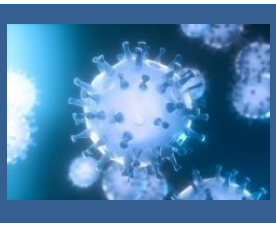

RESEARCH PUBLICATIONS

Publication Date: Jul 28, 2021

Abbreviated Profile of Drugs (APOD): Modeling drug safety profiles to prioritize investigational COVID-19 treatments

Abstract

Safe and effective oral formulation of a drug, that is easy to store, transport, and administer, is imperative to reach the masses including those without adequate facilities and resources, in order to combat globally transmitted coronavirus disease 2019 (COVID-19). In this decision analytic modeling study, the safety of investigational COVID-19 drugs in clinical trials was assessed using the Abbreviated Profile of Drugs (APOD) methodology. The method was extensively tested for various unbiased datasets based on different criteria such as drugs recalled worldwide for failing to meet safety standards, organ-specific toxicities, cytochrome P450 inhibitors, and Food and Drug Administration (FDA) approved drugs with remarkable successes. Experimental validation of the predictions made by APOD were demonstrated by comparison with a progression of multiparametric optimization of a series of cancer drugs that led to a potent drug (GDC-0941) which went into the clinical development. The drugs were classified into three categories of safety profiles: strong, moderate and weak. A total of 3556 drugs available in public databases were examined. According to the results, drugs with strong safety profiles included molnupiravir (EIDD-2801), moderate safety profiles included dexamethasone, and weak safety profiles included lopinavir. In this analysis, the physicochemical-pharmacokinetic APOD fingerprint was associated with the drug safety profile of withdrawn, approved, as well as drugs in clinical trials and the APOD method facilitated decision-making and prioritization of the investigational treatments.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(21)01769-2

IFITM proteins promote SARS-CoV-2 infection and are targets for virus inhibition *in vitro*

Abstract

Interferon-induced transmembrane proteins (IFITMs 1, 2 and 3) can restrict viral pathogens, but pro- and anti-viral activities have been reported for coronaviruses. Here, it was shown that artificial overexpression of IFITMs blocks SARS-CoV-2 infection. However, endogenous IFITM expression supports efficient infection of SARS-CoV-2 in human lung cells. The results indicated that the SARS-CoV-2 Spike protein interacts with IFITMs and hijacks them for efficient viral infection. IFITM proteins were expressed and further induced by interferons in human lung, gut, heart and brain cells. IFITM-derived peptides and targeting antibodies inhibit SARS-CoV-2 entry and replication in human lung cells, cardiomyocytes and gut organoids. The results show that IFITM proteins are cofactors for efficient SARS-CoV-2 infection of human cell types representing *in vivo* targets for viral transmission, dissemination and pathogenesis and are potential targets for therapeutic approaches.

Reference

https://www.nature.com/articles/s41467-021-24817-y

A surrogate virus neutralization test to quantify antibody-mediated inhibition of SARS-CoV-2 in finger stick dried blood spot samples

Abstract

The spike protein of SARS-CoV-2 engages the human angiotensin-converting enzyme 2 (ACE2) receptor to enter host cells, and neutralizing antibodies are effective at blocking this interaction to prevent infection. Widespread application of this important marker of protective immunity is limited by logistical and technical challenges associated with live virus methods and venous blood collection. To address this gap, we validated an immunoassay-based method for quantifying neutralization of the spike-ACE2 interaction in a single drop of capillary whole blood, collected on filter paper as a dried blood spot (DBS) sample. Samples are eluted overnight and incubated in the

presence of spike antigen and ACE2 in a 96-well solid phase plate. Competitive immunoassay with electrochemiluminescent label is used to quantify neutralizing activity. The following measures of assay performance were evaluated: dilution series of confirmed positive and negative samples, agreement with results from matched DBS-serum samples, analysis of results from DBS samples with known COVID-19 status, and precision (intra-assay percent coefficient of variation; %CV) and reliability (inter-assay; %CV). Dilution series produced the expected pattern of dose–response. Agreement between results from serum and DBS samples was high, with concordance correlation = 0.991. Analysis of three control samples across the measurement range indicated acceptable levels of precision and reliability. Median % surrogate neutralization was 46.9 for PCR confirmed convalescent COVID-19 samples and 0.1 for negative samples. Large-scale testing is important for quantifying neutralizing antibodies that can provide protection against COVID-19 in order to estimate the level of immunity in the general population. DBS provides a minimally-invasive, low cost alternative to venous blood collection, and this scalable immunoassay-based method for quantifying inhibition of the spike-ACE2 interaction can be used as a surrogate for virus-based assays to expand testing across a wide range of settings and populations.

Reference

https://www.nature.com/articles/s41598-021-94653-z

An ensemble learning approach to digital corona virus preliminary screening from cough sounds

Abstract

This work develops a robust classifier for a COVID-19 pre-screening model from crowdsourced cough sound data. The crowdsourced cough recordings contain a variable number of coughs, with some input sound files more informative than the others. Accurate detection of COVID-19 from the sound datasets requires overcoming two main challenges (i) the variable number of coughs in each recording and (ii) the low number of COVID-positive cases compared to healthy coughs in the data. Two open datasets of crowdsourced cough recordings were used and then each cough recording was segmented into non-overlapping coughs. The segmentation enriches the original data without oversampling by splitting the original cough sound files into non-

overlapping segments. Splitting the sound files enables us to increase the samples of the minority class (COVID-19) without changing the feature distribution of the COVID-19 samples resulted from applying oversampling techniques. Each cough sound segment is transformed into six image representations for further analyses. We conduct extensive experiments with shallow machine learning, Convolutional Neural Network (CNN), and pre-trained CNN models. The results of the models were compared to other recently published papers that apply machine learning to cough sound data for COVID-19 detection. The method demonstrated a high performance using an ensemble model on the testing dataset with area under receiver operating characteristics curve = 0.77, precision = 0.80, recall = 0.71, F1 measure = 0.75, and Kappa = 0.53. The results show an improvement in the prediction accuracy of our COVID-19 pre-screening model compared to the other models.

Reference

https://www.nature.com/articles/s41598-021-95042-2

Combining a convolutional neural network with autoencoders to predict the survival chance of COVID-19 patients

Abstract

COVID-19 has caused many deaths worldwide. The automation of the diagnosis of this virus is highly desired. Convolutional neural networks (CNNs) have shown outstanding classification performance on image datasets. To date, it appears that COVID computer-aided diagnosis systems based on CNNs and clinical information have not yet been analysed or explored. A novel method was proposed, named the CNN-AE, to predict the survival chance of COVID-19 patients using a CNN trained with clinical information. Notably, the required resources to prepare CT images are expensive and limited compared to those required to collect clinical data, such as blood pressure, liver disease, *etc*. The method was evaluated using a publicly available clinical dataset that it was collected. The dataset properties were carefully analyzed to extract important features and compute the correlations of features. A data augmentation procedure based on autoencoders (AEs) was proposed to balance the dataset. The experimental results revealed that the average accuracy of the CNN-AE (96.05%) was higher than that of the CNN (92.49%). To demonstrate the generality of our augmentation method,

we trained some existing mortality risk prediction methods on the dataset (with and without data augmentation) and compared their performances. It was also evaluated our method using another dataset for further generality verification. To show that clinical data can be used for COVID-19 survival chance prediction, the CNN-AE was compared with multiple pre-trained deep models that were tuned based on CT images.

Reference

https://www.nature.com/articles/s41598-021-93543-8

Publication Date: Jul 27, 2021

Screening of potent neutralizing antibodies against SARS-CoV-2 using convalescent patients-derived phage-display libraries

Abstract

As the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) continues to threaten public health worldwide, the development of effective interventions is urgently needed. Neutralizing antibodies (nAbs) have great potential for the prevention and treatment of SARS-CoV-2 infection. In this study, ten nAbs were isolated from two phage-display immune libraries constructed from the pooled PBMCs of eight COVID-19 convalescent patients. Eight of them, consisting of heavy chains encoded by the immunoglobulin heavy-chain gene-variable region (IGHV)3-66 or IGHV3-53 genes, recognized the same epitope on the receptor-binding domain (RBD), while the remaining two bound to different epitopes. Among the ten antibodies, 2B11 exhibited the highest affinity and neutralization potency against the original wild-type (WT) SARS-CoV-2 virus (KD = 4.76 nM for the S1 protein, IC50 = 6 ng/mL for pseudoviruses, and IC50 = 1 ng/mL for authentic viruses), and potent neutralizing ability against B.1.1.7 pseudoviruses. Furthermore, 1E10, targeting a distinct epitope on RBD, exhibited different neutralization efficiency against WT SARS-CoV-2 and its variants B.1.1.7, B.1.351, and P.1. The crystal structure of the 2B11–RBD complexes revealed that the epitope of 2B11 highly overlaps with the ACE2-binding site. The *in vivo* experiment of 2B11 using AdV5-hACE2-transduced mice showed encouraging therapeutic and prophylactic efficacy against SARS-CoV-2. Taken together, our results suggest that the highly potent SARS-CoV-2-neutralizing antibody, 2B11, could be used against the WT

SARS-CoV-2 and B.1.1.7 variant, or in combination with a different epitope-targeted neutralizing antibody, such as 1E10, against SARS-CoV-2 variants.

