RESEARCH PUBLICATIONS

Association of SARS-CoV-2 clades with clinical, inflammatory and virologic outcomes: An observational study

Abstract

Background: Host determinants of severe coronavirus disease 2019 include advanced age, comorbidities and male sex. Virologic factors may also be important in determining clinical outcome and transmission rates, but limited patient-level data is available.

Methods: An observational cohort study was conducted at seven public hospitals in Singapore. Clinical and laboratory data were collected and compared between individuals infected with different SARS-CoV-2 clades. Firth's logistic regression was used to examine the association between SARS-CoV-2 clade and development of hypoxia, and quasi-Poisson regression to compare transmission rates. Plasma samples were tested for immune mediator levels and the kinetics of viral replication in cell culture were compared.

Findings: 319 Patients with PCR-confirmed SARS-CoV-2 infection had clinical and virologic data available for analysis. 29 (9%) were infected with clade S, 90 (28%) with clade L/V, 96 (30%) with clade G (containing D614G variant), and 104 (33%) with other clades 'O' were assigned to lineage B.6. After adjusting for age and other covariates, infections with clade S (adjusted odds ratio (aOR) 0·030 (95% confidence intervals (CI): 0·0002–0·29)) or clade O (B·6) (aOR 0·26 (95% CI 0·064–0·93)) were associated with lower odds of developing hypoxia requiring supplemental oxygen compared with clade L/V. Patients infected with clade L/V had more pronounced systemic inflammation with higher concentrations of pro-inflammatory cytokines, chemokines and growth factors. No significant difference in the severity of clade G infections was observed (aOR 0·95

(95% CI: 0·35–2·52). Though viral loads were significantly higher, there was no evidence of increased transmissibility of clade G, and replicative fitness in cell culture was similar for all clades.

Interpretation: Infection with clades L/V was associated with increased severity and more systemic release of pro-inflammatory cytokines. Infection with clade G was not associated with changes in severity, and despite higher viral loads there was no evidence of increased transmissibility.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00112-2/fulltext

The emerging association between COVID-19 and acute stroke

Abstract

Prior to COVID-19, only two human-tropic coronaviruses resulted in epidemics, and cerebrovascular disease was rarely reported. Evidence now suggests that 1-6% of hospitalized COVID-19 patients develop stroke. According to some reports, stroke risk is more than sevenfold greater in patients with COVID-19 than influenza. Concerningly, outcomes of COVID-19-related stroke are often worse than in stroke patients without COVID-19 from the same cohorts. In this review, we highlight the emerging association between COVID-19 and stroke and discuss putative pathogenetic mechanisms. Etiology of stroke in COVID-19 patients is likely multifactorial, related to coagulopathy, inflammation, platelet activation, and alterations to the vascular endothelium. Significant work remains to be done to better understand the pathogenesis of COVID-19-related stroke and for designing optimal primary and secondary prevention strategies.

Reference

https://www.cell.com/trends/neurosciences/fulltext/S0166-2236(21)00071-0

Durability of immunity to SARS-CoV-2 and other respiratory viruses

Abstract

Even in non-pandemic times, respiratory viruses account for a vast global burden of disease. They remain a major cause of illness and death and pose a perpetual threat of breaking out into epidemics and pandemics. Many of these respiratory viruses infect

repeatedly and appear to induce only narrow transient immunity, but the situation varies from one virus to another. In the absence of effective specific treatments, understanding the role of immunity in protection, disease and resolution is of paramount importance. These problems have been brought into sharp focus by the coronavirus COVID-19 pandemic. Here, we summarise what is now known about adaptive immunity to SARS-CoV-2 and draw comparisons with immunity to other respiratory viruses, focusing on the longevity of protective responses.

Reference

https://www.cell.com/trends/microbiology/fulltext/S0966-842X(21)00092-5

Italian neonatologists and SARS-CoV-2: Lessons learned to face coming new waves

Abstract

The aim of this review was threefold: (a) to retrieve all SARS-CoV-2 evidences published by Italian neonatologists working in maternity centers and NICUs during the pandemic; (b) to summarize current evidence for the management of term and preterm infants with a SARS-CoV-2-related illness; and (c) to provide an update for dealing with the second wave of COVID-19 and discuss open questions. A review was conducted using MEDLINE/PubMed and the national COVID-19 registry of the Italian Society of Neonatology including citations from December 1, 2019 to October 28, 2020. Sixty-three articles were included. Collected data were divided into the following topics: (a) antenatal management, (b) management in delivery room, (c) postnatal management, (d) mother–baby dyad and breastfeeding management, (e) neonatal emergency transport system reorganization, (f) parents' management and perspective during SARS-CoV-2 pandemic, and (g) future perspective. Evidences have evolved over the pandemic period and the current review can be useful in the management of the mother–neonate dyad during SARS-CoV-2 future waves. Italian neonatologists have played an active role in producing official guidelines and reporting data that have contributed to improve the care of neonates. A joint European action plan is mandatory to face COVID-19 in neonates with more awareness.

Reference

https://www.nature.com/articles/s41390-021-01477-8

Drugs that inhibit TMEM16 proteins block SARS-CoV-2 Spike-induced syncytia

Abstract

Development COVID-19 is a disease with unique characteristics including lung thrombosis, frequent diarrhoea, abnormal activation of the inflammatory response and rapid deterioration of lung function consistent with alveolar oedema. The pathological substrate for these findings remains elusive. Here it was shown that the lungs of patients with COVID-19 contain infected pneumocytes with abnormal morphology and frequent multinucleation. Generation of these syncytia results from activation of the SARS-CoV-2 Spike protein at the cell plasma membrane level. Based on these observations, we performed two high-content microscopy-based screenings with over 3000 approved drugs to search for inhibitors of Spike-driven syncytia. It was converged on the identification of 83 drugs that inhibited Spike-mediated cell fusion, several of which belonged to defined pharmacological classes. The attention was focused on effective drugs that also protected against virus replication and associated cytopathicity. One of the most effective molecules was Niclosamide, which markedly blunted calcium oscillations and membrane conductances in Spike-expressing cells by suppressing the activity of TMEM16F/Anoctamin, a calcium-activated ion channel and scramblase responsible for phosphatidylserine exposure on the cell surface. These findings suggest a potential mechanism for COVID-19 disease pathogenesis and support the repurposing of Niclosamide for therapy.

Reference

https://www.nature.com/articles/s41586-021-03491-6

Cytotoxic T-lymphocyte elicited vaccine against SARS-CoV-2 employing immunoinformatics framework

Abstract

Development of effective counteragents against the novel coronavirus disease (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains, requires clear insights and information for understanding the immune responses

associated with it. This global pandemic has pushed the healthcare system and restricted the movement of people and succumbing of the available therapeutics utterly warrants the development of a potential vaccine to contest the deadly situation. In the present study, highly efficacious, immunodominant cytotoxic T-lymphocyte (CTL) epitopes were predicted by advanced immunoinformatics assays using the spike glycoprotein of SARS-CoV2, generating a robust and specific immune response with convincing immunological parameters (Antigenicity, TAP affinity, MHC binder) engendering an efficient viral vaccine. The molecular docking studies show strong binding of the CTL construct with MHC-1 and host membrane specific TLR2 receptors. The molecular dynamics simulation in an explicit system confirmed the stable and robust binding of CTL epitope with TLR2. Steep magnitude RMSD variation and compelling residual fluctuations existed in terminal residues and various loops of the β linker segments of TLR2-epitope (residues 105-156 and 239-254) to about 0.4 nm. The reduced Rg value (3.3 nm) and stagnant SASA analysis (275 nm/S2/N after 8 ns and 5 ns) for protein surface and its orientation in the exposed and buried regions suggests more compactness due to the strong binding interaction of the epitope. The CTL vaccine candidate establishes a high capability to elicit the critical immune regulators, like T-cells and memory cells as proven by the in silico immunization assays and can be further corroborated through in vitro and in vivo assays.

Reference

https://www.nature.com/articles/s41598-021-86986-6

Evaluation of 11 SARS-CoV-2 antibody tests by using samples from patients with defined IgG antibody titers

Abstract

The performance of 11 SARS-CoV-2 antibody tests were evaluated using a reference set of heat-inactivated samples from 278 unexposed persons and 258 COVID-19 patients, some of whom contributed serial samples. The reference set included samples with a variation in SARS-CoV-2 IgG antibody titers, as determined by an in-house immunofluorescence assay (IFA). The five evaluated rapid diagnostic tests had a specificity of 99.0% and a sensitivity that ranged from 56.3 to 81.6% and decreased with low IFA IgG titers. The specificity was > 99% for five out of six platform-based tests, and

when assessed using samples collected ≥ 22 days after symptom onset, two assays had a sensitivity of > 96%. These two assays also detected samples with low IFA titers more frequently than the other assays. In conclusion, the evaluated antibody tests showed a heterogeneity in their performances and only a few tests performed well with samples having low IFA IgG titers, an important aspect for diagnostics and epidemiological investigations.

