

COVID-19

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RESEARCH PUBLICATIONS

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SARS-CoV-2 shifting transmission dynamics and hidden reservoirs potentially limit efficacy of public health interventions in Italy

Abstract

SARS-CoV-2 transmission dynamics were investigated in Italy, one of the countries hit hardest by the pandemic, using phylodynamic analysis of viral genetic and epidemiological data. The co-circulation of multiple SARS-CoV-2 lineages was observed over time, which were linked to multiple importations and characterized by large transmission clusters concomitant with a high number of infections. Subsequent implementation of a three-phase nationwide lockdown strategy greatly reduced infection numbers and hospitalizations. Yet evidence of sustained viral spread was present among sporadic clusters acting as “hidden reservoirs” during summer 2020. Mathematical modelling shows that increased mobility among residents eventually catalyzed the coalescence of such clusters, thus driving up the number of infections and initiating a new epidemic wave. The results suggest that the efficacy of public health interventions is, ultimately, limited by the size and structure of epidemic reservoirs, which may warrant prioritization during vaccine deployment.

Reference

<https://www.nature.com/articles/s42003-021-02025-0>

Evidence of a dysregulated vitamin D endocrine system in SARS-CoV-2 infected patient's lung cells

Abstract

Although a defective vitamin D endocrine system has been widely suspected to be associated in SARS-CoV-2 pathobiology, the status of the vitamin D endocrine system and vitamin D-modulated genes in lung cells of patients infected with SARS-CoV-2 remains unknown. To understand the significance of the vitamin D endocrine system in SARS-CoV-2 pathobiology, computational approaches were applied to transcriptomic datasets from bronchoalveolar lavage fluid (BALF) cells of such patients or healthy individuals. Levels of vitamin D receptor, retinoid X receptor, and CYP27A1 in BALF cells of patients infected with SARS-CoV-2 were found to be reduced. Additionally, 107 differentially expressed, predominantly downregulated genes, as potentially modulated by vitamin D endocrine system, were identified in transcriptomic datasets from patient's cells. Further analysis of differentially expressed genes provided eight novel genes with a conserved motif with vitamin D-responsive elements, implying the role of both direct and indirect mechanisms of gene expression by the dysregulated vitamin D endocrine system in SARS-CoV-2-infected cells. Protein–protein interaction network of differentially expressed vitamin D-modulated genes were enriched in the immune system, NF- κ B/cytokine signaling, and cell cycle regulation as top predicted pathways that might be affected in the cells of such patients. In brief, the results presented here provide computational evidence to implicate a dysregulated vitamin D endocrine system in the pathobiology of SARS-CoV-2 infection.

Reference

<https://www.nature.com/articles/s41598-021-87703-z>

The construction and visualization of the transmission networks for COVID-19: A potential solution for contact tracing and assessments of epidemics

Abstract

The WHO has described coronavirus disease 2019 (COVID-19) as a pandemic due to the speed and scale of its transmission. Without effective interventions, the rapidly increasing number of COVID-19 cases would greatly increase the burden of clinical

treatments. Identifying the transmission sources and pathways is of vital importance to block transmission and allocate limited public health resources. According to the relationships among cases, we constructed disease transmission network graphs for the COVID-19 epidemic through a visualization technique based on individual reports of epidemiological data. We proposed an analysis strategy of the transmission network with the epidemiological data in Tianjin and Chengdu. The transmission networks showed different transmission characteristics. In Tianjin, an imported case of COVID-19 can produce an average of 2.9 secondary infections and ultimately produce as many as 4 generations of infections, with a maximum of 6 cases being generated before the imported case is identified. In Chengdu, 45 noninformative cases and 24 cases with vague exposure information made accurate information about the transmission network difficult to provide. The proposed analysis framework of visualized transmission networks can trace the transmission source and contacts, assess the current situation of transmission and prevention, and provide evidence for the global response and control of the COVID-19 pandemic.

Reference

<https://www.nature.com/articles/s41598-021-87802-x>

The pathogenic role of epithelial and endothelial cells in early-phase COVID-19 pneumonia: Victims and partners in crime

Abstract

Current understanding of the complex pathogenesis of COVID-19 interstitial pneumonia pathogenesis in the light of biopsies carried out in early/moderate phase and histology data obtained at postmortem analysis is discussed. In autopsies the most observed pattern is diffuse alveolar damage with alveolar-epithelial type-II cell hyperplasia, hyaline membranes, and frequent thromboembolic disease. However, these observations cannot explain some clinical, radiological and physiopathological features observed in SARS-CoV-2 interstitial pneumonia, including the occurrence of vascular enlargement on CT and preserved lung compliance in subjects even presenting with or developing respiratory failure. Histological investigation on early-phase pneumonia on perioperative samples and lung biopsies revealed peculiar morphological and morpho-phenotypical changes including hyper-expression of phosphorylated STAT3 and

immune checkpoint molecules (PD-L1 and IDO) in alveolar-epithelial and endothelial cells. These features might explain in part these discrepancies.

Reference

<https://www.nature.com/articles/s41379-021-00808-8>

RANDGAN: Randomized generative adversarial network for detection of COVID-19 in chest X-ray

Abstract

COVID-19 spread across the globe at an immense rate and has left healthcare systems incapacitated to diagnose and test patients at the needed rate. Studies have shown promising results for detection of COVID-19 from viral bacterial pneumonia in chest X-rays. Automation of COVID-19 testing using medical images can speed up the testing process of patients where health care systems lack sufficient numbers of the reverse-transcription polymerase chain reaction tests. Supervised deep learning models such as convolutional neural networks need enough labeled data for all classes to correctly learn the task of detection. Gathering labeled data is a cumbersome task and requires time and resources which could further strain health care systems and radiologists at the early stages of a pandemic such as COVID-19. In this study, we propose a randomized generative adversarial network (RANDGAN) that detects images of an unknown class (COVID-19) from known and labelled classes (Normal and Viral Pneumonia) without the need for labels and training data from the unknown class of images (COVID-19). We used the largest publicly available COVID-19 chest X-ray dataset, COVIDx, which is comprised of Normal, Pneumonia, and COVID-19 images from multiple public databases. In this work, we use transfer learning to segment the lungs in the COVIDx dataset. Next, we show why segmentation of the region of interest (lungs) is vital to correctly learn the task of classification, specifically in datasets that contain images from different resources as it is the case for the COVIDx dataset. Finally, we show improved results in detection of COVID-19 cases using our generative model (RANDGAN) compared to conventional generative adversarial networks for anomaly detection in medical images, improving the area under the ROC curve from 0.71 to 0.77.

Reference

<https://www.nature.com/articles/s41598-021-87994-2>

Publication Date: Apr 20, 2021

Transmission, infectivity, and neutralization of a spike L452R SARS-CoV-2 variant

Abstract

An emerging SARS-CoV-2 variant was identified by viral whole-genome sequencing of 2,172 nasal/nasopharyngeal swab samples from 44 counties in California, a state in the Western United States. Named B.1.427/B.1.429 to denote its 2 lineages, the variant emerged in May 2020 and increased from 0% to >50% of sequenced cases from September 2020 to January 2021, showing 18.6-24% increased transmissibility relative to wild-type circulating strains. The variant carries 3 mutations in the spike protein, including an L452R substitution. 2-Fold increased was found in B.1.427/B.1.429 viral shedding in vivo and increased L452R pseudovirus infection of cell cultures and lung organoids, albeit decreased relative to pseudoviruses carrying the N501Y mutation common to variants B.1.1.7, B.1.351, and P.1. Antibody neutralization assays revealed 4.0 to 6.7-fold and 2.0-fold decreases in neutralizing titers from convalescent patients and vaccine recipients, respectively. The increased prevalence of a more transmissible variant in California exhibiting decreased antibody neutralization warrants further investigation.