Reference

http://nature.com/articles/s41421-021-00295-w

Factors influencing SARS-CoV-2 transmission and outbreak control measures in densely populated settings

Abstract

Starting with a handful of SARS-CoV-2 infections in dormitory residents in late March 2020, rapid transmission in their dense living environments ensued and by October 2020, more than 50,000 acute infections were identified across various dormitories in Singapore. The aim of the study is to identify combination of factors facilitating SARS-CoV-2 transmission and the impact of control measures in a dormitory through extensive epidemiological, serological and phylogenetic investigations, supported by simulation models. The findings showed that asymptomatic cases and symptomatic cases who did not seek medical attention were major drivers of the outbreak. Furthermore, each resident had about 30 close contacts and each infected resident spread to 4.4 (IQR 3.5–5.3) others at the start of the outbreak. The final attack rate of the current outbreak was 76.2% (IQR 70.6–98.0%) and could be reduced by further 10% under a modified dormitory housing condition. These findings are important when designing living environments in a post COVID-19 future to reduce disease spread and facilitate rapid implementation of outbreak control measures.

Reference

https://www.nature.com/articles/s41598-021-94463-3

Single-cell transcriptome of bronchoalveolar lavage fluid reveals sequential change of macrophages during SARS-CoV-2 infection in ferrets

Abstract

Few studies have used a longitudinal approach to describe the immune response to SARS-CoV-2 infection. Here, single-cell RNA sequencing of bronchoalveolar lavage fluid cells was performed longitudinally obtained from SARS-CoV-2-infected ferrets.

Landscape analysis of the lung immune microenvironment shows distinct changes in cell proportions and characteristics compared to uninfected control, at 2 and 5 days post-infection (dpi). Macrophages are classified into 10 distinct subpopulations with transcriptome changes among monocyte-derived infiltrating macrophages and differentiated M1/M2 macrophages, notably at 2 dpi. Moreover, trajectory analysis reveals gene expression changes from monocyte-derived infiltrating macrophages toward M1 or M2 macrophages and identifies a macrophage subpopulation that has rapidly undergone SARS-CoV-2-mediated activation of inflammatory responses. Finally, we find that M1 or M2 macrophages show distinct patterns of gene modules downregulated by immune-modulatory drugs. Overall, these results elucidate fundamental aspects of the immune response dynamics provoked by SARS-CoV-2 infection.

Reference

https://www.nature.com/articles/s41467-021-24807-0

Comparison of COVID-19 outcomes among shielded and non-shielded populations

Abstract

Many western countries used shielding (extended self-isolation) of people presumed to be at high-risk from COVID-19 to protect them and reduce healthcare demand. To investigate the effectiveness of this strategy, family practitioner, prescribing, laboratory, hospital and death records were linked and compared COVID-19 outcomes among shielded and non-shielded individuals in the West of Scotland. Of the 1.3 million population, 27,747 (2.03%) were advised to shield, and 353,085 (26.85%) were classified a priori as moderate risk. COVID-19 testing was more common in the shielded (7.01%) and moderate risk (2.03%) groups, than low risk (0.73%). Referent to low-risk, the shielded group had higher confirmed infections (RR 8.45, 95% 7.44–9.59), case-fatality (RR 5.62, 95% CI 4.47–7.07) and population mortality (RR 57.56, 95% 44.06–75.19). The moderate-risk had intermediate confirmed infections (RR 4.11, 95% CI 3.82–4.42) and population mortality (RR 25.41, 95% CI 20.36–31.71) but, due to their higher prevalence, made the largest contribution to deaths (PAF 75.30%). Age ≥ 70 years accounted for 49.55% of deaths. In conclusion, in spite of the shielding strategy,

high risk individuals were at increased risk of death. Furthermore, to be effective as a population strategy, shielding criteria would have needed to be widely expanded to include other criteria, such as the elderly.

Reference

https://www.nature.com/articles/s41598-021-94630-6

Mapping each pre-existing condition's association to short-term and long-term COVID-19 complications

Abstract

Understanding the relationships between pre-existing conditions and complications of COVID-19 infection is critical to identifying which patients will develop severe disease. Here, ~1.1 million clinical notes were leveraged from 1803 hospitalized COVID-19 patients and deep neural network models to characterize associations between 21 pre-existing conditions and the development of 20 complications (*e.g.* respiratory, cardiovascular, renal, and hematologic) of COVID-19 infection throughout the course of infection (i.e. 0–30 days, 31–60 days, and 61–90 days). Pleural effusion was the most frequent complication of early COVID-19 infection (89/1803 patients, 4.9%) followed by cardiac arrhythmia (45/1803 patients, 2.5%). Notably, hypertension was the most significant risk factor associated with 10 different complications including acute respiratory distress syndrome, cardiac arrhythmia, and anemia. The onset of new complications after 30 days is rare and most commonly involves pleural effusion (31–60 days: 11 patients, 61–90 days: 9 patients). Lastly, comparing the rates of complications with a propensity-matched COVID-negative hospitalized population confirmed the importance of hypertension as a risk factor for early-onset complications. Overall, the associations between pre-COVID conditions and COVID-associated complications presented here may form the basis for the development of risk assessment scores to guide clinical care pathways.

Reference

https://www.nature.com/articles/s41746-021-00484-7

Lower peripheral blood Toll-like receptor 3 expression is associated with an unfavorable outcome in severe COVID-19 patients

Abstract

The role of innate immunity in COVID-19 is not completely understood. Therefore, this study explored the impact of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection on the expression of Pattern Recognition Receptors (PRRs) in peripheral blood cells and their correlated cytokines. Seventy-nine patients with severe COVID-19 on admission, according to World Health Organization (WHO) classification, were divided into two groups: patients who needed mechanical ventilation and/or deceased (SEVERE, n = 50) and patients who used supplementary oxygen but not mechanical ventilation and survived (MILD, n = 29); a control group (CONTROL, n = 17) was also enrolled. In the peripheral blood, gene expression (mRNA) of Toll-like receptors (TLRs) 3, 4, 7, 8, and 9, retinoic-acid inducible gene I (RIGI), NOD-like receptor family pyrin domain containing 3 (NLRP3), interferon alpha (IFN-α), interferon beta (IFN-β), interferon gamma (IFN-γ), interferon lambda (IFN-λ), pro-interleukin(IL)-1β (pro-IL-1β), and IL-18 was determined on admission, between 5–9 days, and between 10–15 days. Circulating cytokines in plasma were also measured. When compared to the COVID-19 MILD group, the COVID-19 SEVERE group had lower expression of TLR3 and overexpression of TLR4.

Reference

https://www.nature.com/articles/s41598-021-94624-4

Data analytics to evaluate the impact of infectious disease on economy: Case study of COVID-19 pandemic

Abstract

SARS-CoV-2 (COVID-19) is a new strain of coronavirus that is regarded as a respiratory disease and is transmittable among humans. At present, the disease has caused a pandemic, and COVID-19 cases are ballooning out of control. The impact of such turbulent situations can be controlled by tracking the patterns of infected and death cases through accurate prediction and by taking precautions accordingly. COVID-19 case information was collected worldwide and successfully predicted infected victims

and possible death cases around the world and in the United States. In addition, some leading stock market shares were analyzed and successfully forecast their trends. The share market price was also scrutinized by proper reasoning and considered the state of affairs of COVID-19, including geographical dispersity. Developed dashboard was publicly released that presents statistical data of COVID-19 cases, shows predicted results, and reveals the impact of COVID-19 on leading companies and different countries' job markets.

Reference

https://www.cell.com/patterns/fulltext/S2666-3899(21)00158-6

Publication Date: Jul 26, 2021

Single-cell RNA sequencing reveals *ex vivo* signatures of SARS-CoV-2-reactive T cells through 'reverse phenotyping'

Abstract

The *in vivo* phenotypic profile of T cells reactive to severe acute respiratory syndrome (SARS)-CoV-2 antigens remains poorly understood. Conventional methods to detect antigen-reactive T cells require in vitro antigenic re-stimulation or highly individualized peptide-human leukocyte antigen (pHLA) multimers. Here, single-cell RNA sequencing was used to identify and profile SARS-CoV-2-reactive T cells from Coronavirus Disease 2019 (COVID-19) patients. To do so, we induce transcriptional shifts by antigenic stimulation *in vitro* and take advantage of natural T cell receptor (TCR) sequences of clonally expanded T cells as barcodes for 'reverse phenotyping'. This allows identification of SARS-CoV-2-reactive TCRs and reveals phenotypic effects introduced by antigen-specific stimulation. Transcriptional signatures of currently and previously activated SARS-CoV-2-reactive T cells were characterized, and showed correspondence with phenotypes of T cells from the respiratory tract of patients with severe disease in the presence or absence of virus in independent cohorts. Reverse phenotyping is a powerful tool to provide an integrated insight into cellular states of SARS-CoV-2-reactive T cells across tissues and activation states.

