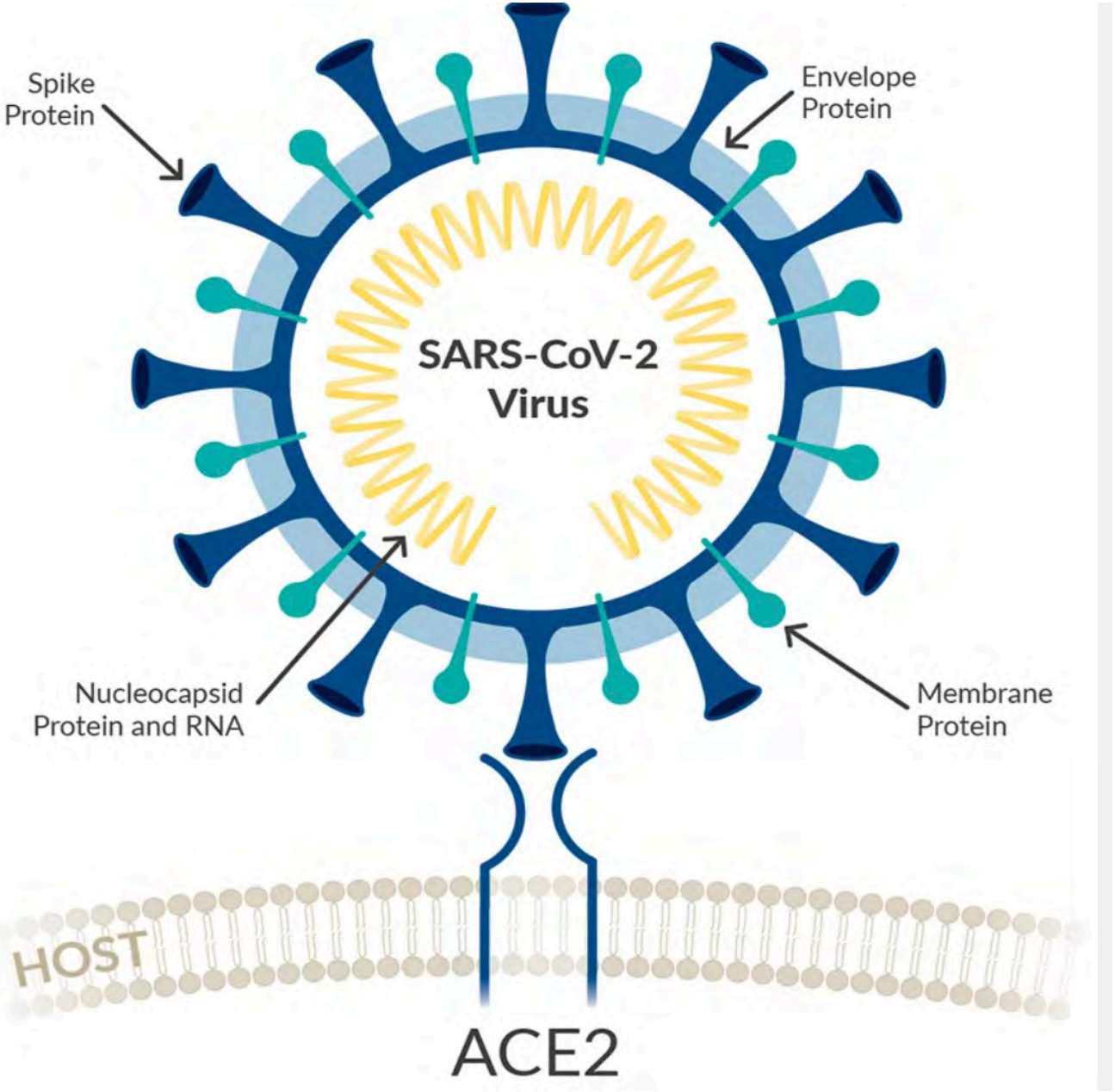
Jon Cohen

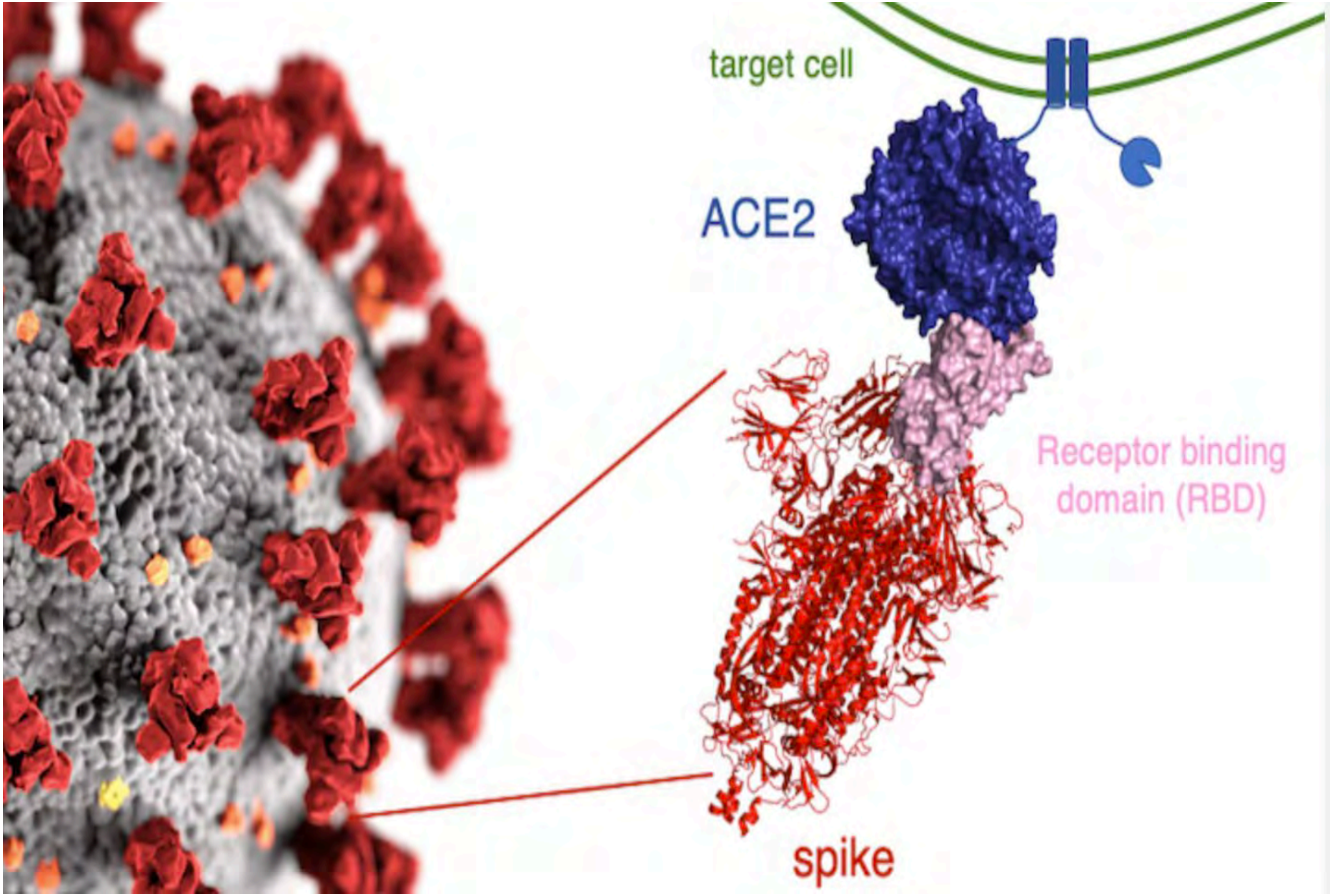
The Wuhan-1 Strain
January 11, 2020

The mRNA vaccines made by Pfizer and Moderna, the vectored virus vaccines made by J&J and AstraZeneca, and the purified protein vaccine made by Novavax were all designed to prevent the Wuhan-1 (or ancestral) strain by inducing antibodies to the SARS-CoV-2 spike (S) protein

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)




Spike Protein
Envelope Protein
SARS-CoV-2 Virus
Nucleocapsid Protein and RNA
Membrane Protein
HOST
ACE2


target cell
ACE2
Receptor binding domain (RBD)
spike

December 10 and 17, 2020:

FDA reviewed phase 3 trials for mRNA vaccines

mRNA vaccines:

Pfizer

First COVID-19 Occurrence From 7 Days After Dose 2

Phase 2/3 Efficacy – Final Analysis

Subjects WITHOUT Evidence of Infection Prior to 7 days after Dose 2

	BNT162b2 (30 µg) N=18,198		Placebo N=18,325				
Efficacy Endpoint	n	Surveillance Time (n)	n	Surveillance Time (n)	VE (%)	(95% CI)	Pr (VE >30%)
First COVID-19 occurrence ≥7 days after Dose 2	8	2.214 (17,411)	162	2.222 (17,511)	95.0	(90.3, 97.6)	>0.9999

Total surveillance time: 1000 person-years for all subjects within each group at risk for the endpoint..
Pr=Posterior probability

mRNA vaccines:

Moderna

Study 301: Primary Efficacy Objective Met, VE Against Confirmed, Symptomatic COVID-19 Cases is > 94%

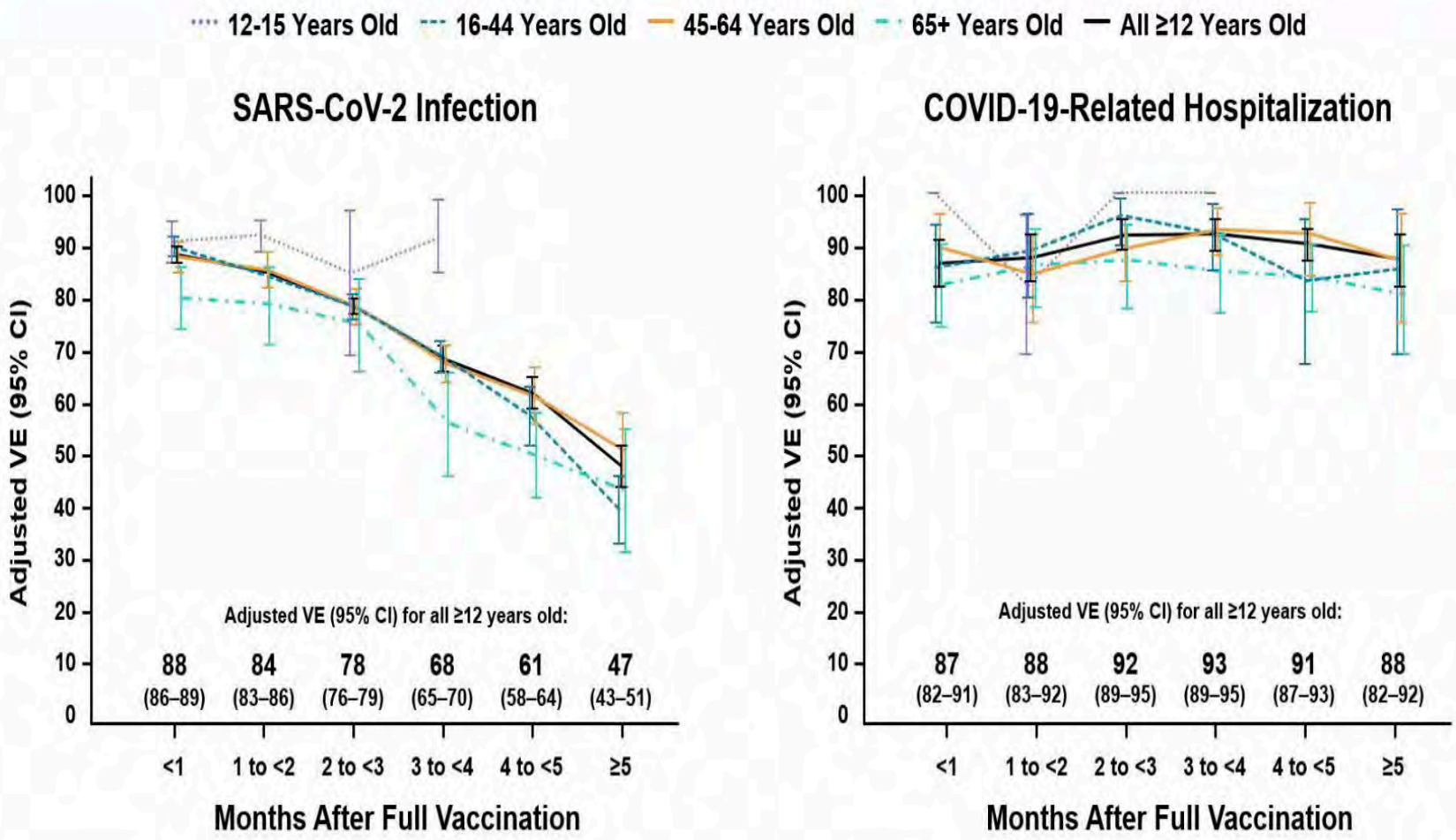
Per Protocol

Confirmed, Symptomatic COVID-19 Cases	Interim Analysis		Primary Efficacy Analysis	
	mRNA-1273 N=13,934	Placebo N=13,883	mRNA-1273 N=14,134	Placebo N=14,073
Number of cases, n (%)	5 (< 0.1%)	90 (0.6%)	11 (< 0.1%)	185 (1.3%)
Vaccine efficacy based on hazard ratio (95% CI)	94.5% (86.5%, 97.8%)		94.1% (89.3%, 96.8%)	
p-value	< 0.0001		< 0.0001	
Incidence rate per 1000 person-years	1.8	33.4	3.3	56.5

Six months later:

Protection against mild illness wasn’t holding up

In All Age Groups, Vaccine Effectiveness Wanes Over Time Against Infections but Not Against Hospitalizations



Tartof SY, et al. Six-Month Effectiveness of BNT162B2 mRNA COVID-19 Vaccine in a Large US Integrated Health System: A Retrospective Cohort Study. Available at SSRN: https://dx.doi.org/10.2139/ssrn.3909743

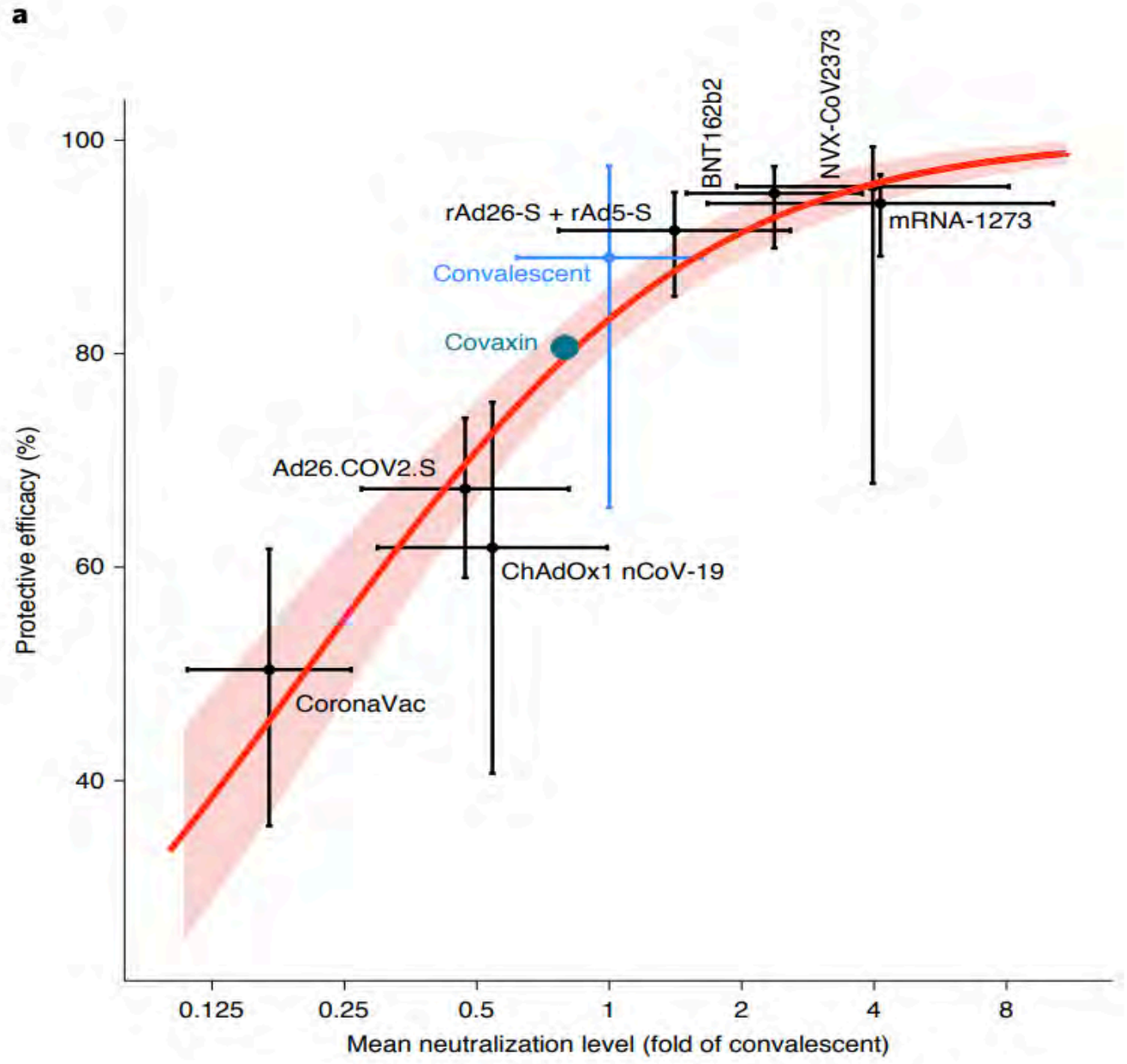
Protection against mild illness is mediated by high-titers of circulating, virus neutralizing antibodies

Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection

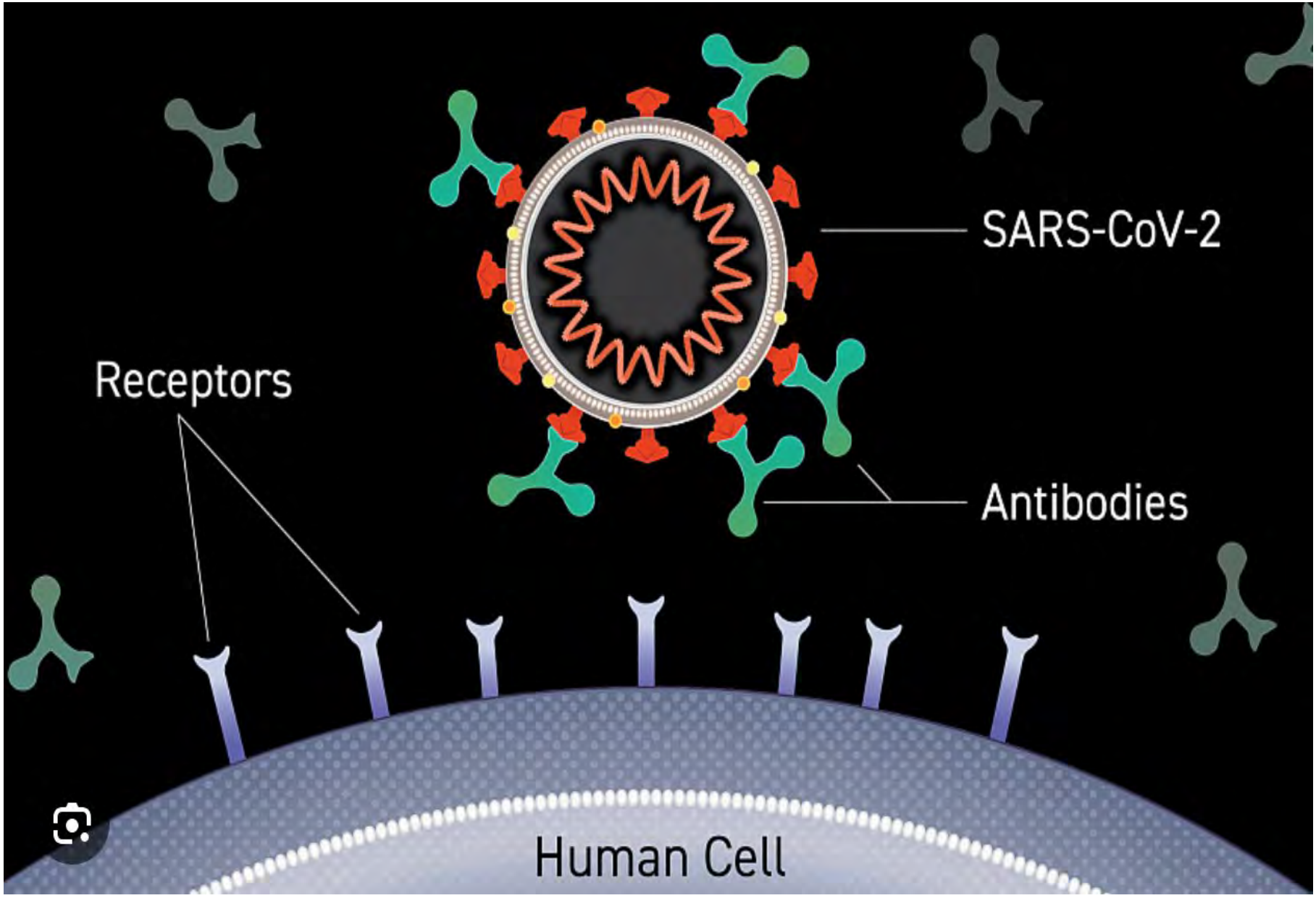
David S. Khoury[1,9], Deborah Cromer[1,9], Arnold Reynaldi[1], Timothy E. Schlub[1,2], Adam K. Wheatley[3], Jennifer A. Juno[3], Kanta Subbarao[3,4], Stephen J. Kent[3,5,6], James A. Triccas[7,8] ✉ and Miles P. Davenport[1] ✉

Predictive models of immune protection from COVID-19 are urgently needed to identify correlates of protection to assist in the future deployment of vaccines. To address this, we analyzed the relationship between in vitro neutralization levels and the observed protection from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection using data from seven current vaccines and from convalescent cohorts. We estimated the neutralization level for 50% protection against detectable SARS-CoV-2 infection to be 20.2% of the mean convalescent level (95% confidence interval (CI) = 14.4–28.4%). The estimated neutralization level required for 50% protection from severe infection was significantly lower (3% of the mean convalescent level; 95% CI = 0.7–13%, $P = 0.0004$). Modeling of the decay of the neutralization titer over the first 250 d after immunization predicts that a significant loss in protection from SARS-CoV-2 infection will occur, although protection from severe disease should be largely retained. Neutralization titers against some SARS-CoV-2 variants of concern are reduced compared with the vaccine strain, and our model predicts the relationship between neutralization and efficacy against viral variants. Here, we show that neutralization level is highly predictive of immune protection, and provide an evidence-based model of SARS-CoV-2 immune protection that will assist in developing vaccine strategies to control the future trajectory of the pandemic.

Khoury, D.S., D. Cromer, A. Reynaldi, et al., "Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection," *Nature Medicine* (2021) 27: 1205-1211.


a
100
80
60
40
Protective efficacy (%)
BNT162b2
NVX-CoV2373
rAd26-S + rAd5-S
mRNA-1273
Convalescent
Covaxin
Ad26.COV2.S
ChAdOx1 nCoV-19
CoronaVac
0.125
0.25
0.5
1
2
4
8
Mean neutralization level (fold of convalescent)

Antibodies provide a first line of defense against viral infections


SARS-CoV-2
Receptors
Antibodies
Human Cell

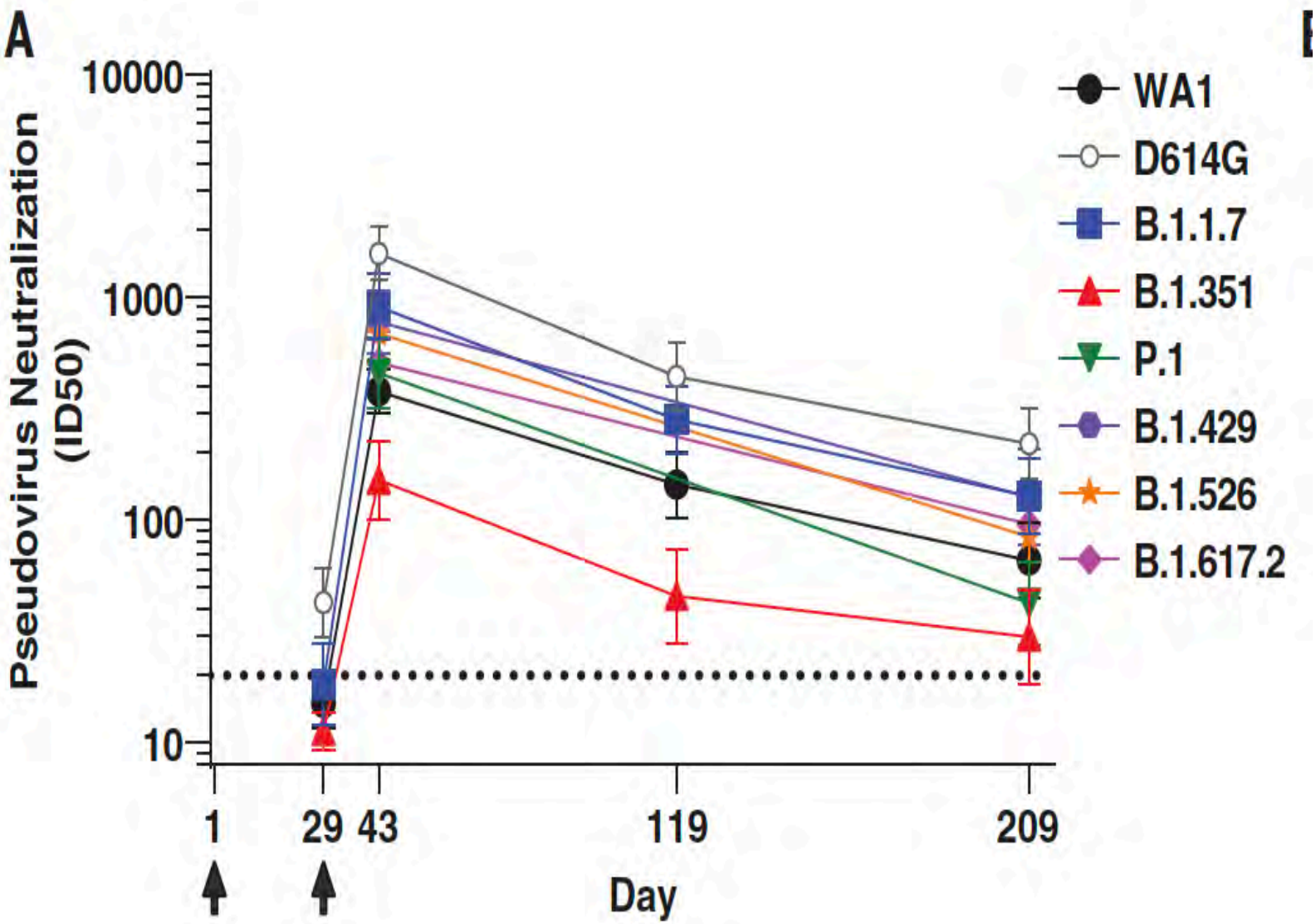
CORONAVIRUS

Durability of mRNA-1273 vaccine–induced antibodies against SARS-CoV-2 variants

Amarendra Pegu[1]†, Sarah E. O'Connell[1]†, Stephen D. Schmidt[1]†, Sijy O'Dell[1]†, Chloe A. Talana[1], Lilin Lai[2], Jim Albert[3], Evan Anderson[2], Hamilton Bennett[4], Kizzmekia S. Corbett[1]‡, Britta Flach[1], Lisa Jackson[5], Brett Leav[4], Julie E. Ledgerwood[1], Catherine J. Luke[6], Mat Makowski[3], Martha C. Nason[1], Paul C. Roberts[6], Mario Roederer[1], Paulina A. Rebolledo[7], Christina A. Rostad[2], Nadine G. Rouphael[7], Wei Shi[1], Lingshu Wang[1], Alicia T. Widge[1], Eun Sung Yang[1], The mRNA-1273 Study Group§, John H. Beigel[6], Barney S. Graham[1], John R. Mascola[1], Mehul S. Suthar[2], Adrian B. McDermott[1], Nicole A. Doria-Rose[1]*

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations may diminish vaccine-induced protective immune responses, particularly as antibody titers wane over time. Here, we assess the effect of SARS-CoV-2 variants B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.429 (Epsilon), B.1.526 (Iota), and B.1.617.2 (Delta) on binding, neutralizing, and angiotensin-converting enzyme 2 (ACE2)–competing antibodies elicited by the messenger RNA (mRNA) vaccine mRNA-1273 over 7 months. Cross-reactive neutralizing responses were rare after a single dose. At the peak of response to the second vaccine dose, all individuals had responses to all variants. Binding and functional antibodies against variants persisted in most subjects, albeit at low levels, for 6 months after the primary series of the mRNA-1273 vaccine. Across all assays, B.1.351 had the lowest antibody recognition. These data complement ongoing studies to inform the potential need for additional boost vaccinations.

Pegu, A., S.E. O'Connell, S.D. Schmidt, et al., "Durability of mRNA-1273 vaccine-induced antibodies against SARS-CoV-2 variants," *Science* (2021) 373: 1372-1375


A
Pseudovirus Neutralization (ID50)
10000
1000
100
10
1
29
43
119
209
Day
WA1
D614G
B.1.1.7
B.1.351
P.1
B.1.429
B.1.526
B.1.617.2

Because virus neutralizing antibodies are short-lived, protection against all symptomatic illness is also short-lived.

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Early Release / Vol. 70
July 30, 2021

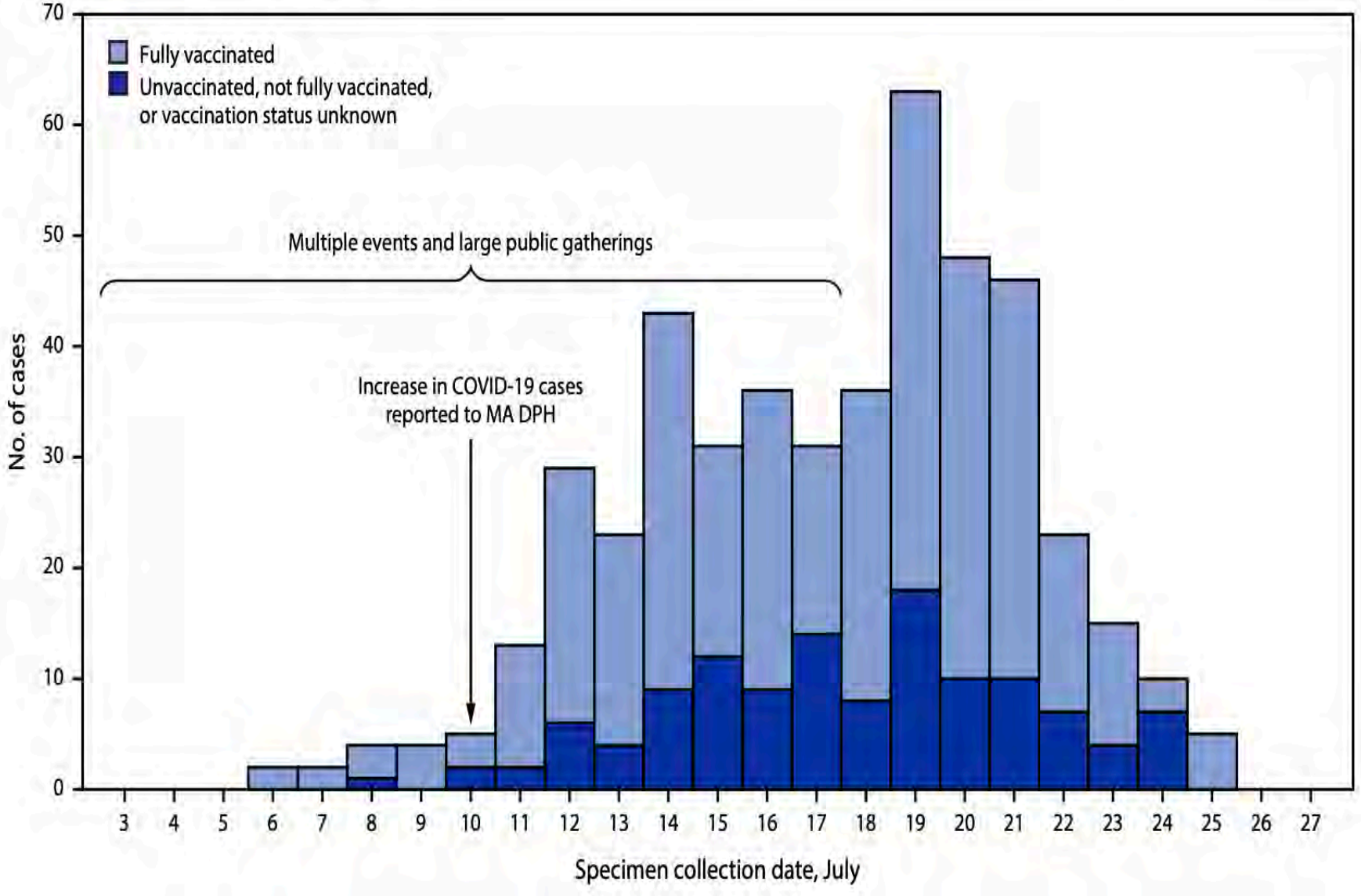
Outbreak of SARS-CoV-2 Infections, Including COVID-19 Vaccine Breakthrough Infections, Associated with Large Public Gatherings — Barnstable County, Massachusetts, July 2021