Reference

[https://www.cell.com/cell/fulltext/S0092-8674\(21\)00505-5](https://www.cell.com/cell/fulltext/S0092-8674(21)00505-5)

SARS-CoV-2 spike protein dictates syncytium-mediated lymphocyte elimination

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus is highly contagious and causes lymphocytopenia, but the underlying mechanisms are poorly understood. We demonstrate here that heterotypic cell-in-cell structures with lymphocytes inside multinucleate syncytia are prevalent in the lung tissues of coronavirus disease 2019 (COVID-19) patients. These unique cellular structures are a direct result of SARS-CoV-2 infection, as the expression of the SARS-CoV-2 spike

glycoprotein is sufficient to induce a rapid (~45.1 nm/s) membrane fusion to produce syncytium, which could readily internalize multiple lines of lymphocytes to form typical cell-in-cell structures, remarkably leading to the death of internalized cells. This membrane fusion is dictated by a bi-arginine motif within the polybasic S1/S2 cleavage site, which is frequently present in the surface glycoprotein of most highly contagious viruses. Moreover, candidate anti-viral drugs could efficiently inhibit spike glycoprotein processing, membrane fusion, and cell-in-cell formation. Together, we delineate a molecular and cellular rationale for SARS-CoV-2 pathogenesis and identify novel targets for COVID-19 therapy.

Reference

<https://www.nature.com/articles/s41418-021-00782-3>

Sensitive detection of SARS-CoV-2 seroconversion by flow cytometry reveals the presence of nucleoprotein-reactive antibodies in unexposed individuals

Abstract

There is an ongoing need of developing sensitive and specific methods for the determination of SARS-CoV-2 seroconversion. For this purpose, we have developed a multiplexed flow cytometric bead array (C19BA) that allows the identification of IgG and IgM antibodies against three immunogenic proteins simultaneously: the spike receptor-binding domain (RBD), the spike protein subunit 1 (S1) and the nucleoprotein (N). Using different cohorts of samples collected before and after the pandemic, we show that this assay is more sensitive than ELISAs performed in our laboratory. The combination of three viral antigens allows for the interrogation of full seroconversion. Importantly, we have detected N-reactive antibodies in COVID-19-negative individuals. Here we present an immunoassay that can be easily implemented and has superior potential to detect low antibody titers compared to current gold standard serology methods.

Reference

<https://www.nature.com/articles/s42003-021-02011-6>

Identification of PBMC-based molecular signature associational with COVID-19 disease severity

Abstract

The longevity of COVID-19 as a global pandemic, and the devastating effects it has had on certain subsets of individuals thus far has highlighted the importance of identifying blood-based biomarkers associated with disease severity. We employed computational and transcriptome analyses of publicly available datasets from PBMCs from 126 patients with COVID-19 admitted to ICU (n=50), COVID-19 not admitted to ICU (n=50), non-COVID-19 admitted to ICU (n=16) and non-COVID-19 not admitted to ICU (n=10), and utilized the Gencode V33 assembly to analyze protein coding mRNA and long noncoding RNA (lncRNA) transcriptomes in the context of disease severity. Our data identified several aberrantly expressed mRNA and lncRNA based biomarkers associated with SARS-CoV-2 severity, which in turn significantly affected canonical, upstream, and disease functions in each group of patients. Immune, interferon, and antiviral responses were severely suppressed in COVID-19 admitted to ICU versus COVID-19 who were not admitted to ICU. Our data suggests a possible therapeutic approach for severe COVID-19 through administration of interferon therapy. Delving further into these biomarkers, roles and their implications on the onset and disease severity of COVID-19 could play a crucial role in patient stratification and identifying varied therapeutic options with diverse clinical implications.

Reference

[https://www.cell.com/heliyon/fulltext/S2405-8440\(21\)00969-5](https://www.cell.com/heliyon/fulltext/S2405-8440(21)00969-5)

An intra-host SARS-CoV-2 dynamics model to assess testing and quarantine strategies for incoming travelers, contact person management and de-isolation

Abstract

Non-pharmaceutical interventions (NPIs) remain decisive tools to contain SARS-CoV-2. Strategies that combine NPIs with testing may improve efficacy and shorten quarantine durations. We develop a stochastic within-host model of SARS-CoV-2 that captures temporal changes in test sensitivities, incubation- and infectious periods. We use the

model to simulate relative transmission risk for (i) isolation of symptomatic individuals, (ii) contact person management and (iii) quarantine of incoming travelers.

It was estimated that testing travelers at entry reduces transmission risks to 21.3% ([20.7, 23.9], PCR) and 27.9% ([27.1, 31.1], rapid diagnostic tests; RDT), compared to unrestricted entry. We calculated that 4 (PCR) vs. 5 (RDT) days pre-test quarantine are non-inferior to a 10 days quarantine for incoming travelers and that 8 (PCR) vs. 10 (RDT) days of pre-test quarantine are non-inferior to 14 days post-exposure quarantine. De-isolation of infected individuals 13 days after symptom onset may reduce the transmission risk to <0.2% [<0.01, 6.0].

Reference

[https://www.cell.com/patterns/fulltext/S2666-3899\(21\)00088-X](https://www.cell.com/patterns/fulltext/S2666-3899(21)00088-X)

Asymptomatic and symptomatic SARS-CoV-2 infections elicit polyfunctional antibodies

Abstract

A large proportion of SARS-CoV-2 infected individuals remains asymptomatic. Little is known about the extent and quality of their antiviral humoral response. Here, we analyze antibody functions in 52 asymptomatic infected individuals, 119 mild and 21 hospitalized COVID-19 patients. We measured anti-Spike IgG, IgA and IgM levels with the S-Flow assay and map IgG-targeted epitopes by Luminex. We also evaluated neutralization, complement deposition and Antibody-Dependent Cellular Cytotoxicity (ADCC) using replication-competent SARS-CoV-2 or reporter cell systems. We show that COVID-19 sera mediate complement deposition and kill infected cells by ADCC. Sera from asymptomatic individuals neutralize the virus, activate ADCC and trigger complement deposition. Antibody levels and functions are lower in asymptomatic individuals than in symptomatic cases. Antibody functions are correlated, regardless of disease severity. Longitudinal samplings show that antibody functions follow similar kinetics of induction and contraction. Overall, asymptomatic SARS-CoV-2 infection elicits polyfunctional antibodies neutralizing the virus and targeting infected cells.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00103-8](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00103-8)

Nanotraps for the containment and clearance of SARS-CoV-2

Abstract

SARS-CoV-2 enters host cells through its viral spike protein binding to angiotensin-converting enzyme 2 (ACE2) receptors on the host cells. Here, we show that functionalized nanoparticles, termed “Nanotraps,” completely inhibited SARS-CoV-2 infection by blocking the interaction between the spike protein of SARS-CoV-2 and the ACE2 of host cells. The liposomal-based Nanotrap surfaces were functionalized with either recombinant ACE2 proteins or anti-SARS-CoV-2 neutralizing antibodies and phagocytosis-specific phosphatidylserines. The Nanotraps effectively captured SARS-CoV-2 and completely blocked SARS-CoV-2 infection to ACE2-expressing human cell lines and primary lung cells; the phosphatidylserine triggered subsequent phagocytosis of the virus-bound, biodegradable Nanotraps by macrophages, leading to the clearance of pseudotyped and authentic virus *in vitro*. Furthermore, the Nanotraps demonstrated an excellent biosafety profile *in vitro* and *in vivo*. Finally, the Nanotraps inhibited pseudotyped SARS-CoV-2 infection in live human lungs in an *ex vivo* lung perfusion system. In summary, Nanotraps represent a new nanomedicine for the inhibition of SARS-CoV-2 infection.

