The Daily COVID-19 Literature Surveillance Summary

April 14, 2021

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COVID-19 Daily Literature Surveillance

COVID19LST

Bringing you real time, distilled information for guiding best practices during the COVID-19 pandemic

LEVEL OF EVIDENCE

Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or *n*-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, *n*-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or *n*-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

*** Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.**

**** As always, a systematic review is generally better than an individual study.**

How to cite the Levels of Evidence Table

OCEBM Levels of Evidence Working Group*. "The Oxford 2011 Levels of Evidence".
Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

** OCEBM Table of Evidence Working Group = Jeremy Howick, Iain Chalmers (James Lind Library), Paul Glasziou, Trish Greenhalgh, Carl Heneghan, Alessandro Liberati, Ivan Moschetti, Bob Phillips, Hazel Thornton, Olive Goddard and Mary Hodgkinson*

EXECUTIVE SUMMARY

Transmission & Prevention

- Binding and neutralization antibody titers after a single vaccine dose in previously infected with SARS-CoV-2 were found to be higher. Researchers of the Institute of Human Virology at the University of Maryland School of Medicine, Baltimore present a serosurvey of 59 healthcare workers who, prior to receiving the first dose of an mRNA SARS-CoV-2 vaccine, were categorized as SARS-CoV-2 IgG negative, IgG positive asymptomatic, and IgG positive symptomatic. At days 0, 7, and 14, plasma was obtained and analyzed to quantify median reciprocal half-maximal binding antibody titers to the spike trimer. At 0, 7, and 14 days they found higher overall titers in both the asymptomatic IgG+ (208, 29 364, and 34 033) and the symptomatic IgG+ (302, 32 301, and 35 460) groups compared to the IgG negative group (<50, <50, and 924). The authors discuss that this data can help to inform vaccination strategies employing single-dose prioritization.

- Antibodies appear to persist through 6 months after the second dose of mRNA-1273 vaccine for COVID-19. Doctorate researchers from the National Institute of Allergy and Infectious Diseases (NIAID) and Emory University School of Medicine investigated 33 healthy adults 6 months after the second dose of Moderna mRNA-1273 COVID-19 vaccine for durability and neutralizing effect of elicited antibodies. An enzyme-linked immunosorbent assay (ELISA) was utilized to measure antibodies by geometric mean endpoint titers (GMTs) and reported that antibodies remained high in all age groups, but 50% inhibitory dilution (ID50) GMTs were lower in 56 to 70 years of age ($p = 0.02$) and >71 years of age ($p = 0.004$) than in those 18 to 55 years of age. This study suggests the continued use of the vaccination for SARS-CoV-2 given the presence of antibodies 180 days after vaccination.

- Emergence of a novel SARS-CoV-2 variant was found in Southern California. Pathology and lab medicine experts from Cedars-Sinai Medical Center in Los Angeles sequenced nasopharyngeal samples collected from 192 patients positive for SARS-CoV-2 between November to December 2020 and conducted phylogenetic analysis using representative genomes from the open source genomic database Nextstrain. They discovered a novel strain with five mutations (CAL.20G) in 22% of all samples (40/185) with a descendent cluster (CAL.20C) accounting for 36.4% (67/185) of cases in Los Angeles. While the CAL.20C strain's significance is unknown, it has now been identified in 25 other states leading the authors to encourage ongoing surveillance for SARS-CoV-2 variants.

TABLE OF CONTENTS

CLIMATE

GLOBAL

THE POTENTIAL FUTURE OF THE COVID-19 PANDEMIC: WILL SARS-COV-2 BECOME A RECURRENT SEASONAL INFECTION?

Murray CJL, Piot P.. JAMA. 2021 Apr 6;325(13):1249-1250. doi: 10.1001/jama.2021.2828.
Level of Evidence: 5 - Expert Opinion

BLUF

An opinion article conducted by physician researchers associated with University of Washington and London School of Hygiene and Tropical Medicine suggests public and health systems should prepare for the possibility that COVID-19 will become a recurrent seasonal disease due to increasing prevalence of COVID-19 variants, reinfection with new variants, and not enough individuals receiving vaccination. This article proposes five strategies including: increased global vaccination efforts, monitoring emergence of new variants and adjusting vaccine accordingly, managing/financing winter hospital surges, reducing transmission in peak months, and physical distancing/precautions for high-risk individuals. The authors suggest there are many uncertainties regarding the future of COVID-19 infection, however preparation for health system changes, public health response, and surveillance based on the prospect of the virus going forward is crucial.

ADULTS

POTENTIAL PROTECTIVE EFFECT FROM COVID-19 CONFERRED BY ALTITUDE: A LONGITUDINAL ANALYSIS IN PERU DURING FULL LOCKDOWN

Thomson TM, Casas F, Guerrero HA, Figueroa-Mujíca R, Villafuerte FC, Machicado C.. High Alt Med Biol. 2021 Mar 29. doi: 10.1089/ham.2020.0202. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Molecular biologists, physiologists, and biophysicists from multiple research institutes in Spain and Peru analyzed geographical factors influencing SARS-CoV-2 transmission and outcomes between April and July 2020 using publicly available datasets. They found altitude >2500 meters was associated with decreased risk of mortality independent of socioeconomic status (Figure 3). Protection was inversely correlated with the presence of hypercholesterolemia and hypertension (Figure 8). Though the study design precludes causal inferences, authors suggest physiologic adaptations to altitude may confer a protective effect against death from COVID-19.

ABSTRACT

Thomson, Timothy M., Fresia Casas, Harold Andre Guerrero, Romulo Figueroa-Mujica, Francisco C. Villafuerte, and Claudia Machicado. Potential protective effect from COVID-19 conferred by altitude: A longitudinal analysis in Peru during full lockdown. High Alt Med Biol. 00:000-000, 2021. Background: The COVID-19 pandemic had a delayed onset in America. Despite the time advantage for the implementation of preventative measures to contain its spread, the pandemic followed growth rates that paralleled those observed before in Europe. Objectives: To analyze the temporal and geographical distribution of the COVID-19 pandemic at district-level in Peru during the full lockdown period in 2020. Methods: Analysis of publicly available data sets, stratified by altitude and geographical localization. Correlation tests of COVID-19 case and death rates to population prevalence of comorbidities. Results: We observe a strong protective effect of altitude from COVID-19 mortality in populations located above 2,500 m. We provide evidence that internal migration through a specific land route is a significant factor progressively overriding the protection from COVID-19 afforded by high altitude. This protection is independent of poverty indexes and is inversely correlated with the prevalence of hypertension and hypercholesterolemia. Discussion: Long-term adaptation to residency at high altitude may be the third general protective factor from COVID-19 severity and death, after young age and female sex. Multisystemic adaptive traits or acclimatization processes in response to chronic hypobaric hypoxia may explain the apparent protective effect of high altitude from COVID-19 death.

