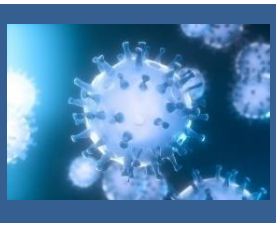

RESEARCH PUBLICATIONS

Publication Date: Jul 20, 2021

Global minimum estimates of children affected by COVID-19-associated orphanhood and deaths of caregivers: A modelling study

Abstract

Background: The COVID-19 pandemic priorities have focused on prevention, detection, and response. Beyond morbidity and mortality, pandemics carry secondary impacts, such as children orphaned or bereft of their caregivers. Such children often face adverse consequences, including poverty, abuse, and institutionalisation. Estimates for the magnitude of this problem resulting from COVID-19 were provided and the need for resource allocation was described.

Methods: Mortality and fertility data was used to model minimum estimates and rates of COVID-19-associated deaths of primary or secondary caregivers for children younger than 18 years in 21 countries. Parents and custodial grandparents were considered as primary caregivers, and co-residing grandparents or older kin (aged 60–84 years) as secondary caregivers. To avoid overcounting, we adjusted for possible clustering of deaths using an estimated secondary attack rate and age-specific infection–fatality ratios for SARS-CoV-2. These estimates were used to model global extrapolations for the number of children who have experienced COVID-19-associated deaths of primary and secondary caregivers.

Findings: Globally, from March 1, 2020, to April 30, 2021, it was estimated that 1 134 000 children (95% credible interval 884 000–1 185 000) experienced the death of primary caregivers, including at least one parent or custodial grandparent. 1 562 000 children (1 299 000–1 683 000) experienced the death of at least one primary or secondary caregiver. Countries in our study set with primary caregiver death rates of at

least one per 1000 children included Peru (10·2 per 1000 children), South Africa (5·1), Mexico (3·5), Brazil (2·4), Colombia (2·3), Iran (1·7), the USA (1·5), Argentina (1·1), and Russia (1·0). Numbers of children orphaned exceeded numbers of deaths among those aged 15–50 years. Between two and five times more children had deceased fathers than deceased mothers.

Interpretation: Orphanhood and caregiver deaths are a hidden pandemic resulting from COVID-19-associated deaths. Accelerating equitable vaccine delivery is key to prevention. Psychosocial and economic support can help families to nurture children bereft of caregivers and help to ensure that institutionalisation is avoided. These data show the need for an additional pillar of our response: prevent, detect, respond, and care for children.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01253-8/fulltext

Three epitope-distinct human antibodies from RenMab mice neutralize SARS-CoV-2 and cooperatively minimize the escape of mutants

Abstract

Coronavirus disease 2019 (COVID-19), a pandemic disease caused by the newly emerging severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has caused more than 3.8 million deaths to date. Neutralizing antibodies are effective therapeutic measures. However, many naturally occurring mutations at the receptor-binding domain (RBD) have emerged, and some of them can evade existing neutralizing antibodies. Here, we utilized RenMab, a novel mouse carrying the entire human antibody variable region, for neutralizing antibody discovery. We obtained several potent RBD-blocking antibodies and categorized them into four distinct groups by epitope mapping. We determined the involved residues of the epitope of three representative antibodies by cryo-electron microscopy (Cryo-EM) studies. Moreover, we performed neutralizing experiments with 50 variant strains with single or combined mutations and found that the mixing of three epitope-distinct antibodies almost eliminated the mutant escape. Our study provides a sound basis for the rational design of fully human antibody cocktails against SARS-CoV-2 and pre-emergent coronaviral threats.

Reference

https://www.nature.com/articles/s41421-021-00292-z

Solar UV-B/A radiation is highly effective in inactivating SARS-CoV-2

Abstract

Solar UV-C photons do not reach Earth's surface, but are known to be endowed with germicidal properties that are also effective on viruses. The effect of softer UV-B and UV-A photons, which copiously reach the Earth's surface, on viruses are instead little studied, particularly on single-stranded RNA viruses. Here measurements of the action spectrum of Covid-19 was combined in response to UV light, Solar irradiation measurements on Earth during the SARS-CoV-2 pandemics, worldwide recorded Covid-19 mortality data and our "Solar-Pump" diffusive model of epidemics to show that (a) UV-B/A photons have a powerful virucidal effect on the single-stranded RNA virus Covid-19 and that (b) the Solar radiation that reaches temperate regions of the Earth at noon during summers, is sufficient to inactivate 63% of virions in open-space concentrations (1.5×10^3 $TCID_{50}$/mL, higher than typical aerosol) in less than 2 min. We conclude that the characteristic seasonality imprint displayed world-wide by the SARS-Cov-2 mortality time-series throughout the diffusion of the outbreak (with temperate regions showing clear seasonal trends and equatorial regions suffering, on average, a systematically lower mortality), might have been efficiently set by the different intensity of UV-B/A Solar radiation hitting different Earth's locations at different times of the year. Our results suggest that Solar UV-B/A play an important role in planning strategies of confinement of the epidemics, which should be worked out and set up during spring/summer months and fully implemented during low-solar-irradiation periods.