Reference

[https://www.cell.com/matter/fulltext/S2590-2385\(21\)00166-1](https://www.cell.com/matter/fulltext/S2590-2385(21)00166-1)

Immunogenicity and efficacy of mRNA COVID-19 vaccine MRT5500 in preclinical animal models

Abstract

Emergency use authorization of COVID vaccines has brought hope to mitigate pandemic of coronavirus disease 2019 (COVID-19). However, there remains a need for additional effective vaccines to meet the global demand and address the potential new viral variants. mRNA technologies offer an expeditious path alternative to traditional vaccine approaches. Here we describe the efforts to utilize an mRNA platform for rational design and evaluations of mRNA vaccine candidates based on the spike (S) glycoprotein of SARS-CoV-2. Several mRNA constructs of S-protein, including wild

type, a pre-fusion stabilized mutant (2P), a furin cleavage-site mutant (GSAS) and a double mutant form (2P/GSAS), as well as others, were tested in animal models for their capacity to elicit neutralizing antibodies (nAbs). The lead 2P/GSAS candidate was further assessed in dose-ranging studies in mice and Cynomolgus macaques, and for efficacy in a Syrian golden hamster model. The selected 2P/GSAS vaccine formulation, designated MRT5500, elicited potent nAbs as measured in neutralization assays in all three preclinical models and more importantly, protected against SARS-CoV-2-induced weight loss and lung pathology in hamsters. In addition, MRT5500 elicited TH1-biased responses in both mouse and non-human primate (NHP), thus alleviating a hypothetical concern of potential vaccine-associated enhanced respiratory diseases known associated with TH2-biased responses. These data position MRT5500 as a viable vaccine candidate for entering clinical development.

Reference

<https://www.nature.com/articles/s41541-021-00324-5>

Neutralizing monoclonal antibodies for treatment of COVID-19

Abstract

Several neutralizing monoclonal antibodies (mAbs) to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed and are now under evaluation in clinical trials. With the US Food and Drug Administration recently granting emergency use authorizations for neutralizing mAbs in non-hospitalized patients with mild-to-moderate COVID-19, there is an urgent need to discuss the broader potential of these novel therapies and to develop strategies to deploy them effectively in clinical practice, given limited initial availability. Here, we review the precedent for passive immunization and lessons learned from using antibody therapies for viral infections such as respiratory syncytial virus, Ebola virus and SARS-CoV infections. We then focus on the deployment of convalescent plasma and neutralizing mAbs for treatment of SARS-CoV-2. We review specific clinical questions, including the rationale for stratification of patients, potential biomarkers, known risk factors and temporal considerations for optimal clinical use. To answer these questions, there is a need to understand factors such as the kinetics of viral load and its correlation with clinical outcomes, endogenous

antibody responses, pharmacokinetic properties of neutralizing mAbs and the potential benefit of combining antibodies to defend against emerging viral variants.

Reference

<https://www.nature.com/articles/s41577-021-00542-x>

Adjuvanting a subunit COVID-19 vaccine to induce protective immunity

Abstract

The development of a portfolio of COVID-19 vaccines to vaccinate the global population remains an urgent public health imperative. Here the capacity of a subunit vaccine was demonstrated, comprising the SARS-CoV-2 spike receptor binding domain displayed on a protein nanoparticle (RBD-NP), to stimulate robust and durable neutralizing antibody (nAb) responses and protection against SARS-CoV-2 in non-human primates. Five adjuvants were evaluated including Essai O/W 1849101, a squalene-in-water emulsion; AS03, an alpha-tocopherol-containing oil-in-water emulsion; AS37, a TLR-7 agonist adsorbed to Alum; CpG1018-Alum, a TLR-9 agonist formulated in Alum; and Alum. RBD-NP immunization with AS03, CpG1018-Alum, AS37 or Alum induced substantial nAb and CD4 T cell responses, and conferred protection against SARS-CoV-2 infection in the pharynx, nares and bronchoalveolar lavage. Live-virus nAb response was maintained up to 180 days post-vaccination with RBD/AS03, and correlated with protection. RBD-NP immunization cross-neutralized the B.1.1.7 variant efficiently but showed a reduced response against the B.1.351 variant. While RBD-NP/AS03 demonstrated a 4.5-fold reduction in neutralization of B.1.351, the RBD-NP/AS37 group showed a 16-fold reduction, suggesting differences in the breadth of the nAb response induced by these adjuvants. Furthermore, RBD-NP/AS03 was as immunogenic as a prefusion stabilized Spike immunogen (Hexapro) adjuvanted with AS03. These data highlight the efficacy of the adjuvanted RBD-NP vaccine in promoting protective immunity against SARS-CoV-2, and have paved the way for the clinical evaluation of this vaccine in Phase I/II clinical trials (NCT04742738 and NCT04750343).

Reference

<https://www.nature.com/articles/s41586-021-03530-2>

Germline variants in UNC13D and AP3B1 are enriched in COVID-19 patients experiencing severe cytokine storms

Abstract

Critically ill coronavirus disease 2019 (COVID-19) is characterized by severe cytokine storms, a hyperinflammatory condition intimately related to the development of fatal outcomes. Why some individuals seem particularly vulnerable to severe cytokine storms is still unknown. Primary immunodeficiency (PID)-related genes are inherited factors that dysregulate host inflammatory responses to infection, especially hemophagocytic lymphohistiocytosis (HLH)-related genes, established as contributors to the development of excessive cytokine storms. The association was analyzed between PID gene variants with severe cytokine storms in COVID-19. Whole-exome sequencing was conducted in 233 hospitalized COVID-19 patients and identified four PID gene (UNC13D, AP3B1, RNF168, DHX58) variants were significantly enriched in COVID-19 patients experiencing severe cytokine storms. The total percentage of COVID-19 patients with variants in UNC13D or AP3B1, two typical HLH genes, was dramatically higher in high-level cytokine group than in low-level group (33.3 vs. 5.7%, $P < 0.001$). Germline variants in UNC13D and AP3B1 were associated with the development of severe cytokine storms, fatal outcomes in COVID-19. These findings advance the understanding of individual susceptibility to severe cytokine storms and help optimize the current management of COVID-19.

Reference

<https://www.nature.com/articles/s41431-021-00886-x>

Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: A randomised, double-blind, placebo-controlled, phase 1 trial

Abstract

Background: Given the scale of the ongoing COVID-19 pandemic, the development of vaccines based on different platforms is essential, particularly in light of emerging viral variants, the absence of information on vaccine-induced immune durability, and potential paediatric use. We aimed to assess the safety and immunogenicity of an

MF59-adjuvanted subunit vaccine for COVID-19 based on recombinant SARS-CoV-2 spike glycoprotein stabilised in a pre-fusion conformation by a novel molecular clamp (spike glycoprotein-clamp [sclamp]).

Methods: A phase 1, double-blind, placebo-controlled, block-randomised trial was done of the sclamp subunit vaccine in a single clinical trial site in Brisbane, QLD, Australia. Healthy adults (aged ≥ 18 to ≤ 55 years) who had tested negative for SARS-CoV-2, reported no close contact with anyone with active or previous SARS-CoV-2 infection, and tested negative for pre-existing SARS-CoV-2 immunity were included. Participants were randomly assigned to one of five treatment groups and received two doses via intramuscular injection 28 days apart of either placebo, sclamp vaccine at 5 μg , 15 μg , or 45 μg , or one dose of sclamp vaccine at 45 μg followed by placebo. Participants and study personnel, except the dose administration personnel, were masked to treatment. The primary safety endpoints included solicited local and systemic adverse events in the 7 days after each dose and unsolicited adverse events up to 12 months after dosing. Here, data are reported up until day 57. Primary immunogenicity endpoints were antigen-specific IgG ELISA and SARS-CoV-2 microneutralisation assays assessed at 28 days after each dose. The study is ongoing and registered with ClinicalTrials.gov, NCT04495933.