Catherine M. Brown, DVM[1]; Johanna Vostok, MPH[1]; Hillary Johnson, MHS[1]; Meagan Burns, MPH[1]; Radhika Gharpure, DVM[2]; Samira Sami, DrPH[2]; Rebecca T. Sabo, MPH[2]; Noemi Hall, PhD[2]; Anne Foreman, PhD[2]; Petra L. Schubert, MPH[1]; Glen R. Gallagher PhD[1]; Timelia Fink[1]; Lawrence C. Madoff, MD[1]; Stacey B. Gabriel, PhD[3]; Bronwyn MacInnis, PhD[3]; Daniel J. Park, PhD[3]; Katherine J. Siddle, PhD[3]; Vaira Harik, MS[4]; Deirdre Arvidson, MSN[4]; Taylor Brock-Fisher, MSc[5]; Molly Dunn, DVM[5]; Amanda Kearns[5]; A. Scott Laney, PhD[2]

During July 2021, 469 cases of COVID-19 associated with multiple summer events and large public gatherings in

transmission might consider expanding prevention strategies, including masking in indoor public settings regardless of vac-

FIGURE 1. SARS-CoV-2 infections (N = 469) associated with large public gatherings, by date of specimen collection and vaccination status* — Barnstable County, Massachusetts, July 2021



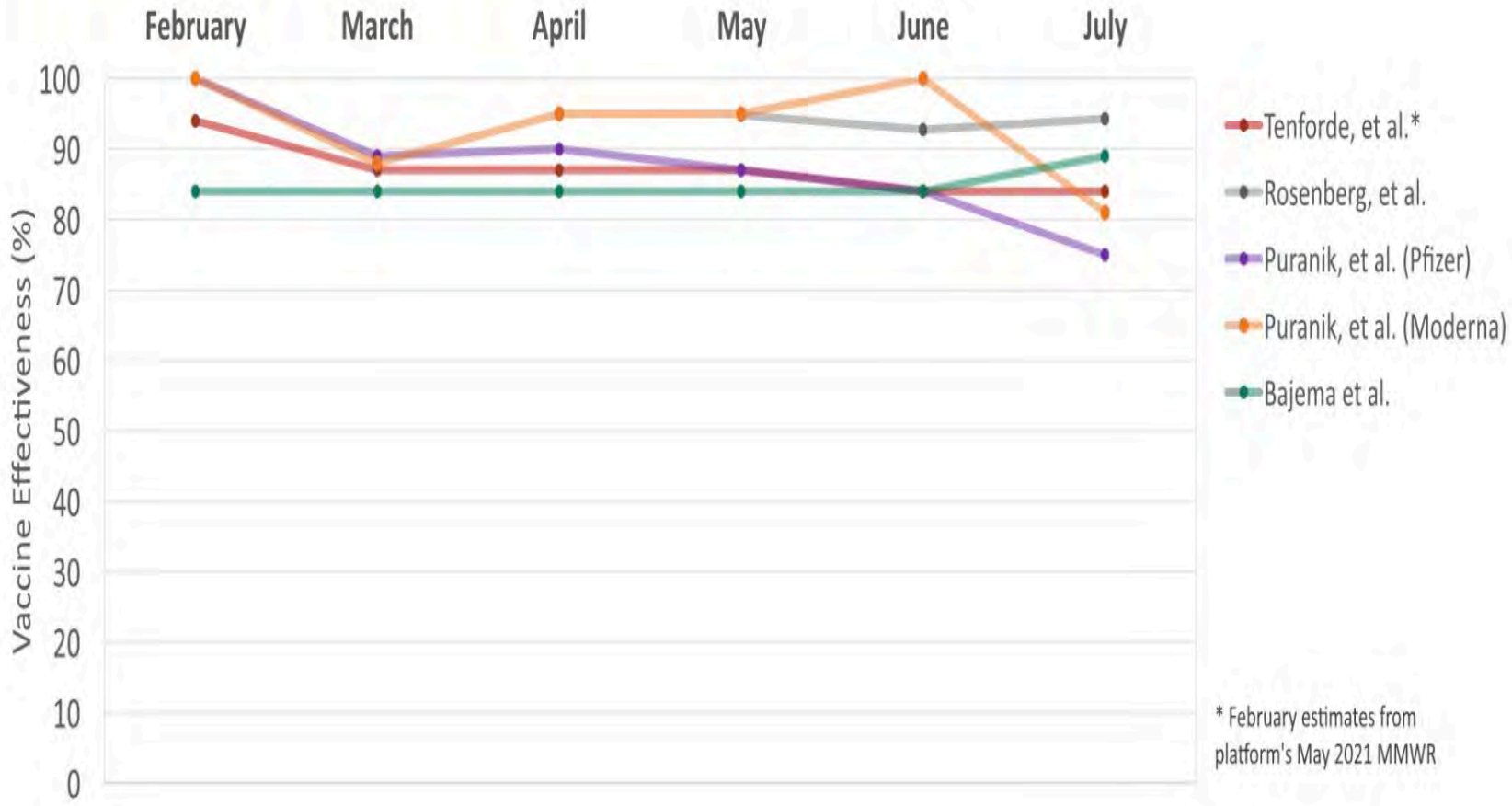
Why did the phase 3 trials of mRNA vaccines show a high level of protection against mild illness?

Six months later:

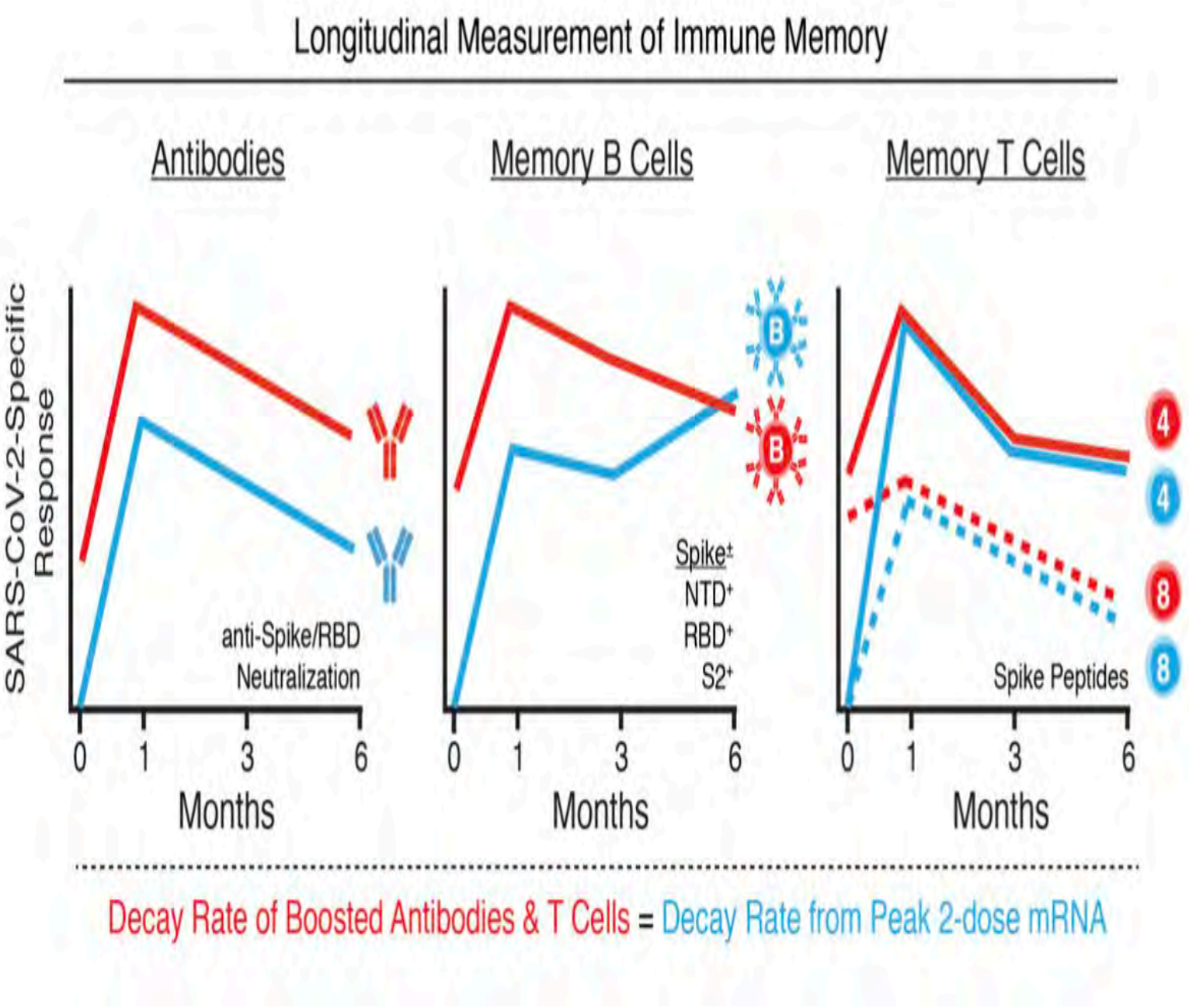
Protection against severe illness was holding up

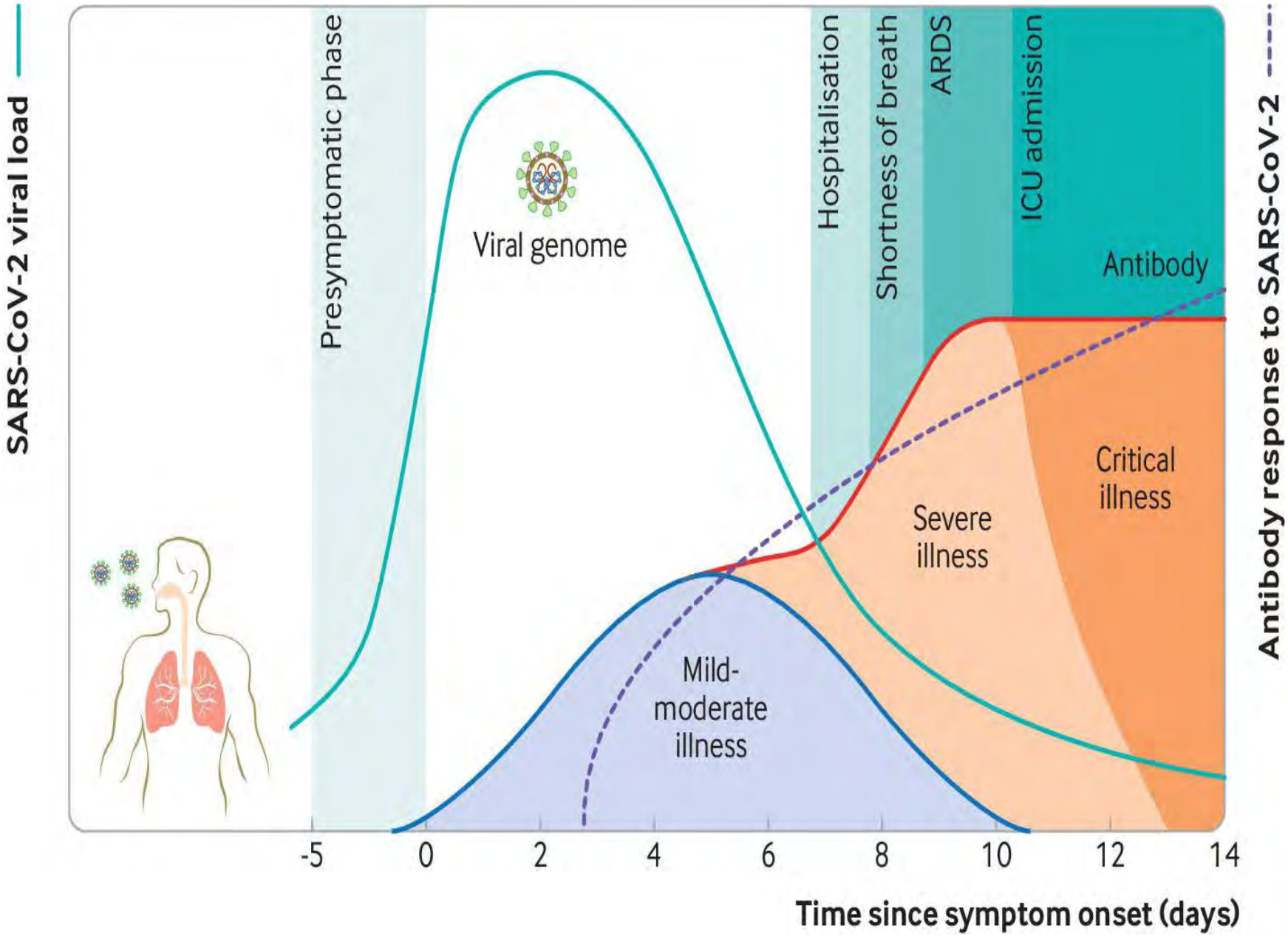
Vaccine effectiveness against **hospitalization** over time

Adults ≥18 years of age



Protection against severe illness is mediated in large part by memory B cells and memory T cells, which are long-lived


Longitudinal Measurement of Immune Memory
Antibodies
Memory B Cells
Memory T Cells
SARS-CoV-2-Specific Response
anti-Spike/RBD Neutralization
Spike±
NTD+
RBD+
S2+
Spike Peptides
0 1 3 6
Months
4
4
8
8
Decay Rate of Boosted Antibodies & T Cells = Decay Rate from Peak 2-dose mRNA


SARS-CoV-2 viral load
Antibody response to SARS-CoV-2
Presymptomatic phase
Viral genome
Hospitalisation
Shortness of breath
ARDS
ICU admission
Antibody
Critical illness
Severe illness
Mild-moderate illness
-5
0
2
4
6
8
10
12
14
Time since symptom onset (days)

December 2021:

One year after vaccines were available, protection against severe disease was holding up

> Clin Infect Dis. 2022 May 17;ciac381. doi: 10.1093/cid/ciac381. Online ahead of print.

Protection of mRNA vaccines against hospitalized COVID-19 in adults over the first year following authorization in the United States

Mark W Tenforde [1], Wesley H Self [2], Yuwei Zhu [2], Eric A Naioti [1], Manjusha Gaglani [3 4], Adit A Ginde [5], Kelly Jensen [5], H Keipp Talbot [2], Jonathan D Casey [2], Nicholas M Mohr [6], Anne Zepeski [6], Tresa McNeal [3 4], Shekhar Ghamande [3 4], Kevin W Gibbs [7], D Clark Files [7], David N Hager [8], Arber Shehu [8], Matthew E Prekker [9], Heidi L Erickson [9], Michelle N Gong [10], Amira Mohamed [10], Nicholas J Johnson [11], Vasisht Srinivasan [11], Jay S Steingrub [12], Ithan D Peltan [13], Samuel M Brown [13], Emily T Martin [14], Arnold S Monto [14], Akram Khan [15], Catherine L Hough [15], Laurence W Busse [16], Caitlin Ten Lohuis [16], Abhijit Duggal [17], Jennifer G Wilson [18], Nida Qadir [19], Steven Y Chang [19], Christopher Mallow [20], Carolina Rivas [20], Hilary M Babcock [21], Jennie H Kwon [21], Matthew C Exline [22], Mena M Botros [22], Adam S Lauring [23], Nathan I Shapiro [24], Natasha Halasa [2], James D Chappell [2], Carlos G Grijalva [2], Todd W Rice [2], Ian D Jones [2], William B Stubblefield [2], Adrienne Baughman [2], Kelsey N Womack [2], Jillian P Rhoads [2], Christopher J Lindsell [2], Kimberly W Hart [2], Caitlin Turbyfill [1], Samantha Olson [1], Nancy Murray [1], Katherine Adams [1], Manish M Patel [1], Influenza and Other Viruses in the Acutely Ill (IVY) Network

Tenforde study

- Study of protection against hospitalization in 8,000 immunocompetent adults between March-December 2021 who received two doses of mRNA vaccine vs. unvaccinated; median age was 60; 81% had more than one medical condition; delta variant predominant.

- Overall: 90% at 3 months and 82% at 9 months.
- Pfizer: 88% at 3 months and 79% at 9 months.
- Moderna: 93% at 3 months and 87% at 9 months.
- 18-64: 91% at 3 months and 87% at 9 months.
- >65: 87% at 3 months and 78% at 9 months.