Reference

https://www.nature.com/articles/s41598-021-94417-9

Development and implementation of a scalable and versatile test for COVID-19 diagnostics in rural communities

Abstract

Rapid and widespread testing of severe acute respiratory coronavirus 2 (SARS-CoV-2) is essential for an effective public health response aimed at containing and mitigating the coronavirus disease 2019 (COVID-19) pandemic. Successful health policy implementation relies on early identification of infected individuals and extensive contact tracing. However, rural communities, where resources for testing are sparse or simply absent, face distinctive challenges to achieving this success. Accordingly, the development of an academic, public land grant University laboratory-based detection assay was reported for the identification of SARS-CoV-2 in samples from various clinical specimens that can be readily deployed in areas where access to testing is limited. The test, which is a quantitative reverse transcription polymerase chain reaction (RT-qPCR)-based procedure, was validated on samples provided by the state laboratory and submitted for FDA Emergency Use Authorization. The test exhibits comparable sensitivity and exceeds specificity and inclusivity values compared to other molecular assays. Additionally, this test can be re-configured to meet supply chain shortages, modified for scale up demands, and is amenable to several clinical specimens. Test development also involved 3D engineering critical supplies and formulating a stable collection media that allowed samples to be transported for hours over a dispersed rural region without the need for a cold-chain. These two elements that were critical when shortages impacted testing and when personnel needed to reach areas that were geographically isolated from the testing center. Overall, using a robust, easy-to-adapt methodology, we show that an academic laboratory can supplement COVID-19 testing needs and help local health departments assess and manage outbreaks. This additional testing capacity is particularly germane for smaller cities and rural regions that would otherwise be unable to meet the testing demand.

Reference

https://www.nature.com/articles/s41467-021-24552-4

Validation of real-time RT-PCR for detection of SARS-CoV-2 in the early stages of the COVID-19 outbreak in the Republic of Korea

Abstract

A real-time reverse transcription polymerase chain reaction (RT-qPCR) assay that does not require Emergency Use Authorization (EUA) reagents was tested and validated for the detection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) during the early stages of the outbreak of coronavirus disease 2019 (COVID-19) in the Republic of Korea. Early diagnosis of COVID-19 enables timely treatment and the implementation of public health measures. The sensitivity, specificity, precision, linearity, accuracy, and robustness of the RT-qPCR assay for SARS-CoV-2 detection was validated and compared its performance with that of several EUA-approved kits. The RT-qPCR assay was highly specific for SARS-CoV-2 as demonstrated by not amplifying 13 other viruses that cause respiratory diseases. The assay showed high linearity using a viral isolate from a patient with known COVID-19 as well as plasmids containing target SARS-CoV-2 genes as templates. The assay showed good repeatability and reproducibility with a coefficient of variation of 3%, and a SARS-CoV-2 limit of detection of 1 PFU/mL. The RT-qPCR-based assay is highly effective and can facilitate the early diagnosis of COVID-19 without the use of EUA-approved kits or reagents in the Republic of Korea.

Reference

https://www.nature.com/articles/s41598-021-94196-3

Post-traumatic stress symptoms in COVID-19 survivors: A self-report and brain imaging follow-up study

Abstract

Previous coronavirus pandemics were associated elevated post-traumatic stress symptoms (PTSS), but the self-report and neurological basis of PTSS in patients who survived coronavirus disease 2019 (COVID-19) are largely unknown. A two-session study was conducted to record PTSS in the COVID-19 survivors discharged from hospitals for a short (i.e., about 3 months, Session 1) to a medium period (*i.e.*, about 6 months, Session 2), as well as brain imaging data in Session 2. The control groups

