The Daily COVID-19 Literature Surveillance Summary

March 30, 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

- mRNA vaccination could boost cross-variant neutralizing antibodies elicited by SARS-CoV-2 infection. Infectious disease experts, microbiologists, and immunologists from the United States and Canada examined whether sera collected from naïve and recovered donors before and after immunization with SARS-CoV-2 mRNA vaccines could neutralize Wuhan-Hu-1 and B.1.351 variants. They found that sera from recovered donors pre-vaccination neutralized the variants, but immunization boosted neutralizing antibody titers against all variants by up to 1,000 times. The authors underscore the importance of vaccinating individuals previously infected with SARS-CoV-2 as a means of producing cross-variant neutralizing antibodies.

Adjusting Practice During COVID-19

- Safety and increased screening need to be further considered for lung transplants during the COVID-19 pandemic. Pediatricians and infectious disease physicians from Texas, Ohio, Virginia, and Pittsburgh present a case involving a solid lung transplant donor, dying from head trauma, with a negative RT-PCR SARS-CoV-2 from upper respiratory tract (URT) sample, as well as negative donor risk assessment interview (UDRAI) determined by organ procurement organizations (OPO). However, shortly after transplant both the recipient and the handling surgeon developed COVID-19, with the recipient ultimately succumbing to disease. As all parties involved had seemingly negative SARS-CoV-2 results prior to surgery, further investigation was performed with a whole genome sequencing from stored bronchoalveolar lavage of lower respiratory tract (LRT) from all three people, revealing a common origin of infection from the donor. The authors suggest, that although an isolated case, this example highlights the need for additional transplant screening during COVID-19 pandemic, especially in the setting of lung transplants.

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ETHNIC MINORITIES AND COVID-19: EXAMINING WHETHER EXCESS RISK IS MEDIATED THROUGH DEPRIVATION

Razieh C, Zaccardi F, Islam N, Gillies CL, Chudasama Y, Rowlands A, Kloecker DE, Davies MJ, Khunti K, Yates T.. Eur J Public Health. 2021 Mar 21:ckab041. doi: 10.1093/eurpub/ckab041. Online ahead of print.
Level of Evidence: 5 - Modeling

BLUF

Epidemiology and diabetes specialists from the UK utilized a four-way decomposition mediation analysis to model the reduction of excess risk in 15,044 South Asian or black (SAB) individuals for testing positive for COVID-19, developing severe disease, or COVID-19 mortality, in comparison to 392,786 white individuals. They found that material deprivation scores were 1.4 in SAB and -2.3 in white individuals (Table 1), and a hypothetical intervention to move 25% of the most materially deprived individuals out of deprivation could eliminate 40-50% of the excess risk outcomes of COVID-19 in SAB communities, while moving 50% of people out of deprivation could eliminate 80% of outcomes (Figure 1). These findings suggest that reducing levels of material deprivation could drastically improve COVID-19 outcomes in SAB communities.

SUMMARY

- The four domains of the mediation analysis were unemployment, non-car ownership, non-home ownership, and household overcrowding

- Material deprivation status was measured by the Townsend score (higher score = greater deprivation)

- SAB individuals had 1.0% positive tests, 0.6% severe cases, and 0.2% deaths due to COVID-19, while white individuals had 0.4%, 0.2%, and 0.1%, showing excess risk outcomes for SAB people

ABSTRACT

BACKGROUND: People from South Asian and black minority ethnic groups are disproportionately affected by the COVID-19 pandemic. It is unknown whether deprivation mediates this excess ethnic risk. METHODS: We used UK Biobank with linked COVID-19 outcomes occurring between 16th March 2020 and 24th August 2020. A four-way decomposition mediation analysis was used to model the extent to which the excess risk of testing positive, severe disease and mortality for COVID-19 in South Asian and black individuals, relative to white individuals, would be eliminated if levels of high material deprivation were reduced within the population. RESULTS: 15,044 (53.0% women) South Asian and black and 392,786 (55.2% women) white individuals were included. There were 151 (1.0%) positive tests, 91 (0.6%) severe cases and 31 (0.2%) deaths due to COVID-19 in South Asian and black individuals compared to 1,471 (0.4%), 895 (0.2%) and 313 (0.1%), respectively, in white individuals. Compared to white individuals, the relative risk of testing positive for COVID-19, developing severe disease and COVID-19 mortality in South Asian and black individuals were 2.73 (95% CI: 2.26, 3.19), 2.96 (2.31, 3.61) and 4.04 (2.54, 5.55), respectively. A hypothetical intervention moving the 25% most deprived in the population out of deprivation was modelled to eliminate between 40-50% of the excess risk of all COVID-19 outcomes in South Asian and black populations, whereas moving the 50% most deprived out of deprivation would eliminate over 80% of the excess risk of COVID-19 outcomes. CONCLUSIONS: The excess risk of COVID-19 outcomes in South Asian and black communities could be substantially reduced with population level policies targeting material deprivation.

FIGURES

Table 1: Cohort characteristics.

	White (n = 392,786)	South Asian and Black (n = 15,044)	Total (n = 407,830)
Age (years)	68.8 (61.2, 74.0)	62.1 (56.3, 69.5)	68.6 (60.9, 73.9)
Women	216874 (55.2%)	7978 (53.0%)	224852 (55.1%)
Men	175912 (44.8%)	7066 (47.0%)	182978 (44.9%)
Deprivation (Townsend score)	-2.3 (-3.7, 0.2)	1.4 (-1.2, 4.1)	-2.2 (-3.7, 0.4)
Positive cases	1471 (0.4%)	151 (1.0%)	1622 (0.4%)
Severe disease	895 (0.2%)	91 (0.6%)	986 (0.2%)
COVID-19 mortality	313 (0.1%)	31 (0.2%)	344 (0.1%)

Data as number (%) or median (IQR).

Table 1. Cohort Characteristics

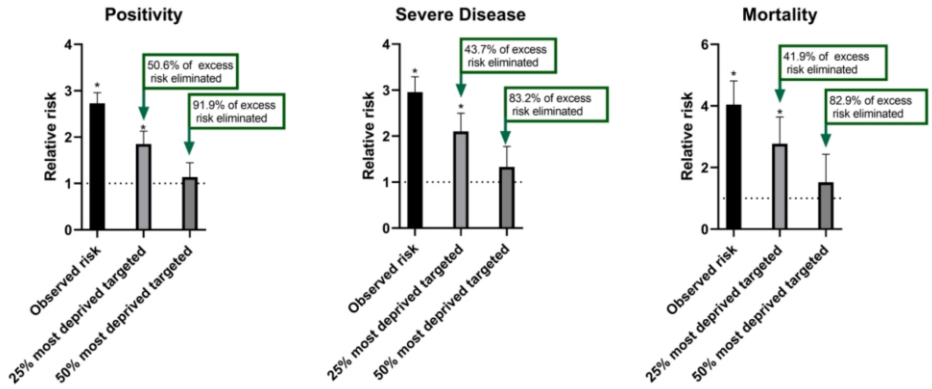

Figure 1: Modeling showing the relative risk of COVID-19 outcomes in black and South Asian relative to white ethnicities and the degree to which the risk is eliminated if the most deprived 25% or 50% in the population were moved out of deprivation.

EPIDEMIOLOGY

NEUTRALIZING ANTIBODIES FOR SARS-COV-2 IN STRAY ANIMALS FROM RIO DE JANEIRO, BRAZIL

Dias HG, Resck MEB, Caldas GC, Resck AF, da Silva NV, Dos Santos AMV, Sousa TDC, Ogrzewalska MH, Siqueira MM, Pauvolid-Corrêa A, Dos Santos FB.. PLoS One. 2021 Mar 25;16(3):e0248578. doi: 10.1371/journal.pone.0248578. eCollection 2021.
Level of Evidence: 3 - Local non-random sample

BLUF

Immunologists, virologists, and veterinarians from the Oswaldo Cruz Institute in Rio de Janeiro, Brazil evaluated serum, and rectal and oropharyngeal samples from 49 cats (40 owned and 9 stray) and 47 dogs (42 owned and 5 stray) for evidence of SARS-CoV-2 infection. No swabs tested positive for SARS-CoV-2 RNA, but oropharyngeal and rectal swabs from one stray dog and one stray cat (both asymptomatic) tested positive for SARS-CoV-2 neutralizing antibodies. While previous research has documented human-pet transmission, authors suggest stray animals are also exposed to SARS-CoV-2.