Findings: Between June 23, 2020, and Aug 17, 2020, of 314 healthy volunteers screened, 120 were randomly assigned ($n=24$ per group), and 114 (95%) completed the study up to day 57 (mean age 32.5 years [SD 10.4], 65 [54%] male, 55 [46%] female). Severe solicited reactions were infrequent and occurred at similar rates in participants receiving placebo (two [8%] of 24) and the SARS-CoV-2 sclamp vaccine at any dose (three [3%] of 96). Both solicited reactions and unsolicited adverse events occurred at a similar frequency in participants receiving placebo and the SARS-CoV-2 sclamp vaccine. Solicited reactions occurred in 19 (79%) of 24 participants receiving placebo and 86 (90%) of 96 receiving the SARS-CoV-2 sclamp vaccine at any dose. Unsolicited adverse events occurred in seven (29%) of 24 participants receiving placebo and 35 (36%) of 96 participants receiving the SARS-CoV-2 sclamp vaccine at any dose. Vaccination with SARS-CoV-2 sclamp elicited a similar antigen-specific response irrespective of dose: 4 weeks after the initial dose (day 29) with 5 μg dose (geometric mean titre [GMT] 6400, 95% CI 3683–11 122), with 15 μg dose (7492, 4959–11 319),

and the two 45 µg dose cohorts (8770, 5526–13 920 in the two-dose 45 µg cohort; 8793, 5570–13 881 in the single-dose 45 µg cohort); 4 weeks after the second dose (day 57) with two 5 µg doses (102 400, 64 857–161 676), with two 15 µg doses (74 725, 51 300–108 847), with two 45 µg doses (79 586, 55 430–114 268), only a single 45 µg dose (4795, 2858–8043). At day 57, 67 (99%) of 68 participants who received two doses of sclamp vaccine at any concentration produced a neutralising immune response, compared with six (25%) of 24 who received a single 45 µg dose and none of 22 who received placebo. Participants receiving two doses of sclamp vaccine elicited similar neutralisation titres, irrespective of dose: two 5 µg doses (GMT 228, 95% CI 146–356), two 15 µg doses (230, 170–312), and two 45 µg doses (239, 187–307).

Interpretation: This first-in-human trial shows that a subunit vaccine comprising mammalian cell culture-derived, MF59-adjuvanted, molecular clamp-stabilised recombinant spike protein elicits strong immune responses with a promising safety profile. However, the glycoprotein 41 peptide present in the clamp created HIV diagnostic assay interference, a possible barrier to widespread use highlighting the criticality of potential non-spike directed immunogenicity during vaccine development. Studies are ongoing with alternative molecular clamp trimerisation domains to ameliorate this response.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00200-0/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00200-0/fulltext)

Safety and immunogenicity of SARS-CoV-2 recombinant protein vaccine formulations in healthy adults: Interim results of a randomised, placebo-controlled, phase 1–2, dose-ranging study

Abstract

Background: CoV2 preS dTM is a stabilised pre-fusion spike protein vaccine produced in a baculovirus expression system being developed against SARS-CoV-2. We present interim safety and immunogenicity results of the first-in-human study of the CoV2 preS dTM vaccine with two different adjuvant formulations.

Methods: This phase 1–2, randomised, double-blind study is being done in healthy, SARS-CoV-2-seronegative adults in ten clinical research centres in the USA.

Participants were stratified by age (18–49 years and ≥ 50 years) and randomly assigned using an interactive response technology system with block randomisation (blocks of varying size) to receive one dose (on day 1) or two doses (on days 1 and 22) of placebo or candidate vaccine, containing low-dose (effective dose 1.3 μg) or high-dose (2.6 μg) antigen with adjuvant AF03 (Sanofi Pasteur) or AS03 (GlaxoSmithKline) or unadjuvanted high-dose antigen (18–49 years only). Primary endpoints were safety, assessed up to day 43, and immunogenicity, measured as SARS-CoV-2 neutralising antibodies (geometric mean titres), assessed on days 1, 22, and 36 serum samples. Safety was assessed according to treatment received in the safety analysis set, which included all randomly assigned participants who received at least one dose. Neutralising antibody titres were assessed in the per-protocol analysis set for immunogenicity, which included participants who received at least one dose, met all inclusion and exclusion criteria, had no protocol deviation, had negative results in the neutralisation test at baseline, and had at least one valid post-dose serology sample. This planned interim analysis reports data up to 43 days after the first vaccination; participants in the trial will be followed up for 12 months after the last study injection. This trial is registered with ClinicalTrials.gov, NCT04537208, and is ongoing.

Findings: Between Sept 3 and Sept 29, 2020, 441 individuals (299 aged 18–49 years and 142 aged ≥ 50 years) were randomly assigned to one of the 11 treatment groups. The interim safety analyses included 439 (>99%) of 441 randomly assigned participants (299 aged 18–49 years and 140 aged ≥ 50 years). Neutralising antibody titres were analysed in 326 (74%) of 441 participants (235 [79%] of 299 aged 18–49 years and 91 [64%] of 142 aged ≥ 50 years). There were no vaccine-related unsolicited immediate adverse events, serious adverse events, medically attended adverse events classified as severe, or adverse events of special interest. Among all study participants, solicited local and systemic reactions of any grade after two vaccine doses were reported in 81% (95% CI 61–93; 21 of 26) of participants in the low-dose plus AF03 group, 93% (84–97; 74 of 80) in the low-dose plus AS03 group, 89% (70–98; 23 of 26) in the high-dose plus AF03 group, 95% (88–99; 81 of 85) in the high-dose plus AS03 group, 29% (10–56; five of 17) in the unadjuvanted high-dose group, and 21% (8–40; six of 29) in the placebo group. A single vaccine dose did not generate neutralising antibody titres above placebo levels in any group at days 22 or 36. Among participants aged 18–49 years, neutralising antibody titres after two vaccine doses were 13.1 (95% CI 6.40–26.9) in the low-dose

plus AF03 group, 20.5 (13.1–32.1) in the low-dose plus AS03 group, 43.2 (20.6–90.4) in the high-dose plus AF03 group, 75.1 (50.5–112.0) in the high-dose plus AS03 group, 5.00 (not calculated) in the unadjuvanted high-dose group, and 5.00 (not calculated) in the placebo group. Among participants aged 50 years or older, neutralising antibody titres after two vaccine doses were 8.62 (1.90–39.0) in the low-dose plus AF03 group, 12.9 (7.09–23.4) in the low-dose plus AS03 group, 12.3 (4.35–35.0) in the high-dose plus AF03 group, 52.3 (25.3–108.0) in the high-dose plus AS03 group, and 5.00 (not calculated) in the placebo group.

Interpretation: The lower than expected immune responses, especially in the older age groups, and the high reactogenicity after dose two were probably due to higher than anticipated host-cell protein content and lower than planned antigen doses in the formulations tested, which was discovered during characterisation studies on the final bulk drug substance. Further development of the AS03-adjuvanted candidate vaccine will focus on identifying the optimal antigen formulation and dose.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00147-X/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00147-X/fulltext)

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Epidemiology, clinical characteristics, and virologic features of COVID-19 patients in Kazakhstan: A nation-wide retrospective cohort study

Abstract

Background: The earliest coronavirus disease-2019 (COVID-19) cases in Central Asia were announced in March 2020 by Kazakhstan. Despite the implementation of aggressive measures to curb infection spread, gaps remain in the understanding of the clinical and epidemiologic features of the regional pandemic.

Methods: A retrospective, observational cohort study was done of patients with laboratory-confirmed COVID-19 hospitalized in Kazakhstan between February and April 2020. Demographic, clinical, laboratory and radiological data of patients was compared with different COVID-19 severities on admission. Logistic regression was used to assess factors associated with disease severity and in-hospital death. Whole-genome SARS-CoV-2 analysis was performed in 53 patients.