Again, immunological studies supported epidemiological observations

Immunological Reviews WILEY

INVITED REVIEW

INVITED REVIEW THEMED ISSUE

Immunological memory to SARS-CoV-2 infection and COVID-19 vaccines

Alessandro Sette[1,2] | Shane Crotty[1,2]

[1]Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology (LJI), La Jolla, California, USA

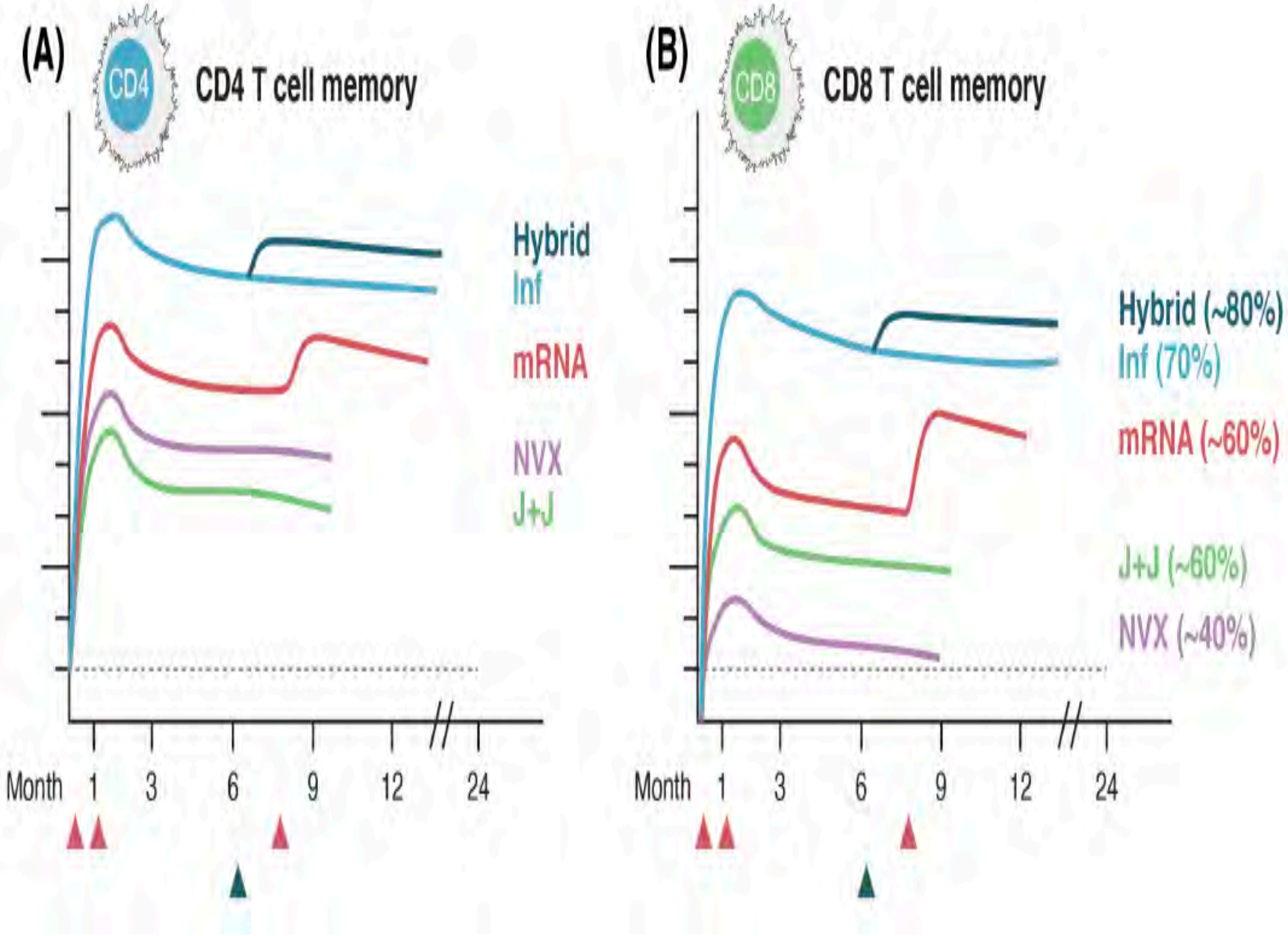
[2]Division of Infectious Diseases and Global Public Health, Department of Medicine, University of California, San Diego (UCSD), La Jolla, California, USA

Correspondence
Shane Crotty, Center for Infectious Disease and Vaccine Research, La Jolla Institute for Immunology (LJI), La Jolla, CA 92037 USA

Abstract

Immunological memory is the basis of protective immunity provided by vaccines and previous infections. Immunological memory can develop from multiple branches of the adaptive immune system, including CD4 T cells, CD8 T cells, B cells, and long-lasting antibody responses. Extraordinary progress has been made in understanding memory to SARS-CoV-2 infection and COVID-19 vaccines, addressing development; quantitative and qualitative features of different cellular and anatomical compartments; and durability of each cellular component and antibodies. Given the sophis-

Sette, A., S. Crotty, *Immunological Reviews* (2022) 310: 27-46


(A)
CD4
CD4 T cell memory
Hybrid
Inf
mRNA
NVX
J+J
Month 1 3 6 9 12 24
(B)
CD8
CD8 T cell memory
Hybrid (~80%)
Inf (70%)
mRNA (~60%)
J+J (~60%)
NVX (~40%)
Month 1 3 6 9 12 24

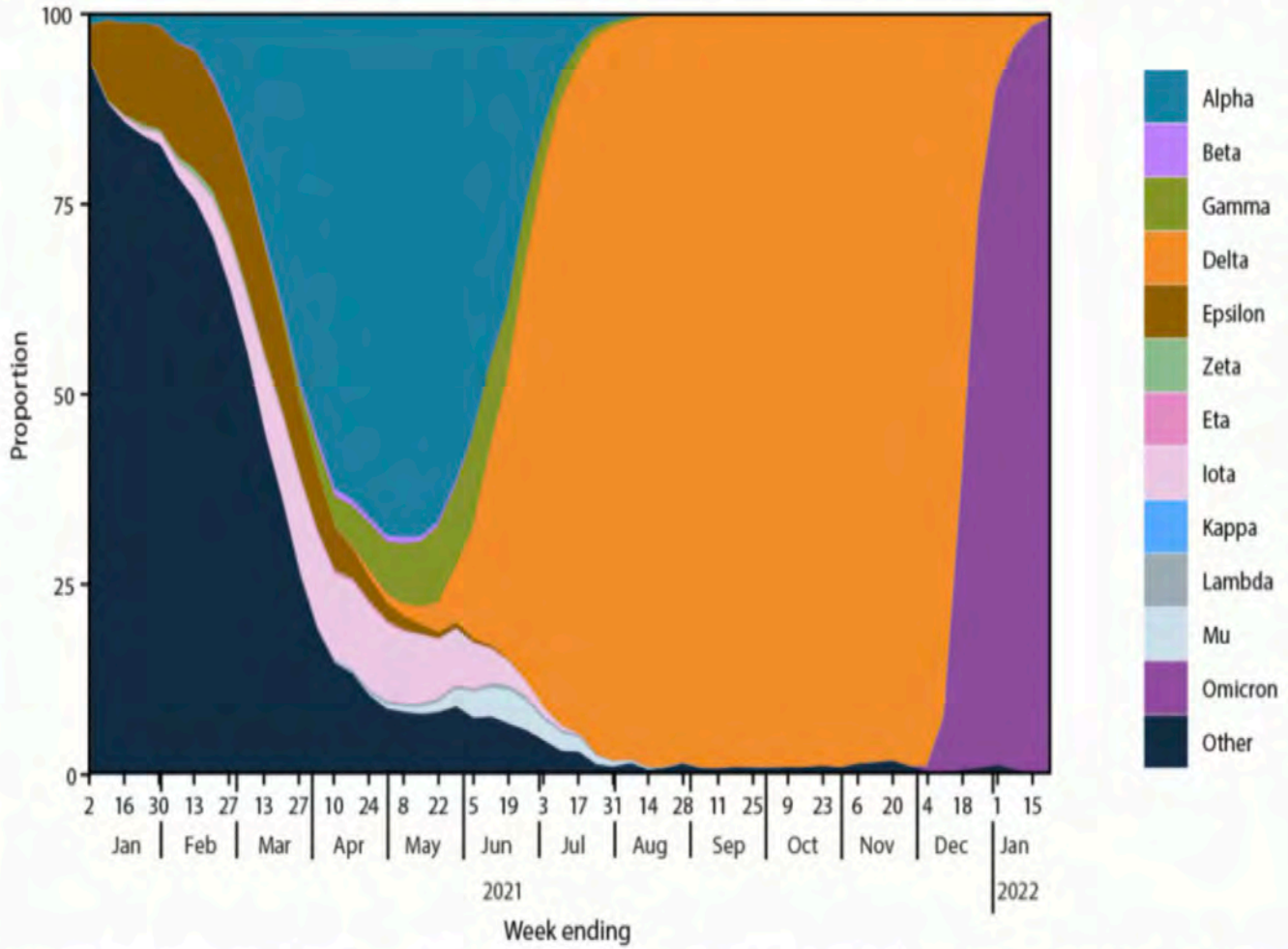
Then, the pandemic entered a new phase

December 1, 2021:

Omicron variant

Changing Landscape of Circulating Variants

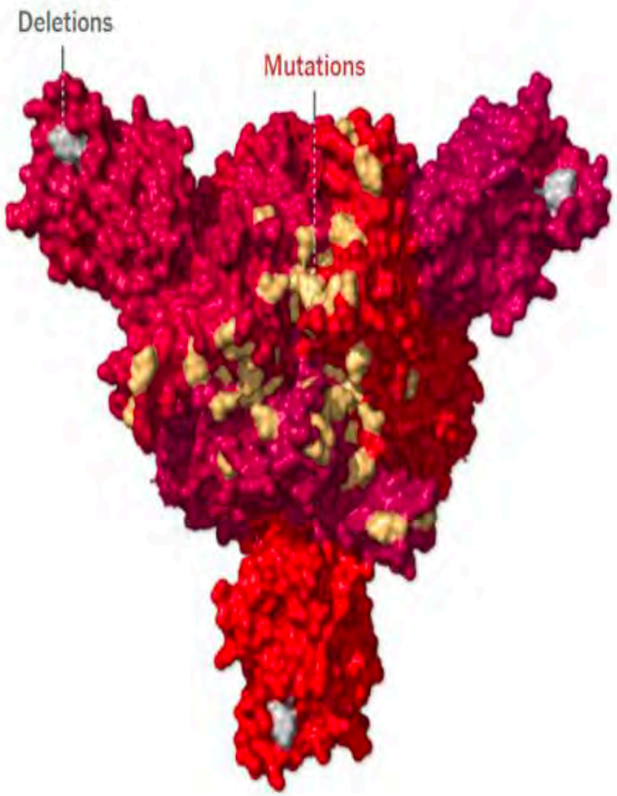
FIGURE 1. National weekly proportion estimates* of SARS-CoV-2 variants† — United States, January 2, 2021–January 22, 2022



Lambrou et al. Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants – United States, June 2021-January 2022 https://www.cdc.gov/mmwr/volumes/71/wr/mm7106a4.htm

SARS-CoV-2 Omicron (B.1.1.529) variant

- Six sub-lineages: BA.1, BA.1.1, BA.2, BA.3, BA.4, and BA.5
- Increased transmissibility and immune evasion, but decreased disease severity
- 30+ mutations in spike gene (S-gene)
  - 15 in receptor binding domain
- Lower vaccine effectiveness
  - Reduced neutralization by sera from vaccinated or convalescent individuals
- Reduction in efficacy of some monoclonal antibody treatments



Key mutations (yellow) in the Omicron spike protein (top view)
Source: New York Times

https://www.cdc.gov/coronavirus/2019-ncov/variants/omicron-variant.html
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/scientific-brief-omicron-variant.html

Article

Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2

https://doi.org/10.1038/s41586-021-04388-0

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Published online: 23 December 2021

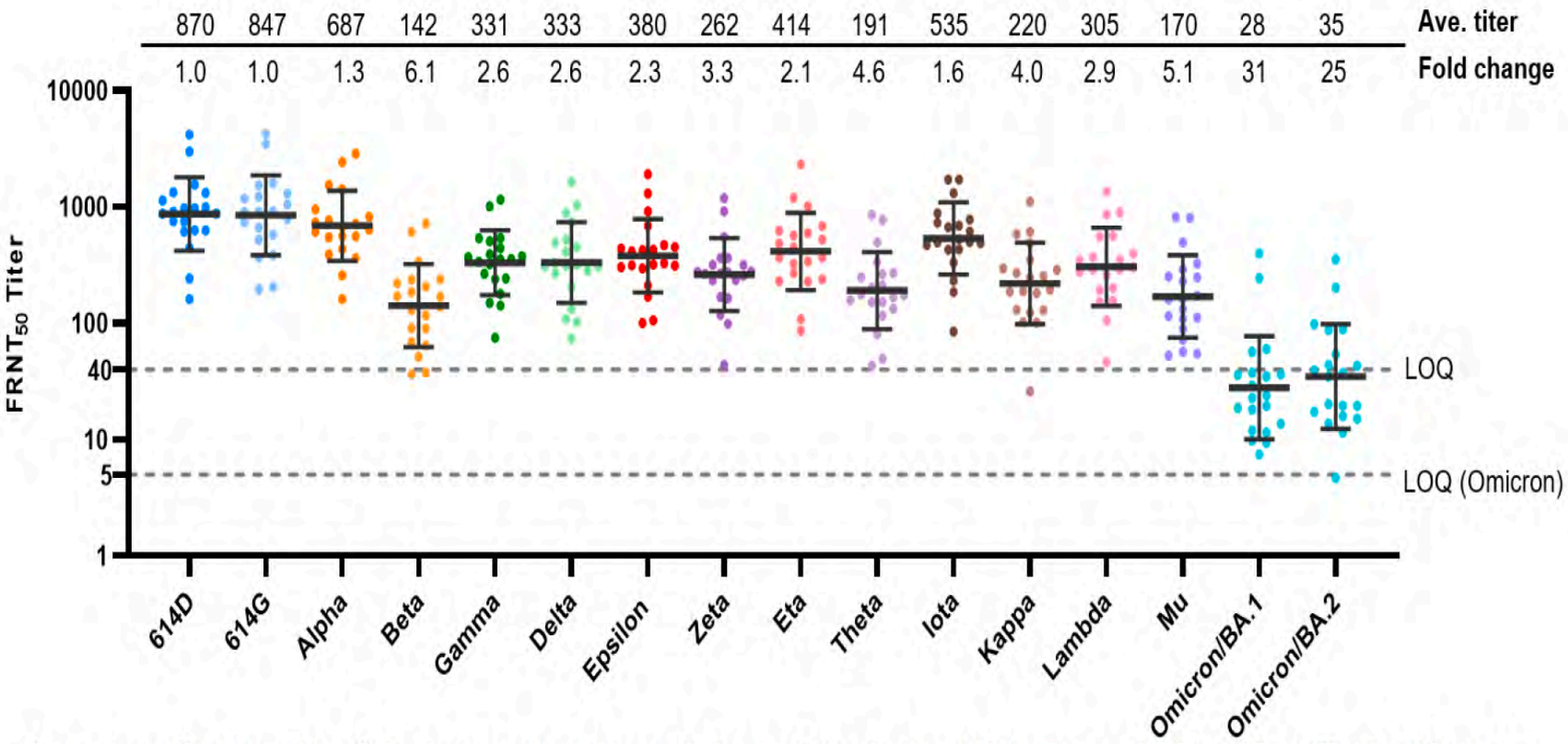
Check for updates

Lihong Liu[1,7], Sho Iketani[1,2,7], Yicheng Guo[1,7], Jasper F.-W. Chan[3,4,7], Maple Wang[1,7], Liyuan Liu[5,7], Yang Luo[1], Hin Chu[3,4], Yiming Huang[5], Manoj S. Nair[1], Jian Yu[1], Kenn K.-H. Chik[4], Terrence T.-T. Yuen[3], Chaemin Yoon[3], Kelvin K.-W. To[3,4], Honglin Chen[3,4], Michael T. Yin[1,6], Magdalena E. Sobieszczyk[1,6], Yaoxing Huang[1], Harris H. Wang[5], Zizhang Sheng[1], Kwok-Yung Yuen[3,4] & David D. Ho[1,2,6]✉

The B.1.1.529/Omicron variant of SARS-CoV-2 was only recently detected in southern Africa, but its subsequent spread has been extensive, both regionally and globally[1]. It is expected to become dominant in the coming weeks[2], probably due to enhanced transmissibility. A striking feature of this variant is the large number of spike mutations[3] that pose a threat to the efficacy of current COVID-19 vaccines and antibody therapies[4]. This concern is amplified by the findings of our study. Here we found that B.1.1.529 is markedly resistant to neutralization by serum not only from patients who recovered from COVID-19, but also from individuals who were vaccinated with one of the four widely used COVID-19 vaccines. Even serum from individuals who were vaccinated and received a booster dose of mRNA-based vaccines exhibited substantially diminished neutralizing activity against B.1.1.529. By evaluating a panel of monoclonal antibodies

Liu, et al., Striking antibody evasion manifested by the Omicron variant of SARS-CoV-2, *Nature* (2022) 602: 676-681

Neutralizing Activity of mRNA Vaccine Sera Against SARS-CoV-2 Variants from Alpha to Omicron



Sera from 2-6 weeks after completing second dose of Moderna (10 sera) and Pfizer-BioNTech (10 sera) vaccines, tested with recombinant SARS-CoV-2 reporter viruses

LOQ=Limit of quantitation. Zhou B, Davis T, Thornburg N, Wentworth D (CDC), *in publication*

Omicron

Because of mutations in the RBD of the spike protein, vaccination or previous infection offered little protection against mild disease

Omicron

However, in otherwise healthy people, vaccination or previous infection were still highly effective at preventing severe disease

Effectiveness of Ad26.COV2.S and BNT162b2 Vaccines against Omicron Variant in South Africa

TO THE EDITOR: The B.1.1.529 (omicron) strain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has rapidly become dominant among the variants of concern in the coronavirus disease 2019 (Covid-19) pandemic in all regions of the world. The omicron variant now

cine against severe Covid-19 caused by the omicron variant. Severe Covid-19 was defined as hospitalization or admission to an intensive care unit (ICU) or to high care. (The latter refers to the practice of locating patients' beds close to the nursing station so that they can be observed

Gray, G., et al. Effectiveness of AD26.COV2.S and BNT162b2 against Omicron Variant in South Africa. *N Engl J Med* (2022) 386: 2243-2245.