ABSTRACT

The epidemic of coronavirus disease 2019 (COVID-19), caused by a novel Betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) became a public health emergency worldwide. Few reports indicate that owned pets from households with at least one human resident that was diagnosed with COVID-19 can be infected by SARS-CoV-2. However, the exposure to SARS-CoV-2 of pets from households with no COVID-19 cases or stray animals remains less assessed. Using real-time reverse transcriptase polymerase chain reaction (RT-PCR) and plaque reduction neutralization test (PRNT90), we investigated the infection and previous exposure of dogs and cats to SARS-CoV-2 during the ongoing COVID-19 epidemic in Rio de Janeiro, Brazil. From June to August 2020, 96 animals were sampled, including 49 cats (40 owned and 9 stray) and 47 dogs (42 owned and 5 stray). Regarding owned pets, 75.6% (62/82) belonged to households with no COVID-19 cases. Samples included serum, and rectal and oropharyngeal swabs. All swabs were negative for SARS-CoV-2 RNA, but serum samples of a stray cat and a stray dog presented neutralizing antibodies for SARS-CoV-2, with PRNT90 titer of 80 and 40, respectively. Serological data presented here suggest that not only owned pets from households with COVID19 cases, but also stray animals are being exposed to SARS-CoV-2 during the COVID-19 pandemic.

MODELING

SUPERSPREADING OF SARS-COV-2 IN THE USA

Pozderac C, Skinner B.. PLoS One. 2021 Mar 25;16(3):e0248808. doi: 10.1371/journal.pone.0248808. eCollection 2021.
Level of Evidence: 5 - Modeling

BLUF

A modeling study conducted by researchers from the Department of Physics at The Ohio State University developed a model using an SIR framework to estimate the mean and variance in SARS-CoV-2 infectiousness and transmission, resulting in a calculation showing clear evidence for superspreading in early stages of the COVID-19 pandemic in the US (Figure 1). This model determined that 81% of new infections were transmitted by the top 10% of most infected individuals and 4.5% of cases arise from 80% of the lowest infected individuals (Figure 3), suggesting that highly infectious persons contributed heavily to the superspreading of new COVID-19 cases in the United States.

FIGURES

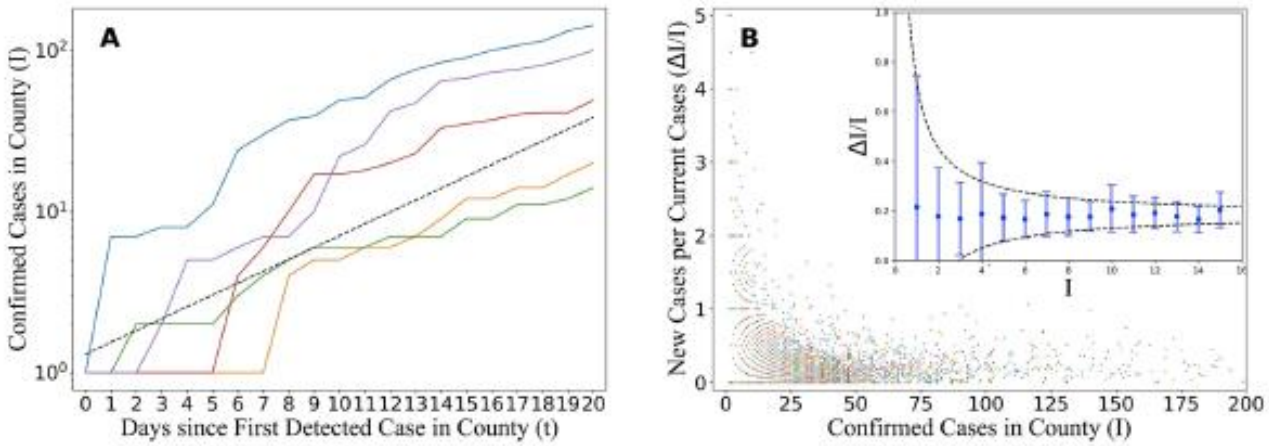

Fig 1. (a) Illustration of the variance in early-time growth rate of new cases. At early times, there is noticeable variance in the growth rate between counties. As the number of cases grows, all counties stabilize towards the average growth rate I &#65533; (1+ μβ)t, (dashed black line) where t is the number of days since the first case in a county. The counties shown are Boulder, CO (blue), St. Mary, LA (purple), Vanderburgh, IN (red), Mesa, CO (orange), and Jones, GA (green). (b) The number of daily infections per infected individual as a function of total infections. In the main figure, each point corresponds to a given county (across all US counties that never report ΔI < 0) at a given time point (within the first 14 days after the first infection reported in that county). As the number of cases increase, all counties converge to the mean infection rate. The mean (points) and variance (bars) of ΔI/ I at a given I are shown in the inset. The variance decreases like ðmb þ s2 bÞ=I (black lines).

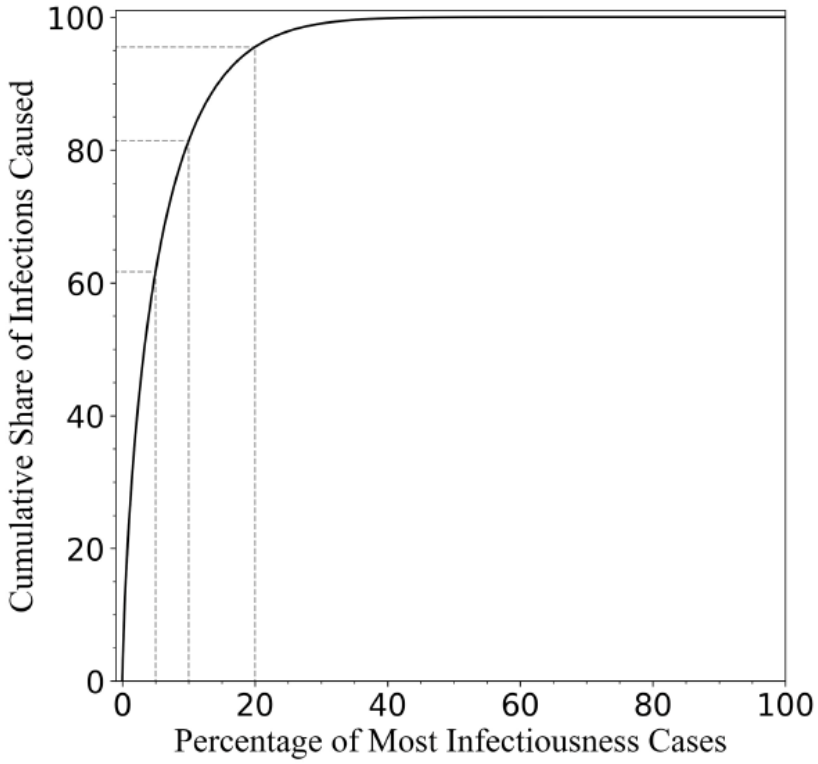

Fig 3. An estimated Lorenz curve for SARS-CoV-2 infections in the USA, which displays the percentage of new cases that are caused by a given cumulative percentage of most infectious individuals (solid black). A few points in the curve are highlighted (dashed grey lines): 61.7%, 81.4%, and 95.5% of new cases are caused by the top 5%, 10%, and 20% infectious cases, respectively. Accounting for undetected and asymptomatic cases would apparently make this curve steeper, corresponding to more severe superspreading.

SPATIO-TEMPORAL PREDICTIVE MODELING FRAMEWORK FOR INFECTIOUS DISEASE SPREAD

Ganesan S, Subramani D.. Sci Rep. 2021 Mar 24;11(1):6741. doi: 10.1038/s41598-021-86084-7.
Level of Evidence: 5 - Modeling

BLUF

Computational data scientists from India developed a predictive partial differential equation-based spatio-temporal framework and used a six-dimensional model to model the spread of COVID-19 in two states in India (Karnataka and Maharashtra), accounting for age distributions, level of infection severity, and infection duration (Figure 1). The model was accurate compared to the actual reported data from Karnataka but underestimated the number of infections in Maharashtra (Figure 2). This fairly accurate model could allow for proper public health intervention/planning such as quarantining, testing, contact tracing, ventilator support, and antiviral treatments, while taking the distribution of infected population into consideration.