Reference

https://www.nature.com/articles/s41598-021-87289-6

From bedside to bench: Regulation of host factors in SARS-CoV-2 infection

Abstract

The zoonotic coronavirus SARS-CoV-2 (severe acute respiratory syndrome coronavirus-2), which causes COVID-19 (coronavirus disease-2019), has resulted in a pandemic. This has led to an urgent need to understand the molecular determinants of SARS-CoV-2 infection, factors associated with COVID-19 heterogeneity and severity, and therapeutic options for these patients. In this review, we discuss the role of host factors in SARS-CoV-2 infection and describe variations in host factor expression as mechanisms underlying the symptoms and severity of COVID-19. The study was focus on two host factors, angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2), implicated in SARS-CoV-2 infection. Genetic variants associated with COVID-19 severity were also discussed, which revealed in selected patients and based on genome-wide association studies (GWASs). Furthermore, important advances in cell and chromatin biology were highlighted, such as single-cell RNA and chromatin sequencing and chromosomal conformation assays, as methods that may aid in the discovery of viral–host interactions in COVID-19. Understanding how regulation of host factor genes varies in physiological and pathological states might explain the heterogeneity observed in SARS-CoV-2 infection, help identify pathways for therapeutic development, and identify patients most likely to progress to severe COVID-19.

Reference

https://www.nature.com/articles/s12276-021-00595-x

The relationship of large city out-of-hospital cardiac arrests and the prevalence of COVID-19

Abstract

Background: Though variable, many major metropolitan cities reported profound and unprecedented increases in out-of-hospital cardiac arrest (OHCA) in early 2020. This study examined the relative magnitude of those increases and their relationship to COVID-19 prevalence.

Methods: EMS (9-1-1 system) medical directors for 50 of the largest U.S. cities agreed to provide the aggregate, de-identified, pre-existing monthly tallies of OHCA among adults (age >18 years) occurring between January and June 2020 within their respective jurisdictions. Identical comparison data were also provided for corresponding time periods in 2018 and 2019. Equivalent data were obtained from the largest cities in Italy, United Kingdom and France, as well as Perth, Australia and Auckland, New Zealand.

Findings: Significant OHCA escalations generally paralleled local prevalence of COVID-19. During April, most U.S. cities (34/50) had >20% increases in OHCA versus 2018–2019 which reflected high local COVID-19 prevalence. Thirteen observed 1·5-fold increases in OHCA and three COVID-19 epicenters had >100% increases (2·5-fold in New York City). Conversely, cities with lesser COVID-19 impact observed unchanged (or even diminished) OHCA numbers. Altogether (n = 50), on average, OHCA cases/city rose 59% during April (p = 0·03). By June, however, after mitigating COVID-19 spread, cities with the highest OHCA escalations returned to (or approached) pre-COVID OHCA numbers while cities minimally affected by COVID-19 during April (and not experiencing OHCA increases), then had marked OHCA escalations when COVID-19 began to surge locally. European, Australian, and New Zealand cities mirrored the U.S. experience.

Interpretation: Most metropolitan cities experienced profound escalations of OHCA generally paralleling local prevalence of COVID-19. Most of these patients were pronounced dead without COVID-19 testing.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00095-X/fulltext

Comparison of seven commercial SARS-CoV-2 rapid point-of-care antigen tests: A single-centre laboratory evaluation study

Abstract

Background: Antigen point-of-care tests (AgPOCTs) can accelerate SARS-CoV-2 testing. As some AgPOCTs have become available, interest is growing in their utility and performance. Here it was aimed to compare the analytical sensitivity and specificity of seven commercially available AgPOCT devices.

Methods: In a single-centre, laboratory evaluation study, AgPOCT products from seven suppliers were compared: the Abbott Panbio COVID-19 Ag Rapid Test, the RapiGEN BIOCREDIT COVID-19 Ag, the Healgen Coronavirus Ag Rapid Test Cassette (Swab), the Coris BioConcept COVID-19 Ag Respi-Strip, the R-Biopharm RIDA QUICK SARS-CoV-2 Antigen, the nal von minden NADAL COVID-19 Ag Test, and the Roche-SD Biosensor SARS-CoV Rapid Antigen Test. Tests were evaluated on recombinant SARS-CoV-2 nucleoprotein, cultured endemic and emerging coronaviruses, stored respiratory samples with known SARS-CoV-2 viral loads, stored samples from patients with respiratory pathogens other than SARS-CoV-2, and self-sampled swabs from healthy volunteers. We estimated analytical sensitivity in terms of approximate viral concentrations (quantified by real-time RT-PCR) that yielded positive AgPOCT results, and specificity in terms of propensity to generate false-positive results.

Findings: In 138 clinical samples with quantified SARS-CoV-2 viral load, the 95% limit of detection (concentration at which 95% of test results were positive) in six of seven AgPOCT products ranged between $2 \cdot 07 \times 10^6$ and $2 \cdot 86 \times 10^7$ copies per swab, with an outlier (RapiGEN) at $1 \cdot 57 \times 10^{10}$ copies per swab. The assays showed no cross-reactivity towards cell culture or tissue culture supernatants containing any of the four endemic human coronaviruses (HCoV-229E, HCoV-NL63, HCoV-OC43, or HCoV-HKU1) or MERS-CoV, with the exception of the Healgen assay in one repeat test on HCoV-HKU1 supernatant. SARS-CoV was cross-detected by all assays. Cumulative specificities among stored clinical samples with non-SARS-CoV-2 infections (n=100) and self-samples from healthy volunteers (n=35; cumulative sample n=135) ranged between 98·5% (95% CI 94·2–99·7) and 100·0% (97·2–100·0) in five products, with two

outliers at 94·8% (89·2–97·7; R-Biopharm) and 88·9% (82·1–93·4; Healgen). False-positive results did not appear to be associated with any specific respiratory pathogen.

Interpretation: The sensitivity range of most AgPOCTs overlaps with SARS-CoV-2 viral loads typically observed in the first week of symptoms, which marks the infectious period in most patients. The AgPOCTs with limit of detections that approximate virus concentrations at which patients are infectious might enable shortcuts in decision making in various areas of health care and public health.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00056-2/fulltext

Publication Date: Apr 06, 2021

A randomized, double-blind, placebo-controlled phase 1 trial of inhaled and intranasal niclosamide: A broad spectrum antiviral candidate for treatment of COVID-19

Abstract

Background: Coronavirus disease 19 (COVID-19) is spreading globally and treatment options remain limited. A formulation of niclosamide, a potent anti-SARS-CoV-2 agent and a broad-spectrum antiviral treatment candidate, optimized for inhalation and intranasal administration (UNI91104) was developed.

Methods: A randomized, placebo-controlled, double-blind, single-centre, dose-ascending Phase 1 trial was conducted to assess the safety of UNI91104 in Denmark (NCT04576312). Healthy volunteers were randomly assigned to a ascending single dose in cohort 1–4 and five doses over 2.5 days in cohort 5. Inclusion criteria included a minimum 80% of predicted lung function. Exclusion criteria included severe, clinically significant allergies and current acute or chronic condition especially airway diseases. Safety was evaluated through adverse events (AEs) and pulmonary function tests including forced expiratory volume in one second (FEV1) and fractional exhaled nitric oxide (FeNO) tests. The primary endpoints were defined as the frequency of reported AEs and the change of safety variables relative to pre-dose. Data from all enroled healthy volunteers receiving any amount of IMP was included in the primary analyses. The pharmacokinetics of UNI91104 was determined.

Findings: The trial was conducted between 29 June 2020 and 08 August 2020. Thirty-four healthy volunteers received UNI91104 and ten placebo. No serious AEs or discontinuation were reported. Mild irritation in the upper respiratory tract following inhalation of UNI91104 was reported as most frequent AE (45 events in 26 healthy volunteers, 59% of all healthy volunteers). Nasal application was well-tolerated. There was no evidence of difference in the change of mean levels of pulmonary function tests between active and placebo group across all cohorts. Five healthy volunteers (11.4%) (1 on placebo) had signs of increased transient FeNO and 4 on active (9.1%) experienced asymptomatic drops in FEV1, which resolved spontaneously or were reversible with a β2-agonist. Niclosamide exhibited dose-proportional pharmacokinetics following inhalation and intranasal administration.

Interpretation: UNI91104, a promising candidate for inhalation and intranasal therapy against COVID-19 and other viral respiratory tract infections is well-tolerated in healthy volunteers and warrants further testing in patient trials.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00061-2/fulltext

Endothelial dysfunction and immunothrombosis as key pathogenic mechanisms in COVID-19

Abstract

Coronavirus disease 2019 (COVID-19) is a clinical syndrome caused by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients with severe disease sho w hyperactivation of the immune system, which can affect multiple organs besides the lungs. Here, it was proposed that SARS-CoV-2 infection induces a process known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels. Microthrombotic complications may contribute to acute respiratory distress syndrome (ARDS) and other organ dysfunctions. Therapeutic strategies aimed at reducing immunothrombosis may therefore be useful. Several antithrombotic and immunomodulating drugs have been proposed as candidates to treat patients with SARS-CoV-2 infection. The growing understanding of SARS-CoV-2 infection pathogenesis and how it contributes to critical illness and its complications may

help to improve risk stratification and develop targeted therapies to reduce the acute and long-term consequences of this disease.