Findings: Of the 1072 patients with laboratory-confirmed COVID-19 in March-April 2020, the median age was 36 years (IQR 24–50) and 484 (45%) were male. On admission, 683 (64%) participants had asymptomatic/mild, 341 (32%) moderate, and 47 (4%) severe-to-critical COVID-19 manifestation; 20 in-hospital deaths (1•87%) were reported by 5 May 2020. Multivariable regression indicated increasing odds of severe disease associated with older age (odds ratio 1•05, 95% CI 1•03-1•07, per year increase; $p<0•001$), the presence of comorbidities (2•34, 95% CI 1•18-4•85; $p=0•017$) and elevated white blood cell count (WBC, 1•13, 95% CI 1•00-1•27; $p=0•044$) on admission, while older age (1•09, 95% CI 1•06-1•13, per year increase; $p<0•001$) and male sex (5•63, 95% CI 2•06-17•57; $p=0•001$) were associated with increased odds of in-hospital death. The SARS-CoV-2 isolates grouped into seven phylogenetic lineages, O/B.4.1, S/A.2, S/B.1.1, G/B.1, GH/B.1.255, GH/B.1.3 and GR/B.1.1.10; 87% of the isolates were O and S sub-types descending from early Asian lineages, while the G, GH and GR isolates were related to lineages from Europe and the Americas.

Interpretation: Older age, comorbidities, increased WBC count, and male sex were risk factors for COVID-19 disease severity and mortality in Kazakhstan. The broad SARS-CoV-2 diversity suggests multiple importations and community-level amplification predating travel restriction.

Reference

[https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762\(21\)00073-9/fulltext](https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762(21)00073-9/fulltext)

Modeling vaccination rollouts, SARS-CoV-2 variants and the requirement for non-pharmaceutical interventions in Italy

Abstract

Despite progress in clinical care for patients with coronavirus disease 2019 (COVID-19)¹, population-wide interventions are still crucial to manage the pandemic, which has been aggravated by the emergence of new, highly transmissible variants. In this study, we combined the SIDARTHE model², which predicts the spread of SARS-CoV-2 infections, with a new data-based model that projects new cases onto casualties and healthcare system costs. Based on the Italian case study, we outline several scenarios: mass vaccination campaigns with different paces, different transmission rates due to new variants and different enforced countermeasures, including the alternation of

opening and closure phases. Our results demonstrate that non-pharmaceutical interventions (NPIs) have a higher effect on the epidemic evolution than vaccination alone, advocating for the need to keep NPIs in place during the first phase of the vaccination campaign. Our model predicts that, from April 2021 to January 2022, in a scenario with no vaccine rollout and weak NPIs ($R_0 = 1.27$), as many as 298,000 deaths associated with COVID-19 could occur. However, fast vaccination rollouts could reduce mortality to as few as 51,000 deaths. Implementation of restrictive NPIs ($R_0 = 0.9$) could reduce COVID-19 deaths to 30,000 without vaccinating the population and to 18,000 with a fast rollout of vaccines. We also show that, if intermittent open–close strategies are adopted, implementing a closing phase first could reduce deaths (from 47,000 to 27,000 with slow vaccine rollout) and healthcare system costs, without substantive aggravation of socioeconomic losses.

Reference

<https://www.nature.com/articles/s41591-021-01334-5>

[mRNA-Based SARS-CoV-2 vaccine candidate CVnCoV induces high levels of virus-neutralising antibodies and mediates protection in rodents](#)

Abstract

mRNA technologies have recently proven clinical efficacy against coronavirus disease 2019 and are among the most promising technologies to address the current pandemic. Here, we show preclinical data for our clinical candidate CVnCoV, a lipid nanoparticle-encapsulated mRNA vaccine that encodes full-length, pre-fusion stabilised severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) spike protein. In contrast to previously published approaches, CVnCoV is exclusively composed of naturally occurring nucleotides. Immunisation with CVnCoV induced strong humoral responses with high titres of virus-neutralising antibodies and robust T-cell responses. CVnCoV vaccination protected hamsters from challenge with wild-type SARS-CoV-2, demonstrated by the absence of viral replication in the lungs. Hamsters vaccinated with a suboptimal dose of CVnCoV leading to breakthrough viral replication exhibited no evidence of vaccine-enhanced disease. Overall, data presented here provide evidence that CVnCoV represents a potent and safe vaccine candidate against SARS-CoV-2.

Reference

<https://www.nature.com/articles/s41541-021-00311-w>

Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model

Abstract

The COVID-19 pandemic progresses unabated in many regions of the world. An effective antiviral against SARS-CoV-2 that could be administered orally for use following high-risk exposure would be of substantial benefit in controlling the COVID-19 pandemic. Herein, we show that MK-4482, an orally administered nucleoside analog, inhibits SARS-CoV-2 replication in the Syrian hamster model. The inhibitory effect of MK-4482 on SARS-CoV-2 replication is observed in animals when the drug is administered either beginning 12 h before or 12 h following infection in a high-risk exposure model. These data support the potential utility of MK-4482 to control SARS-CoV-2 infection in humans following high-risk exposure as well as for treatment of COVID-19 patients.

Reference

<https://www.nature.com/articles/s41467-021-22580-8>

Reconcile the debate over protective effects of BCG vaccine against COVID-19

Abstract

While awaiting the COVID-19 vaccines, researchers have been actively exploring the effectiveness of existing vaccines against the new virus, among which the BCG vaccine (Bacillus Calmette-Guérin) receives the most attention. While many reports suggest a potential role for BCG immunization in ameliorating SARS-CoV-2 infection, these findings remain controversial. With country-level COVID-19 outbreak data from Johns Hopkins University Coronavirus Resource Center, and BCG program data from World Atlas of BCG Policies and Practices and WHO/UNICEF, we estimated a dynamic model to investigate the effect of BCG vaccination across time during the pandemic. Our results reconcile these varying reports regarding protection by BCG against COVID-19 in a variety of clinical scenarios and model specifications. We observe a notable protective effect of the BCG vaccine during the early stage of the pandemic. However, we do not see any strong evidence for protection during the later stages. We also see

that a higher proportion of vaccinated young population may confer some level of communal protection against the virus in the early pandemic period, even when the proportion of vaccination in the older population is low. Our results highlight that while BCG may offer some protection against COVID-19, we should be cautious in interpreting the estimated effectiveness as it may vary over time and depend on the age structure of the vaccinated population.

Reference

<https://www.nature.com/articles/s41598-021-87731-9>

Modeling SARS-CoV-2 infection and its individual differences with ACE2-expressing human iPS cells

Abstract

Genetic differences are a primary reason for differences in the susceptibility and severity of COVID-19. As induced pluripotent stem (iPS) cells maintain the genetic information of the donor, they can be used to model individual differences in SARS-CoV-2 infection in vitro. We found that human iPS cells expressing the SARS-CoV-2 receptor angiotensin-converting enzyme 2 (ACE2) (ACE2-iPS cells) can be infected with SARS-CoV-2. In infected ACE2-iPS cells, the expression of SARS-CoV-2 nucleocapsid protein, budding of viral particles, and production of progeny virus, double membrane spherules, and double-membrane vesicles were confirmed. We performed SARS-CoV-2 infection experiments on ACE2-iPS/ embryonic stem (ES) cells from eight individuals. Male iPS/ES cells were more capable of producing the virus compared with female iPS/ES cells. These findings suggest that ACE2-iPS cells can not only reproduce individual differences in SARS-CoV-2 infection in vitro but also are a useful resource to clarify the causes of individual differences in COVID-19 due to genetic differences.