FIGURES

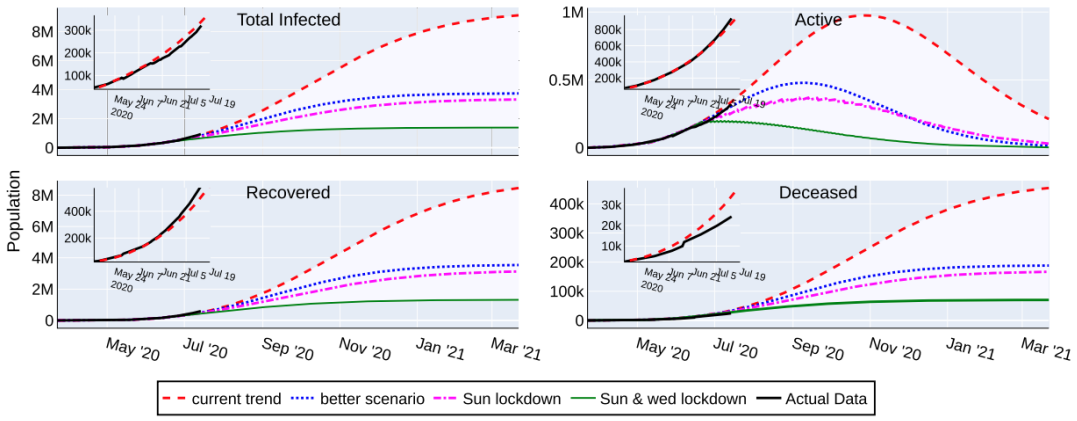

Figure 1. Time series forecast of active, total infections, recovered and deceased cases of Covid-19 in India from Mar 23, 2020 to Mar 22, 2021. The inset shows a zoom with comparison of the model forecast with the data until July 14, 2020.

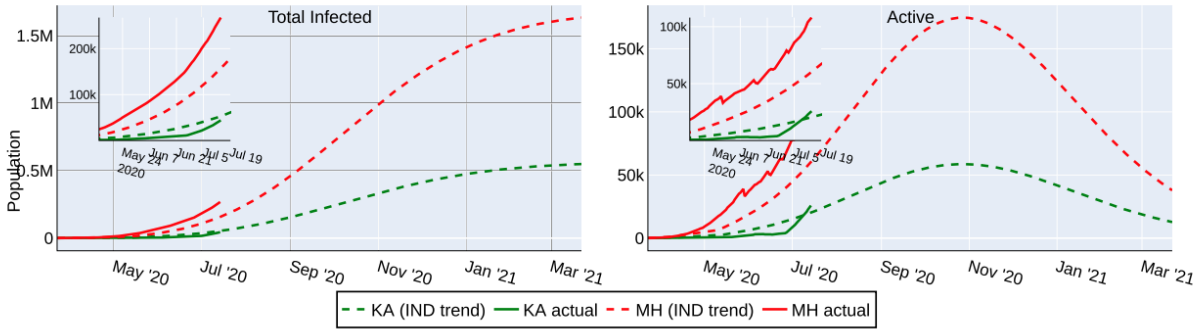

Figure 2. The actual data of KA (green) and MH (red), until July 14, 2020 compared to the estimates computed with the parameters fitted for the reported national data.

ADULTS

OUTCOMES FOR PATIENTS FOLLOWING HOSPITALIZATION FOR COVID-19

Prescott HC.. JAMA. 2021 Mar 17. doi: 10.1001/jama.2021.3430. Online ahead of print.
Level of Evidence: 5 - Opinion

BLUF

An intensivist from the University of Michigan comments on a recently published investigation of the long-term effects of SARS-CoV-2 infection ("long COVID") in a prospective cohort study of 478 participants at Bicêtre Hospital, Paris in spring 2020. Patients reported a variety of symptoms 4 months after hospitalization for COVID-19, with significant heterogeneity between long COVID patients. The author suggests these findings are consistent with findings in studies of recovery from other critical illnesses, but suggests lack of infrastructure and funding will limit proper assessment and management of post-infection long COVID.

UNDERSTANDING THE PATHOLOGY

THE FIRST 12 MONTHS OF COVID-19: A TIMELINE OF IMMUNOLOGICAL INSIGHTS

Carvalho T, Krammer F, Iwasaki A.. Nat Rev Immunol. 2021 Mar 15. doi: 10.1038/s41577-021-00522-1. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Portuguese and American immunologists and microbiologists reviewed literature related to immunology, virology, and vaccine development published since the beginning of the COVID-19 pandemic. They discuss the timeline of discovering antigenic characteristics of SARS-CoV-2, cytokines involved in response to infection (Figure 2), immune-mediated syndromes, antibody-based therapies, and vaccine immunology (see summary, Figure 1). Authors suggest their review highlights both the extraordinary progress made in only a year and research gaps yet to be addressed.

SUMMARY

The timeline reports of important topics in immunology:

1-Finding of SARS-CoV-2 spike protein receptor-binding domain (RBD) and viral entry receptor (ACE2) in the body.
2-Reported Lymphopenia in multiple severe cases.
3-Increased levels of cytokines and Interferons are related to the severity of patients' condition.
4- Assessment of SIRS pathogenesis in COVID-19 patients and finding the similarity to other inflammatory syndromes like HLH (hemophagocytic lymphohistiocytosis) and CRS (cytokine release syndrome), and also starting immunotherapy (tocilizumab against IL-6)
5-Reports of Kawasaki-like illness in children after the viral infection, named multiple inflammatory syndrome in children (MIS-C)
6-Cytokines related to increased mortality: IL-6, IL-8, TNF
7-Starting plasma-therapy without significant improvement in outcome
8-Finding autoantibodies in COVID-19 patients, similar to antibodies in SLE, RA
9-Evaluation of possible role of INF-1 as an important defense mechanism against viral replication and disease progression.

ABSTRACT

Since the initial reports of a cluster of pneumonia cases of unidentified origin in Wuhan, China, in December 2019, the novel coronavirus that causes this disease - severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) - has spread throughout the world, igniting the twenty-first century's deadliest pandemic. Over the past 12 months, a dizzying array of information has emerged from numerous laboratories, covering everything from the putative origin of SARS-CoV-2 to the development of numerous candidate vaccines. Many immunologists quickly pivoted from their existing research to focus on coronavirus disease 2019 (COVID-19) and, owing to this unprecedented convergence of efforts on one viral infection, a remarkable body of work has been produced and disseminated, through both preprint servers and peer-reviewed journals. Here, we take readers through the timeline of key discoveries during the first year of the pandemic, which showcases the extraordinary leaps in our understanding of the immune response to SARS-CoV-2 and highlights gaps in our knowledge as well as areas for future investigations.