Reference

https://www.nature.com/articles/s41577-021-00536-9

Global short-term forecasting of COVID-19 cases

Abstract

The continuously growing number of COVID-19 cases pressures healthcare services worldwide. Accurate short-term forecasting is thus vital to support country-level policy making. The strategies adopted by countries to combat the pandemic vary, generating different uncertainty levels about the actual number of cases. Accounting for the hierarchical structure of the data and accommodating extra-variability is therefore fundamental. A new modelling framework was introduced to describe the pandemic's course with great accuracy and provide short-term daily forecasts for every country in the world. We show that our model generates highly accurate forecasts up to seven days ahead and use estimated model components to cluster countries based on recent events. Statistical novelty was introduced in terms of modelling the autoregressive parameter as a function of time, increasing predictive power and flexibility to adapt to each country. The model can also be used to forecast the number of deaths, study the effects of covariates (such as lockdown policies), and generate forecasts for smaller regions within countries. Consequently, it has substantial implications for global planning and decision making. Forecasts were presented and make all results freely available to any country in the world through an online Shiny dashboard.

Reference

https://www.nature.com/articles/s41598-021-87230-x

Distinct SARS-CoV-2 antibody reactivity patterns in coronavirus convalescent plasma revealed by a coronavirus antigen microarray

Abstract

A coronavirus antigen microarray (COVAM) was constructed containing 11 SARS-CoV-2, 5 SARS-1, 5 MERS, and 12 seasonal coronavirus recombinant proteins. The array is

designed to measure immunoglobulin isotype and subtype levels in serum or plasma samples against each of the individual antigens printed on the array. The COVAM with COVID-19 convalescent plasma (CCP) were probed, which were collected from 99 donors who recovered from a PCR+ confirmed SARS-CoV-2 infection. The results were analyzed using two computational approaches, a generalized linear model (glm) and random forest (RF) prediction model, to classify individual specimens as either Reactive or non-reactive against the SARS-CoV-2 antigens. A training set of 88 pre-COVID-19 specimens (PreCoV) collected in August 2019 and102 positive specimens from SARS-CoV-2 PCR+ confirmed COVID-19 cases, was used for these analyses. Results compared with an FDA emergency use authorized (EUA) SARS-CoV2 S1-based total Ig chemiluminescence immunoassay (Ortho Clinical Diagnostics VITROS Anti-SARS-CoV-2 Total, CoV2T) and with a SARS-CoV-2 S1-S2 spike-based pseudovirus micro neutralization assay (SARS-CoV-2 reporter viral particle neutralization titration (RVPNT) showed high concordance between the three assays. Three CCP specimens that were negative by the VITROS CoV2T immunoassay were also negative by both COVAM and the RVPNT assay. Concordance between VITROS CoV2T and COVAM was 96%, VITROS CoV2T and RVPNT 93%, and RVPNT and COVAM 91%. The discordances were all weakly reactive samples near the cutoff threshold of the VITROS CoV2T immunoassay. The multiplex COVAM allows CCP to be grouped according to antibody reactivity patterns against 11 SARS-CoV-2 antigens. Unsupervised K-means analysis, via the gap statistics, as well as hierarchical clustering analysis revealed three main clusters with distinct reactivity intensities and patterns. These patterns were not recapitulated by adjusting the VITROS CoV2T or RVPNT assay thresholds. Plasma classified by COVAM reactivity patterns offers potential to improve CCP therapeutic efficacy CoV2T alone. The use of a SARS-CoV-2 antigen array can qualify CCP for administration as a treatment for acute COVID-19, and interrogate vaccine immunogenicity and performance in preclinical, clinical studies, and routine vaccination to identify antibody responses predictive of protection from infection and disease.

Reference

https://www.nature.com/articles/s41598-021-87137-7

T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral responses

Abstract

Identification of protective T cell responses against SARS-CoV-2 requires distinguishing people infected with SARS-CoV-2 from those with cross-reactive immunity to other coronaviruses. Here a range of T cell assays were shown that differentially capture immune function to characterise SARS-CoV-2 responses. Strong *ex vivo* ELISpot and proliferation responses to multiple antigens (including M, NP and ORF3) are found in 168 PCR-confirmed SARS-CoV-2 infected volunteers, but are rare in 119 uninfected volunteers. Highly exposed seronegative healthcare workers with recent COVID-19-compatible illness show T cell response patterns characteristic of infection. By contrast, >90% of convalescent or unexposed people show proliferation and cellular lactate responses to spike subunits S1/S2, indicating pre-existing cross-reactive T cell populations. The detection of T cell responses to SARS-CoV-2 is therefore critically dependent on assay and antigen selection. Memory responses to specific non-spike proteins provide a method to distinguish recent infection from pre-existing immunity in exposed populations.

Reference

https://www.nature.com/articles/s41467-021-21856-3

Influenza virus and SARS-CoV-2: Pathogenesis and host responses in the respiratory tract

Abstract

Influenza viruses cause annual epidemics and occasional pandemics of respiratory tract infections that produce a wide spectrum of clinical disease severity in humans. The novel betacoronavirus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 and has since caused a pandemic. Both viral and host factors determine the extent and severity of virus-induced lung damage. The host's response to viral infection is necessary for viral clearance but may be deleterious and contribute to severe disease phenotypes. Similarly, tissue repair mechanisms are required for recovery from infection across the spectrum of disease severity; however,

dysregulated repair responses may lead to chronic lung dysfunction. Understanding of the mechanisms of immunopathology and tissue repair following viral lower respiratory tract infection may broaden treatment options. In this Review, the pathogenesis was discussed, the contribution of the host response to severe clinical phenotypes and highlight early and late epithelial repair mechanisms following influenza virus infection, each of which has been well characterized. Although we are still learning about SARS-CoV-2 and its disease manifestations in humans, throughout the Review we discuss what is known about SARS-CoV-2 in the context of this broad knowledge of influenza virus, highlighting the similarities and differences between the respiratory viruses.

Reference

https://www.nature.com/articles/s41579-021-00542-7

6-Month neurological and psychiatric outcomes in 236 379 survivors of COVID-19: A retrospective cohort study using electronic health records

Abstract

Background: Neurological and psychiatric sequelae of COVID-19 have been reported, but more data are needed to adequately assess the effects of COVID-19 on brain health. It was aimed to provide robust estimates of incidence rates and relative risks of neurological and psychiatric diagnoses in patients in the 6 months following a COVID-19 diagnosis.

Methods: For this retrospective cohort study and time-to-event analysis, we used data obtained from the TriNetX electronic health records network (with over 81 million patients). Our primary cohort comprised patients who had a COVID-19 diagnosis; one matched control cohort included patients diagnosed with influenza, and the other matched control cohort included patients diagnosed with any respiratory tract infection including influenza in the same period. Patients with a diagnosis of COVID-19 or a positive test for SARS-CoV-2 were excluded from the control cohorts. All cohorts included patients older than 10 years who had an index event on or after Jan 20, 2020, and who were still alive on Dec 13, 2020. The incidence of 14 neurological and psychiatric outcomes in the 6 months was estimated after a confirmed diagnosis of COVID-19: intracranial haemorrhage; ischaemic stroke; parkinsonism; Guillain-Barré syndrome; nerve, nerve root, and plexus disorders; myoneural junction and muscle

disease; encephalitis; dementia; psychotic, mood, and anxiety disorders (grouped and separately); substance use disorder; and insomnia. Using a Cox model, we compared incidences with those in propensity score-matched cohorts of patients with influenza or other respiratory tract infections. It was investigated how these estimates were affected by COVID-19 severity, as proxied by hospitalisation, intensive therapy unit (ITU) admission, and encephalopathy (delirium and related disorders). It was assessed the robustness of the differences in outcomes between cohorts by repeating the analysis in different scenarios. To provide benchmarking for the incidence and risk of neurological and psychiatric sequelae, our primary cohort was compared with four cohorts of patients diagnosed in the same period with additional index events: skin infection, urolithiasis, fracture of a large bone, and pulmonary embolism.

Findings: Among 236 379 patients diagnosed with COVID-19, the estimated incidence of a neurological or psychiatric diagnosis in the following 6 months was 33·62% (95% CI 33·17–34·07), with 12·84% (12·36–13·33) receiving their first such diagnosis. For patients who had been admitted to an ITU, the estimated incidence of a diagnosis was 46·42% (44·78–48·09) and for a first diagnosis was 25·79% (23·50–28·25). Regarding individual diagnoses of the study outcomes, the whole COVID-19 cohort had estimated incidences of 0·56% (0·50–0·63) for intracranial haemorrhage, 2·10% (1·97–2·23) for ischaemic stroke, 0·11% (0·08–0·14) for parkinsonism, 0·67% (0·59–0·75) for dementia, 17·39% (17·04–17·74) for anxiety disorder, and 1·40% (1·30–1·51) for psychotic disorder, among others. In the group with ITU admission, estimated incidences were 2·66% (2·24–3·16) for intracranial haemorrhage, 6·92% (6·17–7·76) for ischaemic stroke, 0·26% (0·15–0·45) for parkinsonism, 1·74% (1·31–2·30) for dementia, 19·15% (17·90–20·48) for anxiety disorder, and 2·77% (2·31–3·33) for psychotic disorder. Most diagnostic categories were more common in patients who had COVID-19 than in those who had influenza (hazard ratio [HR] 1·44, 95% CI 1·40–1·47, for any diagnosis; 1·78, 1·68–1·89, for any first diagnosis) and those who had other respiratory tract infections (1·16, 1·14–1·17, for any diagnosis; 1·32, 1·27–1·36, for any first diagnosis). As with incidences, HRs were higher in patients who had more severe COVID-19 (eg, those admitted to ITU compared with those who were not: 1·58, 1·50–1·67, for any diagnosis; 2·87, 2·45–3·35, for any first diagnosis). Results were robust to various sensitivity analyses and benchmarking against the four additional index health events.