Reference

[https://www.cell.com/science/fulltext/S2589-0042\(21\)00396-5](https://www.cell.com/science/fulltext/S2589-0042(21)00396-5)

Multi-platform omics analysis reveals molecular signature for COVID-19 pathogenesis, prognosis and drug target discovery

Abstract

Disease progression prediction and therapeutic drug target discovery for Coronavirus disease 2019 (COVID-19) are particularly important, as there is still no effective strategy for severe COVID-19 patient treatment. Herein, we performed multi-platform omics analysis of serial plasma and urine samples collected from patients during the course of COVID-19. Integrative analyses of these omics data revealed several potential therapeutic targets, such as ANXA1 and CLEC3B. Molecular changes in plasma indicated dysregulation of macrophage and suppression of T cell functions in severe patients compared to those in non-severe patients. Further, we chose 25 important molecular signatures as potential biomarkers for the prediction of disease severity. The prediction power was validated using corresponding urine samples and plasma samples from new COVID-19 patient cohort, with AUC reached to 0.904 and 0.988, respectively. In conclusion, our omics data proposed not only potential therapeutic targets, but also biomarkers for understanding the pathogenesis of severe COVID-19.

Reference

<https://www.nature.com/articles/s41392-021-00508-4>

The effect of eviction moratoria on the transmission of SARS-CoV-2

Abstract

Massive unemployment during the COVID-19 pandemic could result in an eviction crisis in US cities. Here we model the effect of evictions on SARS-CoV-2 epidemics, simulating viral transmission within and among households in a theoretical metropolitan area. We recreate a range of urban epidemic trajectories and project the course of the epidemic under two counterfactual scenarios, one in which a strict moratorium on evictions is in place and enforced, and another in which evictions are allowed to resume at baseline or increased rates. We find, across scenarios, that evictions lead to significant increases in infections. Applying our model to Philadelphia using locally-specific parameters shows that the increase is especially profound in models that

consider realistically heterogeneous cities in which both evictions and contacts occur more frequently in poorer neighborhoods. Our results provide a basis to assess eviction moratoria and show that policies to stem evictions are a warranted and important component of COVID-19 control.

Reference

<https://www.nature.com/articles/s41467-021-22521-5>

Mortality outcomes with hydroxychloroquine and chloroquine in COVID-19 from an international collaborative meta-analysis of randomized trials

Abstract

Substantial COVID-19 research investment has been allocated to randomized clinical trials (RCTs) on hydroxychloroquine/chloroquine, which currently face recruitment challenges or early discontinuation. It was aimed to estimate the effects of hydroxychloroquine and chloroquine on survival in COVID-19 from all currently available RCT evidence, published and unpublished. A rapid meta-analysis of ongoing, completed, or discontinued RCTs was presented on hydroxychloroquine or chloroquine treatment for any COVID-19 patients (protocol: <https://osf.io/QESV4/>). Unpublished RCTs (ClinicalTrials.gov, WHO International Clinical Trials Registry Platform, Cochrane COVID-registry up to June 11, 2020), and published RCTs (PubMed, medRxiv and bioRxiv up to October 16, 2020) were systematically identified. All-cause mortality has been extracted (publications/preprints) or requested from investigators and combined in random-effects meta-analyses, calculating odds ratios (ORs) with 95% confidence intervals (CIs), separately for hydroxychloroquine and chloroquine. Prespecified subgroup analyses include patient setting, diagnostic confirmation, control type, and publication status. Sixty-three trials were potentially eligible. We included 14 unpublished trials (1308 patients) and 14 publications/preprints (9011 patients). Results for hydroxychloroquine are dominated by RECOVERY and WHO SOLIDARITY, two highly pragmatic trials, which employed relatively high doses and included 4716 and 1853 patients, respectively (67% of the total sample size). The combined OR on all-cause mortality for hydroxychloroquine is 1.11 (95% CI: 1.02, 1.20; $I^2 = 0\%$; 26 trials; 10,012 patients) and for chloroquine 1.77 (95%CI: 0.15, 21.13, $I^2 = 0\%$; 4 trials; 307 patients). We identified no subgroup effects. We found that treatment with

hydroxychloroquine is associated with increased mortality in COVID-19 patients, and there is no benefit of chloroquine. Findings have unclear generalizability to outpatients, children, pregnant women, and people with comorbidities.

Reference

<https://www.nature.com/articles/s41467-021-22446-z>

Novel application of automated machine learning with MALDI-TOF-MS for rapid high-throughput screening of COVID-19: A proof of concept

Abstract

The 2019 novel coronavirus infectious disease (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has created an unsustainable need for molecular diagnostic testing. Molecular approaches such as reverse transcription (RT) polymerase chain reaction (PCR) offers highly sensitive and specific means to detect SARS-CoV-2 RNA, however, despite it being the accepted “gold standard”, molecular platforms often require a tradeoff between speed versus throughput. Matrix assisted laser desorption ionization (MALDI)—time of flight (TOF)—mass spectrometry (MS) has been proposed as a potential solution for COVID-19 testing and finding a balance between analytical performance, speed, and throughput, without relying on impacted supply chains. Combined with machine learning (ML), this MALDI-TOF-MS approach could overcome logistical barriers encountered by current testing paradigms. We evaluated the analytical performance of an ML-enhanced MALDI-TOF-MS method for screening COVID-19. Residual nasal swab samples from adult volunteers were used for testing and compared against RT-PCR. Two optimized ML models were identified, exhibiting accuracy of 98.3%, positive percent agreement (PPA) of 100%, negative percent agreement (NPA) of 96%, and accuracy of 96.6%, PPA of 98.5%, and NPA of 94% respectively. Machine learning enhanced MALDI-TOF-MS for COVID-19 testing exhibited performance comparable to existing commercial SARS-CoV-2 tests.

Reference

<https://www.nature.com/articles/s41598-021-87463-w>

A combination of cross-neutralizing antibodies synergizes to prevent SARS-CoV-2 and SARS-CoV pseudovirus infection

Abstract

Coronaviruses have caused several human epidemics and pandemics including the ongoing coronavirus disease 2019 (COVID-19). Prophylactic vaccines and therapeutic antibodies have already shown striking effectiveness against COVID-19. Nevertheless, concerns remain about antigenic drift in SARS-CoV-2 as well as threats from other sarbecoviruses. Cross-neutralizing antibodies to SARS-related viruses provide opportunities to address such concerns. Here, we report on crystal structures of a cross-neutralizing antibody, CV38-142, in complex with the receptor-binding domains from SARS-CoV-2 and SARS-CoV. Recognition of the N343 glycosylation site and water-mediated interactions facilitate cross-reactivity of CV38-142 to SARS-related viruses, allowing the antibody to accommodate antigenic variation in these viruses. CV38-142 synergizes with other cross-neutralizing antibodies, notably COVA1-16, to enhance neutralization of SARS-CoV and SARS-CoV-2, including circulating variants of concern B.1.1.7 and B.1.351. Overall, this study provides valuable information for vaccine and therapeutic design to address current and future antigenic drift in SARS-CoV-2 and to protect against zoonotic SARS-related coronaviruses.

Reference

[https://www.cell.com/cell-host-microbe/fulltext/S1931-3128\(21\)00181-5](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00181-5)

CD8+ T cells specific for an immunodominant SARS-CoV-2 nucleocapsid epitope display high naïve precursor frequency and T cell receptor promiscuity

Abstract

To better understand primary and recall T cell responses during COVID-19, it is important to examine unmanipulated SARS-CoV-2-specific T cells. Using peptide-HLA tetramers for direct ex vivo analysis, we characterized CD8+ T cells specific for SARS-CoV-2 epitopes in COVID-19 patients and unexposed individuals. Unlike CD8+ T cells directed towards subdominant epitopes – B7/N257, A2/S269 and A24/S1208 – CD8+ T cells specific for the immunodominant B7/N105 epitope were detected at high frequency in pre-pandemic samples, and at increased frequency during acute COVID-19 and

convalescence. SARS-CoV-2-specific CD8⁺ T cells in pre-pandemic samples from children, adults and elderly individuals predominantly displayed a naïve phenotype, indicating a lack of previous cross-reactive exposures. T cell receptor (TCR) analyses revealed diverse TCR $\alpha\beta$ repertoires and promiscuous $\alpha\beta$ -TCR pairing within B7/N105+CD8⁺ T cells. Our study demonstrates high naive precursor frequency and TCR $\alpha\beta$ diversity within immunodominant B7/N105-specific CD8⁺ T cells, and provides insight into SARS-CoV-2-specific T cell origins and subsequent responses.