FIGURES

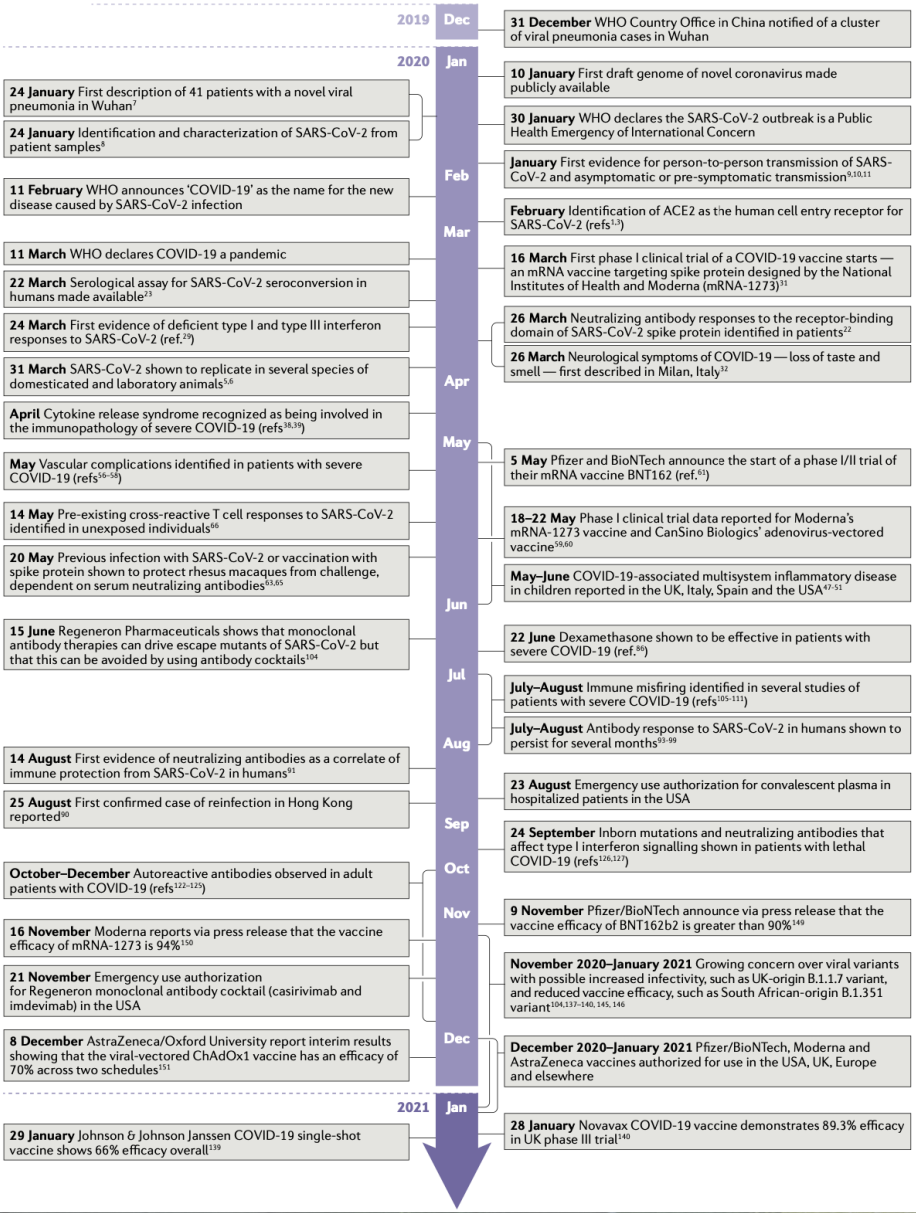

Fig. 1 | Timeline of key discoveries in the immune response to SARS-CoV-2. In the case of data that were posted as preprints before peer-reviewed publication, the timeline follows the date of the preprint but the reference list details the peer-reviewed journal publication. ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

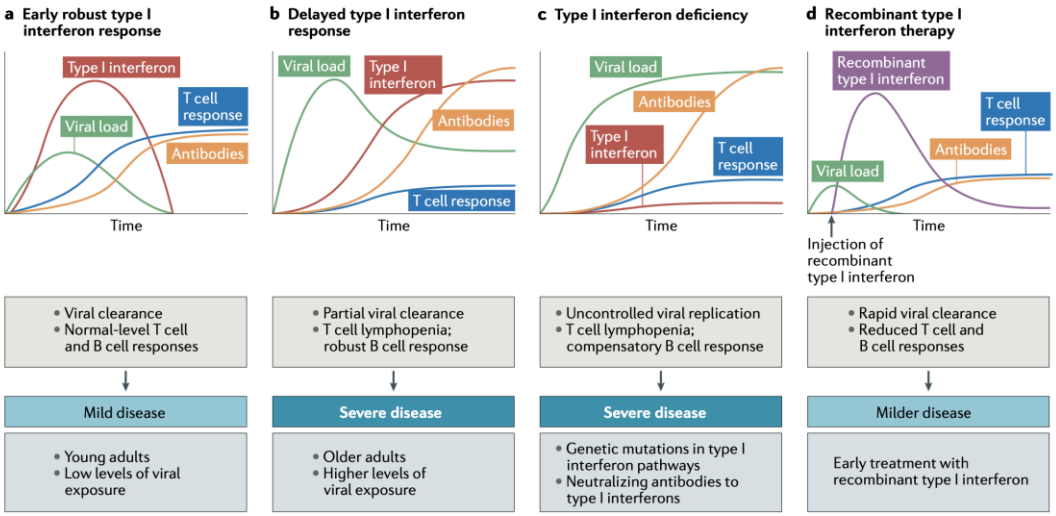

Fig. 2 | **A hypothetical figure showing how the timing of interferon responses might control innate and adaptive immunity to SARS-CoV-2.** **a** | When the type I interferon response to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is early and robust, the viral load is quickly controlled, resulting in mild disease. This is followed by normal-level T cell and B cell responses. This may occur in young people or after low-dose viral exposure. **b** | When the type I interferon response is delayed or reduced early during infection with SARS-CoV-2, viral replication and spread occur. Severe coronavirus disease 2019 (COVID-19) is accompanied by T cell lymphopenia. Despite this, strong antibody responses are induced. Type I interferon induced late during infection may be detrimental in driving pathological responses. This may occur in older adults or after high-dose viral exposure. **c** | In those individuals who are either genetically or serologically deficient in type I interferon, the replication of SARS-CoV-2 occurs unopposed, causing severe to life-threatening COVID-19. T cell lymphopenia is observed. Compensatory activation of antibody responses occurs but is insufficient to control disease. **d** | Early post-exposure prophylaxis with recombinant type I interferon can reduce the viral load of SARS-CoV-2 and hasten recovery. However, this leads to reduced antigen load and reduced adaptive immune responses.

Fig. 2 A hypothetical figure showing how the timing of interferon responses might control innate and adaptive immunity to SARS-CoV-2.

a | When the type I interferon response to infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is early and robust, the viral load is quickly controlled, resulting in mild disease. This is followed by normal-level T cell and B cell responses. This may occur in young people or after low-dose viral exposure.

b | When the type I interferon response is delayed or reduced early during infection with SARS-CoV-2, viral replication and spread occur. Severe coronavirus disease 2019 (COVID-19) is accompanied by T cell lymphopenia. Despite this, strong antibody responses are induced. Type I interferon induced late during infection may be detrimental in driving pathological responses. This may occur in older adults or after high-dose viral exposure.

c | In those individuals who are either genetically or serologically deficient in type I interferon, the replication of SARS-CoV-2 occurs unopposed, causing severe to life-threatening COVID-19. T cell lymphopenia is observed. Compensatory activation of antibody responses occurs but is insufficient to control disease.

d | Early post-exposure prophylaxis with recombinant type I interferon can reduce the viral load of SARS-CoV-2 and hasten recovery. However, this leads to reduced antigen load and reduced adaptive immune responses.

MRNA VACCINATION BOOSTS CROSS-VARIANT NEUTRALIZING ANTIBODIES ELICITED BY SARS-COV-2 INFECTION

Stamatatos L, Czartoski J, Wan YH, Homad LJ, Rubin V, Glantz H, Neradilek M, Seydoux E, Jennewein MF, MacCamy AJ, Feng J, Mize G, De Rosa SC, Finzi A, Lemos MP, Cohen KW, Moodie Z, McElrath MJ, McGuire AT.. Science. 2021 Mar 25:eabg9175. doi: 10.1126/science.abg9175. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Infectious disease experts, microbiologists, and immunologists from the United States and Canada examined whether sera collected from naïve and recovered donors before and after immunization with SARS-CoV-2 mRNA vaccines could neutralize Wuhan-Hu-1 and B.1.351 variants. They found that sera from recovered donors pre-vaccination neutralized the variants (Figure 1), but immunization boosted neutralizing antibody titers against all variants by up to 1,000 times (Figure 2, Figure 3). The authors underscore the importance of vaccinating individuals previously infected with SARS-CoV-2 as a means of producing cross-variant neutralizing antibodies.

ABSTRACT

Emerging SARS-CoV-2 variants have raised concerns about resistance to neutralizing antibodies elicited by previous infection or vaccination. We examined whether sera from recovered and naive donors collected prior to, and following immunizations with existing mRNA vaccines, could neutralize the Wuhan-Hu-1 and B.1.351 variants. Pre-vaccination sera from recovered donors neutralized Wuhan-Hu-1 and sporadically neutralized B.1.351, but a single immunization boosted neutralizing titers against all variants and SARS-CoV-1 by up to 1000-fold. Neutralization was due to antibodies targeting the receptor binding domain and was not boosted by a second immunization. Immunization of naive donors also elicited cross-neutralizing responses, but at lower titers. Our study highlights the importance of vaccinating both uninfected and previously infected persons to elicit cross-variant neutralizing antibodies.