FIGURES

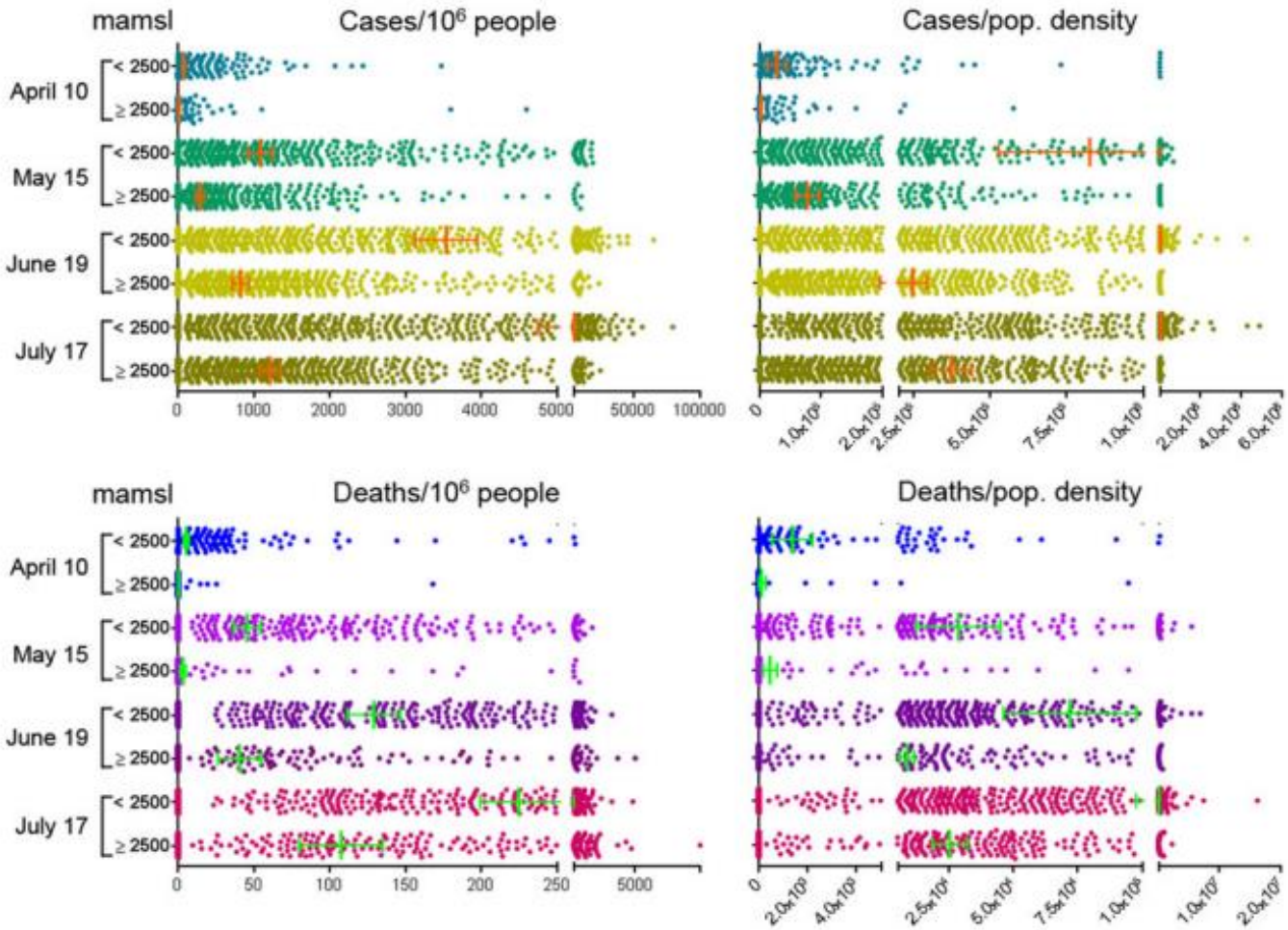


FIG. 3. Distribution of case and death rates per million people or population density in districts located below or above 2,5 00 m of altitude. Cumulative deaths and cases per 106 population or population density were plotted on each of the four indicated dates. Green and orange vertical lines denote mean values and horizontal lines 95% confidence intervals. All pairwise comparisons between low- and high- altitude strata on all four dates yielded p-values <0.0001 (Mann–Whitney nonparametric test). mamsl, meters above mean sea level.