Interpretation: The study provides evidence for substantial neurological and psychiatric morbidity in the 6 months after COVID-19 infection. Risks were greatest in, but not limited to, patients who had severe COVID-19. This information could help in service planning and identification of research priorities. Complementary study designs, including prospective cohorts, are needed to corroborate and explain these findings

Reference

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00084-5/fulltext

An evaluation of the mental health impact of SARS-CoV-2 on patients, general public and healthcare professionals: A systematic review and meta-analysis

Abstract

Background: The global impact of COVID-19 pandemic continues to affect the lives of billions of people with recurrent waves. Healthcare systems are struggling to manage pre-existing patient care and recurring covid-19 demands. As a result, it was evaluated that the mental health impact using systematic review and meta-analysis.

Methods: A comprehensive search was undertaken from April 2020 to 22nd January 2021 using multiple electronic databases. A systematic review protocol was developed and published on PROSPERO registration; CRD42020181481. A random-effects model was used to compute pooled estimates of anxiety, depression, PTSD, insomnia and suicidal thoughts.

Findings: The search yielded 11,295 studies and of those 287 met the inclusion criteria. The meta-analysis of 206 studies revealed minimal differences in prevalence of anxiety, depression, and PTSD among HCPs compared with the public during the pandemic but higher prevalence of suicidal thoughts/ideation or self-harm (11% vs 5.8%) and lower prevalence of wellbeing (28.2% vs 52.6%) among the public compared to HCPs.

Interpretation: The pandemic has led to a high mental health burden especially amongst HCPs and higher suicidal ideation and lower wellbeing in general public which warrants further investigation and management globally. These findings highlight an emerging critical public health issue that requires urgent solutions.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00086-9/fulltext

Functional comparison of SARS-CoV-2 with closely related pangolin and bat coronaviruses

Abstract

The origin and intermediate host for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is yet to be determined. Coronaviruses found to be closely related to SARS-CoV-2 include RaTG13 derived from bat and two clusters (PCoV-GD and PCoV-GX) of coronaviruses identified in pangolin. Here, the infectivity and antigenicity patterns of SARS-CoV-2 were studied, and the three related coronaviruses. Compared with the other three viruses, RaTG13 showed almost no infectivity to a variety of cell lines. The two pangolin coronaviruses and SARS-CoV-2 showed similar infectious activity. However, in SARS-CoV-2-susceptible cell lines, the pangolin coronaviruses presented even higher infectivity. The striking difference between the SARS-CoV-2 and pangolin coronaviruses is that the latter can infect porcine cells, which could be partially attributed to an amino acid difference at the position of 498 of the spike protein. The infection by SARS-CoV-2 was mainly mediated by Furin and TMPRSS2, while PCoV-GD and PCoV-GX mainly depend on Cathepsin L. Extensive cross-neutralization was found between SARS-CoV-2 and PCoV-GD. However, almost no cross-neutralization was observed between PCoV-GX and SARS-CoV-2 or PCoV-GD. More attention should be paid to pangolin coronaviruses and to investigate the possibility of these coronaviruses spreading across species to become zoonoses among pigs or humans.

Reference

https://www.nature.com/articles/s41421-021-00256-3

Elevated COVID19 mortality risk in detroit area hospitals among patients from census tracts with extreme socioeconomic vulnerability

Abstract

Background: The incidence of novel coronavirus disease (COVID19) is elevated in areas with heightened socioeconomic vulnerability. Early reports from US hospitals also implicated social disadvantage and chronic disease history as COVID19 mortality risk

factors. However, the relationship between race and COVID19 mortality remains unclear.

Methods: In-hospital COVID19 mortality risk factors were examined in a multi-hospital tertiary health care system that serves greater Detroit, Michigan, a predominantly African American city with high rates of poverty and chronic disease. Consecutive adult patients who presented to emergency departments and tested positive for COVID19 from 3/11/2020 through 4/18/2020 were included. Using log-binomial regression, we assessed the relationship between in-hospital mortality and residence in census tracts that were flagged for extreme socioeconomic vulnerability, patient-level demographics, and clinical comorbidities.

Findings: A total of 1,015 adults tested positive for COVID19 during the study period; 80% identified as Black people, 52% were male and 53% were ≥ 65 years of age. The median body mass index was 30•4 and the median Charlson Comorbidity Index score was 4. Patients from census tracts that were flagged for vulnerability related to socioeconomic status had a higher mortality rate than their peers who resided in less vulnerable census tracts (β 0.26, standard error (SE) 0.11, degrees of freedom (df) 378, t-value (t) 2.27, exp(β) 1.29, p-value 0.02). Adjustment for age category, Black race, sex and/or the Charlson Comorbidity Index score category reduced the magnitude of association by less than 10% [exp(β) 1.29 vs. 1.21]. Black race [p = 0.38] and sex [p = 0.62] were not associated with mortality in this sample.

Interpretation: People who lived in areas flagged for extreme socioeconomic vulnerability had elevated mortality risk in our predominantly African-American cohort of COVID19 patients who were able to seek hospital care during the so-called 'first wave' of the pandemic. By contrast, Black race was not associated with mortality in our sample.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00094-8/fulltext

Secondary analysis of transcriptomes of SARS-CoV-2 infection models to characterize COVID-19

Abstract

Standard transcriptomic analyses alone have limited power in capturing the molecular mechanisms driving disease pathophysiology and outcomes. To overcome this, unsupervised network analyses are used to identify clusters of genes that can be associated with distinct molecular mechanisms and outcomes for a disease. In this study, we developed an integrated network analysis framework that integrates transcriptional signatures from multiple model systems with protein-protein interaction data to find gene modules. Through a meta-analysis of different enriched features from these gene modules, communities of highly interconnected features were extracted. These clusters of higher-order features, working as a multifeatured machine, enable collective assessment of their contribution for disease or phenotype characterization. It was shown the utility of this workflow using transcriptomics data from three different models of SARS-CoV-2 infection and identify several pathways and biological processes that could enable in understanding or hypothesizing molecular signatures inducing pathophysiological changes, risks, or sequelae of COVID-19.

Reference

https://www.cell.com/patterns/fulltext/S2666-3899(21)00067-2

Clinical features and predictors of severity in COVID-19 patients with critical illness in Singapore

Abstract

It was aimed to describe a case series of critically and non-critically ill COVID-19 patients in Singapore. This was a multicentered prospective study with clinical and laboratory details. Details for fifty uncomplicated COVID-19 patients and ten who required mechanical ventilation were collected. It was compared clinical features between the groups, assessed predictors of intubation, and described ventilatory management in ICU patients. Ventilated patients were significantly older, reported more dyspnea, had elevated C-reactive protein and lactate dehydrogenase. A multivariable

logistic regression model identified respiratory rate (aOR 2.83, 95% CI 1.24–6.47) and neutrophil count (aOR 2.39, 95% CI 1.34–4.26) on admission as independent predictors of intubation with area under receiver operating characteristic curve of 0.928 (95% CI 0.828–0.979). Median APACHE II score was 19 (IQR 17–22) and PaO2/FiO2 ratio before intubation was 104 (IQR 89–129). Median peak FiO2 was 0.75 (IQR 0.6–1.0), positive end-expiratory pressure 12 (IQR 10–14) and plateau pressure 22 (IQR 18–26) in the first 24 h of ventilation. Median duration of ventilation was 6.5 days (IQR 5.5–13). There were no fatalities. Most COVID-19 patients in Singapore who required mechanical ventilation because of ARDS were extubated with no mortality.

Reference

https://www.nature.com/articles/s41598-021-81377-3

Clinical characteristics and outcomes of COVID-19 patients with diabetes mellitus in Kuwait

Abstract

Background: COVID-19 has a highly variable clinical presentation, ranging from asymptomatic to severe respiratory symptoms and death. Diabetes seems to be one of the main comorbidities contributing to a worse COVID-19 outcome.

Objective: In here the clinical characteristics and outcomes of diabetic COVID-19 patients Kuwait, were analyzed.

Methods: In this single-center, retrospective study of 417 consecutive COVID-19 patients, we analyze and compare disease severity, outcome, associated complications, and clinical laboratory findings between diabetic and non-diabetic COVID-19 patients.