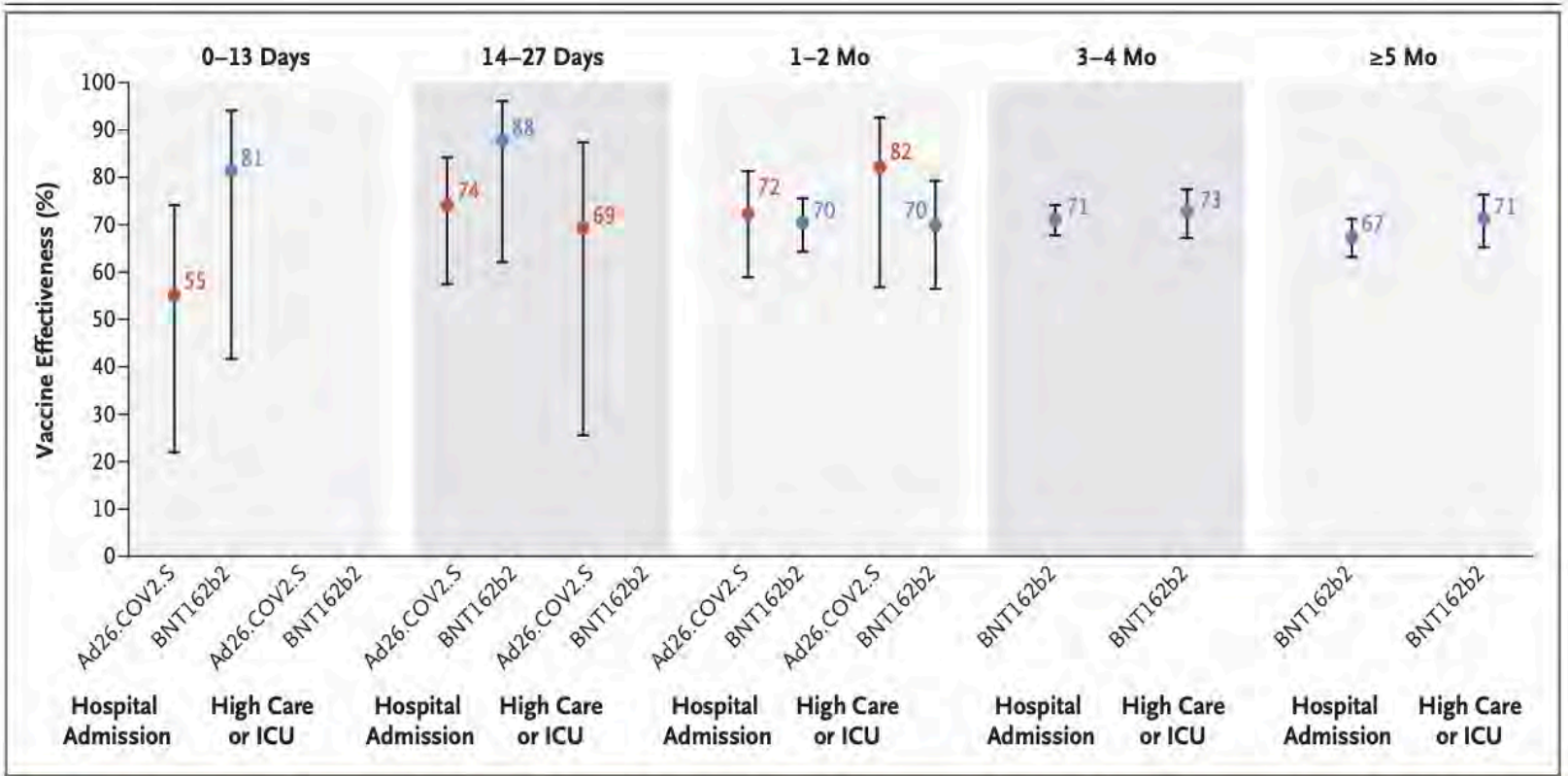


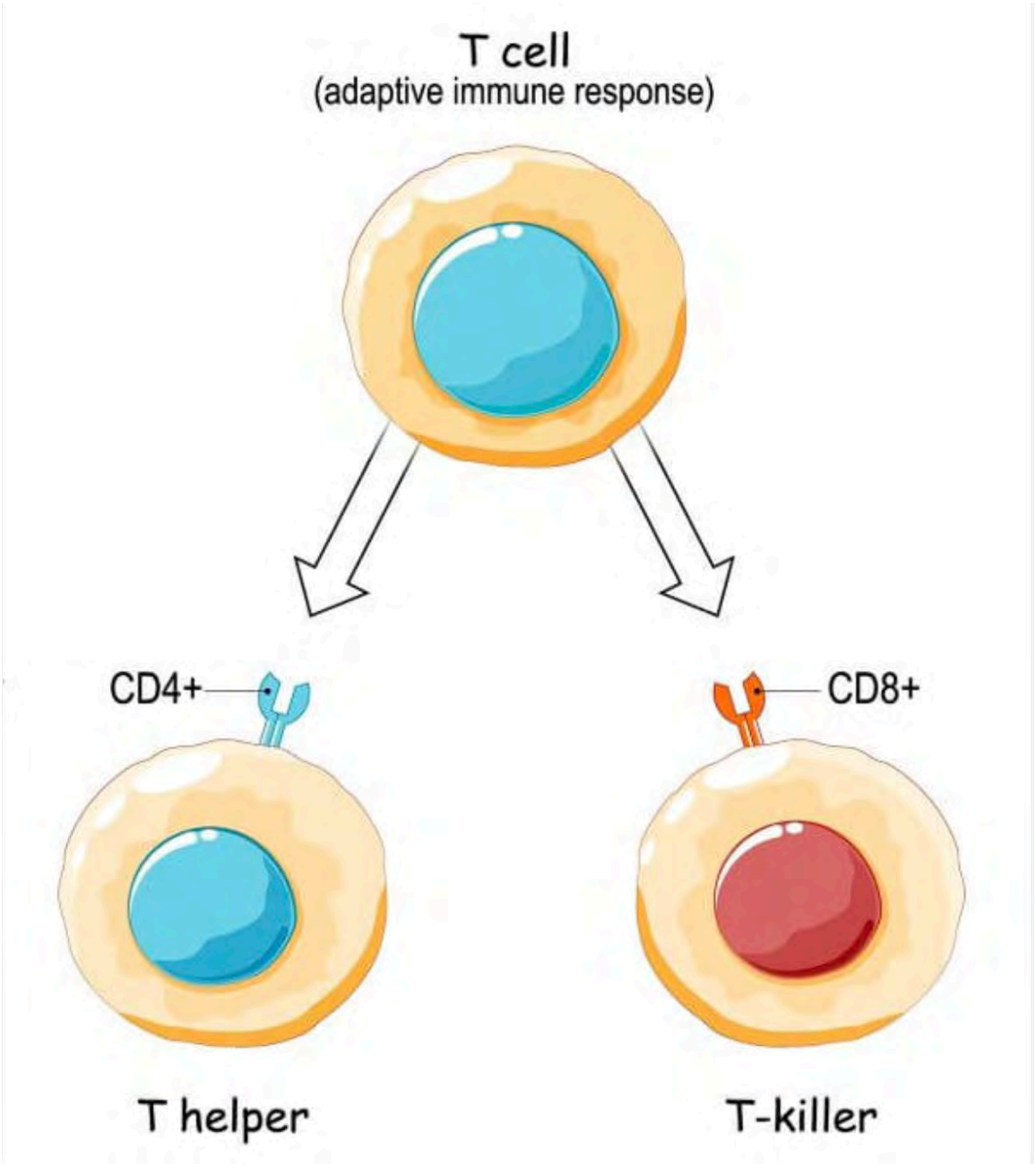
Figure 1. Vaccine Effectiveness against Severe Covid-19 during a Surge of the Omicron Variant in South Africa (November 15, 2021, to January 14, 2022).

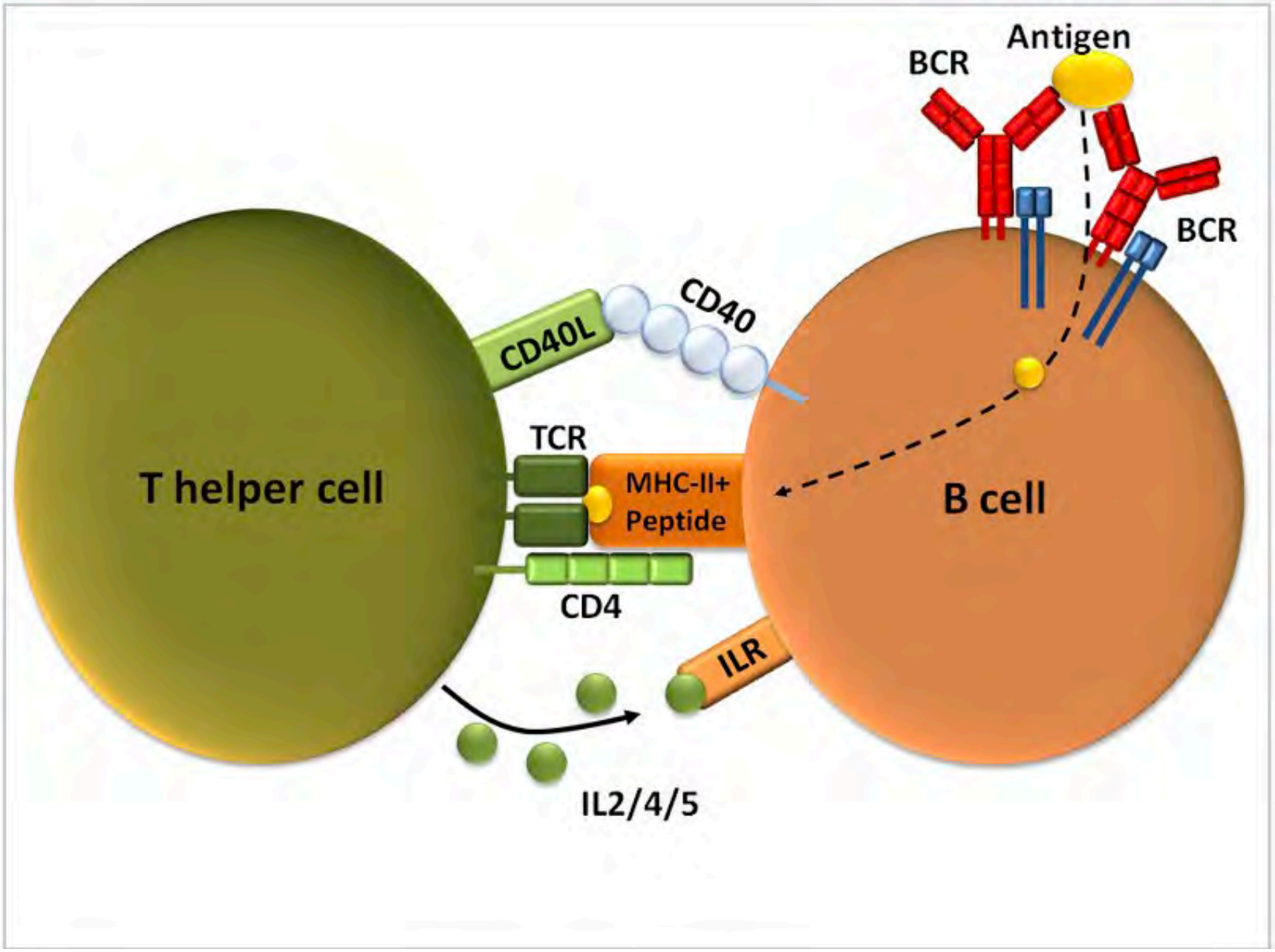
Shown is the estimated effectiveness of the BNT162b2 messenger RNA vaccine (Pfizer–BioNTech) and the Ad26.COV2.S vaccine (Johnson & Johnson–Janssen) against severe Covid-19, which was defined as disease resulting in hospitalization or admission to an intensive care unit (ICU) or to high care (the practice of locating patients' beds close to the nursing station for 24-hour observation). Effectiveness data are shown according to the time period after the administration of the second dose of vaccine. If no value is provided for a specific time period in either vaccine group, data were not collected for that vaccine during that time period. I bars indicate 95% confidence intervals.

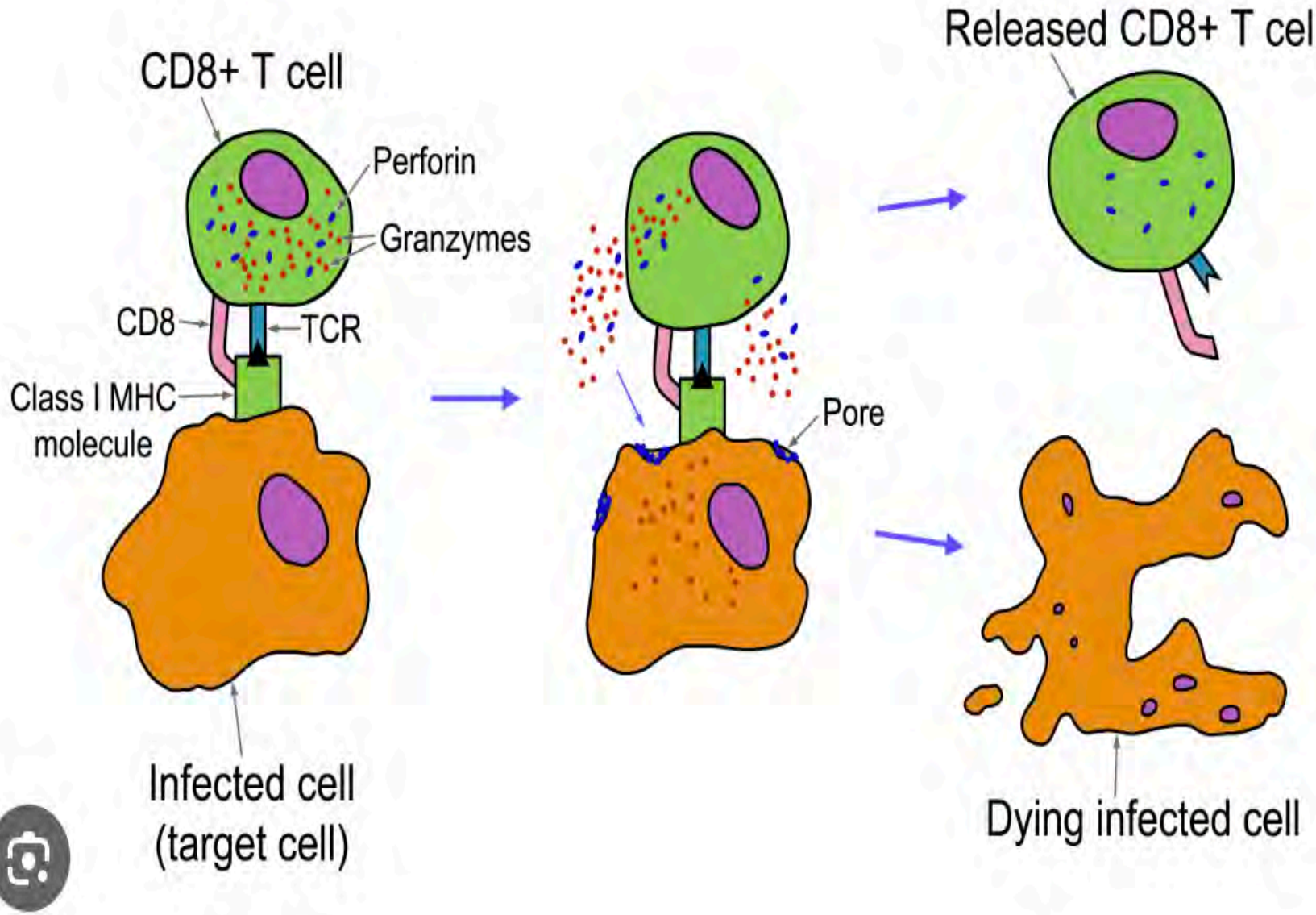
Gray, G., et al. Effectiveness of AD26.COV2.S and BNT162b2 against Omicron Variant in South Africa. *N Engl J Med* (2022) 386: 2243-2245.

Why?