FIGURES

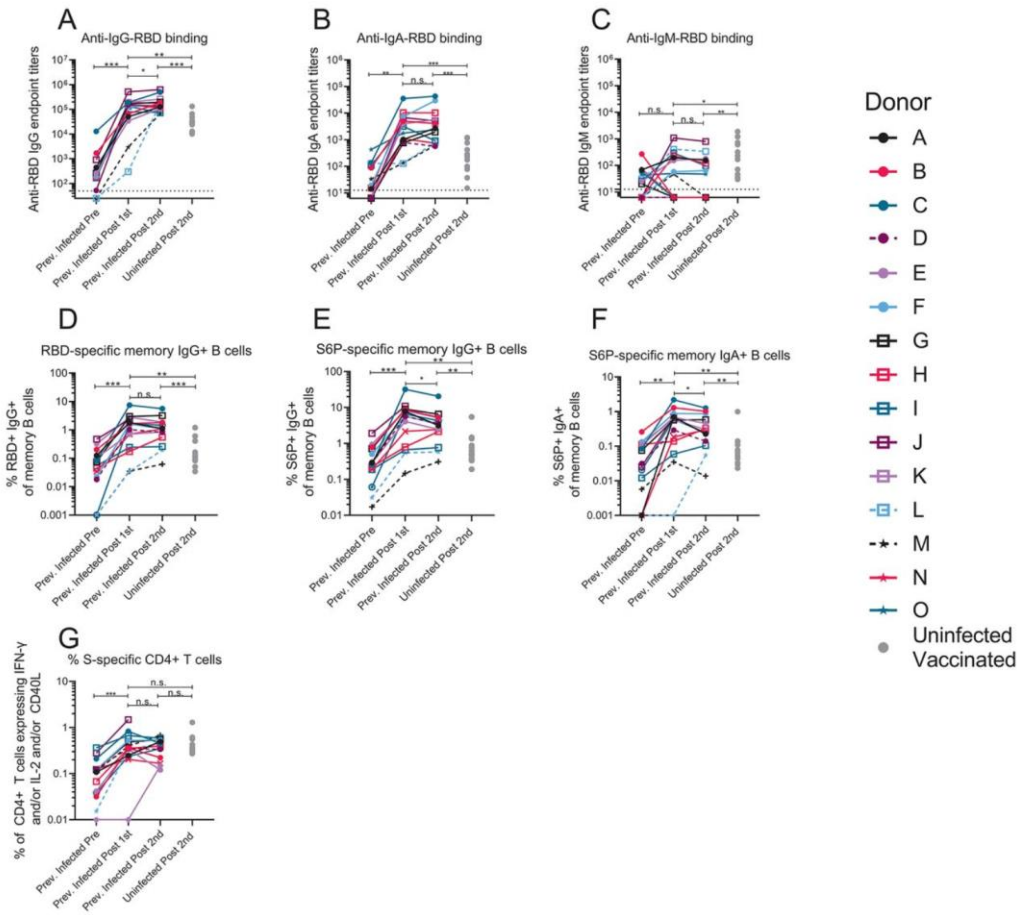

Fig. 2 A single dose of a spike-derived mRNA vaccine elicits a strong recall response.

IgG (A), IgA (B) and IgM (C) end-point antibody titers specific to the receptor binding domain of the Wuhan-Hu-1 variant were measured in serum collected from donors previously infected with SARS-CoV-2 before and after one or two immunizations with the Pfizer/BioNTech or Moderna mRNA vaccines by ELISA, as indicated. Endpoint titers measured in sera from uninfected donors following two vaccine doses are shown for comparison (gray dots). (D) Frequency of Wuhan-Hu-1 RBD-specific IgG+ memory B cells (live, IgD-, CD19+, CD20+, CD3-, CD14, CD56-, singlet, lymphocytes) in PBMC from previously infected donors was measured before and after one or two immunizations. The frequency of S6P-specific IgG+ (E) and IgA+ (F) memory B cells in PBMC previously infected donors were measured before and after one or two immunizations. The frequency of memory B cells from uninfected donors following two vaccine doses are shown for comparison in D-F (gray dots). (G) The frequency of S-specific CD4+ T cells expressing IFN-γ and/or IL-2 and/or CD40L in PBMC from previously infected donors was measured before and after one or two immunizations. The frequency of S-specific CD4+ T cells in PBMC from uninfected donors following two vaccine doses are shown for comparison (gray dots). Experiments were performed once. Significant differences in infected donors before or after vaccination (A-D) or between pseudoviruses (E) were determined using a Wilcoxon signed rank test (*p<0.05, ** p<0.01 and ***p<0.001). Significant differences between previously infected and uninfected donors (A-D) were determined using a Wilcoxon rank sum test (*p<0.05, **p<0.01 and **p<0.001).

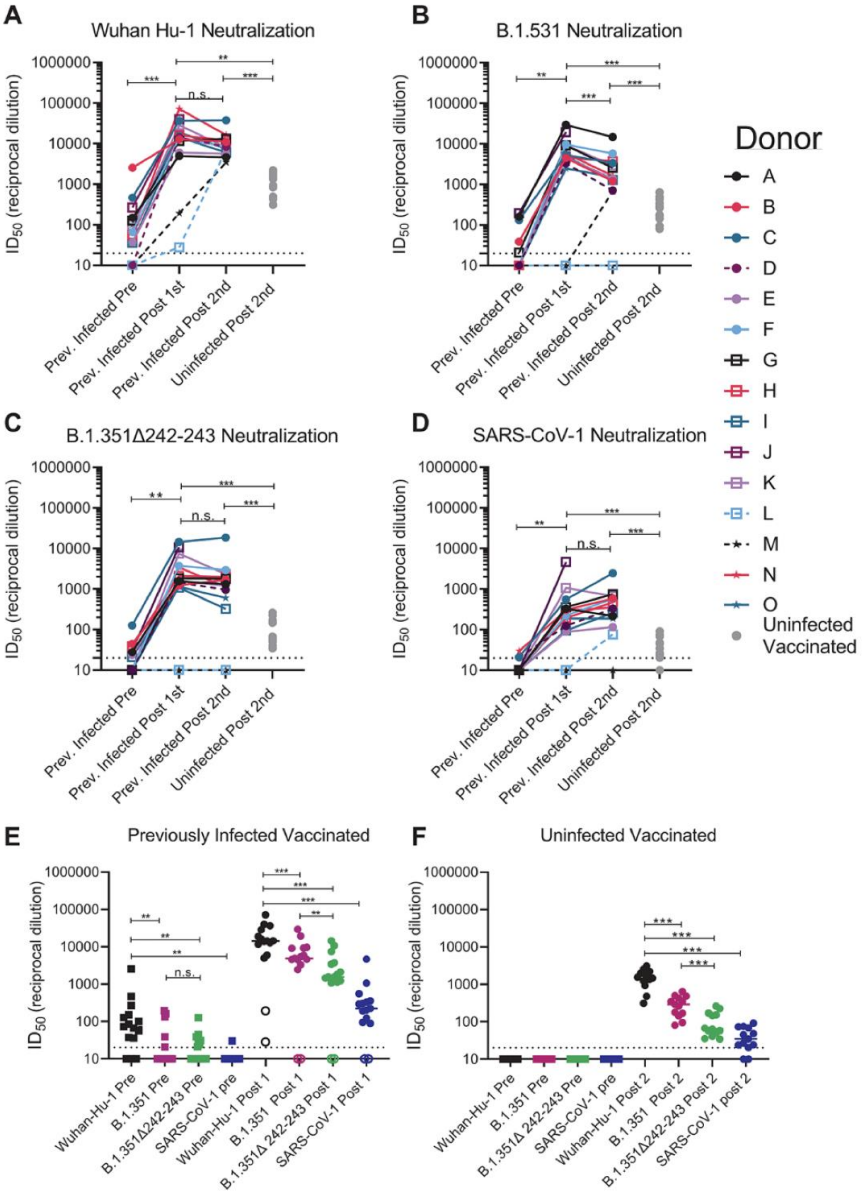

Fig. 3. Pre-existing SARS-CoV-2 neutralizing antibody responses are boosted by a single dose of a spike- derived mRNA vaccine. The serum dilution resulting in 50% neutralization (ID50) of (A) Wuhan-Hu- 1, (B) B.1.351, (C) B.1.351Δ242-243, and (D) SARS-CoV-1 pseudoviruses was measured in recovered COVID-19 donors prior to and following a one or two immunizations with the Pfizer/BioNTech or Moderna vaccines, and in uninfected donors following two vaccine doses as indicated. Data points between previously infected donors who were symptomatic and asymptomatic are connected by solid and dashed lines, respectively in A-D. (E) Serum dilution resulting in 50% neutralization (ID50) from recovered donors prior to (squares) and following a single immunization (circles) with the Pfizer/BioNTech or Moderna vaccines against Wuhan-Hu-1, B.1.351, B.1.351Δ242-243 and SARS-CoV-1 pseudoviruses as indicated. Previously infected donors who were asymptomatic, negative for anti-IgG RBD antibodies, and RBD-specific IgG+ memory B cells prior to vaccination are shown as open circles. (F) Neutralizing potency (ID50) of serum from uninfected donors following two immunizations with the Pfizer/BioNTech or Moderna vaccines against the indicated pseudoviruses. Each data point represents a different donor and the horizonal bars represent the medians in E and F. The dashed lines demarcate the lowest serum dilutions tested. Experiments were performed once. Significant differences in infected donors before or after vaccination, or from the same timepoint against different variants (*p<0.05, ** p<0.01 and ***p<0.001) were determined using a Wilcoxon signed rank test. Significant differences between previously infected and uninfected donors (*p<0.05, **p<0.01 and ***p<0.001) were determined using a Wilcoxon rank sum test.