Reference

https://www.nature.com/articles/s41467-021-24730-4

Neutralizing activity of Sputnik V vaccine sera against SARS-CoV-2 variants

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected at least 180 million people since its identification as the cause of the current COVID-19 pandemic. The rapid pace of vaccine development has resulted in multiple vaccines already in use worldwide. The contemporaneous emergence of SARS-CoV-2 'variants of concern' (VOC) across diverse geographic locales underscores the need to monitor the efficacy of vaccines being administered globally. All WHO designated VOC carry spike (S) polymorphisms thought to enable escape from neutralizing antibodies. Here, the neutralizing activity of post-Sputnik V vaccination sera was characterized against the ensemble of S mutations present in alpha (B.1.1.7) and beta (B.1.351) VOC. Using de novo generated replication-competent vesicular stomatitis virus expressing various SARS-CoV-2-S in place of VSV-G (rcVSV-CoV2-S), coupled with a clonal 293T-ACE2 + TMPRSS2 + cell line optimized for highly efficient S-mediated infection, we determine that only 1 out of 12 post-vaccination serum samples shows effective neutralization (IC_{90}) of rcVSV-CoV2-S: B.1.351 at full serum strength. The same set of sera efficiently neutralize S from B.1.1.7 and exhibit only moderately reduced activity against S carrying the E484K substitution alone. Taken together, the data suggest that control of some emergent SARS-CoV-2 variants may benefit from updated vaccines.

Reference

https://www.nature.com/articles/s41467-021-24909-9

Immunogenicity and reactogenicity of heterologous ChAdOx1 nCoV-19/mRNA vaccination

Abstract

Heterologous priming with the ChAdOx1 nCoV-19 vector vaccine followed by boosting with a messenger RNA vaccine (BNT162b2 or mRNA-1273) is currently recommended in Germany, although data on immunogenicity and reactogenicity are not available. In this observational study it was shown that, in healthy adult individuals (n = 96), the heterologous vaccine regimen induced spike-specific IgG, neutralizing antibodies and spike-specific CD4 T cells, the levels of which were significantly higher than after

homologous vector vaccine boost (n = 55) and higher or comparable in magnitude to homologous mRNA vaccine regimens (n = 62). Moreover, spike-specific CD8 T cell levels after heterologous vaccination were significantly higher than after both homologous regimens. Spike-specific T cells were predominantly polyfunctional with largely overlapping cytokine-producing phenotypes in all three regimens. Recipients of both the homologous vector regimen and the heterologous vector/mRNA combination reported greater reactogenicity following the priming vector vaccination, whereas heterologous boosting was well tolerated and comparable to homologous mRNA boosting. Taken together, heterologous vector/mRNA boosting induces strong humoral and cellular immune responses with acceptable reactogenicity profiles.

Reference

https://www.nature.com/articles/s41591-021-01464-w

S494 O-glycosylation site on the SARS-CoV-2 RBD affects the virus affinity to ACE2 and its infectivity; A molecular dynamics study

Abstract

SARS-CoV-2 is a strain of Coronavirus family that caused the ongoing pandemic of COVID-19. Several studies showed that the glycosylation of virus spike (S) protein and the Angiotensin-Converting Enzyme 2 (ACE2) receptor on the host cell is critical for the virus infectivity. Molecular Dynamics (MD) simulations were used to explore the role of a novel mutated O-glycosylation site (D494S) on the Receptor Binding Domain (RBD) of S protein. This site was suggested as a key mediator of virus-host interaction. By exploring the dynamics of three O-glycosylated models and the control systems of unglcosylated S4944 and S494D complexes, it was shown that the decoration of S494 with elongated O-glycans results in stabilized interactions on the direct RBD-ACE2. Calculation of the distances between RBD and two major H1, H2 helices of ACE2 and the interacting pairs of amino acids in the interface showed that the elongated O-glycan maintains these interactions by forming several polar contacts with the neighbouring residues while it would not interfere in the direct binding interface. Relative binding free energy of RBD-ACE2 is also more favorable in the O-glycosylated models with longer glycans. The increase of RBD binding affinity to ACE2 depends on the size of attached O-glycan. By increasing the size of O-glycan, the RBD-ACE2 binding affinity will

increase. Hence, this crucial factor must be taken into account for any further inhibitory approaches towards RBD-ACE2 interaction.

Reference

https://www.nature.com/articles/s41598-021-94602-w

ChAdOx1 nCoV-19 protection against SARS-CoV-2 in rhesus macaque and ferret challenge models

Abstract

Vaccines against SARS-CoV-2 are urgently required, but early development of vaccines against SARS-CoV-1 resulted in enhanced disease after vaccination. Careful assessment of this phenomena is warranted for vaccine development against SARS CoV-2. Here detailed immune profiling was reported after ChAdOx1 nCoV-19 (AZD1222) and subsequent high dose challenge in two animal models of SARS-CoV-2 mediated disease. The lung pathology was demonstrated in rhesus macaques, caused by SARS-CoV-2 mediated pneumonia is reduced by prior vaccination with ChAdOx1 nCoV-19 which induced neutralizing antibody responses after a single intramuscular administration. In a second animal model, ferrets, ChAdOx1 nCoV-19 reduced both virus shedding and lung pathology. Antibody titre was boosted by a second dose. Data from these challenge models on the absence of enhanced disease and the detailed immune profiling, support the continued clinical evaluation of ChAdOx1 nCoV-19.

Reference

https://www.nature.com/articles/s42003-021-02443-0

Clinical outcomes of hospitalized COVID-19 patients with renal injury: A multi-hospital observational study from Wuhan

Abstract

Renal injury is common in patients with coronavirus disease 2019 (COVID-19). We aimed to determine the relationship of estimated glomerular filtration rate (eGFR) and acute kidney injury (AKI) with the characteristics, progression, and prognosis of COVID-19 in-patients. We retrospectively reviewed 1851 COVID-19 patients admitted to 3 hospitals in Wuhan, China. Clinical, laboratory, radiological, treatment, complication,

and outcome data were analyzed. Patients were stratified according to levels of eGFR (≥ 90 vs. 60–89 vs. < 60 mL/min/1.73 m^2). The risk of reaching the composite endpoint—intensive care unit admission, invasive ventilation, or death—was compared. On admission, 25.5% patients had renal impairment (eGFR < 90 mL/min/1.73 m^2), but only 2.6% patients had chronic kidney disease (CKD). The overall in-hospital AKI incidence was 6.7%. Severe illness and comorbidities (hypertension, diabetes, CKD, and cardiovascular/cerebrovascular diseases) were more common among patients with low eGFR (< 90 mL/min/1.73 m^2). Despite the more frequent use of intensive oxygen therapy, continuous blood purification, and glucocorticoid treatment, the prognosis of these patients was unsatisfactory, with the incidence of the composite endpoint (15.4% vs. 19.6% vs. 54.5%; P = 0.000) and complications (AKI, respiratory failure, cardiac injury, coagulation disorders, sepsis, etc.) increasing with decreasing eGFR. Kaplan–Meier survival analysis revealed that patients with eGFR < 90 mL/min/1.73 m^2 or AKI had significantly escalated risks of reaching the composite endpoint. Multivariate regression analysis showed that renal insufficiency (eGFR < 60 mL/min/1.73 m^2) on admission and in-hospital AKI independently predicted poor prognosis among COVID-19 in-patients. And renal impairment on admission was a greater predictor of poor prognosis in non-elderly patients than that in elderly patients. Early and continuous renal-function monitoring and early AKI diagnosis are necessary to predict and prevent the progression of COVID-19.

Reference

https://www.nature.com/articles/s41598-021-94570-1

An ultra-portable, self-contained point-of-care nucleic acid amplification test for diagnosis of active COVID-19 infection

Abstract

There is currently a high level of demand for rapid COVID-19 tests, that can detect the onset of the disease at point of care settings. An ultra-portable, self-contained, point-of-care nucleic acid amplification test was developed for diagnosis of active COVID-19 infection, based on the principle of loop mediated isothermal amplification (LAMP). The LAMP assay is 100% sensitive and specific to detect a minimum of 300 RNA copies/reaction of SARS-CoV-2. All of the required sample transportation, lysing and

amplification steps are performed in a standalone disposable cartridge, which is controlled by a battery operated, pocket size (6x9x4cm^3) unit. The test is easy to operate and does not require skilled personnel. The total time from sample to answer is approximately 35 min; a colorimetric readout indicates positive or negative results. This portable diagnostic platform has significant potential for rapid and effective testing in community settings. This will accelerate clinical decision making, in terms of effective triage and timely therapeutic and infection control interventions.

Reference

https://www.nature.com/articles/s41598-021-94652-0

A realistic transfer method reveals low risk of SARS-CoV-2 transmission *via* contaminated euro coins and banknotes

Abstract

The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has created a significant threat to global health. While respiratory aerosols or droplets are considered as the main route of human-to-human transmission, secretions expelled by infected individuals can also contaminate surfaces and objects, potentially creating the risk of fomite-based transmission. Consequently, frequently touched objects such as paper currency and coins have been suspected as potential transmission vehicle. To assess the risk of SARS-CoV-2 transmission by banknotes and coins, the stability of SARS-CoV-2 and bovine coronavirus was examined, as surrogate with lower biosafety restrictions, on these different means of payment and developed a touch transfer method to examine transfer efficiency from contaminated surfaces to fingertips. Although we observed prolonged virus stability, the results indicate that transmission of SARS-CoV-2 *via* contaminated coins and banknotes is unlikely and requires high viral loads and a timely order of specific events.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00876-2

Safety, tolerability, and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults: Preliminary report of an open-label and randomised phase 1 clinical trial

Abstract

Background: SARS-CoV-2 has caused millions of deaths, and, since Aug 11, 2020, 20 intramuscular COVID-19 vaccines have been approved for use. We aimed to evaluate the safety and immunogenicity of an aerosolised adenovirus type-5 vector-based COVID-19 vaccine (Ad5-nCoV) in adults without COVID-19 from China.