Results: COVID-19 patients with diabetes had more I CU admission than non-diabetic COVID-19 patients (20.1% vs. 16.8%, p < 0.001). Diabetic COVID-19 patients also recorded higher mortality in comparison to non-diabetic COVID-19 patients (16.7% vs. 12.1%, p < 0.001). Diabetic COVID-19 patients had significantly higher prevalence of comorbidities, such as hypertension. Laboratory investigations also highlighted notably higher levels of C-reactive protein in diabetic COVID019 patients and lower estimated glomerular filtration rate. They also showed a higher incidence of complications. logistic regression analysis showed that every 1 mmol/L increase in fasting blood glucose in

COVID-19 patients is associated with 1.52 (95% CI: 1.34–1.72, p < 0.001) times the odds of dying from COVID-19.

Conclusion: Diabetes is a major contributor to worsening outcomes in COVID-19 patients. Understanding the pathophysiology underlining these findings could provide insight into better management and improved outcome of such cases.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)00809-4

A single dose of self-transcribing and replicating RNA based SARS-CoV-2 vaccine produces protective adaptive immunity in mice

Abstract

A self-transcribing and replicating RNA (STARRTM) based vaccine (LUNAR®-COV19) has been developed to prevent SARS-CoV-2 infection. The vaccine encodes an alphavirus-based replicon and the SARS-CoV-2 full length spike glycoprotein. Translation of the replicon produces a replicase complex that amplifies and prolong SARS-CoV-2 spike glycoprotein expression. A single prime vaccination in mice led to robust antibody responses, with neutralizing antibody titers increasing up to day 60. Activation of cell mediated immunity produced a strong viral antigen specific CD8+ T lymphocyte response. Assaying for intracellular cytokine staining for IFN-γ and IL-4 positive CD4+ T helper lymphocytes as well as anti-spike glycoprotein IgG2a/IgG1 ratios supported a strong Th1 dominant immune response. Finally, single LUNAR-COV19 vaccination at both 2 μg and 10 μg doses completely protected human ACE2 transgenic mice from both mortality and even measurable infection following wild-type SARS-CoV-2 challenge. Our findings collectively suggest the potential of LUNAR-COV19 as a single dose vaccine.

Reference

https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00188-X

Design and identification of novel annomontine analogues against SARS-CoV-2: An *in-silico* approach

Abstract

Aims: COVID-19 has currently emerged as the major global pandemic affecting the lives of people across the globe. It broke out from Wuhan Province of China, first reported to WHO on 31st December 2019 as "*Pneumonia of unknown cause*". Over time more people were infected with this virus, and the only tactic to ensure safety was to take precautionary measures due to the lack of any effective treatment or vaccines. As a result of unavailability of desired efficacy for previously repurposed drugs, exploring novel scaffolds against the virus has become the need of the hour.

Main methods: In the present study, 23 new annomontine analogues were designed representing β-carboline based scaffolds. A hypothesis on its role as an effective ligand was laid for target-specific binding in SARS-CoV-2. These molecules were used for molecular docking analysis against the multiple possible drug targets using the Maestro Interface. To ensure the drug safety of these molecules ADME/Tox analysis was also performed.

Key findings: The molecular docking analysis of the 23 novel molecules indicated the efficiency of these derivates against COVID-19. The efficiency of molecules was computed by the summation of the docking score against each target defined as LigE Score and compared against Hydroxycholoquine as a standard. Based on the docking score, the majority of the annomontine derivatives were found to have increased binding affinity with targets as compared to hydroxycholoquine.

Significance: Due to the lack of efficiency, effectiveness, and failure of already repurposed drugs against the COVID-19, the exploration of the novel scaffold that can act as effective treatment is much needed. The current study hence emphasizes the potential of annomontine based-*β*-varboline derivatives as a potential drug candidate against COVID-19.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)00760-X

Early introductions and transmission of SARS-CoV-2 variant B.1.1.7 in the United States

Abstract

The emergence and spread of SARS-CoV-2 lineage B.1.1.7, first detected in the United Kingdom, has become a global public health concern because of its increased transmissibility. Over 2500 COVID-19 cases associated with this variant have been detected in the US since December 2020, but the extent of establishment is relatively unknown. Using travel, genomic, and diagnostic data, it was highlighted that the primary ports of entry for B.1.1.7 in the US were in New York, California, and Florida. Furthermore, we found evidence for many independent B.1.1.7 establishments starting in early December 2020, followed by interstate spread by the end of the month. Finally, we project that B.1.1.7 will be the dominant lineage in many states by mid to late March. Thus, genomic surveillance for B.1.1.7 and other variants urgently needs to be enhanced to better inform the public health response.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00434-7

Bridging animal and clinical research during SARS-CoV-2 pandemic: A new-old challenge

Abstract

Many milestones in medical history rest on animal modeling of human diseases. The SARS-CoV-2 pandemic has evoked a tremendous investigative effort primarily centered on clinical studies. However, several animal SARS-CoV-2/COVID-19 models have been developed and pre-clinical findings aimed at supporting clinical evidence rapidly emerge. In this review, the existing animal models were characterized exposing their relevance and limitations as well as outline their utility in COVID-19 drug and vaccine development. Concurrently, the status of clinical trial research was summarized, and discussed the novel tactics utilized in the largest multi-center trials aiming to accelerate generation of reliable results that may subsequently shape COVID-19 clinical treatment practices. Areas of improvement for animal studies were also highlighted in order to elevate their translational utility. In pandemics, to optimize the use of strained resources

in a short time-frame, optimizing and strengthening the synergy between the preclinical and clinical domains is pivotal.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00084-0/fulltext

Genetic variability in COVID-19-related genes in the Brazilian population

Abstract

SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease (TMPRSS2) to infect human lung cells. Previous studies have suggested that different host ACE2 and TMPRSS2 genetic backgrounds might contribute to differences in the rate of SARS-CoV-2 infection or COVID-19 severity. Recent studies have also shown that variants in 15 genes related to type I interferon immunity to influenza virus might predispose patients toward life-threatening COVID-19 pneumonia. Other genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1, IL6, CTSL, ABO, and FURIN) and HLA alleles have also been implicated in the response to infection with SARS-CoV-2. Currently, Brazil has recorded the third-highest number of COVID-19 cases worldwide. It was aimed to investigate the genetic variation present in COVID-19-related genes in the Brazilian population. 27 Candidate genes and HLA alleles were analyzed in 954 admixed Brazilian exomes. It was used that the information available in two public databases (http://www.bipmed.org and http://abraom.ib.usp.br/) and additional exomes from individuals born in southeast Brazil, the region of the country with the highest number of COVID-19 patients. Variant allele frequencies were compared with the 1000 Genomes Project phase 3 (1KGP) and gnomAD databases. 395 Nonsynonymous variants were detected; of these, 325 were also found in the 1KGP and/or gnomAD. Six of these variants were previously reported to influence the rate of infection or clinical prognosis of COVID-19. The remaining 70 variants were identified exclusively in the Brazilian sample, with a mean allele frequency of 0.0025. *In silico* analysis revealed that seven of these variants are predicted to affect protein function. Furthermore, we identified HLA alleles previously associated with the COVID-19 response at loci DQB1 and DRB1. The results showed genetic variability common to other populations and rare and ultrarare variants exclusively found in the Brazilian population. These findings might lead to differences in the rate of infection or

response to infection by SARS-CoV-2 and should be further investigated in patients with this disease.

Reference

https://www.nature.com/articles/s41439-021-00146-w

Plasma biomarker profiling of PIMS-TS, COVID-19 and SARS-CoV2 seropositive children – a cross-sectional observational study from southern India

Abstract

Background: SARS-CoV-2 infection in children can present with varied clinical phenotypes and understanding the pathogenesis is essential, to inform about the clinical trajectory and management.

Methods: A multiplex immune assay analysis was performed and compared the plasma biomarkers of Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 infection (PIMS-TS), acute COVID-19 infection (COVID-19), SARS-CoV-2 seropositive and control children admitted to a tertiary care children's hospital in Chennai, India. Pro-inflammatory cytokines, chemokines and growth factors were correlated with SARS-CoV-2 clinical phenotypes.

Findings: PIMS-TS children had significantly elevated levels of cytokines, IFNγ, IL-2, TNFα, IL-1α, IFNα, IFNβ, IL-6, IL-15, IL-17A, GM-CSF, IL-10, IL-33 and IL-Ra; elevated chemokines, CCL2, CCL19, CCL20 and CXCL10 and elevated VEGF, Granzyme B and PDL-1 in comparison to COVID-19, seropositive and controls. COVID-19 children had elevated levels of IFNγ, IL-2, TNFα, IL-1α, IFNα, IFNβ, IL-6, IL-17A, IL-10, CCL2, CCL5, CCL11, CXCL10 and VEGF in comparison to seropositive and/or controls. Similarly, seropositive children had elevated levels of IFNγ, IL-2, IL-1α, IFNβ, IL-17A, IL-10, CCL5 and CXCL10 in comparison to control children. Plasma biomarkers in PIMS-TS and COVID-19 children showed a positive correlation with CRP and a negative correlation with the lymphocyte count and sodium levels.