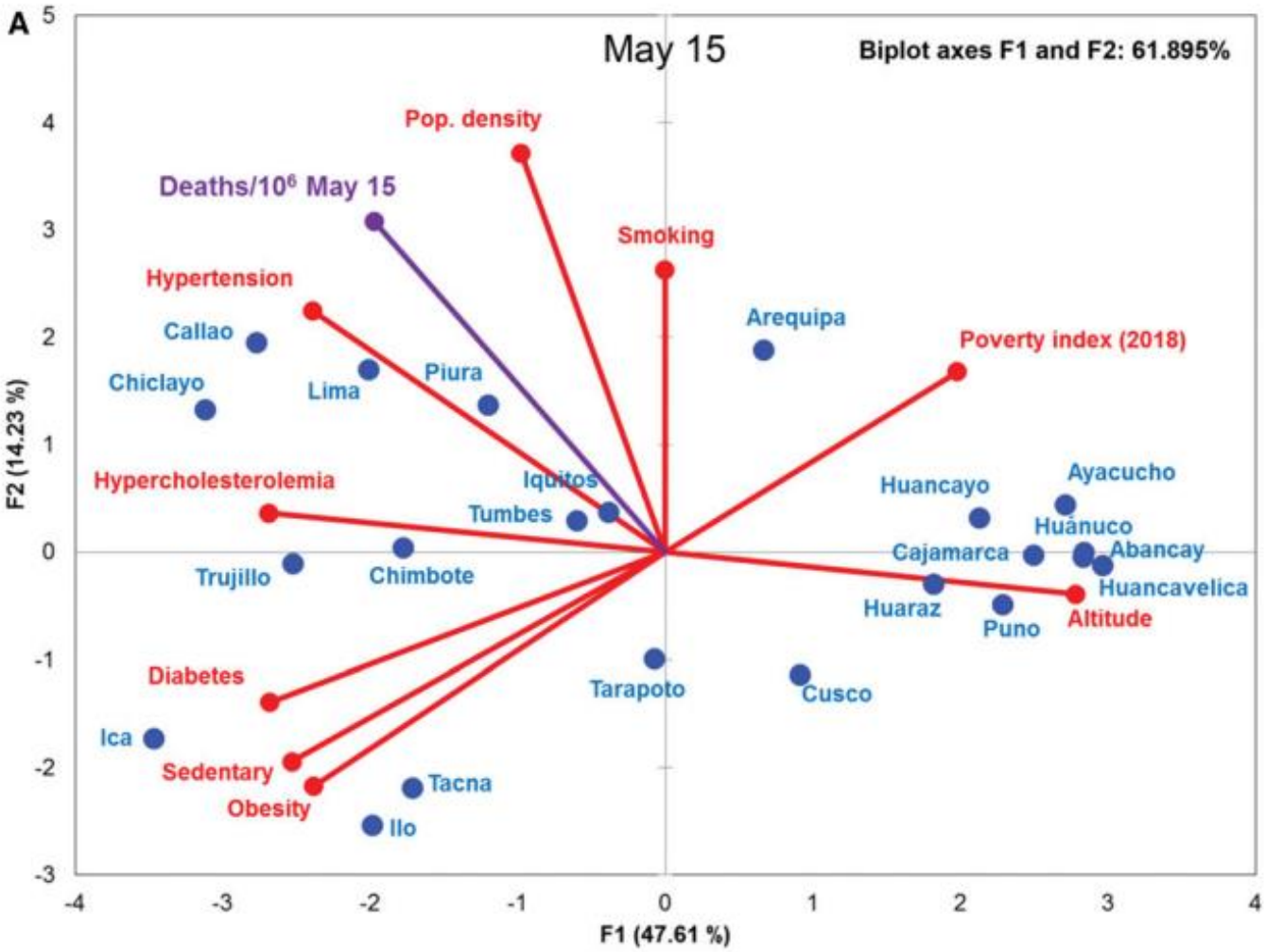


FIG. 8. Correlation analyses of COVID-19 death rates, nontransmissible morbidity prevalence, and altitude in major Peruvian cities. (A) Principal component analysis of COVID-19 deaths registered from May 15 through June 19 (rates per 106 population), together with morbidity prevalence, altitude, and poverty index.

ARE ANTIPHOSPHOLIPID ANTIBODIES JUST A COMMON EPIPHENOMENON OR ARE THEY CAUSATIVE OF IMMUNE-MEDIATED COAGULOPATHY IN COVID-19?

Castillo-Martínez D, Torres Z, Amezcua-Guerra LM, Pineda C.. Clin Rheumatol. 2021 Apr 7. doi: 10.1007/s10067-021-05724-5. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

A perspective article conducted by physician researchers affiliated with various medical institutions in Mexico City, Mexico analyzed case reports and case studies to explain the high frequency of antiphospholipid antibodies (aPLs) in COVID-19 infection and found high diversity and frequency of aPLs suggest active induction during acute infection, more often associated with severe or critical illness. APL positivity corresponded with presence of thrombophilias and low natural anticoagulant likely contributing to coagulopathy, and contradictory results on aPLs involvement in thrombotic events (Table 1). Concurrence of thrombotic complications and aPLs suggests an active role for antibodies and resembles catastrophic antiphospholipid syndrome, thus it is important to define whether aPLs are an epiphenomenon or actively involved in hemostatic abnormalities to uncover novel mechanisms and prognostic bookmarks for immune-mediated thrombosis and devastating disease.

ABSTRACT

The coronavirus disease 2019 (COVID-19) is the largest public health emergency in recent times. A significant number of patients develop a severe form of COVID-19 characterized by coagulopathy, organ failure, and elevated mortality. In addition, an unusually high frequency of antiphospholipid antibodies (aPLs) has been found in patients with COVID-19. These clinical and serological manifestations closely resemble those seen in the antiphospholipid syndrome (APS), especially in its catastrophic form, suggesting a role of aPLs in immune-associated coagulopathy. However, government bodies such as the American Society of Hematology have spoken out against the systematic search for aPLs in patients with COVID-19. In an attempt to bridge the gap on this hot topic, we conducted a comprehensive review of currently available cohort studies and case series systematically evaluating aPLs in COVID-19 patients. In this Perspective, we seek to identify both the frequency and the type of aPLs found in patients with COVID-19, as well as the potential association of these aPLs with vascular thrombosis and other distinctive characteristics of COVID-19. Furthermore, we investigated whether there is evidence that allows us to define the occurrence of aPLs in COVID-19 as an epiphenomenon, as has been observed in other systemic viral infections, or as antibodies against self-antigens bearing hallmarks that suggest a pathogenic role in immune-mediated thrombosis. Defining whether aPLs represent an epiphenomenon or they are actually involved in hemostatic abnormalities of COVID-19 is crucial both for uncovering novel mechanisms of immune-mediated thrombosis and for identifying potential prognostic biomarkers in this devastating disease.

FIGURES

Table 1: Summary of the main findings of studies on positive antiphospholipid antibodies in COVID-19.