Method: This was a randomised, single-centre, open-label, phase 1 trial done in Zhongnan Hospital (Wuhan, China), to evaluate the safety and immunogenicity of the Ad5-nCoV vaccine by aerosol inhalation in adults (≥18 years) seronegative for SARS-CoV-2. Breastfeeding or pregnant women and people with major chronic illnesses or history of allergies were excluded. Participants were enrolled and randomly assigned (1:1:1:1:1) into five groups to be vaccinated via intramuscular injection, aerosol inhalation, or both. Randomisation was stratified by sex and age (18–55 years or ≥56 years) using computer-generated randomisation sequences (block sizes of five). Only laboratory staff were masked to group assignment. The participants in the two aerosol groups received an initial high dose (2 × 1010 viral particles; HDmu group) or low dose (1 × 1010 viral particles; LDmu group) of Ad5-nCoV vaccine on day 0, followed by a booster on day 28. The mixed vaccination group received an initial intramuscular (5 × 1010 viral particles) vaccine on day 0, followed by an aerosolised booster (2 × 1010 viral particles) vaccine on day 28 (MIX group). The intramuscular groups received one dose (5 × 1010 viral particles; 1Dim group) or two doses (10 × 1010 viral particles; 2Dim group) of Ad5-nCoV on day 0. The primary safety outcome was adverse events 7 days after each vaccination, and the primary immunogenicity outcome was anti-SARS-CoV-2 spike receptor IgG antibody and SARS-CoV-2 neutralising antibody geometric mean titres at day 28 after last vaccination. This trial is registered with ClinicalTrials.gov, number NCT04552366.

Findings: Between Sept 28, 2020, and Sept 30, 2020, 230 individuals were screened for inclusion, of whom 130 (56%) participants were enrolled into the trial and randomly assigned into one of the five groups (26 participants per group). Within 7 days after

vaccination, adverse events occurred in 18 (69%) in the HDmu group, 19 (73%) in the LDmu group, 19 (73%) in the MIX group, 19 (73%) in the 1Dim group, and 15 (58%) in the 2Dim group. The most common adverse events reported 7 days after the first or booster vaccine were fever (62 [48%] of 130 participants), fatigue (40 [31%] participants), and headache (46 [35%] participants). More adverse events were reported in participants who received intramuscular vaccination, including participants in the MIX group (49 [63%] of 78 participants), than those who received aerosol vaccine (13 [25%] of 52 participants) after the first vaccine vaccination. No serious adverse events were noted within 56 days after the first vaccine. At days 28 after last vaccination, geometric mean titres of SARS-CoV-2 neutralising antibody was 107 (95% CI 47–245) in the HDmu group, 105 (47–232) in the LDmu group, 396 (207–758) in the MIX group, 95 (61–147) in the 1Dim group, and 180 (113–288) in the 2Dim group. The geometric mean concentrations of receptor binding domain-binding IgG was 261 EU/mL (95% CI 121–563) in the HDmu group, 289 EU/mL (138–606) in the LDmu group, 2013 EU/mL (1180–3435) in the MIX group, 915 EU/mL (588–1423) in the 1Dim group, and 1190 EU/mL (776–1824) in the 2Dim group.

Interpretation: Aerosolised Ad5-nCoV is well tolerated, and two doses of aerosolised Ad5-nCoV elicited neutralising antibody responses, similar to one dose of intramuscular injection. An aerosolised booster vaccination at 28 days after first intramuscular injection induced strong IgG and neutralising antibody responses. The efficacy and cost-effectiveness of aerosol vaccination should be evaluated in future studies.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00396-0/fulltext

Emergence of an early SARS-CoV-2 epidemic in the United States

Abstract

The emergence of the COVID-19 epidemic in the United States (U.S.) went largely undetected due to inadequate testing. New Orleans experienced one of the earliest and fastest accelerating outbreaks, coinciding with Mardi Gras. To gain insight into the emergence of SARS-CoV-2 in the U.S. and how large-scale events accelerate transmission, SARS-CoV-2 genomes were sequenced during the first wave of the COVID-19 epidemic in Louisiana. We show that SARS-CoV-2 in Louisiana had limited

diversity compared to other U.S. states, and that one introduction of SARS-CoV-2 led to almost all of the early transmission in Louisiana. By analyzing mobility and genomic data, we show that SARS-CoV-2 was already present in New Orleans before Mardi Gras, and the festival dramatically accelerated transmission. The study provides an understanding of how superspreading during large-scale events played a key role during the early outbreak in the U.S. and can greatly accelerate epidemics.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00889-8

Publication Date: Jul 25, 2021

Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study

Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant, Gamma, emerged in the city of Manaus in late 2020 during a large resurgence of coronavirus disease (COVID-19), and has spread throughout Brazil. The effectiveness of vaccines in settings with widespread Gamma variant transmission has not been reported.

Methods: A matched test-negative case-control study was performed to estimate the effectiveness of an inactivated vaccine, CoronaVac, in healthcare workers (HCWs) in Manaus, where the Gamma variant accounted for 86% of genotyped SARS-CoV-2 samples at the peak of its epidemic. An early analysis of effectiveness was performed following administration of at least one vaccine dose and an analysis of effectiveness of the two-dose schedule. The primary outcome was symptomatic SARS-CoV-2 infection.

Findings: For the early at-least-one-dose and two-dose analyses the study population was, respectively, 53,176 and 53,153 HCWs residing in Manaus and aged 18 years or older, with complete information on age, residence, and vaccination status. Among 53,153 HCWs eligible for the two-dose analysis, 47,170 (89%) received at least one dose of CoronaVac and 2,656 individuals (5%) underwent RT-PCR testing from 19

January, 2021 to 13 April, 2021. Of 3,195 RT-PCR tests, 885 (28%) were positive. 393 and 418 case-control pairs were selected for the early and two-dose analyses, respectively, matched on calendar time, age, and neighbourhood. Among those who had received both vaccine doses before the RT-PCR sample collection date, the average time from second dose to sample collection date was 14 days (IQR 7-24). In the early analysis, vaccination with at least one dose was associated with a 0.50-fold reduction (adjusted vaccine effectiveness (VE), 49.6%, 95% CI 11.3 to 71.4) in the odds of symptomatic SARS-CoV-2 infection during the period 14 days or more after receiving the first dose. However, low effectiveness (adjusted VE 36.8%, 95% CI -54.9 to 74.2) of the two-dose schedule was estimated against symptomatic SARS-CoV-2 infection during the period 14 days or more after receiving the second dose. A finding that vaccinated individuals were much more likely to be infected than unvaccinated individuals in the period 0-13 days after first dose (aOR 2.11, 95% CI 1.36-3.27) suggests that unmeasured confounding led to downward bias in the vaccine effectiveness estimate.

Interpretation: Evidence from this test-negative study of the effectiveness of CoronaVac was mixed, and likely affected by bias in this setting. Administration of at least one vaccine dose showed effectiveness against symptomatic SARS-CoV-2 infection in the setting of epidemic Gamma variant transmission. However, the low estimated effectiveness of the two-dose schedule underscores the need to maintain non-pharmaceutical interventions while vaccination campaigns with CoronaVac are being implemented.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00017-X/fulltext

Publication Date: Jul 23, 2021

SARS-CoV-2 activates lung epithelial cell proinflammatory signaling and leads to immune dysregulation in COVID-19 patients

Abstract

Background: The outbreak of Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 infection has become a global health emergency. It was aimed to decipher

SARS-CoV-2 infected cell types, the consequent host immune response and their interplay in lung of COVID-19 patients.

Methods: Single-cell RNA sequencing (scRNA-seq) data of bronchoalveolar lavage fluid (BALF) samples was analyzed from 10 healthy donors, 6 severe COVID-19 patients and 3 mild recovered patients. The expressions of SARS-CoV-2 receptors (*ACE2* and *TMPRSS2*) were examined among different cell types. The immune cells infiltration patterns, their expression profiles, and interplays between immune cells and SARS-CoV-2 target cells were further investigated.

Findings: Compared to healthy controls, *ACE2* and *TMPRSS2* expressions were significantly higher in lung epithelial cells of COVID-19 patients, in particular club and ciliated cells. SARS-CoV-2 activated pro-inflammatory genes and interferon/cytokine signaling in these cells. In severe COVID-19 patients, significantly higher neutrophil, but lower macrophage in lung was observed along with markedly increased cytokines expression compared with healthy controls and mild patients. By contrast, neutrophil and macrophage returned to normal level whilst more T and NK cells accumulation were observed in mild patients. Moreover, SARS-CoV-2 infection altered the community interplays of lung epithelial and immune cells: interactions between the club and immune cells were higher in COVID-19 patients compared to healthy donors; on the other hand, immune-immune cells interactions appeared the strongest in mild patients.