T cells


T cell
(adaptive immune response)
CD4+
CD8+
T helper
T-killer


Antigen
BCR
BCR
CD40
CD40L
TCR
MHC-II+
Peptide
T helper cell
B cell
CD4
ILR
IL2/4/5


CD8+ T cell
Perforin
Granzymes
CD8
TCR
Class I MHC molecule
Infected cell (target cell)
Pore
Released CD8+ T cell
Dying infected cell

Cytotoxic T cells provide a second line of defense against viral infections

Unlike epitopes on the receptor binding domain of the spike protein, T cell epitopes are largely conserved across variants

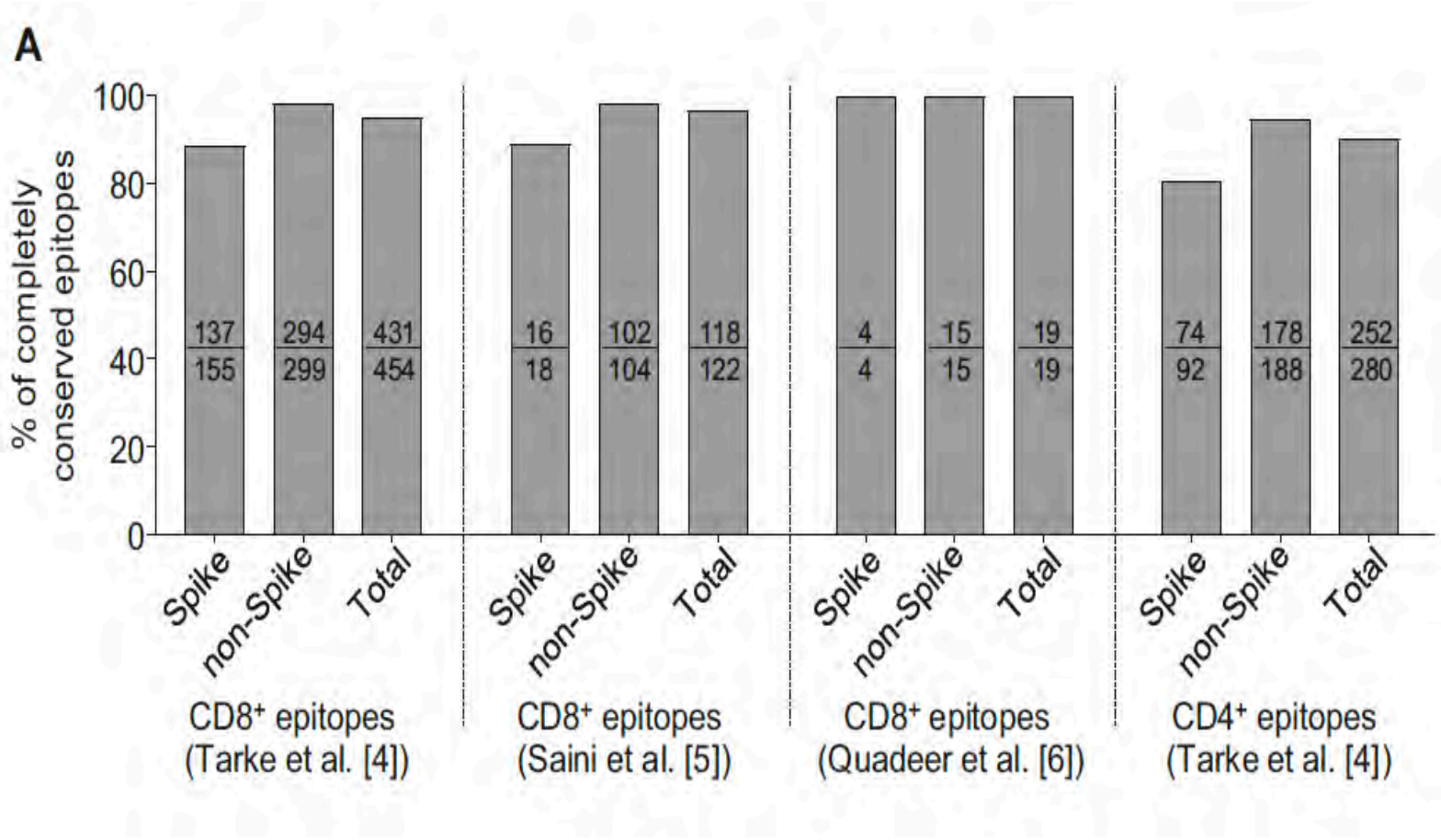
T cell epitopes in SARS-CoV-2 proteins are substantially conserved in the Omicron variant

Seong Jin Choi[1,7], Dong-Uk Kim[2,7], Ji Yun Noh[2,3], Sangwoo Kim[4], Su-Hyung Park[2], Hye Won Jeong[2,5] and Eui-Cheol Shin[2,6]✉

Cellular & Molecular Immunology (2022) 19:447–448; https://doi.org/10.1038/s41423-022-00838-5

In November 2021, the Omicron variant (B.1.1.529) emerged and was designated a variant of concern (VOC) by the World Health Organization. Recently, Omicron was reported to extensively escape neutralizing antibodies elicited by COVID-19 vaccination or natural infection [1–3]. However, whether Omicron evades the T cell immunity elicited by COVID-19 vaccination or natural infection

original SARS-CoV-2 strain and Omicron. PBMCs were obtained from individuals who had recovered from infection with the original SARS-CoV-2 and individuals vaccinated with BNT162b2. Among convalescent individuals, the frequency of IFN-γ^+ cells after stimulation with the Omicron spike OLPs was 76.74% and 88.03% of the frequency after stimulation with the original spike



Epitopes recognized by CD4$^+$ and CD8$^+$ T cells are conserved between Wuhan-1 and Omicron strains

Also, unlike circulating antibodies, memory T cells are long-lasting

Article

Longitudinal analysis shows durable and broad immune memory after SARS-CoV-2 infection with persisting antibody responses and memory B and T cells

Kristen W. Cohen,[1,10] Susanne L. Linderman,[2,3,10] Zoe Moodie,[1] Julie Czartoski,[1] Lilin Lai,[2,4,5] Grace Mantus,[2,4,6] Carson Norwood,[2,4,6] Lindsay E. Nyhoff,[2,4] Venkata Viswanadh Edara,[2,4,5] Katharine Floyd,[2,4,5] Stephen C. De Rosa,[1,7] Hasan Ahmed,[8] Rachael Whaley,[1] Shivan N. Patel,[6] Brittany Prigmore,[1] Maria P. Lemos,[1] Carl W. Davis,[2,3] Sarah Furth,[1] James B. O'Keefe,[6] Mohini P. Gharpure,[2,3] Sivaram Gunisetty,[2,3] Kathy Stephens,[4] Rustom Antia,[8] Veronika I. Zarnitsyna,[2,3] David S. Stephens,[6] Srilatha Edupuganti,[6,9] Nadine Rouphael,[6,9] Evan J. Anderson,[4] Aneesh K. Mehta,[6] Jens Wrammert,[2,4,11] Mehul S. Suthar,[2,4,5,11] Rafi Ahmed,[2,3,11,*] and M. Juliana McElrath[1,7,11,12,*]

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https://doi.org/10.1016/j.xcrm.2021.100354

Cohen, K.W., et al. *Cell Reports Medicine*, July 20, 2021

Cohen, et al. (2021)

- Study of 254 Covid-19 patients followed for 8 months.
- CD4+ and CD8+ T cells had a half-life of about 200 days.
- Most importantly, whereas CD4+ T cells equally targeted all four SARS-CoV-2 structural proteins, CD8+ T cells showed preferential recognition for the nucleoprotein.

What is the evidence that cytotoxic T cells are important in protection against severe Covid?

Preclinical studies

CORONAVIRUS

Dual spike and nucleocapsid mRNA vaccination confer protection against SARS-CoV-2 Omicron and Delta variants in preclinical models

Renee L. Hajnik[1,2]†, Jessica A. Plante[1,3,4]†, Yuejin Liang[1]†, Mohamad-Gabriel Alameh[5], Jinyi Tang[6,7,8], Srinivasa Reddy Bonam[1], Chaojie Zhong[1], Awadalkareem Adam[1], Dionna Scharton[1,4], Grace H. Rafael[1], Yang Liu[9], Nicholas C. Hazell[1,2], Jiaren Sun[1,3,10], Lynn Soong[1,3,10], Pei-Yong Shi[3,9,10], Tian Wang[1,3,10], David H. Walker[2,3,11], Jie Sun[6,7,8], Drew Weissman[5], Scott C. Weaver[1,3,4,10], Kenneth S. Plante[1,3,4]*, Haitao Hu[1,3,10]*‡

Emergence of SARS-CoV-2 variants of concern (VOCs), including the highly transmissible Omicron and Delta strains, has posed constant challenges to the current COVID-19 vaccines that principally target the viral spike protein (S). Here, we report a nucleoside-modified messenger RNA (mRNA) vaccine that expresses the more conserved viral nucleoprotein (mRNA-N) and show that mRNA-N vaccination alone can induce modest control of SARS-CoV-2. Critically, combining mRNA-N with the clinically proven S-expressing mRNA vaccine (mRNA-S+N) induced robust protection against both Delta and Omicron variants. In the hamster models of SARS-CoV-2 VOC challenge, we demonstrated that, compared to mRNA-S alone, combination mRNA-S+N vaccination not only induced more robust control of the Delta and Omicron variants in the lungs but also provided enhanced protection in the upper respiratory tract. In vivo $CD8^+$ T cell depletion suggested a potential role for $CD8^+$ T cells in protection conferred by mRNA-S+N vaccination. Antigen-specific immune analyses indicated that N-specific immunity, as well as augmented S-specific immunity, was associated with enhanced protection elicited by the combination mRNA vaccination. Our findings suggest that combined mRNA-S+N vaccination is an effective approach for promoting broad protection against SARS-CoV-2 variants.

Hajnik R.L., et al. *Science Translational Medicine* (2022) 14: eabq1945.

Hajnick, et al. (2022)

- Hamsters inoculated with mRNA coding for the SARS-Cov-2 spike (S) protein, nucleoprotein (N), or spike plus nucleoprotein. All three combinations were protective. However, the combination of spike plus nucleoprotein offered the broadest protection against variants.
- Depletion of CD8+ T cells abrogated protection for all three groups.
- “Our findings suggest that combined mRNA-S + N vaccination is an effective approach for promoting broad protection against SARS-CoV-2 variants.”

CORONAVIRUS

CD8 T Cells Contribute to Vaccine Protection Against SARS-CoV-2 in Macaques

Jinyan Liu[1]*, Jingyou Yu[1]*, Katherine McMahan[1]*, Catherine Jacob-Dolan[1,2]*, Xuan He[1]*, Victoria Giffin[1]*, Cindy Wu[1], Michaela Sciacca[1], Olivia Powers[1], Felix Nampanya[1], Jessica Miller[1], Michelle Lifton[1], David Hope[1], Kevin Hall[1], Nicole P. Hachmann[1], Benjamin Chung[1], Tochi Anioke[1], Wenjun Li[3], Jeanne Muench[4], Adrienne Gamblin[4], Mona Boursiquot[4], Anthony Cook[4], Mark G. Lewis[4], Hanne Andersen[4], Dan H. Barouch[1,2]†

Spike-specific neutralizing antibodies (NAbs) are generally considered key correlates of vaccine protection against SARS-CoV-2 infection. Recently, robust vaccine prevention of severe disease with SARS-CoV-2 variants that largely escape NAb responses has been reported, suggesting a role for other immune parameters for virologic control. However, direct data demonstrating a role of $CD8^+$ T cells in vaccine protection has not yet been reported. In this study, we show that vaccine-elicited $CD8^+$ T cells contribute substantially to virologic control following SARS-CoV-2 challenge in rhesus macaques. We vaccinated 30 macaques with a single immunization of the adenovirus vector-based vaccine Ad26.COV2.S or sham and then challenged them with $5x10^5$ $TCID_{50}$ SARS-CoV-2 B.1.617.2 (Delta) by the intranasal and intratracheal routes. All vaccinated animals were infected by this high-dose challenge but showed rapid virologic control in nasal swabs and bronchoalveolar lavage by day 4 following challenge. However, administration of an anti-CD8α or anti-CD8β depleting monoclonal antibody in vaccinated animals prior to SARS-CoV-2 challenge resulted in higher levels of peak and day 4 virus in both the upper and lower respiratory tracts. These data demonstrate that $CD8^+$ T cells contribute substantially to vaccine protection against SARS-CoV-2 replication in macaques.

Liu, J., et al. *Science Immunology*, August 9, 2022.

Liu, et al. (2022)

- Study of 30 rhesus macaques inoculated with the Ad26.Cov.5 vaccine and challenged with SARS-CoV-2 by the intranasal and intratracheal routes.
- All animals showed rapid virological control of the infection within 4 days of challenge. Administration of anti-CD8+ monoclonal antibodies resulted in substantially higher levels of virus in both the upper and lower respiratory tracts.
- “These data demonstrate that CD8+ T cells contribute substantially to vaccine-induced protection against SARS-CoV-2 in macaques.”

Human studies

CD8+ T cells contribute to survival in COVID-19 patients with hematologic cancers

A full list of authors and affiliations appears at the end of the article.

[#] These authors contributed equally to this work.

Abstract

Cancer patients have high mortality from COVID-19, and the immune parameters that dictate clinical outcomes remain unknown. In a cohort of 100 cancer patients hospitalized for COVID-19, patients with hematologic cancers had higher mortality relative to solid cancers. In two additional cohorts, flow cytometric and serologic analyses demonstrated that solid cancer and non-cancer patients had a similar immune phenotype during acute COVID-19 whereas hematologic cancer patients had impairment of B cells and SARS-CoV-2-specific antibody responses. Despite the impaired humoral immunity and high mortality in hematologic cancer patients with COVID-19, those with a greater number of CD8 T cells had improved survival, including those treated with anti-CD20 therapy. Further, 77% of hematologic cancer patients had detectable SARS-CoV-2 specific T-cell responses. Thus, CD8 T cells may influence recovery from COVID-19 when humoral immunity is deficient. These observations suggest that CD8 T cell responses to vaccination might provide protection in hematologic cancer patients even in the setting of limited humoral responses.

Bange, E.M., et al., *Nature Medicine* (2021). 27: 1280-1289.

Bange, et al. (2021)

- Study of 100 hematologic cancer patients hospitalized with Covid-19.
- Despite the impaired humoral immunity and high mortality in hematologic cancer patients with Covid-19, those with a greater number of CD8+ T cells had the highest incidence of survival, including those treated with anti-CD-20 (a pan-B cell marker).
- “These observations suggest that CD8+ T cell responses might provide protection in hematologic cancer patients even in the setting of limited humoral responses.”

ARTICLES
https://doi.org/10.1038/s41590-021-01084-z
nature immunology

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An immunodominant $NP_{105-113}$-B*07:02 cytotoxic T cell response controls viral replication and is associated with less severe COVID-19 disease

Yanchun Peng[1,2,27], Suet Ling Felce[2,3,4,27], Danning Dong[1,2,5,27], Frank Penkava[6,27], Alexander J. Mentzer[3,4,27], Xuan Yao[2,4,27], Guihai Liu[2,4,7,27], Zixi Yin[1,2,4,27], Ji-Li Chen[1,2,27], Yongxu Lu[8], Dannielle Wellington[1,2], Peter A. C. Wing[2,4], Delaney C. C. Dominey-Foy[2,4], Chen Jin[2,4], Wenbo Wang[2,4], Megat Abd Hamid[2,4], Ricardo A. Fernandes[2,4], Beibei Wang[2,4], Anastasia Fries[3,4], Xiaodong Zhuang[4], Neil Ashley[9], Timothy Rostron[10], Craig Waugh[11], Paul Sopp[11], Philip Hublitz[12], Ryan Beveridge[13], Tiong Kit Tan[1], Christina Dold[14], Andrew J. Kwok[3,4]

Peng, Y., et al. *Nature Immunology* (2022) 23: 50-61.

Peng, et al. (2022)

- Study of 52 Covid-19 patients; 30 with mild and 22 with severe disease.
- Protection against severe disease was most closely correlated with CD8+ responses directed against the SARS-CoV-2 nucleoprotein.
- “Our data show that nucleoprotein-specific T cell responses associate with mild disease and high antiviral efficacy, pointing to inclusion for future vaccine design.”