Table 1 Summary of the main findings of studies on positive antiphospholipid antibodies in COVID-19

Ref. (country)	Cases (% male)	Age, years	aPL + (any)	aCL + IgM	aCL + IgG	aβ$_2$GPI + IgM	aβ$_2$GPI + IgG	LA +	Non-criteria aPL +
5 (Spain)	24 (58)	64 ± 14	8%	8.3%	0	8.3%	0	–	–
6 (France)	25 (68)	47 (35–64)	96%	52%	48%	0	4%	92%	aCL IgA=28% aβ$_2$GPI IgA=12% aPL IgM=56% aPL IgG=60%
8 (France)	56 (–)	–	~50%	10% of patients had aCL or aβ$_2$GPI IgG/IgM, no disaggregated information is reported.				45%	–
9 (Mexico)	21 (43)	*m* 62 (54–67)	57%	14%	10%	0	5%	–	aPT IgM=5% aPS IgM=14% aPS IgG=10% aAnnV IgM=19% aAnnV IgG=5%
10 (USA)	172 (–)	–	52%	23%	4.7%	5.2%	2.9%	–	aCL IgA=3.5% aβ$_2$GPI IgA=4.1% aPS/aPT IgM=18% aPS/aPT IgG=24%
11 (China)	79 (57)	60	47%	2.5%	5%	1.2%	15.1%	2.5%	aCL IgA=21.5% aβ$_2$GPI IgA=24% aPS/aPT IgM=8.8% aPS/aPT IgG=0%
12 (China)	19 (53)	*m* 65 (60–70)	52%	5.2%	10.5%	0	31.5%	5.2%	aCL IgA=31.5% aβ$_2$GPI IgA=36.8%
13 (Belgium)	31 (90)	*m* 63 (38–82)	74%	3%	19%	3%	9.6%	67.7%	aCL IgA=9.6% aβ2GPI IgA=9.6% aPS/aPT IgG=6.4% aPS/aPT IgM=12.9%
14 (Italy)	122 (51)	54 ± 19	~50%	2.7%	13.4%	7.1%	6.3%	22.2%	aCL IgA=1.7% aβ$_2$GPI IgM=3.3%
16 (France)	150 (81)	*m* 63 (53–71)	–	–	–	–	–	87.4%	–
17 (Spain)	27 (44)	58 (20–90)	25%	0	0	0	0	22.2%	aβ$_2$GPI IgA=3.7%
18 (France)	89 (68)	*m* 68 (63–71)	72%	2.2%	5.6%	2.2%	5.6%	66.3%	–
19 (UK)	35 (69)	56 (18–83)	91%	–	–	–	–	91%	–
20 (USA)	68 (50)	~56	44%	1.4%	0	1.4%	0	44%	–
21 (China)	86 (62)	66 ± 11	37%	–	–	–	–	–	–
23 (Italy)	33 (51)	*m* 70 (22–90)	24%	15%	9%	6%	6%	–	–
24 (Italy)	122 (63)	68 ± 16	–	6.6%	5.7%	9%	15.6%	–	aPS/aPT IgG=2.5% aPS/aPT IgM=9.8% aβ2GPI IgA =6.6%
25 (France)	74 (–)	*m* ~64	88%	12% (any aCL or aβ$_2$GPI in IgM/IgG isotypes)				85%	–
Total	1233 (60)	–	~54%	~10.4%	~10%	~3.3%	~7.8%	~52.5%	–

Age is presented as mean ± standard deviation unless otherwise specified; *m* denotes median (interquartile range)

aPL, antiphospholipid antibodies; *aCL*, anticardiolipin antibodies; *aβ2GPI*, anti-β$_2$ glycoprotein-I antibodies; *LA*, lupus anticoagulant; *aPT*, anti-prothrombin antibodies; *aPS*, anti-phosphatidylserine antibodies; *aAnnV*, anti-annexin V antibodies

BINDING AND NEUTRALIZATION ANTIBODY TITERS AFTER A SINGLE VACCINE DOSE IN HEALTH CARE WORKERS PREVIOUSLY INFECTED WITH SARS-COV-2

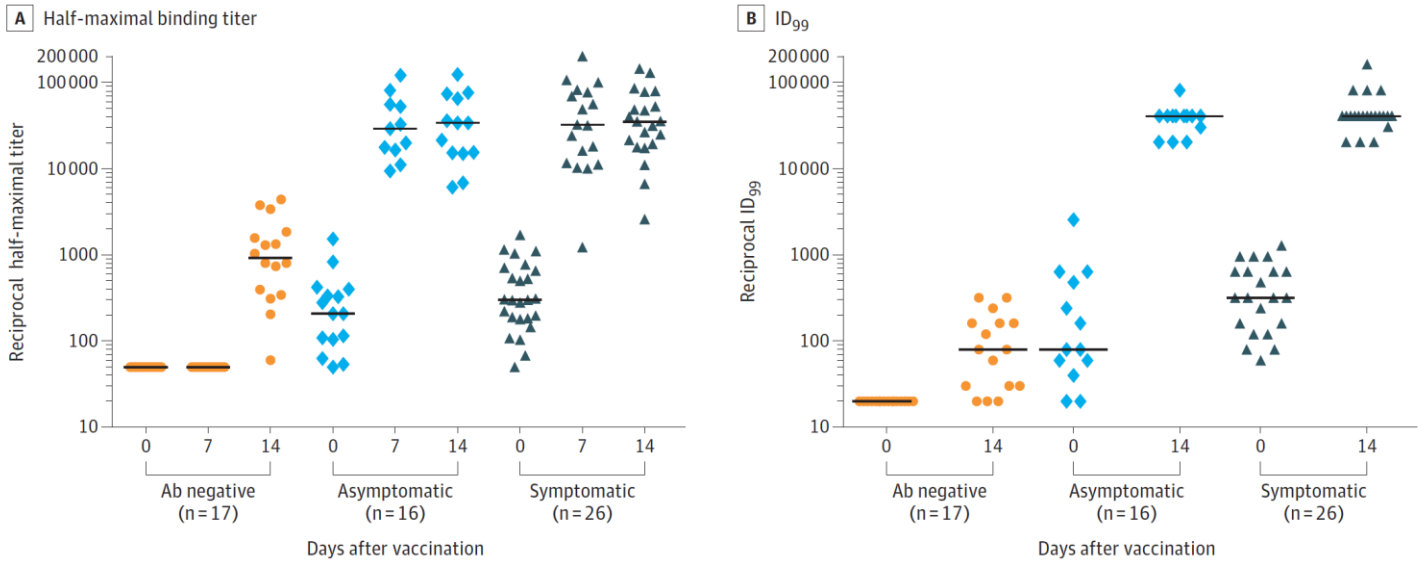
Saadat S, Rikhtegaran Tehrani Z, Logue J, Newman M, Frieman MB, Harris AD, Sajadi MM.. JAMA. 2021 Apr 13;325(14):1467-1469. doi: 10.1001/jama.2021.3341.
Level of Evidence: 5 - Guidelines and Recommendations

BLUF

Researchers of the Institute of Human Virology at the University of Maryland School of Medicine, Baltimore present a serosurvey of 59 healthcare workers who, prior to receiving the first dose of an mRNA SARS-CoV-2 vaccine, were categorized as SARS-CoV-2 IgG negative, IgG positive asymptomatic, and IgG positive symptomatic. At days 0, 7, and 14, plasma was obtained and analyzed to quantify median reciprocal half-maximal binding antibody titers to the spike trimer. At 0, 7, and 14 days they found higher overall titers in both the asymptomatic IgG+ (208, 29 364, and 34 033) and the symptomatic IgG+ (302, 32 301, and 35 460) groups compared to the IgG negative group (<50, <50, and 924). The authors discuss that this data can help to inform vaccination strategies employing single-dose prioritization.