Interpretation: A comprehensive plasma biomarker profile of children with different clinical spectrum of SARS-CoV-2 infection was described from a low- and middle-income country (LMIC) and observed that PIMS-TS is a distinct and unique

immunopathogenic paediatric illness related to SARS-CoV-2 presenting with cytokine storm different from acute COVID-19 infection and other hyperinflammatory conditions

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00110-9/fulltext

The contrasting role of nasopharyngeal angiotensin converting enzyme 2 (ACE2) transcription in SARS-CoV-2 infection: A cross-sectional study of people tested for COVID-19 in British Columbia, Canada

Abstract

Background: Angiotensin converting enzyme 2 (ACE2) protein serves as the host receptor for SARS-CoV-2, with a critical role in viral infection. We aim to understand population level variation of nasopharyngeal ACE2 transcription in people tested for COVID-19 and the relationship between ACE2 transcription and SARS-CoV-2 viral load, while adjusting for expression of: (i) the complementary protease, Transmembrane serine protease 2 (TMPRSS2), (ii) soluble ACE2, (iii) age, and (iv) biological sex. The ACE2 gene was targeted to measure expression of transmembrane and soluble transcripts.

Methods: A cross-sectional study of n = 424 "participants" aged 1–104 years referred for COVID-19 testing was performed in British Columbia, Canada. Patients who tested positive for COVID-19 were matched by age and biological sex to patients who tested negative. Viral load and host gene expression were assessed by quantitative reverse-transcriptase polymerase chain reaction. Bivariate analysis and multiple linear regression were performed to understand the role of nasopharyngeal ACE2 expression in SARS-CoV-2 infection.

Findings: Analysis showed no association between age and nasopharyngeal ACE2 transcription in those who tested negative for COVID-19 (P = 0•092). Mean relative transcription of transmembrane (P = 0•00012) and soluble (P<0•0001) ACE2 isoforms, as well as TMPRSS2 (P<0•0001) was higher in COVID-19-negative participants than COVID--19 positive ones, yielding a negative correlation between targeted host gene expression and positive COVID-19 diagnosis. In bivariate analysis of COVID-19-positive participants, transcription of transmembrane ACE2 positively correlated with SARS-

CoV-2 viral RNA load (B = 0•49, R2=0•14, P<0•0001), transcription of soluble ACE2 negatively correlated (B= -0•85, R2= 0•26, P<0•0001), and no correlation was found with TMPRSS2 transcription (B= -0•042, R2=<0•10, P = 0•69). Multivariable analysis showed that the greatest viral RNA loads were observed in participants with high transmembrane ACE2 transcription (B= 0•89, 95%CI: [0•59 to 1•18]), while transcription of the soluble isoform appears to protect against high viral RNA load in the upper respiratory tract (B= -0•099, 95%CI: [-0•18 to -0•022]).

Interpretation: Nasopharyngeal ACE2 transcription plays a dual, contrasting role in SARS-CoV-2 infection of the upper respiratory tract. Transcription of the transmembrane ACE2 isoform positively correlates, while transcription of the soluble isoform negatively correlates with viral RNA load after adjusting for age, biological sex, and transcription of TMPRSS2.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00109-2/fulltext

Publication Date: Apr 01, 2021

Analysis of SARS-CoV-2 genomic epidemiology reveals disease transmission coupled to variant emergence and allelic variation

Abstract

The spread of SARS-CoV-2 created a pandemic crisis with > 150,000 cumulative cases in > 65 countries within a few months. The reproductive number (R) is a metric to estimate the transmission of a pathogen during an outbreak. Preliminary published estimates were based on the initial outbreak in China. Whole genome sequences (WGS) analysis found mutational variations in the viral genome; however, previous comparisons failed to show a direct relationship between viral genome diversity, transmission, and the epidemic severity. COVID-19 incidences from different countries were modeled over the epidemic curve. Estimates of the instantaneous R (Wallinga and Teunis method) with a short and standard serial interval were done. WGS were used to determine the populations genomic variation and that underpinned creation of the pathogen genome identity (GENI) score, which was merged with the outbreak curve in four distinct phases. Inference of transmission time was based on a mutation rate of 2

mutations/month. R estimates revealed differences in the transmission and variable infection dynamics between and within outbreak progression for each country examined. Outside China, our R estimates observed propagating dynamics indicating that other countries were poised to move to the takeoff and exponential stages. Population density and local temperatures had no clear relationship to the outbreak progression. Integration of incidence data with the GENI score directly predicted increases in cases as the genome variation increased that led to new variants. Integrating the outbreak curve, dynamic R, and SNP variation found a direct association between increasing cases and transmission genome evolution. By defining the epidemic curve into four stages and integrating the instantaneous country-specific R with the GENI score, we directly connected changes in individual outbreaks based on changes in the virus genome via SNPs. This resulted in the ability to forecast potential increases in cases as well as mutations that may defeat PCR screening and the infection process. By using instantaneous R estimations and WGS, outbreak dynamics were defined to be linked to viral mutations, indicating that WGS, as a surveillance tool, is required to predict shifts in each outbreak that will provide actionable decision making information. Integrating epidemiology with genome sequencing and modeling allows for evidence-based disease outbreak tracking with predictive therapeutically valuable insights in near real time.

Reference

https://www.nature.com/articles/s41598-021-86265-4

Neutralization potency of monoclonal antibodies recognizing dominant and subdominant epitopes on SARS-CoV-2 Spike is impacted by the B.1.1.7 variant

Abstract

Interaction of the SARS-CoV-2 Spike receptor binding domain (RBD) with the receptor ACE2 on host cells is essential for viral entry. RBD is the dominant target for neutralizing antibodies, and several neutralizing epitopes on RBD have been molecularly characterized. Analysis of circulating SARS-CoV-2 variants has revealed mutations arising in the RBD, N-terminal domain (NTD) and S2 subunits of Spike. To understand how these mutations affect Spike antigenicity, we isolated and characterized >100 monoclonal antibodies targeting epitopes on RBD, NTD, and S2

from SARS-CoV-2-infected individuals. Approximately 45% showed neutralizing activity, of which ~20% were NTD specific. NTD-specific antibodies formed two distinct groups: the first was highly potent against infectious virus, whereas the second was less potent and displayed glycan-dependant neutralization activity. Mutations present in B.1.1.7 Spike frequently conferred neutralization resistance to NTD-specific antibodies. This work demonstrates that neutralizing antibodies targeting subdominant epitopes should be considered when investigating antigenic drift in emerging variants.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00135-7

Antibody responses to the BNT162b2 mRNA vaccine in individuals previously infected with SARS-CoV-2

Abstract

In a cohort of BNT162b2 (Pfizer–BioNTech) mRNA vaccine recipients (n = 1,090), we observed that spike-specific IgG antibody levels and ACE2 antibody binding inhibition responses elicited by a single vaccine dose in individuals with prior SARS-CoV-2 infection (n = 35) were similar to those seen after two doses of vaccine in individuals without prior infection (n = 228). Post-vaccine symptoms were more prominent for those with prior infection after the first dose, but symptomology was similar between groups after the second dose.

Reference

https://www.nature.com/articles/s41591-021-01325-6

Lead compounds for the development of SARS-CoV-2 3CL protease inhibitors

Abstract

We report the identification of three structurally diverse compounds – compound 4, GC376, and MAC-5576 – as inhibitors of the SARS-CoV-2 3CL protease. Structures of each of these compounds in complex with the protease revealed strategies for further development, as well as general principles for designing SARS-CoV-2 3CL protease inhibitors. These compounds may therefore serve as leads for the basis of building effective SARS-CoV-2 3CL protease inhibitors.

Reference

https://www.nature.com/articles/s41467-021-22362-2

Systems serology detects functionally distinct coronavirus antibody features in children and elderly

Abstract

The hallmarks of COVID-19 are higher pathogenicity and mortality in the elderly compared to children. Examining baseline SARS-CoV-2 cross-reactive immunological responses, induced by circulating human coronaviruses (hCoVs), is needed to understand such divergent clinical outcomes. Here we show analysis of coronavirus antibody responses of pre-pandemic healthy children (n = 89), adults (n = 98), elderly (n = 57), and COVID-19 patients (n = 50) by systems serology. Moderate levels of cross-reactive, but non-neutralizing, SARS-CoV-2 antibodies are detected in pre-pandemic healthy individuals. SARS-CoV-2 antigen-specific Fcγ receptor binding accurately distinguishes COVID-19 patients from healthy individuals, suggesting that SARS-CoV-2 infection induces qualitative changes to antibody Fc, enhancing Fcγ receptor engagement. Higher cross-reactive SARS-CoV-2 IgA and IgG are observed in healthy elderly, while healthy children display elevated SARS-CoV-2 IgM, suggesting that children have fewer hCoV exposures, resulting in less-experienced but more polyreactive humoral immunity. Age-dependent analysis of COVID-19 patients, confirms elevated class-switched antibodies in elderly, while children have stronger Fc responses which we demonstrate are functionally different. These insights will inform COVID-19 vaccination strategies, improved serological diagnostics and therapeutics.