Interpretation: SARS-CoV-2 could infect lung epithelium, alter communication patterns between lung epithelial cells and immune system, and drive dysregulated host immune response in COVID-19 patients.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00293-0/fulltext

SARS-Cov-2 prevalence, transmission, health-related outcomes and control strategies in homeless shelters: Systematic review and meta-analysis

Abstract

Background: People experiencing homelessness (PEH) may be at risk for COVID19. We synthesised evidence on SARS-Cov-2 infection, transmission, outcomes of disease,

effects of non-pharmaceutical interventions (NPI), and the effectiveness of strategies for infection prevention and control (IPC).

Methods: Systematic review of articles, indexed in electronic databases (EMBASE, WHO Covid19, Web of Science), institutional websites and the Norwegian Institute of Public Health's live map of COVID-19 evidence, and published from December 1st, 2019, to March 3rd, 2021. Empirical papers of any study design addressing Covid-19 and health(-related) outcomes in PEH or shelters' staff were included. (PROSPERO-2020-CRD42020187033)

Findings: Of 536 publications, 37 studies were included (two modelling, 31 observational, four qualitative studies). Random-effect meta-analysis yields a baseline SARS-Cov-2 prevalence of 2•32% (95% Confidence-Interval, 95%CI=1•30–3•34) in PEH and 1•55% (95%CI=0•79–2•31) in staff. In outbreaks, the pooled prevalence increases to 31•59% (95%CI=20•48–42•71) in PEH and 14•80% (95%CI=10•73–18•87) in staff. Main IPC strategies were universal rapid testing, expansion of non-congregate housing, and in-shelter measures (bed spacing, limited staff rotation, reduction in number of residents).

Interpretation: 32% of PEH and 15% staff are infected during outbreaks of SARS-Cov-2 in homeless shelters. Most studies were conducted in the USA. No studies were found quantifying health-related outcomes of NPI. Overview and evaluation of IPC strategies for PEH, a better understanding of disease transmission, and reliable data on PEH within Covid-19 notification systems are needed. Qualitative studies may serve to voice PEH and shelter staff experiences, and guide future evaluations and IPC strategies.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00312-6/fulltext

A prospective observational safety study on ChAdOx1 nCoV-19 corona virus vaccine (recombinant) use in healthcare workers-first results from India

Abstract

Background: We provide the first post-approval safety analysis of COVISHIELD in health care workers (HCWs) in northern India.

Methods: This continuing prospective observational study (February 2021 to May 2022) enrolled participants ≥18 years receiving COVISHIELD vaccination. Primary outcome was safety and reactogenicity. Categories (FDA toxicity grading) and outcomes of adverse events following immunization (AEFIs) were recorded, causality assessment performed, and risk factors analysed.

Findings: The results of an interim analysis of 804 participants, were present. AEFIs following first dose were reported in 321 (40%; systemic involvement in 248). Among 730 participants who completed a 7-day follow-up post second dose, AEFIs occurred in 115 (15.7%; systemic in 99). Majority of AEFIs were mild-moderate and resolved spontaneously. Serious AEFIs, leading to hospitalization was noticed in 1 (0.1%) participant with suspicion of immunization stress related response (ISRR). AEFIs of grade 3 severity (FDA) were recorded in 4 participants (0.5%). No deaths were recorded. Regression analysis showed increased risk of AEFIs in younger individuals, a two times higher odds in females, those with hypertension or with history of allergy; and three times higher odds in individuals with hypothyroidism.

Interpretation: COVISHIELD carries an overall favourable safety profile with AEFI rates much less than reported for other adenoviral vaccines. Females, those with hypertension, individuals with history of allergy and hypothyroidism may need watchful vaccine administration. This being an interim analysis and based on healthcare workers who may not reflect the general population demographics, larger inclusive studies are warranted for confirming the findings.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00318-7/fulltext

RBM15-mediated N6-methyladenosine modification affects COVID-19 severity by regulating the expression of multitarget genes

Abstract

Severe coronavirus disease 2019 (COVID-19) is characterized by symptoms of lymphopenia and multiorgan damage, but the underlying mechanisms remain unclear. To explore the function of N6-methyladenosine (m6A) modifications in COVID-19, microarray analyses were performed to comprehensively characterize the m6A

epitranscriptome. The results revealed distinct global m6A profiles in severe and mild COVID-19 patients. Programmed cell death and inflammatory response were the major biological processes modulated by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Further, RBM15, a major m6A methyltransferase, was significantly elevated and positively correlated with disease severity. Silencing RBM15 drastically reduced lymphocyte death *in vitro*. Knockdown of RBM15 remarkably suppressed the expression levels of multitarget genes related to programmed cell death and inflammatory response. This study shows that SARS-CoV-2 infection alters the m6A epitranscriptome of lymphocytes, particularly in the case of severe patients. RBM15 regulated host immune response to SARS-CoV-2 by elevating m6A modifications of multitarget genes. These findings indicate that RBM15 can serve as a target for the treatment of COVID-19.

Reference

http://nature.com/articles/s41419-021-04012-z

G6PD distribution in sub-Saharan Africa and potential risks of using chloroquine/hydroxychloroquine based treatments for COVID-19

Abstract

Chloroquine/hydroxychloroquine have been proposed as potential treatments for COVID-19. These drugs have warning labels for use in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Analysis of whole genome sequence data of 458 individuals from sub-Saharan Africa showed significant G6PD variation across the continent. Nine variants were identified, of which four are potentially deleterious to G6PD function, and one (rs1050828) that is known to cause G6PD deficiency. Data was supplemented for the rs1050828 variant with genotype array data from over 11,000 Africans. Although this variant is common in Africans overall, large allele frequency differences exist between sub-populations. African sub-populations in the same country can show significant differences in allele frequency (e.g. 16.0% in Tsonga vs 0.8% in Xhosa, both in South Africa, $p = 2.4 \times 10-3$). The high prevalence of variants in the G6PD gene found in this analysis suggests that it may be a significant interaction factor in clinical trials of chloroquine and hydroxychloroquine for treatment of COVID-19 in Africans.

Reference

https://www.nature.com/articles/s41397-021-00242-8

Repeated cross-sectional analysis of hydroxychloroquine deimplementation in the AHA COVID-19 CVD Registry

Abstract

There is little data describing trends in the use of hydroxychloroquine for COVID-19 following publication of randomized trials that failed to demonstrate a benefit of this therapy. 13,957 Patients admitted for active COVID-19 were identified at 85 U.S. hospitals participating in a national registry between March 1 and August 31, 2020. The overall proportion of patients receiving hydroxychloroquine peaked at 55.2% in March and April and decreased to 4.8% in May and June and 0.8% in July and August. At the hospital-level, median use was 59.4% in March and April (IQR 48.5–71.5%, range 0–100%) and decreased to 0.3% (IQR 0–5.4%, range 0–100%) by May and June and 0% (IQR 0–1.3%, range 0–36.4%) by July and August. The rate and hospital-level uniformity in deimplementation of this ineffective therapy for COVID-19 reflects a rapid response to evolving clinical information and further study may offer strategies to inform deimplementation of ineffective clinical care.

Reference

https://www.nature.com/articles/s41598-021-94203-7

The effect of high-dose parenteral vitamin D3 on COVID-19-related inhospital mortality in critical COVID-19 patients during intensive care unit admission: An observational cohort study

Abstract

Background: In many studies, vitamin D has been found to be low in COVID-19 patients. In this study, we aimed to investigate the relationship between clinical course and inhospital mortality with parenteral administration of high-dose vitamin D3 within the first 24 h of admission to patients who were hospitalized in the intensive care unit (ICU) because of COVID-19 with vitamin D deficiency.

Methods: This study included 175 COVID-19 patients with vitamin D deficiency [25(OH) D <12 ng/mL] who were hospitalized in the ICU. Vitamin D3 group (n = 113) included patients who received a single dose of 300,000 IU vitamin D3 intramuscularly. Vitamin D3 was not administered to the control group (n = 62).

Results: Median C-reactive protein level was 10.8 mg/dL in the vitamin D3 group and 10.6 mg/dL in the control group (p = 0.465). Thirty-nine percent (n = 44) of the patients in the vitamin D3 group were intubated endotracheally, and 50% (n = 31) of the patients in the control group were intubated endotracheally (p = 0.157). Parenteral vitamin D3 administration was not associated with inhospital mortality by multivariate logistic regression analysis. According to Kaplan–Meier survival analysis, the median survival time was 16 d in the vitamin D3 group and 17 d in the control group (log-rank test, p = 0.459).

Conclusion: In this study, which was performed for the first time in the literature, it was observed that high-dose parenteral vitamin D3 administration in critical COVID-19 patients with vitamin D deficiency during admission to the ICU did not reduce the need for intubation, length of hospital stay, and inhospital mortality.

Reference

https://www.nature.com/articles/s41430-021-00984-5

Publication Date: Jul 22, 2021

Humoral immunity to SARS-CoV-2 and seasonal coronaviruses in children and adults in north-eastern France

Abstract

Background: Children are underrepresented in the COVID-19 pandemic and often experience milder disease than adolescents and adults. Reduced severity is possibly due to recent and more frequent seasonal human coronaviruses (HCoV) infections. The seroprevalence of SARS-CoV-2 and seasonal HCoV specific antibodies were assessed in a large cohort in north-eastern France.