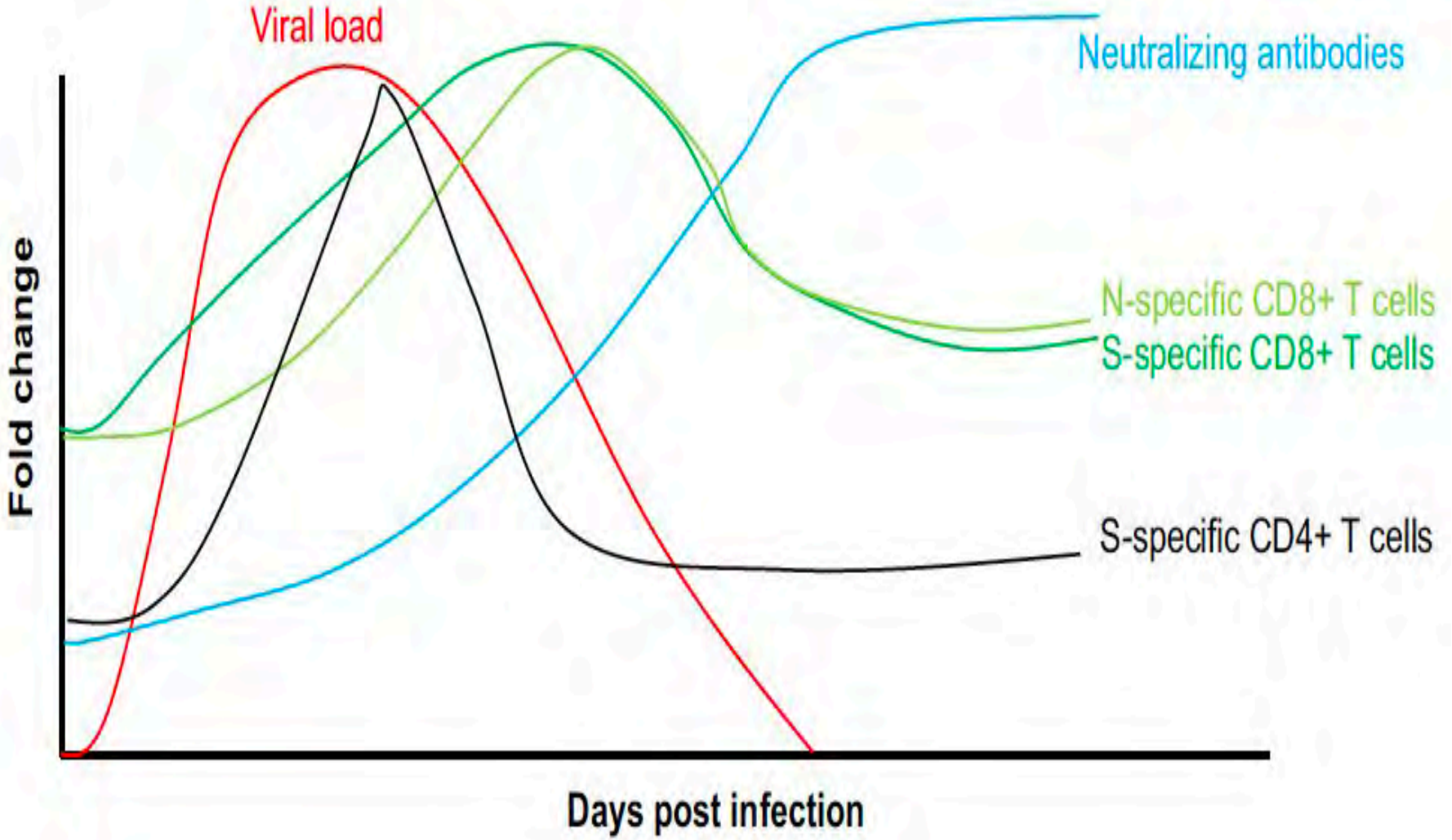
SARS-CoV-2 clearance after breakthrough infection correlates with fit and happy T cells

Marc Veldhoen[1] & Antonio Bertoletti[2,3]

1 Instituto de Medicina Molecular, João Lobo Antunes, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal
2 Emerging Infectious Diseases Program, Duke-NUS Medical School, Singapore, Singapore
3 Singapore Immunology Network, A*STAR, Singapore, Singapore

Immunology & Cell Biology 2023; 1–3; doi: 10.1111/imcb.12654

Veldhoen, M. A. Bertoletti, Immunology and Cell Biology (2023) 1-3.



Decrease in SARS-CoV-2 viral load most correlates with CD8+ T cell response during re-exposure

VIEWPOINT: COVID-19

T cell immunity to COVID-19 vaccines

T cell immunity may be critical for long-term protection by COVID-19 vaccines

By **E. John Wherry**[1] *and* **Dan H. Barouch**[2]

The development of multiple COVID-19 vaccines in record time is a major biomedical achievement, but mechanistic immune correlates of vaccine protection remain to be determined. Most studies on COVID-19 vaccines have focused on neutralizing antibody (NAb) responses, with little emphasis on cellular immunity. However, accumulating data suggest that T cell responses play an important role in

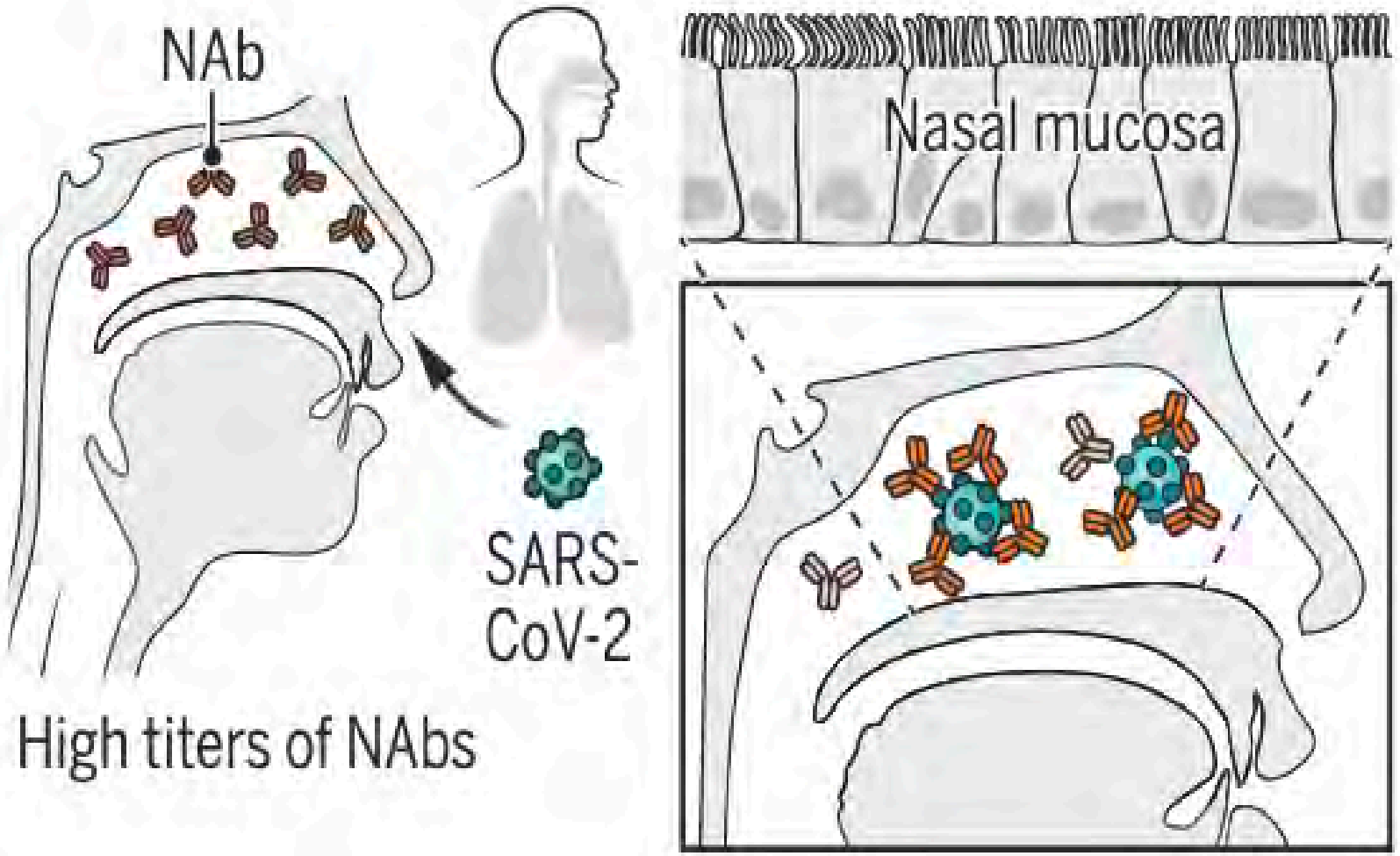
Immunological memory to SARS-CoV-2 from vaccination or infection can protect the host through multiple mechanisms. If virus breaches NAb defenses in the upper respiratory tract, protection from severe disease could still be mediated if immune mechanisms prevent virus spread to the lower respiratory tract and control virus replication in the lungs. Such protection can involve antibodies, but T cells are ideally suited to limit virus replication by eliminating virus-infected cells. Thus, although an ideal vac-

severe disease has largely been maintained in otherwise healthy individuals. For example, data from South Africa during the Omicron surge have shown that both BNT162b2 and Ad26.COV2.S vaccines still provided robust protection against hospitalization even in the absence of high-titer NAbs (*5*, *6*, *9*). These data suggest that other mechanisms protect from severe disease.

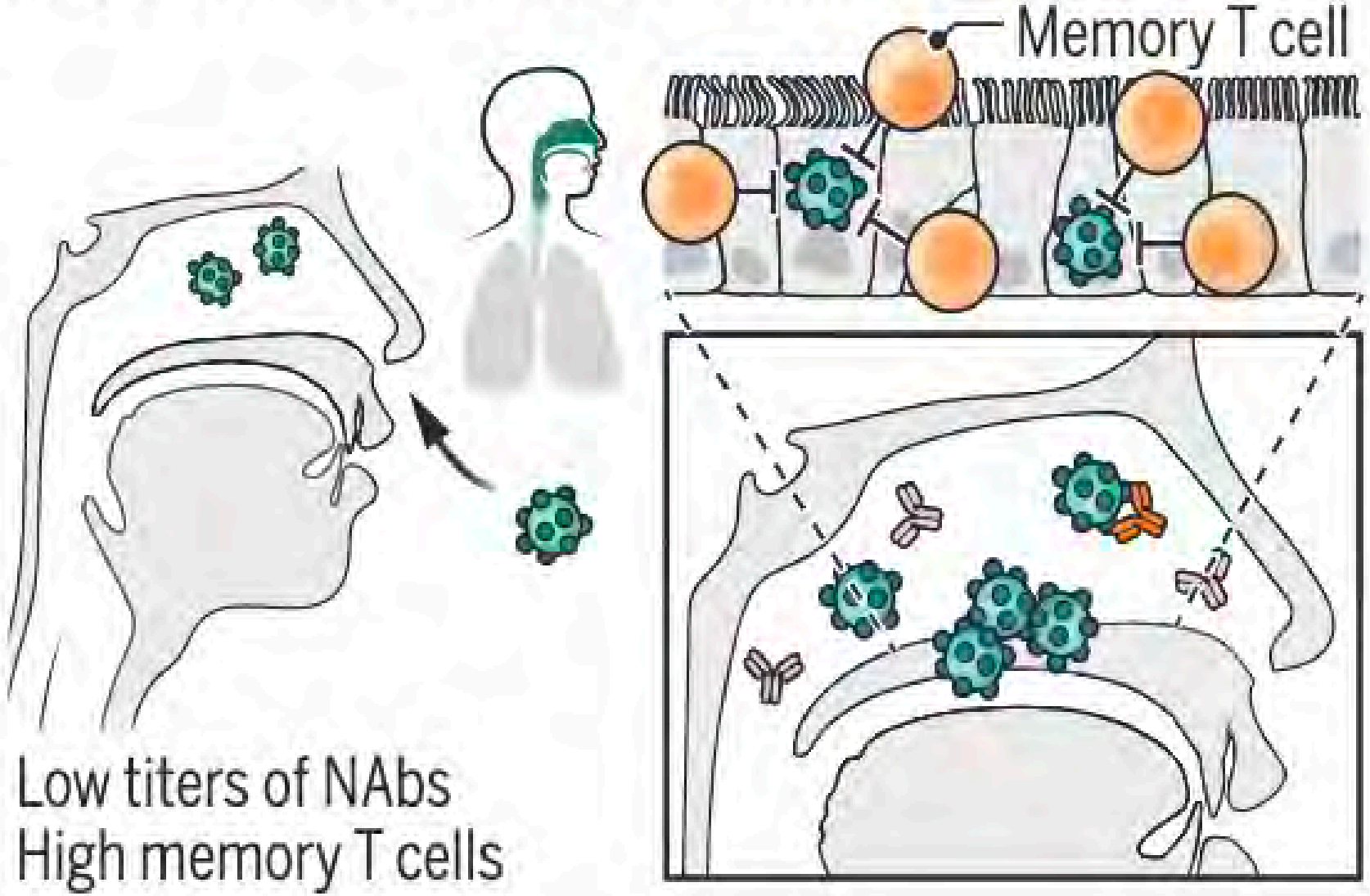
Multiple layers of the immune system contribute to immunological memory and protective immunity to viruses. Antibody re-

Wherry, J., D.H. Barouch, *Science* (2022) 377: 821-822.