Reference

https://www.nature.com/articles/s41467-021-22236-7

Pathophysiology of SARS-CoV-2: the Mount Sinai COVID-19 autopsy experience

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its associated clinical syndrome COVID-19 are causing overwhelming morbidity and mortality around the globe and disproportionately affected New York City between March and May 2020. Here, we report on the first 100 COVID-19-positive autopsies performed at the Mount

Sinai Hospital in New York City. Autopsies revealed large pulmonary emboli in six cases. Diffuse alveolar damage was present in over 90% of cases. We also report microthrombi in multiple organ systems including the brain, as well as hemophagocytosis. We additionally provide electron microscopic evidence of the presence of the virus in our samples. Laboratory results of our COVID-19 cohort disclose elevated inflammatory markers, abnormal coagulation values, and elevated cytokines IL-6, IL-8, and TNFα. The autopsy series of COVID-19-positive patients reveals that this disease, often conceptualized as a primarily respiratory viral illness, has widespread effects in the body including hypercoagulability, a hyperinflammatory state, and endothelial dysfunction. Targeting of these multisystemic pathways could lead to new treatment avenues as well as combination therapies against SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41379-021-00793-y

Modeling the first wave of Covid-19 pandemic in the Republic of Cyprus

Abstract

Different data analytic methodologies were presented that have been applied in order to understand the evolution of the first wave of the Coronavirus disease 2019 in the Republic of Cyprus and the effect of different intervention measures that have been taken by the government. Change point detection has been used in order to estimate the number and locations of changes in the behaviour of the collected data. Count time series methods have been employed to provide short term projections and a number of various compartmental models have been fitted to the data providing with long term projections on the pandemic's evolution and allowing for the estimation of the effective reproduction number.

Reference

https://www.nature.com/articles/s41598-021-86606-3

PaO₂/FiO₂ and IL-6 are risk factors of mortality for intensive care COVID-19 patients

Abstract

To identify the risk factors of mortality for the coronavirus disease 19 (COVID-19) patients admitted to intensive care units (ICUs) through a retrospective analysis. The demographic, clinical, laboratory, and chest imaging data of patients admitted to the ICU of Huoshenshan Hospital from February 10 to April 10, 2020 were retrospectively analyzed. Student's t-test and Chi-square test were used to compare the continuous and categorical variables, respectively. The logistic regression model was employed to ascertain the risk factors of mortality. This retrospective study involved 123 patients, including 64 dead and 59 survivors. Among them, 57 people were tested for interleukin-6 (IL-6) (20 died and 37 survived). In all included patients, the oxygenation index (PaO2/FiO2) was identified as an independent risk factor (odd ratio [OR] = 0.96, 95% confidence interval [CI]: 0.928–0.994, p = 0.021). The area under the curve (AUC) was 0.895 (95% CI: 0.826–0.943, p < 0.0001). Among the patients tested for IL-6, the PaO2/FiO2 (OR = 0.955, 95%CI: 0.915–0.996, p = 0.032) and IL-6 (OR = 1.013, 95%CI: 1.001–1.025, p = 0.028) were identified as independent risk factors. The AUC was 0.9 (95% CI: 0.791–0.964, p < 0.0001) for IL-6 and 0.865 (95% CI: 0.748–0.941, p < 0.0001) for PaO₂/FiO₂. PaO₂/FiO₂ and IL-6 could potentially serve as independent risk factors for predicting death in COVID-19 patients requiring intensive care.

Reference

https://www.nature.com/articles/s41598-021-86676-3

Association between pre-existing respiratory disease and its treatment, and severe COVID-19: A population cohort study

Abstract

Background: Previous studies suggested that the prevalence of chronic respiratory disease in patients hospitalized with COVID-19 was lower than its prevalence in the general population. The aim of this study was to assess whether chronic lung disease or use of inhaled corticosteroids (ICS) affects the risk of contracting severe COVID-19.

Methods: In this population cohort study, records from 1205 general practices in England that contribute to the QResearch database were linked to Public Health England's database of SARS-CoV-2 testing and English hospital admissions, intensive care unit (ICU) admissions, and deaths for COVID-19. All patients aged 20 years and older who were registered with one of the 1205 general practices on Jan 24, 2020, were included in this study. With Cox regression, we examined the risks of COVID-19-related hospitalization, admission to ICU, and death in relation to respiratory disease and use of ICS, adjusting for demographic and socioeconomic status and comorbidities associated with severe COVID-19.

Findings: Between Jan 24 and April 30, 2020, 8 256 161 people were included in the cohort and observed, of whom 14 479 (0·2%) were admitted to hospital with COVID-19, 1542 (<0·1%) were admitted to ICU, and 5956 (0·1%) died. People with some respiratory diseases were at an increased risk of hospitalisation (chronic obstructive pulmonary disease [COPD] hazard ratio [HR] 1·54 [95% CI 1·45–1·63], asthma 1·18 [1·13–1·24], severe asthma 1·29 [1·22–1·37; people on three or more current asthma medications], bronchiectasis 1·34 [1·20–1·50], sarcoidosis 1·36 [1·10–1·68], extrinsic allergic alveolitis 1·35 [0·82–2·21], idiopathic pulmonary fibrosis 1·59 [1·30–1·95], other interstitial lung disease 1·66 [1·30–2·12], and lung cancer 2·24 [1·89–2·65]) and death (COPD 1·54 [1·42–1·67], asthma 0·99 [0·91–1·07], severe asthma 1·08 [0·98–1·19], bronchiectasis 1·12 [0·94–1·33], sarcoidosis 1·41 [0·99–1·99), extrinsic allergic alveolitis 1·56 [0·78–3·13], idiopathic pulmonary fibrosis 1·47 [1·12–1·92], other interstitial lung disease 2·05 [1·49–2·81], and lung cancer 1·77 [1·37–2·29]) due to COVID-19 compared with those without these diseases. Admission to ICU was rare, but the HR for people with asthma was 1·08 (0·93–1·25) and severe asthma was 1·30 (1·08–1·58). In a post-hoc analysis, relative risks of severe COVID-19 in people with respiratory disease were similar before and after shielding was introduced on March 23, 2020. In another post-hoc analysis, people with two or more prescriptions for ICS in the 150 days before study start were at a slightly higher risk of severe COVID-19 compared with all other individuals (ie, no or one ICS prescription): HR 1·13 (1·03–1·23) for hospitalisation, 1·63 (1·18–2·24) for ICU admission, and 1·15 (1·01–1·31) for death.

Interpretation: The risk of severe COVID-19 in people with asthma is relatively small. People with COPD and interstitial lung disease appear to have a modestly increased

risk of severe disease, but their risk of death from COVID-19 at the height of the epidemic was mostly far lower than the ordinary risk of death from any cause. Use of inhaled steroids might be associated with a modestly increased risk of severe COVID-19.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00095-3/fulltext

CORRESPONDANCE

COVID-19 vaccines in high-risk ethnic groups

Viruses Black, Asian, and minority ethnic communities worldwide have a disproportionate risk of severe COVID-19. In the UK, as of May 19, 2020, 36% of critically ill patients with COVID-19 requiring intensive care were from Black, Asian, or minority ethnic groups. According to Public Health England, the mortality risk from COVID-19, after accounting for sex, age, deprivation score, and geographical region, is double in Bangladeshi people and up to 50% higher in Black and south Asian people compared with White British people. This finding contrasts with age-adjusted all-cause mortality from previous years, which was lower in Asian and Black people than in White British people. These data imply that COVID-19 has more serious effects in Black and Asian people. The ethnic groups most affected by COVID-19 are under-represented in the COVID-19 vaccine trial data published so far. Despite efforts to encourage participation from Black, Asian, and minority ethnic groups, of the 552 participants in the phase 2/3 Oxford–AstraZeneca trial (based in Southampton and Oxford, UK), only one participant was Black and 19 were Asian. Large-scale trials also have a smaller proportion of minority groups compared with the populations sampled (appendix). For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00624-3/fulltext

COMMENT

Distinguishing the real from the hyperglycaemia: Does COVID-19 induce diabetes?

Reports noting the deleterious impact of diabetes on people infected with SARS-CoV-2 arose in the earliest weeks of the COVID-19 pandemic. Over time, obesity, hyperglycaemia, type-2 diabetes, and type-1 diabetes have each been reported to be associated with increased COVID-19 morbidity and mortality, as well as expanded therapeutic needs during hospital admission. More controversial, however, has been the question of whether SARS-CoV-2 specifically is, in and of itself, capable of inducing diabetes; and, if so, in which of its forms. Beyond this question, hypotheses abound as to whether such a disease-provoking activity (if it exists) is due to acceleration of an underlying and potentially pathogenic feature associated with traditional diabetes pathogenesis (ie, type 1 or type 2 diabetes), or incitement of a new variant of diabetes involving either acute β-cell destruction or impairment of insulin secretion. What does seem clear is that SARS-CoV-2 infection, like many other infections, has the ability to induce hyperglycaemia in people without a previous diagnosis of diabetes, be it through diminished insulin secretion, enhanced release of counter-regulatory hormones, excessive hepatic glucose production, impaired glucose disposal, or a combination of these factors.