Methods: In this cross-sectional seroprevalence study, serum samples were collected from children and adults requiring hospital admission for non-COVID-19 between

February and August 2020. Antibody responses to SARS-CoV-2 and seasonal HCoV (229E, HKU1, NL63, OC43) were assessed using a bead-based multiplex assay, Luciferase-Linked ImmunoSorbent Assay, and a pseudotype neutralisation assay.

Findings: In 2,408 individuals, seroprevalence of SARS-CoV-2-specific antibodies was 7-8% with three different immunoassays. Antibody levels to seasonal HCoV increased substantially up to the age of 10. Antibody responses in SARS-CoV-2 seropositive individuals were lowest in adults 18-30 years. In SARS-CoV-2 seronegative individuals, we observed cross-reactivity between antibodies to the four HCoV and SARS-CoV-2 Spike. In contrast to other antibodies to SARS-CoV-2, specific antibodies to sub-unit 2 of Spike (S2) in seronegative samples were highest in children. Upon infection with SARS-CoV-2, antibody levels to Spike of betacoronavirus OC43 increased across the whole age spectrum. No SARS-CoV-2 seropositive individuals with low levels of antibodies to seasonal HCoV were observed.

Interpretation: The findings underline significant cross-reactivity between antibodies to SARS-CoV-2 and seasonal HCoV, but provide no significant evidence for cross-protective immunity to SARS-CoV-2 infection due to a recent seasonal HCoV infection. In particular, across all age groups we did not observe SARS-CoV-2 infected individuals with low levels of antibodies to seasonal HCoV.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00288-7/fulltext

Shorter leukocyte telomere length is associated with adverse COVID-19 outcomes: A cohort study in UK Biobank

Abstract

Background: Older age is the most powerful risk factor for adverse coronavirus disease-19 (COVID-19) outcomes. It is uncertain whether leucocyte telomere length (LTL), previously proposed as a marker of biological age, is also associated with COVID-19 outcomes.

Methods: LTL values obtained from participants recruited into UK Biobank (UKB), were associated during 2006–2010 with adverse COVID-19 outcomes recorded by 30 November 2020, defined as a composite of any of the following: hospital admission,

need for critical care, respiratory support, or mortality. Using information on 130 LTL-associated genetic variants, we conducted exploratory Mendelian randomisation (MR) analyses in UKB to evaluate whether observational associations might reflect cause-and-effect relationships.

Findings: Of 6775 participants in UKB who tested positive for infection with SARS-CoV-2 in the community, there were 914 (13.5%) with adverse COVID-19 outcomes. The odds ratio (OR) for adverse COVID-19 outcomes was 1·17 (95% CI 1·05–1·30; P = 0·004) per 1-SD shorter usual LTL, after adjustment for age, sex and ethnicity. Similar ORs were observed in analyses that: adjusted for additional risk factors; disaggregated the composite outcome and reduced the scope for selection or collider bias. In MR analyses, the OR for adverse COVID-19 outcomes was directionally concordant but non-significant.

Interpretation: Shorter LTL is associated with higher risk of adverse COVID-19 outcomes, independent of several major risk factors for COVID-19 including age. Further data are needed to determine whether this association reflects causality.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00278-4/fulltext

Cognitive deficits in people who have recovered from COVID-19

Abstract

Background: There is growing concern about possible cognitive consequences of COVID-19, with reports of 'Long COVID' symptoms persisting into the chronic phase and case studies revealing neurological problems in severely affected patients. However, there is little information regarding the nature and broader prevalence of cognitive problems post-infection or across the full spread of disease severity.

Methods: It was sought to confirm whether there was an association between cross-sectional cognitive performance data from 81,337 participants who between January and December 2020 undertook a clinically validated web-optimized assessment as part of the Great British Intelligence Test, and questionnaire items capturing self-report of suspected and confirmed COVID-19 infection and respiratory symptoms.

Findings: People who had recovered from COVID-19, including those no longer reporting symptoms, exhibited significant cognitive deficits versus controls when controlling for age, gender, education level, income, racial-ethnic group, pre-existing medical disorders, tiredness, depression and anxiety. The deficits were of substantial effect size for people who had been hospitalised (N = 192), but also for non-hospitalised cases who had biological confirmation of COVID-19 infection (N = 326). Analysing markers of premorbid intelligence did not support these differences being present prior to infection. Finer grained analysis of performance across sub-tests supported the hypothesis that COVID-19 has a multi-domain impact on human cognition.

Interpretation: These results accord with reports of 'Long Covid' cognitive symptoms that persist into the early-chronic phase. They should act as a clarion call for further research with longitudinal and neuroimaging cohorts to plot recovery trajectories and identify the biological basis of cognitive deficits in SARS-COV-2 survivors.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00324-2/fulltext

Humoral and cellular immunity to SARS-CoV-2 vaccination in renal transplant versus dialysis patients: A prospective, multicenter observational study using mRNA-1273 or BNT162b2 mRNA vaccine

Abstract

Background: Dialysis and kidney transplant patients are vulnerable populations for COVID-19 related disease and mortality.

Methods: We conducted a prospective study exploring the eight week time course of specific cellular (interferon-γ release assay and flow cytometry) or/and humoral immune responses (ELISA) to SARS-CoV-2 boost vaccination in more than 3100 participants including medical personnel, dialysis patients and kidney transplant recipients using mRNA vaccines BNT162b2 or mRNA-1273.

Results: SARS-CoV-2-vaccination induced seroconversion efficacy in dialysis patients was similar to medical personnel (> 95%), but markedly impaired in kidney transplant recipients (42%). T-cellular immunity largely mimicked humoral results. Major risk factors of seroconversion failure were immunosuppressive drug number and type

(belatacept, MMF-MPA, calcineurin-inhibitors) as well as vaccine type (BNT162b2 mRNA). Seroconversion rates induced by mRNA-1273 compared to BNT162b2 vaccine were 97% to 88% ($p < 0.001$) in dialysis and 49% to 26% in transplant patients, respectively. Specific IgG directed against the new binding domain of the spike protein (RDB) were significantly higher in dialysis patients vaccinated by mRNA-1273 (95%) compared to BNT162b2 (85%, $p < 0.001$). Vaccination appeared safe and highly effective demonstrating an almost complete lack of symptomatic COVID-19 disease after boost vaccination as well as ceased disease incidences during third pandemic wave in dialysis patients.

Conclusion: Dialysis patients exhibit a remarkably high seroconversion rate of 95% after boost vaccination, while humoral response is impaired in the majority of transplant recipients. Immunosuppressive drug number and type as well as vaccine type (BNT162b2) are major determinants of seroconversion failure in both dialysis and transplant patients suggesting immune monitoring and adaption of vaccination protocols.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00155-1/fulltext

Anosmia, ageusia, and other COVID-19-like symptoms in association with a positive SARS-CoV-2 test, across six national digital surveillance platforms: An observational study

Abstract

Background: Multiple voluntary surveillance platforms were developed across the world in response to the COVID-19 pandemic, providing a real-time understanding of population-based COVID-19 epidemiology. During this time, testing criteria broadened and health-care policies matured. It was aimed to test whether there were consistent associations of symptoms with SARS-CoV-2 test status across three surveillance platforms in three countries (two platforms per country), during periods of testing and policy changes.

Methods: For this observational study, data of observations was used from three volunteer COVID-19 digital surveillance platforms (Carnegie Mellon University and

University of Maryland Facebook COVID-19 Symptom Survey, ZOE COVID Symptom Study app, and the Corona Israel study) targeting communities in three countries (Israel, the UK, and the USA; two platforms per country). The study population included adult respondents (age 18–100 years at baseline) who were not health-care workers. We did logistic regression of self-reported symptoms on self-reported SARS-CoV-2 test status (positive or negative), adjusted for age and sex, in each of the study cohorts. We compared odds ratios (ORs) across platforms and countries, and meta-analyses were did assuming a random effects model. Testing policy changes, COVID-19 incidence, and time scales of duration of symptoms and symptom-to-test time were also evaluated.

Findings: Between April 1 and July 31, 2020, 514 459 tests from over 10 million respondents were recorded in the six surveillance platform datasets. Anosmia–ageusia was the strongest, most consistent symptom associated with a positive COVID-19 test (robust aggregated rank one, meta-analysed random effects OR 16·96, 95% CI 13·13–21·92). Fever (rank two, 6·45, 4·25–9·81), shortness of breath (rank three, 4·69, 3·14–7·01), and cough (rank four, 4·29, 3·13–5·88) were also highly associated with test positivity. The association of symptoms with test status varied by duration of illness, timing of the test, and broader test criteria, as well as over time, by country, and by platform.

Interpretation: The strong association of anosmia–ageusia with self-reported positive SARS-CoV-2 test was consistently observed, supporting its validity as a reliable COVID-19 signal, regardless of the participatory surveillance platform, country, phase of illness, or testing policy. These findings show that associations between COVID-19 symptoms and test positivity ranked similarly in a wide range of scenarios. Anosmia, fever, and respiratory symptoms consistently had the strongest effect estimates and were the most appropriate empirical signals for symptom-based public health surveillance in areas with insufficient testing or benchmarking capacity. Collaborative syndromic surveillance could enhance real-time epidemiological investigations and public health utility globally.