Reference

[https://www.cell.com/immunity/fulltext/S1074-7613\(21\)00171-0](https://www.cell.com/immunity/fulltext/S1074-7613(21)00171-0)

SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: A prospective cohort study

Abstract

Background: Whether young adults who are infected with SARS-CoV-2 are at risk of subsequent infection is uncertain. We investigated the risk of subsequent SARS-CoV-2 infection among young adults seropositive for a previous infection.

Methods: This analysis was performed as part of the prospective COVID-19 Health Action Response for Marines study (CHARM). CHARM included predominantly male US Marine recruits, aged 18–20 years, following a 2-week unsupervised quarantine at home. After the home quarantine period, upon arrival at a Marine-supervised 2-week quarantine facility (college campus or hotel), participants were enrolled and were assessed for baseline SARS-CoV-2 IgG seropositivity, defined as a dilution of 1:150 or more on receptor-binding domain and full-length spike protein ELISA. Participants also completed a questionnaire consisting of demographic information, risk factors, reporting of 14 specific COVID-19-related symptoms or any other unspecified symptom, and brief medical history. SARS-CoV-2 infection was assessed by PCR at weeks 0, 1, and 2 of quarantine and participants completed a follow-up questionnaire, which included questions about the same COVID-19-related symptoms since the last study visit. Participants were excluded at this stage if they had a positive PCR test during quarantine. Participants who had three negative swab PCR results during quarantine and a baseline serum serology test at the beginning of the supervised quarantine that identified them as seronegative or seropositive for SARS-CoV-2 then went on to basic

training at Marine Corps Recruit Depot—Parris Island. Three PCR tests were done at weeks 2, 4, and 6 in both seropositive and seronegative groups, along with the follow-up symptom questionnaire and baseline neutralising antibody titres on all subsequently infected seropositive and selected seropositive uninfected participants (prospective study period).

Findings: Between May 11, 2020, and Nov 2, 2020, we enrolled 3249 participants, of whom 3168 (98%) continued into the 2-week quarantine period. 3076 (95%) participants, 2825 (92%) of whom were men, were then followed up during the prospective study period after quarantine for 6 weeks. Among 189 seropositive participants, 19 (10%) had at least one positive PCR test for SARS-CoV-2 during the 6-week follow-up (1.1 cases per person-year). In contrast, 1079 (48%) of 2247 seronegative participants tested positive (6.2 cases per person-year). The incidence rate ratio was 0.18 (95% CI 0.11–0.28; $p < 0.001$). Among seropositive recruits, infection was more likely with lower baseline full-length spike protein IgG titres than in those with higher baseline full-length spike protein IgG titres (hazard ratio 0.45 [95% CI 0.32–0.65]; $p < 0.001$). Infected seropositive participants had viral loads that were about 10-times lower than those of infected seronegative participants (ORF1ab gene cycle threshold difference 3.95 [95% CI 1.23–6.67]; $p = 0.004$). Among seropositive participants, baseline neutralising titres were detected in 45 (83%) of 54 uninfected and in six (32%) of 19 infected participants during the 6 weeks of observation (ID50 difference $p < 0.0001$).

Interpretation: Seropositive young adults had about one-fifth the risk of subsequent infection compared with seronegative individuals. Although antibodies induced by initial infection are largely protective, they do not guarantee effective SARS-CoV-2 neutralisation activity or immunity against subsequent infection. These findings might be relevant for optimisation of mass vaccination strategies.

Reference

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00158-2/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00158-2/fulltext)

Underlying conditions and risk of hospitalisation, ICU admission and mortality among those with COVID-19 in Ireland: A national surveillance study

Abstract

Background: To date, over 2 million people worldwide have died with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To describe the experience in Ireland, this study examined associations between underlying conditions and the following outcomes: mortality, admission to hospital or admission to the intensive care unit (ICU) among those infected with COVID-19.

Methods: This study used data from the Health Protection Surveillance Centre in Ireland and included confirmed cases of COVID-19 from the first wave of the pandemic between March and July 2020. Two cohorts were included: all cases (community and hospital) and hospital admissions only. For all cases, health outcome data included mortality and hospitalisation. For hospitalised cases, outcome data included mortality and ICU admission. Logistic regression was used to examine associations between underlying conditions and outcomes across both cohorts. Results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CIs).

Findings: There were 19,789 cases included in analysis, which encompassed 1,476 (7.5%) deaths, 2,811 (14.2%) hospitalisations, and 438 (2.2%) ICU admissions of whom 90 (20.5%) died. Significantly higher risk of mortality, hospitalisation and ICU admission was associated with having chronic heart disease, a BMI ≥ 40 kg/m² and male sex. Additionally, diagnosis of a chronic neurological condition (OR 1.41; 95%CI:1.17, 1.69), chronic kidney disease (OR 1.74; 95%CI:1.35, 2.24) and cancer (OR 2.77; 95%CI:2.21, 3.47) were significantly associated with higher risk of mortality among all cases, with similar patterns of association observed for mortality among hospitalised cases.

Interpretation: The identification of underlying conditions among COVID-19 cases may help identify those at highest risk of the worst health outcomes and inform preventive strategies to improve outcomes.

Reference

[https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762\(21\)00074-0/fulltext](https://www.thelancet.com/journals/lanepi/article/PIIS2666-7762(21)00074-0/fulltext)

REPORT

Publication Date: Apr 17, 2021

Increased resistance of SARS-CoV-2 variant P.1 to antibody neutralization

Abstract

The emergence of SARS-CoV-2 variants has raised concerns about altered sensitivity to antibody-mediated immunity. The relative resistance of SARS-CoV-2 variants B.1.1.7 and B.1.351 to antibody neutralization has been recently investigated. We report that another emergent variant from Brazil, P.1, is not only refractory to multiple neutralizing monoclonal antibodies but also more resistant to neutralization by convalescent plasma and vaccinee sera. The magnitude of resistance is greater for monoclonal antibodies than vaccinee sera and evident with both pseudovirus and authentic P.1 virus. The cryoelectron microscopy structure of a soluble prefusion-stabilized spike reveals that the P.1 trimer adopts exclusively a conformation in which one of the receptor-binding domains is in the “up” position, which is known to facilitate binding to entry receptor ACE2. The functional impact of P.1 mutations thus appears to arise from local changes instead of global conformational alterations. The P.1 variant threatens current antibody therapies but less so protective vaccine efficacy.