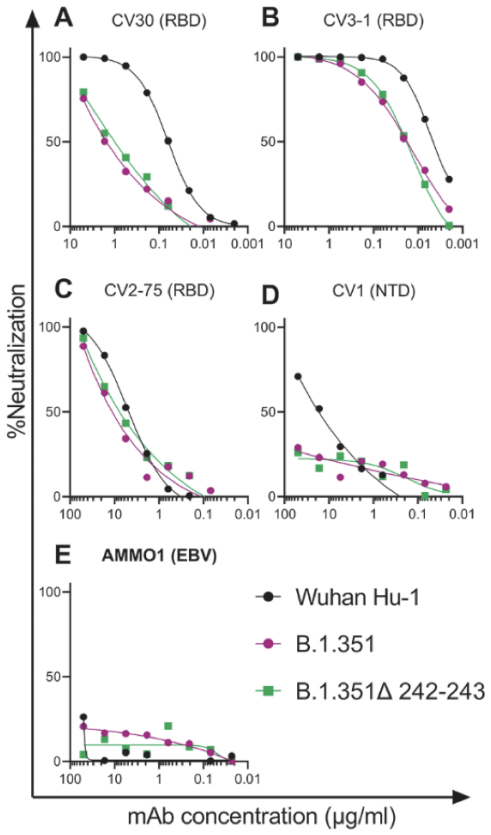

Fig. 1. B.1.351 variants show decreased susceptibility to neutralizing monoclonal antibodies. (A to E) The ability of the indicated monoclonal antibodies (mAbs) to neutralize Wuhan-Hu-1, B.1.351 and B.1.351Δ242-243 pseudovirus infectivity in 293T-hACE2 cells was measured as indicated. The epitope specificity of each mAb is shown in parentheses (RBD: receptor binding domain; NTD: N-terminal domain; EBV: Epstein-Barr virus). Data points represent the mean of two technical replicates. Data are representative of two independent experiments.

SARS-COV-2 VARIANTS OF CONCERN IN THE UNITED STATES-CHALLENGES AND OPPORTUNITIES

Walensky RP, Walke HT, Fauci AS.. JAMA. 2021 Mar 16;325(11):1037-1038. doi: 10.1001/jama.2021.2294.
Level of Evidence: 5 - Expert Opinion

BLUF

Dr. Anthony Fauci and collaborators from the Centers for Disease Control and National Institute of Allergy and Infectious Diseases addressed the concern that SARS-CoV-2 B.1.1.7 and B.1.351 variants may be more contagious or result in more severe disease. They note that the Department of Health and Human Services (HHS) has established an Interagency Group (SIG) to improve coordination efforts among several government agencies to address the spread of these SARS-CoV-2 variants. Because variants have the potential to worsen the trajectory of the pandemic, the authors emphasize the importance of a multi-faceted public health response, especially during this period of increasing vaccination efforts.

INACTIVATED RABIES VIRUS VECTORED SARS-COV-2 VACCINE PREVENTS DISEASE IN A SYRIAN HAMSTER MODEL

Kurup D, Malherbe DC, Wirblich C, Lambert R, Ronk AJ, Zabihi Diba L, Bukreyev A, Schnell MJ.. PLoS Pathog. 2021 Mar 25;17(3):e1009383. doi: 10.1371/journal.ppat.1009383. Online ahead of print.
Level of Evidence: 5 - Mechanism-based reasoning

BLUF

Microbiologists and immunologists from Jefferson University injected 12 Syrian hamsters with an inactivated rabies vectored SARS-CoV-2 S1 vaccine (CORAVAX) and evaluated the resulting immune response. Serology studies demonstrated high levels of virus neutralizing antibodies compared to control vaccine FILORAB1 (rabies vectored ebola vaccine) (Figure 2), with significantly reduced lung viral replication and pathology (Figures 5, 7). Authors suggest these vaccines are suitable candidates for human clinical trials, especially due to the ease of their production relative to other methods.

ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emergent coronavirus that has caused a worldwide pandemic. Although human disease is often asymptomatic, some develop severe illnesses such as pneumonia, respiratory failure, and death. There is an urgent need for a vaccine to prevent its rapid spread as asymptomatic infections accounting for up to 40% of transmission events. Here we further evaluated an inactivated rabies vectored SARS-CoV-2 S1 vaccine CORAVAX in a Syrian hamster model. CORAVAX adjuvanted with MPLA-AddaVax, a TRL4 agonist, induced high levels of neutralizing antibodies and generated a strong Th1-biased immune response. Vaccinated hamsters were protected from weight loss and viral replication in the lungs and nasal turbinates three days after challenge with SARS-CoV-2. CORAVAX also prevented lung disease, as indicated by the significant reduction in lung pathology. This study highlights CORAVAX as a safe, immunogenic, and efficacious vaccine that warrants further assessment in human trials.

FIGURES

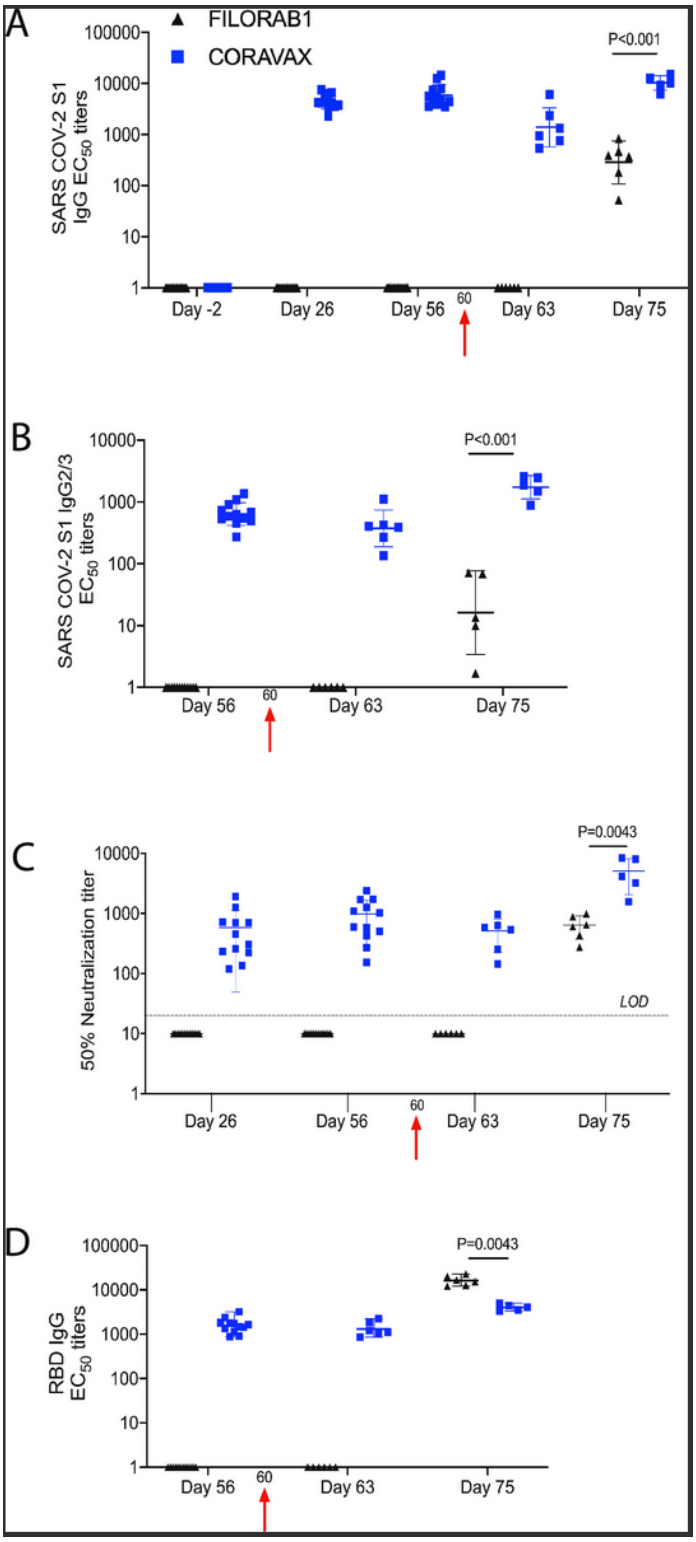

Fig 2. SARS CoV-2 immune responses.