Reference

https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00115-1/fulltext

Immediate effect of the COVID-19 pandemic on patient health, health-care use, and behaviours: Results from an international survey of people with rheumatic diseases

Abstract

Background: The impact and consequences of the COVID-19 pandemic on people with rheumatic disease are unclear. The COVID-19 Global Rheumatology Alliance Patient Experience Survey was developed to assess the effects of the COVID-19 pandemic on people with rheumatic disease worldwide.

Methods: Survey questions were developed by key stakeholder groups and disseminated worldwide through social media, websites, and patient support organisations. Questions included demographics, rheumatic disease diagnosis, COVID-19 diagnosis, adoption of protective behaviours to mitigate COVID-19 exposure, medication access and changes, health-care access and communication with rheumatologists, and changes in employment or schooling. Adults age 18 years and older with inflammatory or autoimmune rheumatic diseases were eligible for inclusion. We included participants with and without a COVID-19 diagnosis. We excluded participants reporting only non-inflammatory rheumatic diseases such as fibromyalgia or osteoarthritis.

Findings: 12 117 Responses to the survey were received between April 3 and May 8, 2020, and of these, 10 407 respondents had included appropriate age data. We included complete responses from 9300 adults with rheumatic disease (mean age 46·1 years; 8375 [90·1%] women, 893 [9·6%] men, and 32 [0·3%] participants who identified as non-binary). 6273 (67·5%) of respondents identified as White, 1565 (16·8%) as Latin American, 198 (2·1%) as Black, 190 (2·0%) as Asian, and 42 (0·5%) as Native American or Aboriginal or First Nation. The most common rheumatic disease diagnoses included rheumatoid arthritis (3636 [39·1%] of 9300), systemic lupus erythematosus (2882 [31·0%]), and Sjögren's syndrome (1290 [13·9%]). Most respondents (6921 [82·0%] of 8441) continued their antirheumatic medications as prescribed. Almost all (9266 [99·7%] of 9297) respondents adopted protective behaviours to limit SARS-CoV-2 exposure. A change in employment status occurred in 2524 (27·1%) of 9300) of

respondents, with a 13·6% decrease in the number in full-time employment (from 4066 to 3514).

Interpretation: People with rheumatic disease maintained therapy and followed public health advice to mitigate the risks of COVID-19. Substantial employment status changes occurred, with potential implications for health-care access, medication affordability, mental health, and rheumatic disease activity.

Reference

https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00175-2/fulltext

Altered oral and gut microbiota and its association with SARS-CoV-2 viral load in COVID-19 patients during hospitalization

Abstract

The human oral and gut commensal microbes play vital roles in the development and maintenance of immune homeostasis, while its association with susceptibility and severity of SARS-CoV-2 infection is barely understood. In this study, the dynamics of the oral and intestinal flora were investigated before and after the clearance of SARS-CoV-2 in 53 COVID-19 patients, and then examined their microbiome alterations in comparison to 76 healthy individuals. A total of 140 throat swab samples and 81 fecal samples from these COVID-19 patients during hospitalization, and 44 throat swab samples and 32 fecal samples from sex and age-matched healthy individuals were collected and then subjected to 16S rRNA sequencing and viral load inspection. It was found that SARS-CoV-2 infection was associated with alterations of the microbiome community in patients as indicated by both alpha and beta diversity indexes. Several bacterial taxa were identified related to SARS-CoV-2 infection, wherein elevated *Granulicatella* and *Rothia mucilaginosa* were found in both oral and gut microbiome. The SARS-CoV-2 viral load in those samples was also calculated to identify potential dynamics between COVID-19 and the microbiome. These findings provide a meaningful baseline for microbes in the digestive tract of COVID-19 patients and will shed light on new dimensions for disease pathophysiology, potential microbial biomarkers, and treatment strategies for COVID-19.

Reference

https://www.nature.com/articles/s41522-021-00232-5

A single dose of replication-competent VSV-vectored vaccine expressing SARS-CoV-2 S1 protects against virus replication in a hamster model of severe COVID-19

Abstract

The development of effective countermeasures against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the agent responsible for the COVID-19 pandemic, is a priority. ConVac, a replication-competent vesicular stomatitis virus (VSV) vaccine vector, was designed and produced that expresses the S1 subunit of SARS-CoV-2 spike protein. Golden Syrian hamsters were used as animal models of severe COVID-19 to test the efficacy of the ConVac vaccine. A single vaccine dose elicited high levels of SARS-CoV-2 specific binding and neutralizing antibodies; following intranasal challenge with SARS-CoV-2, animals were protected from weight loss and viral replication in the lungs. No enhanced pathology was observed in vaccinated animals upon challenge, but some inflammation was still detected. The data indicate rapid control of SARS-CoV-2 replication by the S1-based VSV-vectored SARS-CoV-2 ConVac vaccine.

Reference

https://www.nature.com/articles/s41541-021-00352-1

Liposome-mediated detection of SARS-CoV-2 RNA-positive extracellular vesicles in plasma

Abstract

Plasma SARS-CoV-2 RNA may represent a viable diagnostic alternative to respiratory RNA levels, which rapidly decline after infection. Quantitative PCR with reverse transcription (RT–qPCR) reference assays exhibit poor performance with plasma, probably reflecting the dilution and degradation of viral RNA released into the circulation, but these issues could be addressed by analysing viral RNA packaged into extracellular vesicles. Here an assay approach was described in which extracellular vesicles directly captured from plasma are fused with reagent-loaded liposomes to

sensitively amplify and detect a SARS-CoV-2 gene target. This approach accurately identified patients with COVID-19, including challenging cases missed by RT–qPCR. SARS-CoV-2-positive extracellular vesicles were detected at day 1 post-infection, and plateaued from day 6 to the day 28 endpoint in a non-human primate model, while signal durations for 20–60 days were observed in young children. This nanotechnology approach uses a non-infectious sample and extends virus detection windows, offering a tool to support COVID-19 diagnosis in patients without SARS-CoV-2 RNA detectable in the respiratory tract.

Reference

https://www.nature.com/articles/s41565-021-00939-8

Discovery of SARS-CoV-2-E channel inhibitors as antiviral candidates

Abstract

Lack of efficiency has been a major problem shared by all currently developed anti-SARS-CoV-2 therapies. The previous study shows that SARS-CoV-2 structural envelope (2-E) protein forms a type of cation channel, and heterogeneously expression of 2-E channels causes host cell death. In this study, a cell-based high throughput screening (HTS) assay was developed and used it to discover inhibitors against 2-E channels. Among 4376 compounds tested, 34 hits with cell protection activity were found. Followed by an anti-viral analysis, 15 compounds which could inhibit SARS-CoV-2 replication were identified. In electrophysiological experiments, three representatives showing inhibitory effect on 2-E channels were chosen for further characterization. Among them, proanthocyanidins directly bound to 2-E channel with binding affinity (KD) of 22.14 μM in surface plasmon resonance assay. Molecular modeling and docking analysis revealed that proanthocyanidins inserted into the pore of 2-E N-terminal vestibule acting as a channel blocker. Consistently, mutations of Glu 8 and Asn 15, two residues lining the proposed binding pocket, abolished the inhibitory effects of proanthocyanidins. The natural product proanthocyanidins are widely used as cosmetic, suggesting a potential of proanthocyanidins as disinfectant for external use. This study further demonstrates that 2-E channel is an effective antiviral drug target and provides a potential antiviral candidate against SARS-CoV-2.

Reference

https://www.nature.com/articles/s41401-021-00732-2

Effect of time and titer in convalescent plasma therapy for COVID-19

Abstract

The clinical benefit of convalescent plasma (CP) for patients with coronavirus disease (COVID)-19 is still debated. In this systematic review and meta-analysis, we selected 10 randomized clinical trials (RCTs) and 15 non-randomized studies (total number of patients = 22,591) of CP treatment and evaluated two different scenarios: (1) disease stage of plasma recipients and (2) donated plasma antibody titer, considering all-cause mortality at the latest follow-up. The results show that, when provided at early stages of the disease, CP significantly reduced mortality: risk ratio (RR) 0.72 (0.68, 0.77), $p < 0.00001$, while provided in severe or critical conditions, it did not (RR: 0.94 [0.86, 1.04], $p = 0.22$). On the other hand, the benefit on mortality was not increased by using plasma with a high-antibody titer compared with unselected plasma. This meta-analysis might promote CP usage in patients with early-stage COVID-19 in further RCTs to maximize its benefit in decreasing mortality, especially in less affluent countries.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00866-X

Systemic IL-15, IFN-γ, and IP-10/CXCL10 signature associated with effective immune response to SARS-CoV-2 in BNT162b2 mRNA vaccine recipients