FIGURES

Figure. Anti–SARS-CoV-2 Antibody Responses After a Single Dose of Vaccine in Health Care Workers



After COVID-19 vaccination, plasma was drawn at 0, 7, and 14 days; IgG binding titers against spike trimer were measured by enzyme-linked immunosorbent assay and live virus neutralization was assessed at days 0 and 14. A, IgG spike trimer half-maximal titers. By 7 days and continuing through 14 days following vaccination, both groups of health care workers with prior infection (asymptomatic and symptomatic) who received a single vaccine dose developed higher peak IgG titers than the antibody (Ab)-negative group. B, Live virus neutralization ID99 (the 99%inhibitory dose, the dilution at which 99%of cells were protected). At 14 days, both groups of health care workers with prior infection (asymptomatic and symptomatic) who received a single vaccine dose developed higher neutralization titers than the Ab-negative group. Horizontal black lines represent median values.

ANTIBODY PERSISTENCE THROUGH 6 MONTHS AFTER THE SECOND DOSE OF MRNA-1273 VACCINE FOR COVID-19

Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, Ledgerwood JE, Mascola JR, Graham BS, Lin BC, O'Dell S, Schmidt SD, Widge AT, Edara VV, Anderson EJ, Lai L, Floyd K, Rouphael NG, Zarnitsyna V, Roberts PC, Makhene M, Buchanan W, Luke CJ, Beigel JH, Jackson LA, Neuzil KM, Bennett H, Leav B, Albert J, Kunwar P; mRNA-1273 Study Group.. N Engl J Med. 2021 Apr 6. doi: 10.1056/NEJMc2103916. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

Doctorate researchers from the National Institute of Allergy and Infectious Diseases (NIAID) and Emory University School of Medicine investigated 33 healthy adults 6 months after the second dose of Moderna mRNA-1273 COVID-19 vaccine for durability and neutralizing effect of elicited antibodies. An enzyme-linked immunosorbent assay (ELISA) was utilized to measure antibodies by geometric mean endpoint titers (GMTs) and reported that antibodies remained high in all age groups, but 50% inhibitory dilution (ID50) GMTs were lower in 56 to 70 years of age ($p = 0.02$) and >71 years of age ($p = 0.004$) than in those 18 to 55 years of age (Figure 1). This study suggests the continued use of the vaccination for SARS-CoV-2 given the the presence of antibodies 180 days after vaccination.