Serum samples collected from each hamster were evaluated for SARS-CoV-2 S-specific immune responses by A) ELISA, Anti-SARS CoV-2 S1 IgG responses represented as EC50 titers over time, B) ELISA, Anti-SARS CoV-2 IgG2/3 responses, C) Virus neutralizing antibodies, and D) ELISA, Anti-SARS COV- 2 S RBD IgG responses. The CORAVAX vaccine group is shown in blue and the FILORAB1 group in black. For A-D, mean titers ± SD are depicted for each group per time point. P values determined by Mann-Whitney test. Only significant differences are depicted.

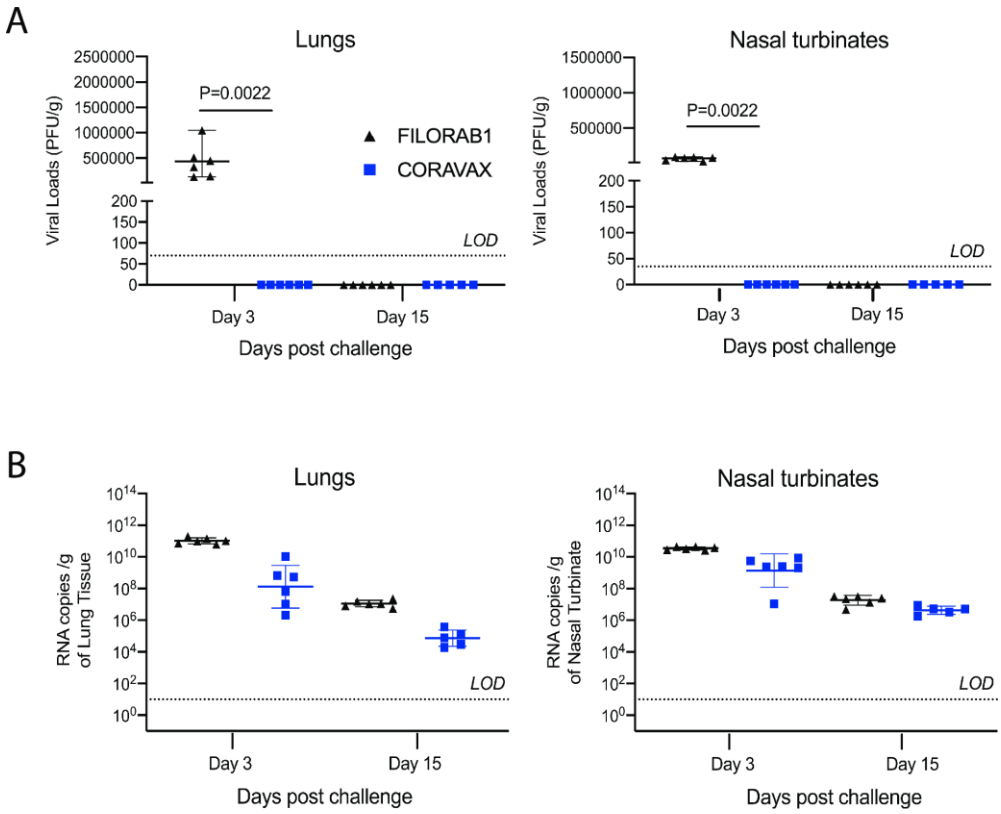

Fig 5. SARS-CoV-2 tissue viral load in hamsters.

Hamsters were challenged intranasally with 105 PFU SARS-CoV-2, and half of the animals in each group were euthanized at days 3 and 15 p.c. Right lungs (A, C) and nasal turbinates (B, D) from each animal were homogenized in media and viral loads were determined by plaque assays on Vero E6 cells (A, B) or by qRT-PCR (C, D). The limit of detection for the plaque assay was 70 PFU per lung and 35 PFU per nasal turbinate. The limit of detection for the qRT-PCR assay is 10 copies. The CORAVAX vaccine group is shown in blue and the FILORAB1 group in black. Data represent mean ± S.D., N = 6 for FILORAB1 group day 3 and day 15 time points, and N = 6 for CORAVAX group day 3 and N = 5 for CORAVAX group day 15 time points. P values determined by Mann-Whitney test. Only significant differences are depicted.

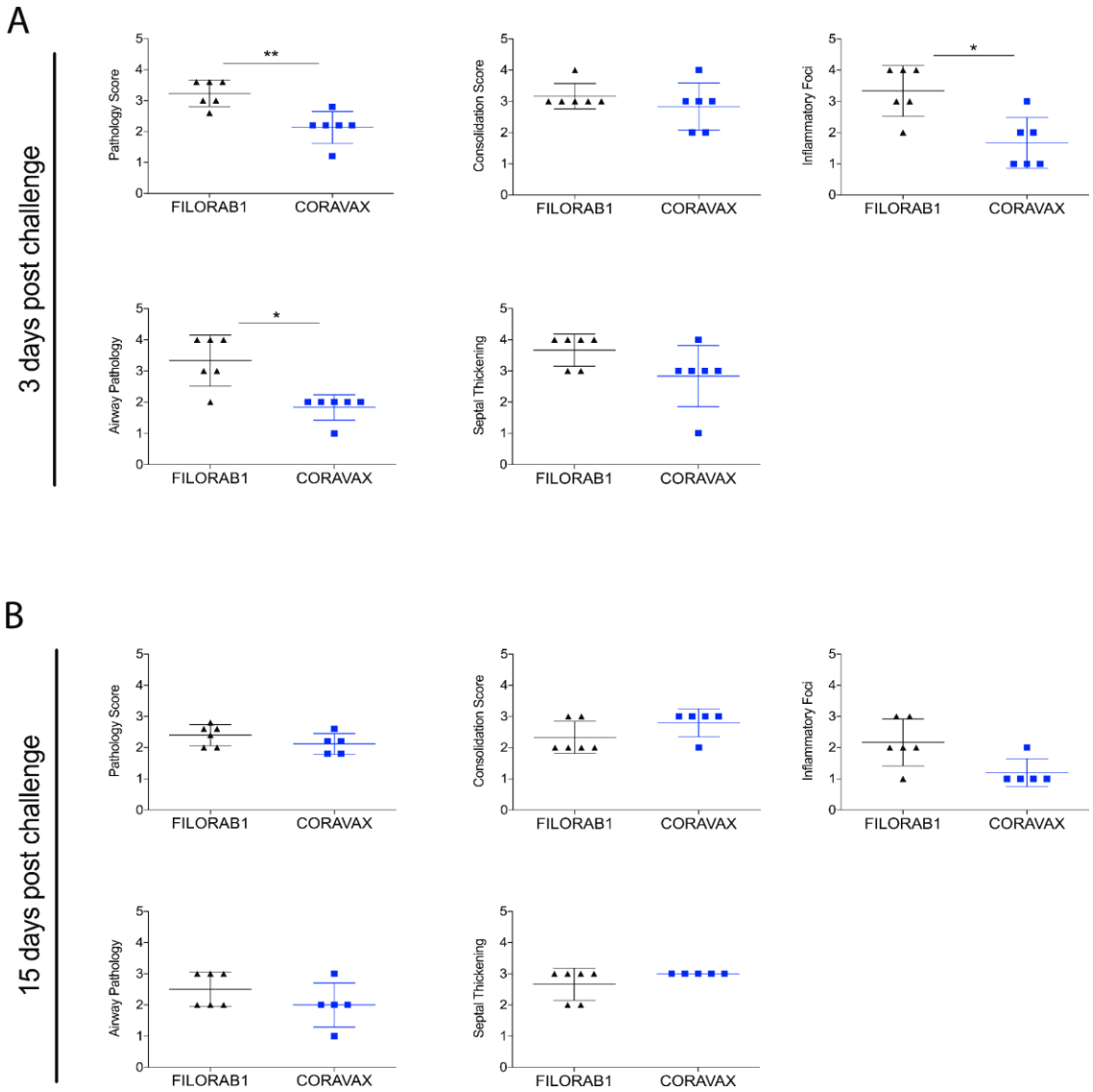

Fig 7. Comparative pathology scores for lungs from CORAVAX vaccinated and control hamsters post SARS-CoV-2 challenge. Scores at 3 days (A) and 15 days (B) p.c. Scores are displayed for overall lung pathology and individual criteria, including consolidation or extent of inflammation, type inflammatory foci, airway pathology, and septal thickening. The pathology scores (mean) were calculated based on the criteria described in S1 Table. The CORAVAX vaccine group is shown in blue and the control group in black. Data represent mean ± S.D., N = 6 for FILORAB1 group day 3 and day 15 time points and N = 6 for CORAVAX vaccine group at day 3 and N = 5 for CORAVAX day 15 time points. P > 0.123 (ns), P < 0.033 (*), P < 0.002 (**), P < 0.001 (***). Only significant differences are depicted.