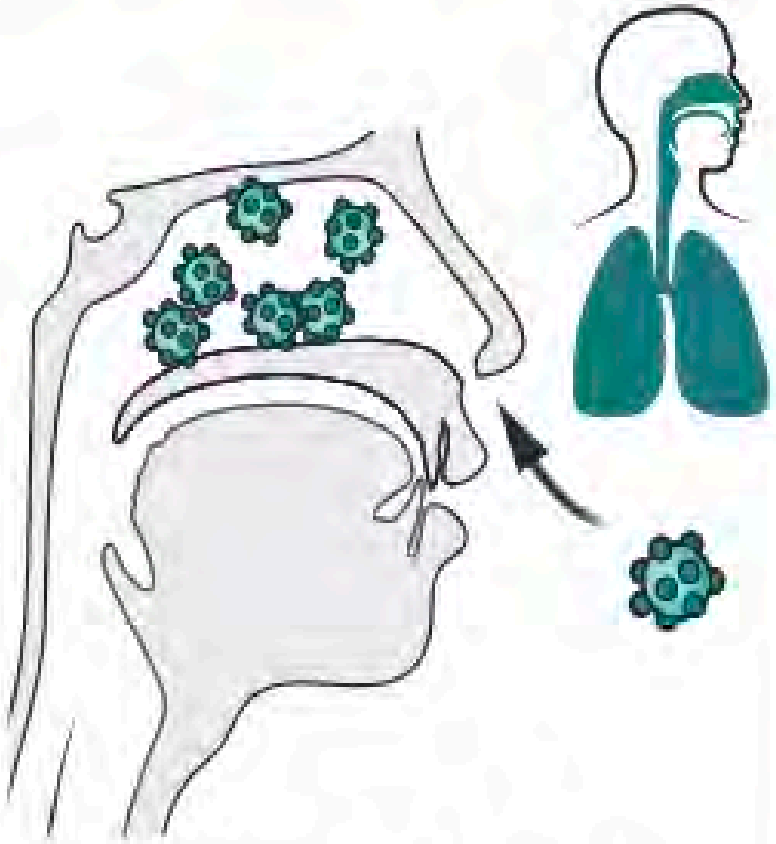
Protection from infection



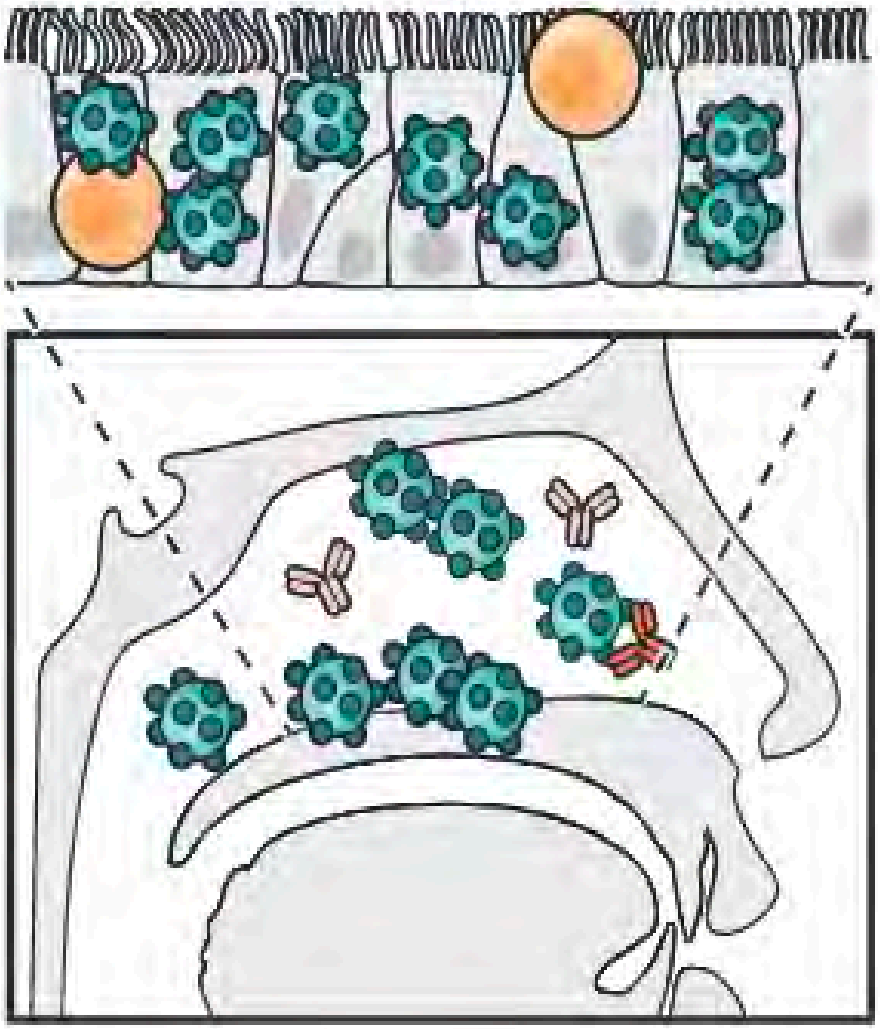
Protection from severe disease



Viral dissemination and severe disease

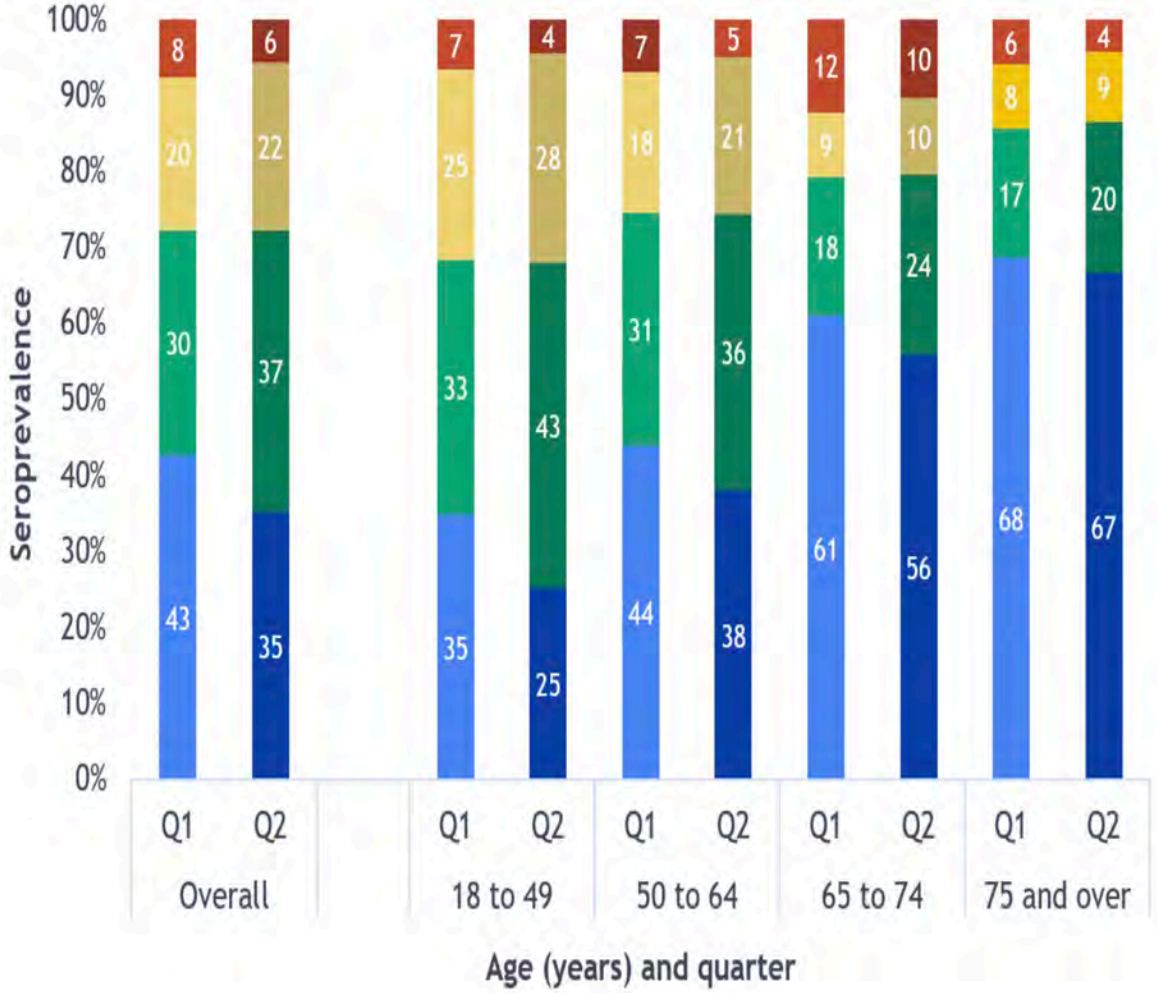


Low titers of NAbs
Low memory T cells



We are at a different stage of this pandemic

Seroprevalence by Vaccine and Infection History Among U.S. Adult Blood Donors by Age Group, January-June 2022



No immunity

Infection only induced immunity

Both vaccine and infection induced immunity

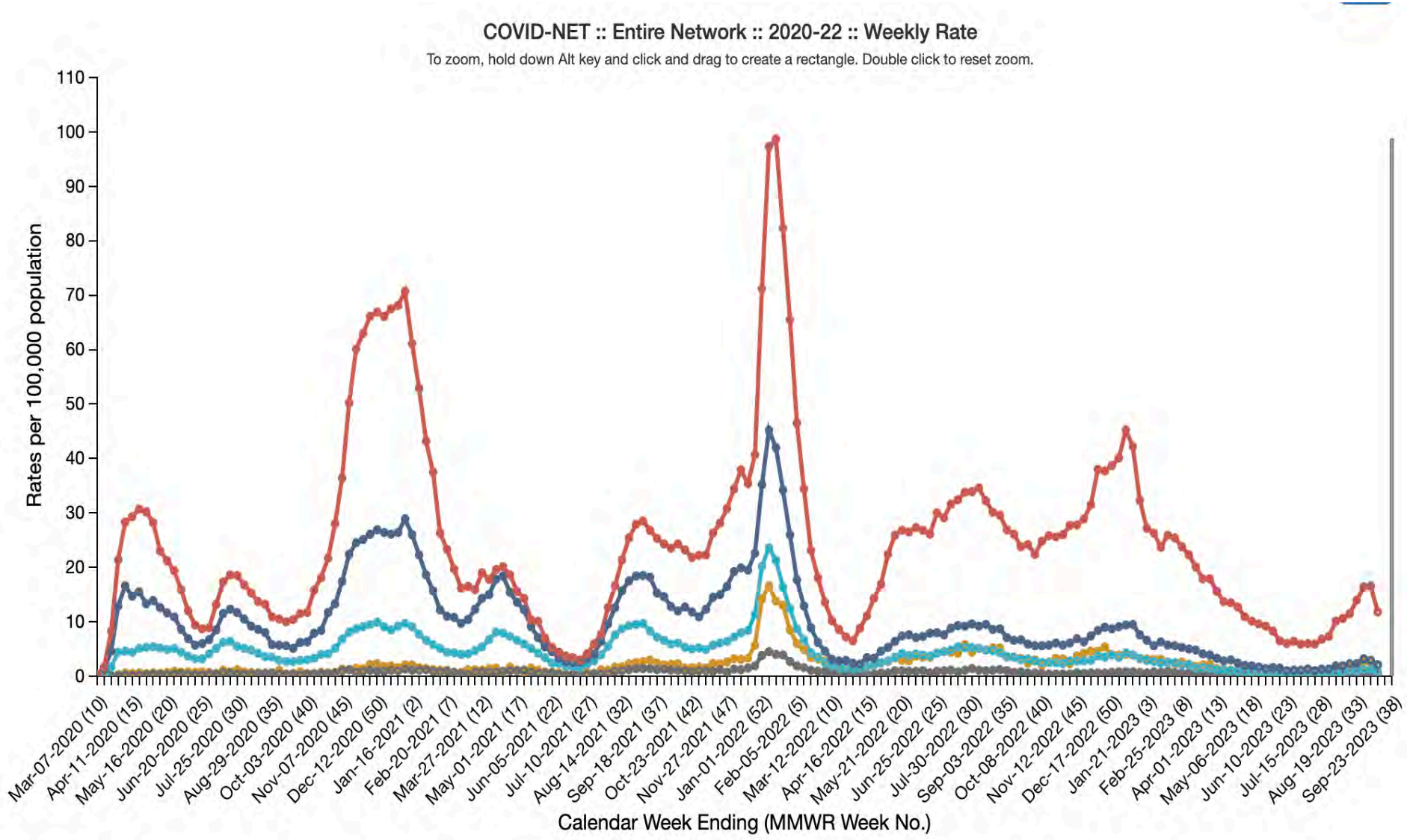
Vaccine only induced immunity

Q1 = Jan. - Mar. 2022

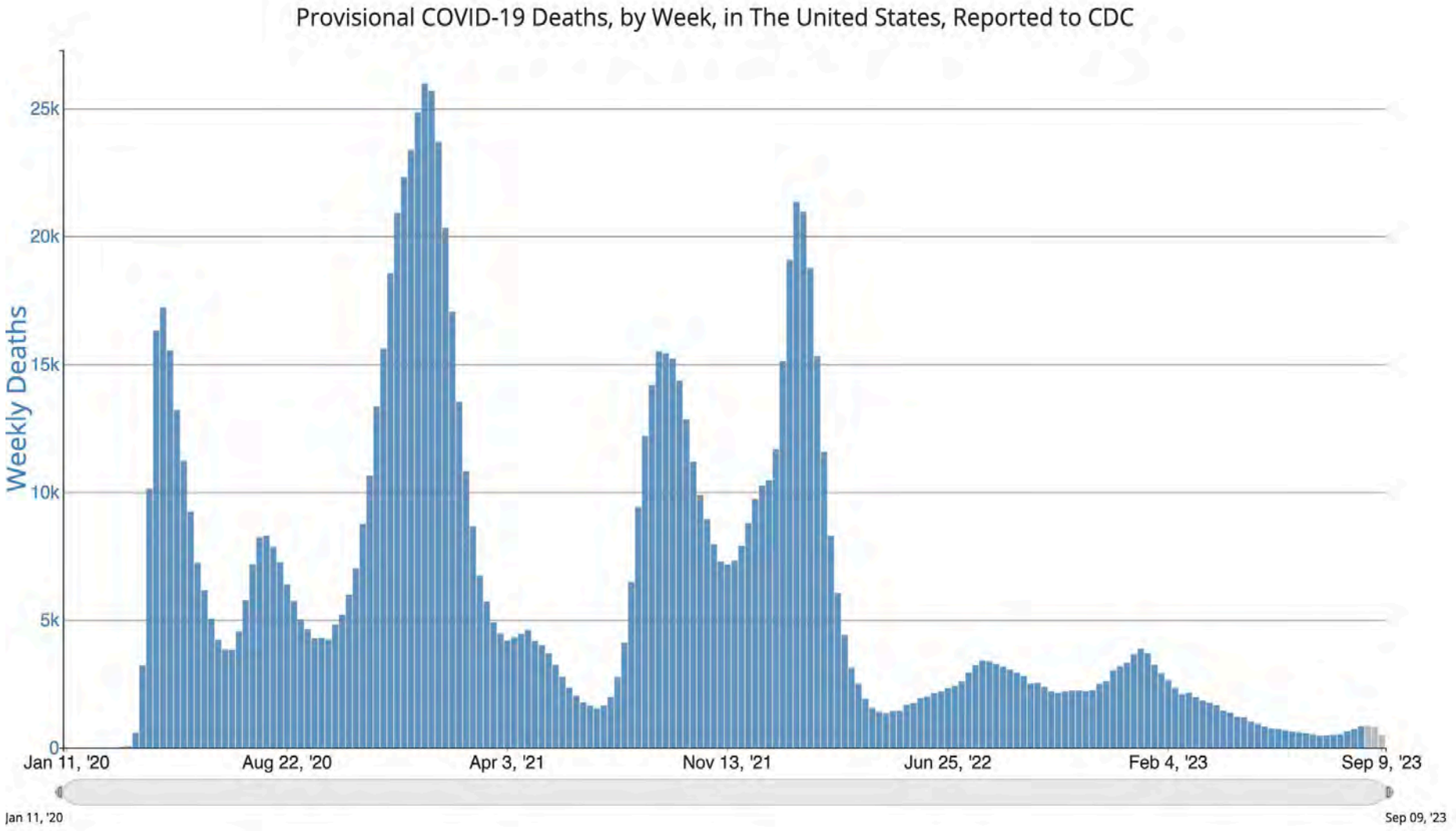
Q2 = Apr. - Jun. 2022

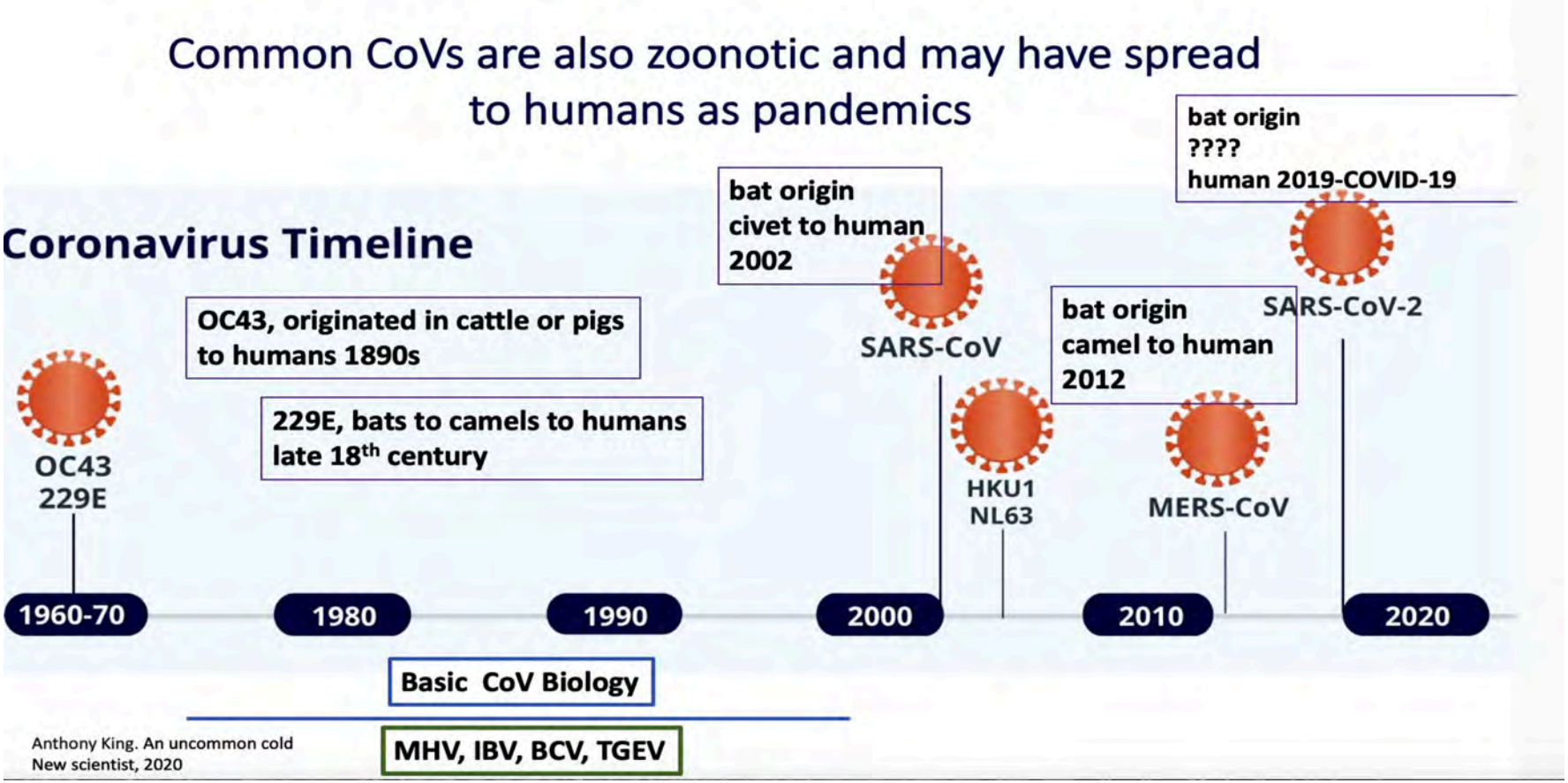
Source: https://covid.cdc.gov/covid-data-tracker/#nationwide-blood-donor-seroprevalence-2022

Weekly Covid-19 Hospitalization Rates, USA



Weekly Covid-19 Death Rates, USA





1. SARS-CoV-2 virus will be circulating for decades, if not longer.
2. Need to continue to protect those at highest risk of hospitalization and death.

The future of Covid-19 vaccines

- Memory cytotoxic T cells, which are generally long-lived, are important in protecting against severe disease.
- Cytotoxic T cells primarily recognize the SARS-CoV-2 nucleoprotein (N), which is antigenically conserved across all variants.
- Wouldn’t it make sense to include the N protein in future vaccines.

Critical question moving forward

- What is the best priming and boosting strategy to ensure long-lived memory T cell responses?
- The answer will likely be dependent on the age and comorbidity status of various populations.

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