FIGURES

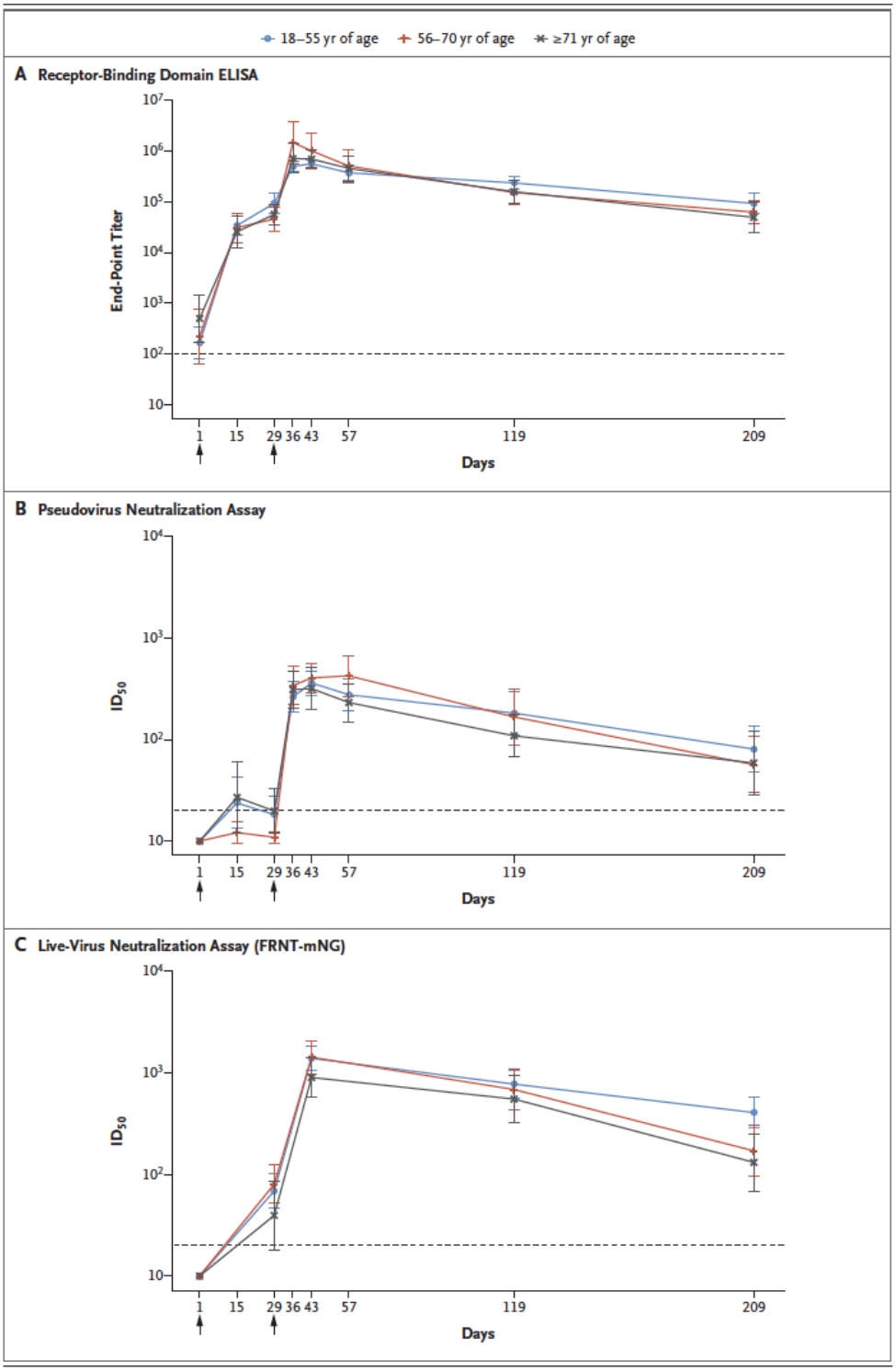


Figure 1 (facing page). Time Course of SARS-CoV-2 Antibody Binding and Neutralization Responses after mRNA-1273 Vaccination. All the participants received 100 μg of mRNA-1273 on days 1 and 29, indicated by arrows. The numbers of participants in each age group with data available at day 209 are as follows: 18 to 55 years, 15 participants; 56 to 70 years, 9 participants; and 71 years or older, 9 participants. The titers shown are the binding to spike receptor–binding domain protein (the end-point dilution titer) assessed on enzyme-linked immunosorbent assay (ELISA) on days 1, 15, 29, 36, 43, 57, 119, and 209 (Panel A); the 50% inhibitory dilution (ID50) titer on pseudovirus neutralization assay on days 1, 15, 29, 36, 43, 57, 119, and 209 (Panel B); and the ID50 titer on the live-virus focus-reduction neutralization mNeon-Green test (FRNT-mNG) on days 1, 29, 43, 119, and 209 (Panel C). Lines show geometric mean titers for each age group; I bars indicate 95% confidence intervals. The dashed line indicates the limit of detection for each assay.

EMERGENCE OF A NOVEL SARS-COV-2 VARIANT IN SOUTHERN CALIFORNIA

Zhang W, Davis BD, Chen SS, Sincuir Martinez JM, Plummer JT, Vail E.. JAMA. 2021 Apr 6;325(13):1324-1326. doi: 10.1001/jama.2021.1612.
Level of Evidence: 5 - Local non-random sample

BLUF

Pathology and lab medicine experts from Cedars-Sinai Medical Center in Los Angeles sequenced nasopharyngeal samples collected from 192 patients positive for SARS-CoV-2 between November to December 2020 and conducted phylogenetic analysis using representative genomes from the open source genomic database Nextstrain (Figure 1). They discovered a novel strain with five mutations (CAL.20G) in 22% of all samples (40/185) with a descendent cluster (CAL.20C) accounting for 36.4% (67/185) of cases in Los Angeles (Figure 2). While the CAL.20C strain's significance is unknown, it has now been identified in 25 other states leading the authors to encourage ongoing surveillance for SARS-CoV-2 variants.

FIGURES

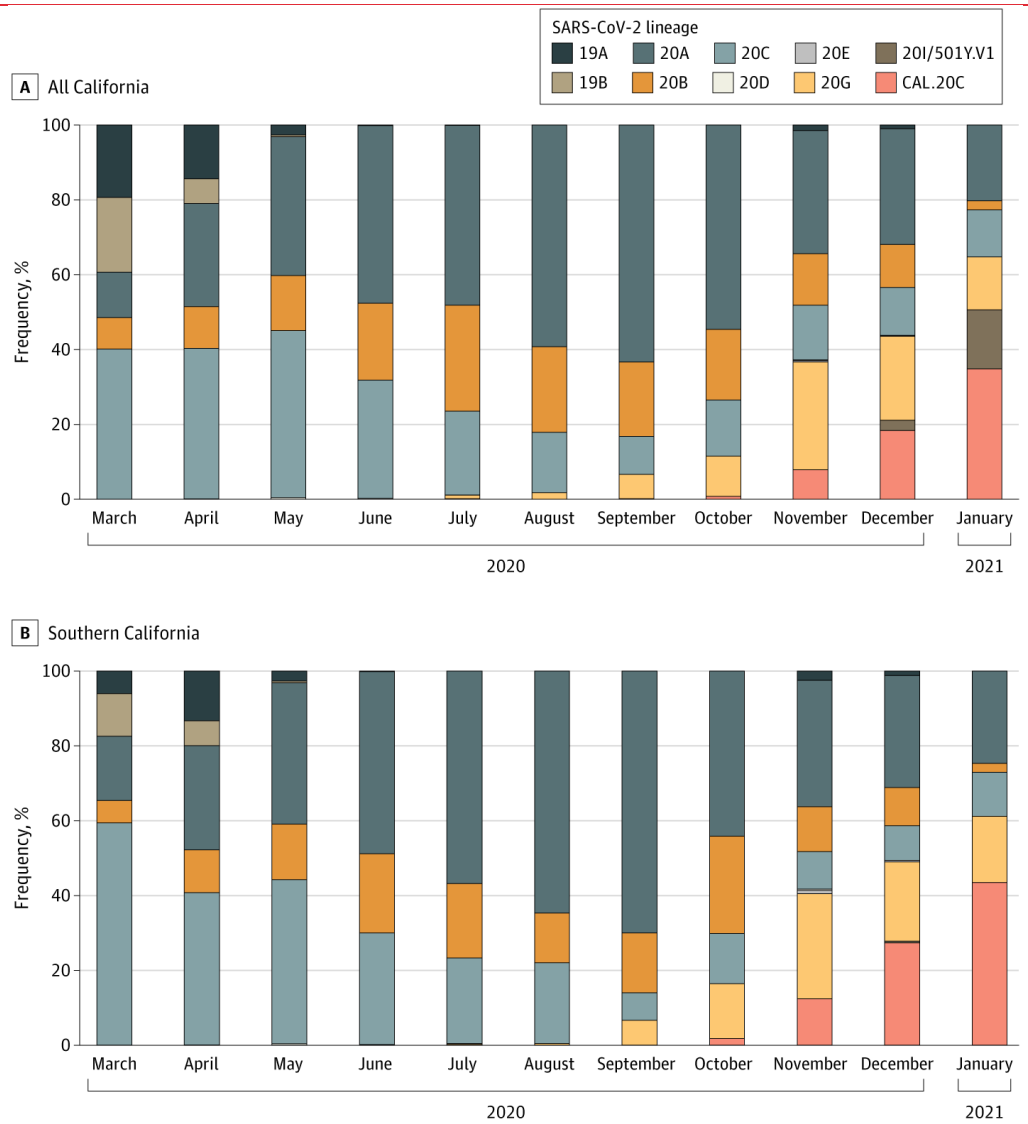


Figure 2. Timeline for the Emergence of a Novel Southern California Variant, CAL.20C, Among All SARS-CoV-2 Circulating Variants Observed. Diagrammatic representation of circulating SARS-CoV-2 variant frequencies. A, Includes 10 431 samples from the state of California. B, Includes 4829 samples from Southern California.