Abstract

Early responses to vaccination are important for shaping both humoral and cellular protective immunity. Dissecting innate vaccine signatures may predict immunogenicity to help optimize the efficacy of mRNA and other vaccine strategies. Here, the cytokine and chemokine responses were characterized to the 1st and 2nd dose of the BNT162b2 mRNA (Pfizer/BioNtech) vaccine in antigen-naive and in previously coronavirus disease 2019 (COVID-19)-infected individuals (NCT04743388). Transient increases in interleukin-15 (IL-15) and interferon gamma (IFN-γ) levels early after boost correlate with Spike antibody levels, supporting their use as biomarkers of effective humoral immunity development in response to vaccination. A systemic signature was identified

including increases in IL-15, IFN-γ, and IP-10/CXCL10 after the 1st vaccination, which were enriched by tumor necrosis factor alpha (TNF-α) and IL-6 after the 2nd vaccination. In previously COVID-19-infected individuals, a single vaccination results in both strong cytokine induction and antibody titers similar to the ones observed upon booster vaccination in antigen-naive individuals, a result with potential implication for future public health recommendations.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00932-3

Memory B cell repertoire for recognition of evolving SARS-CoV-2 spike

Abstract

Memory B cell reserves can generate protective antibodies against repeated SARS-CoV-2 infections, but with unknown reach from original infection to antigenically drifted variants. Memory B cell receptor-encoded antibodies were charted from 19 COVID-19 convalescent subjects against SARS-CoV-2 spike (S) and found seven major antibody competition groups against epitopes recurrently targeted across individuals. Inclusion of published and newly determined structures of antibody-S complexes identified corresponding epitopic regions. Group assignment correlated with cross-CoV-reactivity breadth, neutralization potency, and convergent antibody signatures. Although emerging SARS-CoV-2 variants of concern escaped binding by many members of the groups associated with the most potent neutralizing activity, some antibodies in each of those groups retained affinity—suggesting that otherwise redundant components of a primary immune response are important for durable protection from evolving pathogens. The results furnish a global atlas of S-specific memory B cell repertoires and illustrate properties driving viral escape and conferring robustness against emerging variants.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00884-9

Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19

Abstract

SARS-CoV-2 infection can cause severe respiratory COVID-19. However, many individuals present with isolated upper respiratory symptoms, suggesting potential to constrain viral pathology to the nasopharynx. Which cells SARS-CoV-2 primarily targets and how infection influences the respiratory epithelium remains incompletely understood. scRNA-seq was performed on nasopharyngeal swabs from 58 healthy and COVID-19 participants. During COVID-19, expansion of secretory, loss of ciliated, and epithelial cell repopulation were observed *via* deuterosomal cell expansion. In mild and moderate COVID-19, epithelial cells express anti-viral/interferon-responsive genes, while cells in severe COVID-19 have muted anti-viral responses despite equivalent viral loads. SARS-CoV-2 RNA+ host-target cells are highly heterogenous, including developing ciliated, interferon-responsive ciliated, AZGP1high goblet, and KRT13+ “hillock”-like cells, and genes were identified associated with susceptibility, resistance, or infection response. The study defines protective and detrimental responses to SARS-CoV-2, the direct viral targets of infection, and suggests that failed nasal epithelial anti-viral immunity may underlie and precede severe COVID-19.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(21)00882-5

Spatiotemporal invasion dynamics of SARS-CoV-2 lineage B.1.1.7 emergence

Abstract

Understanding the causes and consequences of the emergence of SARS-CoV-2 variants of concern is crucial to pandemic control yet difficult to achieve, as they arise in the context of variable human behavior and immunity. The spatial invasion dynamics of lineage B.1.1.7 were investigated by jointly analyzing UK human mobility, virus genomes, and community-based PCR data. A multi-stage spatial invasion process was identified in which early B.1.1.7 growth rates were associated with mobility and asymmetric lineage export from a dominant source location, enhancing the effects of B.1.1.7’s increased intrinsic transmissibility. It was further explored how B.1.1.7 spread was shaped by non-pharmaceutical interventions and spatial variation in previous attack

rates. The findings show that careful accounting of the behavioral and epidemiological context within which variants of concern emerge is necessary to interpret correctly their observed relative growth rates.

Reference

https://science.sciencemag.org/content/early/2021/07/22/science.abj0113

Publication Date: Jul 21, 2021

Dapagliflozin in patients with cardiometabolic risk factors hospitalised with COVID-19 (DARE-19): A randomised, double-blind, placebo-controlled, phase 3 trial

Abstract

Background: COVID-19 can lead to multiorgan failure. Dapagliflozin, a SGLT2 inhibitor, has significant protective benefits for the heart and kidney. We aimed to see whether this agent might provide organ protection in patients with COVID-19 by affecting processes dysregulated during acute illness.

Methods: DARE-19 was a randomised, double-blind, placebo-controlled trial of patients hospitalised with COVID-19 and with at least one cardiometabolic risk factor (ie, hypertension, type 2 diabetes, atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease). Patients critically ill at screening were excluded. Patients were randomly assigned 1:1 to dapagliflozin (10 mg daily orally) or matched placebo for 30 days. Dual primary outcomes were assessed in the intention-to-treat population: the outcome of prevention (time to new or worsened organ dysfunction or death), and the hierarchial composite outcome of recovery (change in clinical status by day 30). Safety outcomes, in patients who received at least one study medication dose, included serious adverse events, adverse events leading to discontinuation, and adverse events of interest. This study is registered with ClinicalTrials.gov, NCT04350593.

Findings: Between April 22, 2020 and Jan 1, 2021, 1250 patients were randomly assigned with 625 in each group. The primary composite outcome of prevention showed organ dysfunction or death occurred in 70 patients (11·2%) in the dapagliflozin group, and 86 (13·8%) in the placebo group (hazard ratio [HR] 0·80, 95% CI 0·58–1·10; p=0·17). For the primary outcome of recovery, 547 patients (87·5%) in the dapagliflozin

group and 532 (85·1%) in the placebo group showed clinical status improvement, although this was not statistically significant (win ratio 1·09, 95% CI 0·97–1·22; p=0·14). There were 41 deaths (6·6%) in the dapagliflozin group, and 54 (8·6%) in the placebo group (HR 0·77, 95% CI 0·52–1·16). Serious adverse events were reported in 65 (10·6%) of 613 patients treated with dapagliflozin and in 82 (13·3%) of 616 patients given the placebo.

Interpretation: In patients with cardiometabolic risk factors who were hospitalised with COVID-19, treatment with dapagliflozin did not result in a statistically significant risk reduction in organ dysfunction or death, or improvement in clinical recovery, but was well tolerated.

Reference

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00180-7/fulltext

PERSPECTIVE

Publication Date: Jul 27, 2021

Vaccination as a preventative measure contributing to immune fitness

The primary goal of vaccination is the prevention of pathogen-specific infection. The indirect consequences may include maintenance of homeostasis through prevention of infection-induced complications; trained immunity that re-programs innate cells to respond more efficiently to later, unrelated threats; slowing or reversing immune senescence by altering the epigenetic clock, and leveraging the pool of memory B and T cells to improve responses to new infections. Vaccines may exploit the plasticity of the immune system to drive longer-term immune responses that promote health at a broader level than just the prevention of single, specific infections. In this perspective, we discuss the concept of “immune fitness” and how to potentially build a resilient immune system that could contribute to better health. It was argued that vaccines may contribute positively to immune fitness in ways that are only beginning to be understood, and that life-course vaccination is a fundamental tool for achieving healthy aging.

Reference

https://www.nature.com/articles/s41541-021-00354-z

REPORT

Publication Date: Jul 27, 2021

Performance of Crisis standards of care guidelines in a cohort of critically Ill COVID-19 Patients in the United States

Many US states published crisis standards of care (CSC) guidelines for allocating scarce critical care resources during the COVID-19 pandemic. However, the performance of these guidelines in maximizing population benefit has not been well tested. In 2,272 adults with COVID-19 requiring ICU admission drawn from the STOP-COVID multicenter cohort, we tested three approaches to CSC algorithms: SOFA scores grouped into ranges, SOFA score ranges plus comorbidities, and a hypothetical approach using raw SOFA scores not grouped into ranges. It was found that area under receiver operating characteristic (AUROC) curves for all three algorithms demonstrate only modest discrimination for 28-day mortality. Adding comorbidity scoring modestly improves algorithm performance over SOFA scores alone. The algorithm incorporating comorbidities has modestly worse predictive performance for Black compared to White patients. CSC algorithms should be empirically examined to refine approaches to the allocation of scarce resources during pandemics and to avoid potential exacerbation of racial inequities. For more details, read the link given below.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00230-5

No evidence of human genome integration of SARS-CoV-2 found by long-read DNA sequencing

A recent study proposed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) hijacks the LINE-1 (L1) retrotransposition machinery to integrate into the DNA of infected cells. If confirmed, this finding could have significant clinical implications. Here, we apply deep (>50×) long-read Oxford Nanopore Technologies (ONT) sequencing to HEK293T cells infected with SARS-CoV-2, and do not find the virus integrated into the genome. By examining ONT data from separate HEK293T cultivars, we completely resolve 78 L1 insertions arising in vitro in the absence of L1 overexpression systems. ONT sequencing applied to hepatitis B virus (HBV) positive liver cancer tissues located

a single HBV insertion. These experiments demonstrate reliable resolution of retrotransposon and exogenous virus insertions *via* ONT sequencing. That we find no evidence of SARS-CoV-2 integration suggests such events are, at most, extremely rare in vivo, and therefore are unlikely to drive oncogenesis or explain post-recovery detection of the virus. For more details, read the link given below.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00961-X