Reference

[https://www.cell.com/cell-host-microbe/fulltext/S1931-3128\(21\)00183-9](https://www.cell.com/cell-host-microbe/fulltext/S1931-3128(21)00183-9)

BNT162b2 vaccination effectively prevents the rapid rise of SARS-CoV-2 variant B.1.1.7 in high-risk populations in Israel

Abstract

Since the emergence of the SARS-CoV-2 pandemic, various genetic variants have been described. The B.1.1.7 variant, which emerged in England during December 2020, is associated with increased infectivity. Therefore, its pattern of spread is of great importance. The Israeli government established three national programs: massive RT-PCR testing, focused surveillance in nursing homes, and robust prioritized vaccination with BNT162b2. To define the impact of the aforementioned programs, we analyze data

from ~300,000 RT-PCR samples collected from December 6, 2020, to February 10, 2021. We reveal that the B.1.1.7 is 45% (95% confidence interval [CI]: 20%–60%) more transmissible than the wild-type strain and has become the dominant strain in Israel within 3.5 weeks. Despite the rapid increase in viral spread, focused RT-PCR testing and prioritized vaccination programs are capable of preventing the spread of the B.1.1.7 variant in the elderly. Therefore, proactive surveillance programs, combined with prioritized vaccination, are achievable and can reduce severe illness and subsequent death.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00080-X](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00080-X)

COMMENT

Publication Date: Apr 19, 2021

Response to first vaccination against SARS-CoV-2 in patients with multiple myeloma

Multiple myeloma is a malignancy of plasma cells, which is highly associated with immune suppression. Consistent with this, reports of outcomes of COVID-19 infection in patients with multiple myeloma show higher rates of severe disease than in the general population. Protection of this vulnerable patient group from COVID-19 infection is crucial but response to the new vaccines in patients with multiple myeloma is unknown. A recent report showing low anti-SARS-CoV-2 IgG response to the Pfizer vaccine in patients with cancer included 38 patients with haematological malignancies (nine patients with multiple myeloma) and showed only a 13% response rate, raising concerns that multiple myeloma might be associated with attenuated vaccine response. In the UK, both Pfizer and AstraZeneca vaccines have been used with spacing of 12 weeks between the first and second doses. We retrospectively assessed serological response following the first SARS-CoV-2 vaccine dose in patients with multiple myeloma in our centre. Patients were eligible if they had a diagnosis of multiple myeloma and an anti-SARS-CoV-2 spike protein S1 IgG antibody result 21 days or more post-vaccination. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026\(21\)00110-1/fulltext](https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(21)00110-1/fulltext)

Soluble interleukin-6 receptor in the COVID-19 cytokine storm syndrome

Data suggest that interleukin (IL)-6 blockade could reduce mortality in severe COVID-19, yet IL-6 is only modestly elevated in most patients. Chen *et al.* describe the role of soluble interleukin-6 receptor (sIL-6R) in IL-6 *trans*-signaling and how understanding the IL-6:sIL-6R axis might help define and treat COVID-19 cytokine storm syndrome.

Reference

[https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791\(21\)00091-4](https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00091-4)

Saliva as a gold-standard sample for SARS-CoV-2 detection

As COVID-19 continues to strain public health systems and vaccination programmes race against new variants that might be more transmissible or capable of evading immune responses, the urgent need for simple, accessible, and frequent testing remains. Inexpensive, scalable, and sustainable strategies that allow easily repeatable testing over time need to be made widely available. This is possible by testing saliva. The gold-standard sample for SARS-CoV-2 detection defaulted to the nasopharyngeal swab because of its role in detection of other upper respiratory tract pathogens. Demand for swabs drove a cascading collapse of supply chains and worsened shortages of personal protective equipment (PPE) required by health-care workers for sample collection. As the need for mass testing and frequent, repeated sampling surged, the urgency for alternative sample types became apparent. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/lanres/article/PIIS2213-2600\(21\)00178-8/fulltext](https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00178-8/fulltext)

Recombinant protein vaccines against SARS-CoV-2

The development of vaccines against SARS-CoV-2 has proceeded at an unprecedented pace, resulting in emergency use approvals and accelerated deployment of multiple vaccines. This development and deployment has occurred within a year of the Public Health Emergency of International Concern declaration by WHO. However, some attempts to develop vaccines have run into difficulties in early clinical development.

Paul Goepfert and colleagues describe clinical studies of CoV2 preS dTM, a stabilised pre-fusion spike protein vaccine produced in a baculovirus expression system administered alone or with one of two oil-in-water adjuvants (AS03 or AF03), in younger or older adults (299 aged 18–49 years and 142 aged ≥ 50 years). Alternate vaccination regimens were assessed including one or two doses and at different dose concentrations. After the trial commenced, it was discovered that a reagent used to quantitate the spike protein antigen cross-reacted with glycosylated baculovirus protein present in the formulation, resulting in an underestimate of antigen concentration of approximately four to six times, with either 1.3 μg (low dose) or 2.6 μg (high dose)

administered. Immunogenicity was lower than expected, whereas reactogenicity was higher after the second dose of the adjuvanted vaccines. Some useful conclusions can be drawn from the study—for example, in individuals who are seronegative, an adjuvant is required, with AS03 resulting in greater immunogenicity than AF03. The higher dose with AS03 consistently resulted in the induction of neutralising antibodies in younger adults, although only 62.5% of those older than 60 years seroconverted for neutralising antibodies. The manufacturing process can now be optimised to achieve a higher antigen content and reduced host-cell protein contamination. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00227-9/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00227-9/fulltext)

Mounting evidence of impaired viral control in severe COVID-19

Substantial gaps in knowledge regarding the evolution and pathogenesis of COVID-19 remain after 1 year of the SARS-CoV-2 pandemic. At the start of the pandemic, a biphasic model to explain the physiopathology of COVID-19 became popular. This model divided the disease course into an initial viral response phase, followed by the inflammatory response phase. In the inflammatory response phase, the virus is thought to have a minor role, and host inflammatory responses are the predominant mediators of pathophysiology, by triggering tissue damage leading to acute respiratory distress syndrome. Growing evidence from our group and others suggest that this model might need revising. Patients with the most severe forms of the disease show the highest viral RNA loads in respiratory samples and prolonged viral shedding. Most critically ill patients with COVID-19 show SARS-CoV-2 RNAemia, with viral RNA load in plasma correlating with the degree of severity and the risk of mortality.^{5, 6} Non-survivors show more frequent antigenaemia.⁶ Furthermore, autopsies from COVID-19 patients demonstrate viral dissemination by the presence of viral particles and viral RNA in different organs. All these findings suggest that the virus is a key driver of pathogenesis in severe COVID-19. Some immunological signatures denote an impaired ability to control viral replication in patients with severe COVID-19; in critically ill patients, absent or insufficient specific anti-SARS-CoV-2 S antibodies correlate with the presence of antigenaemia, high viral RNA loads in plasma, and mortality.⁶ Patients with severe

COVID-19 also show impaired interferon type I response, which is associated with a persistent blood viral load.

Although inflammation appears to be a central pathogenic event in severe COVID-19 (as demonstrated by the success of steroids and interleukin (IL)-6 pathway blockers in clinical trials), we should not forget what drives the inflammatory process in these patients. Our results show a direct correlation between the concentrations of viral RNA in plasma and those of pro-inflammatory cytokines (C-X-C motif chemokine ligand, monocyte chemoattractant protein-1, IL-6, IL-15, and granulocyte-macrophage colony-stimulating factor) and anti-inflammatory or immunosuppressor mediators (IL-10 and programmed death-ligand 1). Previous findings in SARS, H5N1 influenza, and pandemic H1N1 influenza already described a close connection between viral load, hypercytokinaemia, and disease severity. Consequently, hypercytokinaemia would be an additional clue supporting that severe COVID-19 patients have difficulties in controlling SARS-CoV-2 replication. For more details, read the link given below.

Reference

[https://www.thelancet.com/journals/laninf/article/PIIS1473-3099\(21\)00227-9/fulltext](https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00227-9/fulltext)

PREVIEW

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Uncovering the complexities of biological structures with network-based learning: An application in SARS-CoV-2

Abstract

Network-based learning enables the identification of possible undiscovered interactions in biological systems. In this issue of Patterns, Du et al. show that applying these methods to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reveals potential infection targets of the virus and possible interactions between SARS-CoV-2 proteins and human proteins.

Reference

[https://www.cell.com/patterns/fulltext/S2666-3899\(21\)00085-4](https://www.cell.com/patterns/fulltext/S2666-3899(21)00085-4)