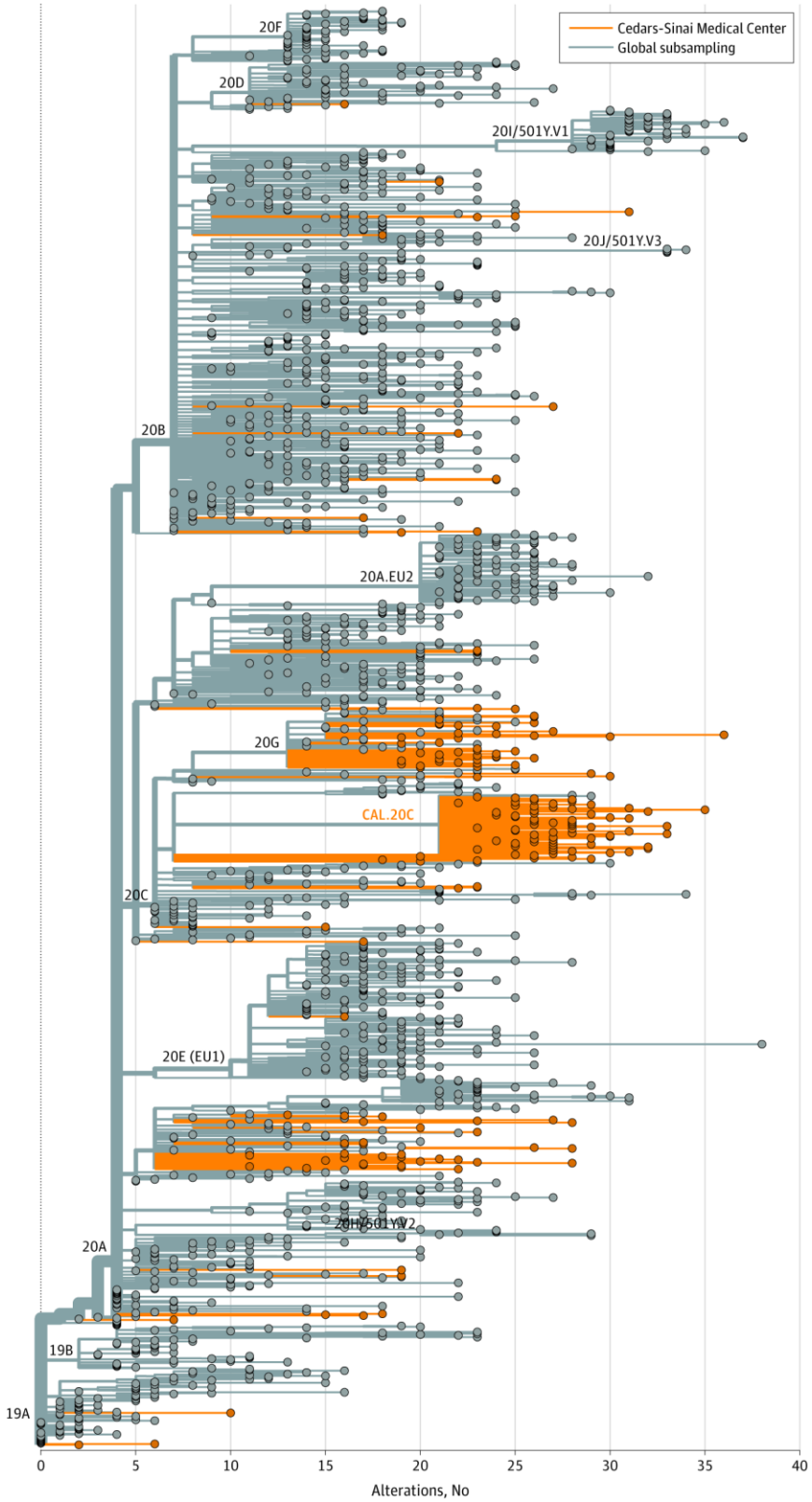


Figure 1. Phylogenetic Relationship of CSMC Samples to Global SARS-CoV-2 Genomes. Phylogenetic tree of 185 Cedars-Sinai Medical Center (CSMC) SARS-CoV-2 isolates and a global subsampling of 1480 isolates collected from December 2019 to January 2021 reveals a novel subcluster within 20C that share 5 mutations (ORF1a: I4205V, ORF1b: D1183Y, S: S13I; W152C; L452R), designated as CAL.20C (20C/S.452R). The phylogenetic tree shows the relationship of CAL.20C to other circulating lineages. The branch length (x-axis) reflects numbers of mutations accumulated before being discovered, and clades are designated based on Nextstrain nomenclature. The UK variant (501Y.V1), South African variant (501Y.V2), and Brazil variant (501Y.V3) are shown.

GASTROENTEROLOGY

SAFETY OF TOFACITINIB IN THE COVID-19 PANDEMIC-ENOUGH IS NOT ENOUGH

Reuken PA, Teich N, Stallmach A.. Inflamm Bowel Dis. 2021 Mar 30:izab051. doi: 10.1093/ibd/izab051. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

Gastroenterologists from Jena University Hospital in Germany comment on a report by Agrawal et al which suggested the use of tofacitinib in patients with inflammatory bowel disease is not associated with poor outcomes from COVID-19. The current authors argue the numerous uncontrolled confounding variables and low event number limits causal inferences. Due to other reports of poor outcomes in patients treated with tofacitinib and relative safety of anti-TNFs, authors suggest providers continue to use tofacitinib cautiously.

PREPARING FOR THE FUTURE - NANOBODIES FOR COVID-19?