Diabetes onset has been noted, in case reports, to occur simultaneously with acute SARS-CoV-2 infection or in the weeks to months following recovery from the infection. However, findings from epidemiological studies have been conflicting: for example, work from the UK showed an increase in type-1 diabetes incidence during the COVID-19 pandemic, whereas a larger study from Germany showed no such change, although neither study confirmed COVID-19 diagnosis or accounted for viral load as a potential contributing factor. Recent summaries of the available scientific literature suggest that a causal association between COVID-19 and the onset of type-1 diabetes is unlikely, but there is need for further investigation. Indeed, taken together, the available information

provides a strong rationale for the recently formed CoviDiab Registry, which seeks to proactively address such questions. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00087-5/fulltext

Short-term safety of the BNT162b2 mRNA COVID-19 vaccine in patients with cancer treated with immune checkpoint inhibitors

Viruses On Dec 20, 2020, the Israeli Ministry of Health launched a national COVID-19 vaccination campaign that aimed to rapidly vaccinate all high-risk individuals by the end of January, 2021, using the Pfizer BNT162b2 mRNA vaccine. Vaccines were readily available and free of charge. Patients with cancer who have been treated with systemic anticancer therapy are at a significantly increased risk of mortality from COVID-19, and therefore should be considered as a high-priority group for COVID-19 vaccination.

Because the pivotal vaccination study for BNT162b2 included only healthy individuals or those with stable chronic medical conditions, a major obstacle faced by the Ministry of Health and by the National Council for the Prevention Diagnosis and Treatment of Malignant Disease was an absence of data regarding the safety and efficacy of the vaccine in patients with cancer who have been or are being treated. Based on available knowledge regarding other routinely used vaccines (*eg*, the influenza vaccine) the Ministry of Health recommended vaccination of all patients with cancer. However, some experts at the National Council raised concerns regarding the ability of the vaccine to provoke or enhance immune-related side-effects in patients who are being treated with immune checkpoint inhibitors. Thus, the Ministry of Health left the decision about vaccinating individuals treated with immune checkpoint inhibitors to the discretion of their treating physician. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(21)00155-8/fulltext

REPORT

Hypoxic and pharmacological activation of HIFs inhibits SARS-CoV-2 infection of lung epithelial cells

Abstract

COVID-19, caused by the novel coronavirus SARS-CoV-2, is a global health issue with more than 2 million fatalities to date. Viral replication is shaped by the cellular microenvironment and one important factor to consider is oxygen tension, where hypoxia inducible factor (HIF) regulates transcriptional responses to hypoxia. SARS-CoV-2 primarily infects cells of the respiratory tract, entering *via* its Spike glycoprotein binding to angiotensin-converting enzyme (ACE2). It was demonstrated that hypoxia and the HIF prolyl hydroxylase inhibitor Roxadustat reduce ACE2 expression and inhibit SARS-CoV-2 entry and replication in lung epithelial cells *via* a HIF-1α dependent pathway. Hypoxia and Roxadustat inhibit SARS-CoV-2 RNA replication showing that post-entry steps in the viral life cycle are oxygen-sensitive. This study highlights the importance of HIF signalling in regulating multiple aspects of SARS-CoV-2 infection and raises the potential use of HIF prolyl hydroxylase inhibitors in the prevention or treatment of COVID-19.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00334-X

SARS-CoV-2 mutations acquired in mink reduce antibody-mediated neutralization

Abstract

Transmission of SARS-CoV-2 from humans to farmed mink was observed in Europe and the US. In the infected animals viral variants arose that harbored mutations in the spike (S) protein, the target of neutralizing antibodies, and these variants were transmitted back to humans. This raised concerns that mink might become a constant source of human infection with SARS-CoV-2 variants associated with an increased

threat to human health and resulted in mass culling of mink. Here, it was reported that mutations frequently found in the S proteins of SARS-CoV-2 from mink were mostly compatible with efficient entry into human cells and its inhibition by soluble ACE2. In contrast, mutation Y453F reduced neutralization by an antibody with emergency use authorization for COVID-19 therapy and by sera/plasma from COVID-19 patients. These results suggest that antibody responses induced upon infection or certain antibodies used for treatment might offer insufficient protection against SARS-CoV-2 variants from mink.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00331-4

X-ray screening identifies active site and allosteric inhibitors of SARS-CoV-2 main protease

Abstract

The coronavirus disease (COVID-19) caused by SARS-CoV-2 is creating tremendous human suffering. To date, no effective drug is available to directly treat the disease. In a search for a drug against COVID-19, a high-throughput X-ray crystallographic screen of two repurposing drug libraries against the SARS-CoV-2 main protease (Mpro) were performed, which is essential for viral replication. In contrast to commonly applied X-ray fragment screening experiments with molecules of low complexity, the screen tested already approved drugs and drugs in clinical trials. From the three-dimensional protein structures, we identified 37 compounds that bind to Mpro. In subsequent cell-based viral reduction assays, one peptidomimetic and six non-peptidic compounds showed antiviral activity at non-toxic concentrations. Two allosteric binding sites representing attractive targets for drug development against SARS-CoV-2 were identified.

Reference

https://science.sciencemag.org/content/early/2021/03/31/science.abf7945

Rapid decline of neutralizing antibodies is associated with decay of IgM in adults recovered from mild COVID-19 disease

Abstract

The fate of protective immunity following mild SARS-CoV-2 infection remains ill defined. Here we characterize antibody responses in a cohort of participants recovered from mild SARS-CoV-2 infection with follow up to 6 months. IgA, IgM, and IgG binding and avidity to viral antigens were measured and assess neutralizing antibody responses over time. Further, the effect of fever, gender, age, and time was correlated since symptom onset with antibody responses. It was observed that total anti-*S* trimer, anti-RBD, and anti-NP IgG are relatively stable over 6 months of follow-up and anti-S and anti-RBD avidity increases over time, and that fever is associated with higher levels of antibodies. However, neutralizing antibody responses rapidly decay and are strongly associated with declines in IgM levels. Thus, while total antibody against SARS-CoV-2 may persist, functional antibody, particularly IgM, is rapidly lost. These observations have implications for the duration of protective immunity following mild SARS-CoV-2 infection.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00069-0

Complete map of SARS-CoV-2 RBD mutations that escape the monoclonal antibody LY-CoV555 and its cocktail with LY-CoV016

Abstract

Monoclonal antibodies and antibody cocktails are a promising therapeutic and prophylaxis for coronavirus disease 2019 (COVID-19). However, ongoing evolution of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) can render monoclonal antibodies ineffective. Here, all of the mutations were completely mapped to the SARS-CoV-2 spike receptor-binding domain (RBD) that escape binding by a leading monoclonal antibody, LY-CoV555, and its cocktail combination with LY-CoV016. Individual mutations that escape binding by each antibody are combined in the circulating B.1.351 and P.1 SARS-CoV-2 lineages (E484K escapes LY-CoV555, K417N/T escapes LY-CoV016). In addition, the L452R mutation in the B.1.429 lineage

escapes LY-CoV555. Furthermore, single amino acid changes were identified that escape the combined LY-CoV555+LY-CoV016 cocktail. It was suggested that future efforts diversify the epitopes targeted by antibodies and antibody cocktails to make them more resilient to the antigenic evolution of SARS-CoV-2.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00071-9

Establishment of a reverse genetics system for SARS-CoV-2 using circular polymerase extension reaction

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified as the causative agent of coronavirus disease 2019 (COVID-19). Although multiple mutations have been observed in SARS-CoV-2, functional analysis of each mutation of SARS-CoV-2 has been limited by the lack of convenient mutagenesis methods. In this study, we establish a PCR-based, bacterium-free method to generate SARS-CoV-2 infectious clones. Recombinant SARS-CoV-2 could be rescued at high titer with high accuracy after assembling 10 SARS-CoV-2 cDNA fragments by circular polymerase extension reaction (CPER) and transfection of the resulting circular genome into susceptible cells. The construction of infectious clones for reporter viruses and mutant viruses could be completed in two simple steps: introduction of reporter genes or mutations into the desirable DNA fragments ($\sim$5,000 base pairs) by PCR and assembly of the DNA fragments by CPER. This reverse genetics system may potentially advance further understanding of SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00328-4

PERSPECTIVE

Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination

When vaccines are in limited supply, expanding the number of people who receive some vaccine, such as by halving doses or increasing the interval between doses, can reduce disease and mortality compared with concentrating available vaccine doses in a subset of the population. A corollary of such dose-sparing strategies is that the vaccinated individuals may have less protective immunity. Concerns have been raised that expanding the fraction of the population with partial immunity to SARS-CoV-2 could increase selection for vaccine-escape variants, ultimately undermining vaccine effectiveness. It was argued that, although this is possible, preliminary evidence instead suggests such strategies should slow the rate of viral escape from vaccine or naturally induced immunity. As long as vaccination provides some protection against escape variants, the corresponding reduction in prevalence and incidence should reduce the rate at which new variants are generated and the speed of adaptation. Because there is little evidence of efficient immune selection of SARS-CoV-2 during typical infections, these population-level effects are likely to dominate vaccine-induced evolution.

Reference

https://www.nature.com/articles/s41577-021-00544-9