GASTROENTEROLOGY

COVID-19 TRANSMISSION FOLLOWING OUTPATIENT ENDOSCOPY DURING PANDEMIC ACCELERATION PHASE INVOLVING SARS-COV-2 VOC 202012/01 VARIANT IN UK

Hayee B; SCOTS II Project group, Bhandari P, Rees CJ, Penman I.. Gut. 2021 Mar 24:gutjnl-2021-324354. doi: 10.1136/gutjnl-2021-324354. Online ahead of print.
Level of Evidence: 3 - Local non-random sample

BLUF

A prospective multicenter study conducted by researchers from multiple gastroenterology institutions throughout the United Kingdom (UK) investigated data from 8 UK centers regarding 2,440 patients who underwent endoscopy between December 14-31, 2020 and found 30 patients developed symptoms suspicious for COVID-19 post-procedure with 16 testing positive via nasopharyngeal swab (NPS) (Table 1); 3 cases were attributed to potential transmission from endoscopy attendance (Figure 2). Compared to a study performed before the novel SARS-CoV-2 variant (VOC 202012/01) surge occurred in which no SARS-CoV-2 transmission were recorded in over 6,200 patients, the rate of transmission among these patients is ~0.5%. Thus, the risk of acquiring COVID-19 from endoscopy remains very low, however there is still need for strict adherence to infection prevention and control measures to limit potential transmission.

FIGURES

Case	Hospital	Total endoscopy activity (cases)	Procedure	Days from endoscopy to symptom onset	Cause identified on review	Attributed to endoscopy?
1	A	440	Colonoscopy	12	Attended for CT scan on day 5 after endoscopy (non-swab)	No
2	B	458	OGD	7	No other likely source identified	Yes
3			Colonoscopy	5	Attended emergency department on day prior to endoscopy	No
4	C	263	Colonoscopy	6	No other likely source identified	Yes
5			Colonoscopy	3	Family member with confirmed infection prior to attendance*	No
6			Sigmoidoscopy	2	Multiple family members with confirmed infection†	No
7			Colonoscopy	4	Attended for CT scan 3 days prior to endoscopy (non-swab)	No
8	D	462	ERCP	5	Temporary admission to ward where outbreak occurred	No
9			Colonoscopy	2	Family member had confirmed infection prior to attendance*	No
10			OGD	5	Family member had confirmed infection prior to attendance*	No
11			Colonoscopy	8	Hospital staff; returned to work immediately after endoscopy	No
12			Colonoscopy	2	Family member had confirmed infection prior to attendance*	No
13	E	194	ERCP	13	Family member had confirmed infection after attendance*	No
14			ERCP	11	No other likely source identified	Yes
15			OGD	1	Family member had confirmed infection prior to attendance*	No
16	F	472	OGD	4	NHS employee (administrative) with multiple duties in hospital	No

Table 1: Analysis of COVID-19 cases confirmed by nasopharyngeal swab (NPS) after symptom onset

2 – secondary care; 3 – tertiary care; *; .
*Cases known only in retrospect, between preprocedure NPS and attendance.
†History not disclosed by patient prior to attendance (preprocedure telephone questionnaire).
ERCP, endoscopic retrograde pancreatography; OGD, oesophagogastroduodenoscopy

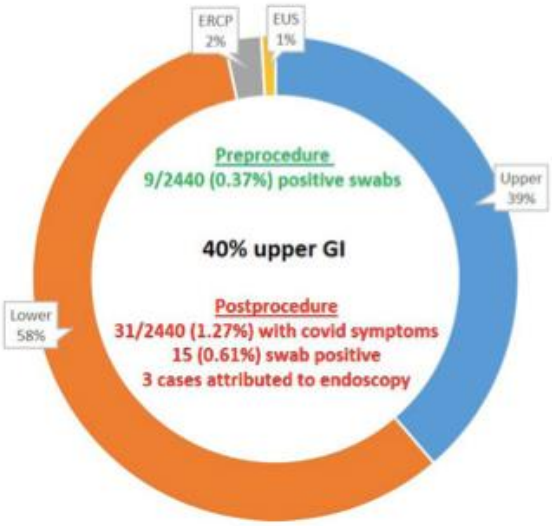

Figure 2: Proportions of procedures performed.

TRANSPLANT SURGERY

RISK AND REWARD: BALANCING SAFETY AND MAXIMIZING LUNG DONORS DURING THE COVID-19 PANDEMIC

La Hoz RM, Danziger-Isakov LA, Klassen DK, Michaels MG.. Am J Transplant. 2021 Mar 23. doi: 10.1111/ajt.16575. Online ahead of print.
Level of Evidence: 5 - Case Report

BLUF

Pediatricians and infectious disease physicians from Texas, Ohio, Virginia, and Pittsburgh present a case involving a solid lung transplant donor, dying from head trauma, with a negative RT-PCR SARS-CoV-2 from upper respiratory tract (URT) sample, as well as negative donor risk assessment interview (UDRAI) determined by organ procurement organizations (OPO). However, shortly after transplant both the recipient and the handling surgeon developed COVID-19, with the recipient ultimately succumbing to disease. As all parties involved had seemingly negative SARS-CoV-2 results prior to surgery, further investigation was performed with a whole genome sequencing from stored bronchoalveolar lavage of lower respiratory tract (LRT) from all three people, revealing a common origin of infection from the donor. The authors suggest, that although an isolated case, this example highlights the need for additional transplant screening during COVID-19 pandemic, especially in the setting of lung transplants.

ABSTRACT

During the early phase of the Coronavirus Disease 2019 (COVID-19) pandemic there was an abrupt decline in the number of transplants in the United States (1). The possibility of donor derived COVID-19 was one of the contributing factors and a consequence of the limited availability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) donor testing. As solid organ transplant rates have returned to the pre-pandemic time despite the on-going pandemic, the optimal approach to screen solid organ donors for SARS-CoV-2 is uncertain. Ideally, donor screening should minimize the risk of disease transmission and maximize organ utilization.

RESEARCH PROGRESS IN LABORATORY DETECTION OF SARS-COV-2

Wang HJ, Xiang YH, Hu R, Ji R, Wang YP.. Ir J Med Sci. 2021 Mar 24. doi: 10.1007/s11845-021-02604-4. Online ahead of print.
Level of Evidence: 5 - Review / Literature Review

BLUF

Researchers from the First Hospital of Lanzhou University in Lanzhou, China review the current detection methods of SARS-CoV-2 detailing the advantages, disadvantages, and accuracy of each. RT-PCR is the most commonly used detection method, with fastest results using either nasopharyngeal, oropharyngeal, or alveolar lavage, and the highest sensitivity reaching 96.6% when SARS-CoV-2 nucleocapsid protein gene is used as primer detection target. Other detection methods examined include antibody detection of IgG, IgM, and IgA, colloidal gold method, enzyme linked immunosorbent assay, clusters of regular interval short palindromes (CRISPR), reverse transcription loop-mediated isothermal amplification (RT-LAMP), and digital PCR. Advancements of technology will continue to improve the detection of SARS-CoV-2.

ABSTRACT

BACKGROUND: Nucleic acid testing is a reliable method for diagnosing viral infection in clinical samples. However, when the number of cases is huge and there are individual differences in the virus itself, the probability of false-negative results increases. With the advancement in research on the new coronavirus, new detection technologies that use serum-specific antibodies as detection targets have been developed. These detection technologies have high efficiency and shorter turnaround time, which ultimately shortens the time required for diagnosis. This article summarizes the methods that have been reported to date for the detection of the new coronavirus and discusses their principles and technical characteristics. AIMS: Compare the advantages and disadvantages of various SARS-CoV-2 detection methods and analyze their principles. METHODS: Searched reports on SARS-CoV-2 detection methods published so far, extracted the data and analyzed them. Use the primer blast function of NCBI to analyze the primers used in qRT-PCR detection. RESULTS: The detection sensitivity was the highest when nucleocapsid protein gene was used as the target, reaching 96.6%. The detection efficiency of the remaining targets ranged from 66.7% to 96.0%. Various new detection methods, like Serum specific antibody detection, can speed up the test time. However, due to the complexity of the method and higher testing requirements, it seems that it cannot be used as a complete replacement for qRT-PRC testing. CONCLUSIONS: With the advancement of technology and the improvement of methods, the detection methods of SARSCoV-2 have become more mature. These advances provided great help to the detection of SARS-CoV-2.

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CONTRIBUTORS

Ankita Dharmendran
Hamza Sultan
Leah Merker
Michael Wang
Nicolas Longobardi
Renate Meckl
Reza Aghaei
Veronica Graham

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