Sasisekharan R.. N Engl J Med. 2021 Apr 7. doi: 10.1056/NEJMcibr2101205. Online ahead of print.
Level of Evidence: 5 - Expert Opinion

BLUF

A bioengineer from the Koch Institute for Integrative Cancer Research at the Massachusetts Institute of Technology reviewed current research on the viability and adaptability of neutralizing nanobodies in the treatment of SARS-CoV-2 infections. They review data showing biparatopic nanobodies effectively recognize common spike protein epitopes (Figures 1, 2), may be both easier to administer than traditional monoclonal antibodies, and are likely to work even in the presence of viral mutations. The author suggests nanobodies are a promising therapeutic for SARS-CoV-2.

FIGURES

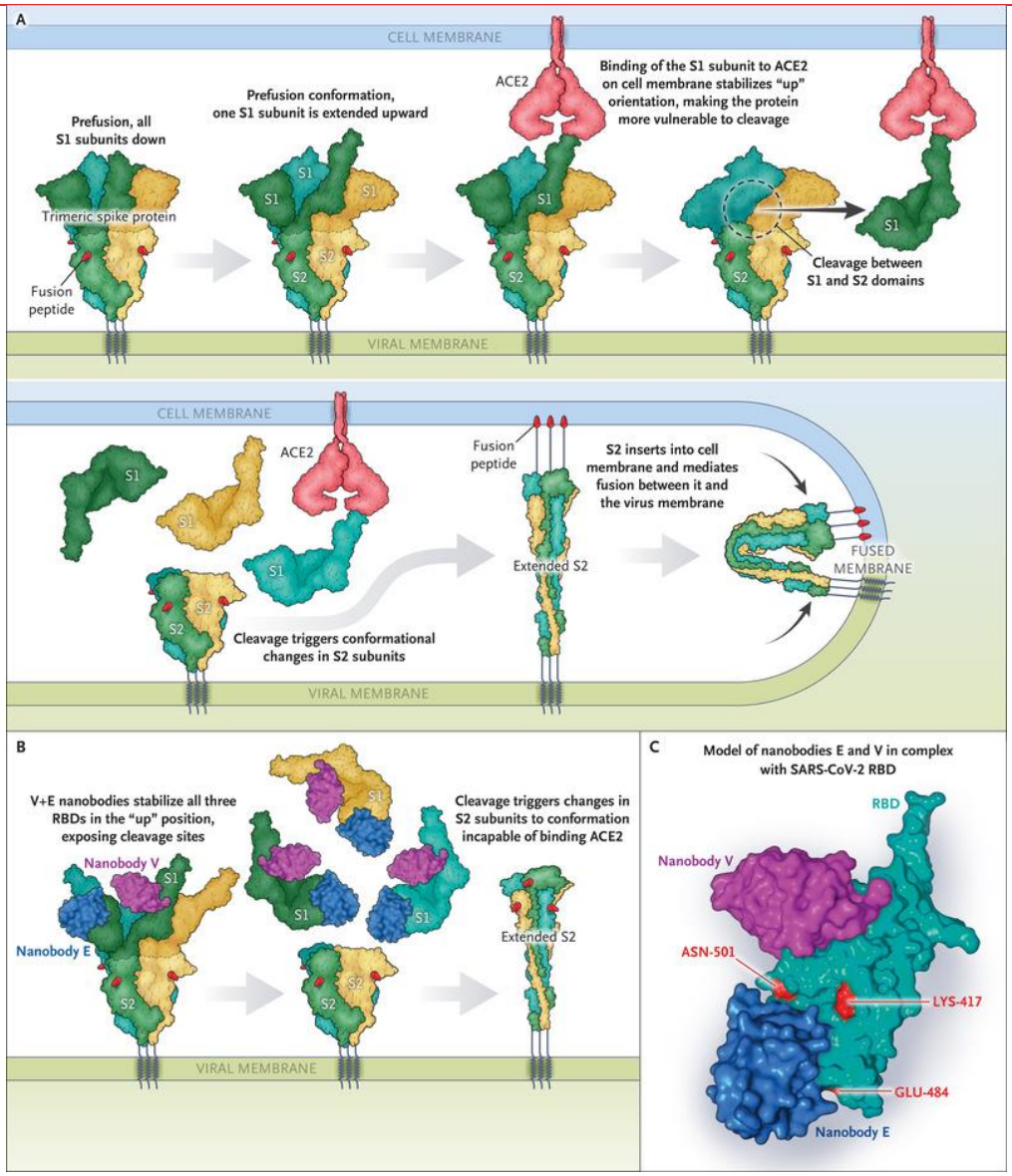


Figure 1.
SARS-CoV-2 Membrane Fusion Process and Footprints of V and E Nanobodies.

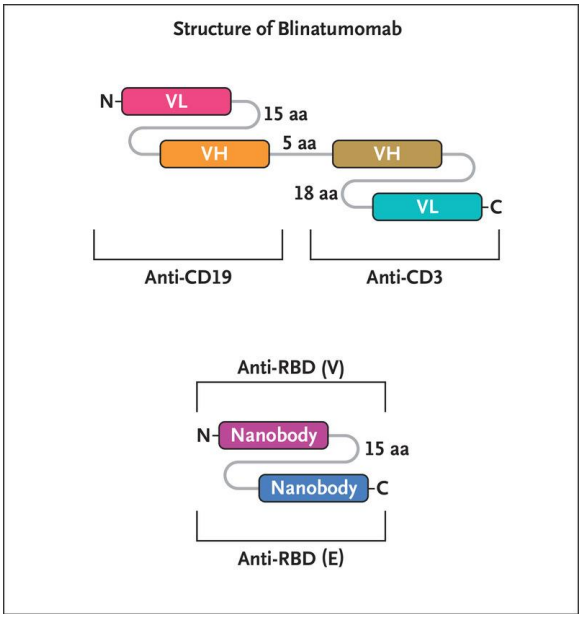


Figure 2.
Modular Organization of Bispecific Blinatumomab and a Biparatopic SARS-CoV-2 Nanobody.

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CONTRIBUTORS

Hamza Sultan
Michael Wang
Renate Meckl
Reza Aghaei

EDITORS

Julia Ghering
Maresa Woodfield

SENIOR EDITORS

Allison Hansen
Avery Forrow

SENIOR EXECUTIVE EDITOR

Thamanna Nishath

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