were non-COVID-19 locals. Session 1 was completed for 126 COVID-19 survivors and 126 controls. Session 2 was completed for 47 COVID-19 survivors and 43 controls. The total score of post-traumatic stress disorder (PTSD) checklist for DSM-5 (PCL-5) score was significantly higher in COVID-19 survivors compared with controls in both sessions. The PCL-5 score in COVID-19 survivors was positively correlated with the duration after discharge ($r = 0.27$, $p = 0.003$ for Session 1), and increased by 20% from Session 1 to Session 2 for the survivors who participated both sessions. The increase was positively correlated with individual's test-retest duration ($r = 0.46$, $p = 0.03$). Brain structural volume and functional activity in bilateral hippocampus and amygdala were significantly larger in COVID-19 survivors compared with controls. However, the volumes of the left hippocampus and amygdala were negatively correlated with the PCL-5 score for the COVID-19 survivors. The study suggests that COVID-19 survivors might face possible PTSS deteriorations, and highlights the importance of monitoring mental wellness of COVID-19 survivors.

Reference

https://www.nature.com/articles/s41380-021-01223-w

Longitudinal metabolomics of human plasma reveals prognostic markers of COVID-19 disease severity

Abstract

There is an urgent need to identify which COVID-19 patients will develop life-threatening illness so that medical resources can be optimally allocated and rapid treatment can be administered early in the disease course, when clinical management is most effective. To aid in the prognostic classification of disease severity, we perform untargeted metabolomics on plasma from 339 patients, with samples collected at six longitudinal time points. Using the temporal metabolic profiles and machine learning, we build a predictive model of disease severity. It was discovered that a panel of metabolites measured at the time of study entry successfully determines disease severity. Through analysis of longitudinal samples, we confirm that most of these markers are directly related to disease progression and that their levels return to baseline upon disease recovery. Finally, it was validated that these metabolites are also altered in a hamster model of COVID-19.

Reference

https://www.cell.com/cell-reports-medicine/fulltext/S2666-3791(21)00223-8

A benchmarking study of SARS-CoV-2 whole-genome sequencing protocols using COVID-19 patient samples

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging new type of coronavirus that is responsible for the COVID-19 pandemic and the unprecedented global health emergency. Whole-genome sequencing (WGS) of SARS-CoV-2 plays a critical role in understanding the disease. Performance variation exists across SARS-CoV-2 viral WGS technologies, but there is currently no benchmarking study comparing different WGS sequencing protocols. Seven different SARS-CoV-2 WGS library protocols were compared using RNA from patient nasopharyngeal swab samples under two storage conditions with low and high viral inputs. Large differences were found in mappability and genome coverage, and variations in sensitivity, reproducibility, and precision of single-nucleotide variant calling across different protocols. For certain amplicon-based protocols, an appropriate primer trimming step is critical for accurate single-nucleotide variant calling. The performance of protocols were ranked based on six different metrics. The findings offer guidance in choosing appropriate WGS protocols to characterize SARS-CoV-2 and its evolution.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042(21)00860-9

Publication Date: Jul 19, 2021

Ethnic differences in SARS-CoV-2 vaccine hesitancy in United Kingdom healthcare workers: Results from the UK-REACH prospective nationwide cohort study

Abstract

Background: In most countries, healthcare workers (HCWs) represent a priority group for vaccination against severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) due to their elevated risk of COVID-19 and potential contribution to nosocomial SARS-

CoV-2 transmission. Concerns have been raised that HCWs from ethnic minority groups are more likely to be vaccine hesitant (defined by the World Health Organisation as refusing or delaying a vaccination) than those of White ethnicity, but there are limited data on SARS-CoV-2 vaccine hesitancy and its predictors in UK HCWs.

Methods: Nationwide prospective cohort study and qualitative study in a multi-ethnic cohort of clinical and non-clinical UK HCWs. Ethnic differences were analyzed in SARS-CoV-2 vaccine hesitancy adjusting for demographics, vaccine trust, and perceived risk of COVID-19. Reasons were explored for hesitancy in qualitative data using a framework analysis.

Findings: 11,584 HCWs were included in the cohort analysis. 23% (2704) reported vaccine hesitancy. Compared to White British HCWs (21.3% hesitant), HCWs from Black Caribbean (54.2%), Mixed White and Black Caribbean (38.1%), Black African (34.4%), Chinese (33.1%), Pakistani (30.4%), and White Other (28.7%) ethnic groups were significantly more likely to be hesitant. In adjusted analysis, Black Caribbean (aOR 3.37, 95% CI 2.11 - 5.37), Black African (aOR 2.05, 95% CI 1.49 - 2.82), White Other ethnic groups (aOR 1.48, 95% CI 1.19 - 1.84) were significantly more likely to be hesitant. Other independent predictors of hesitancy were younger age, female sex, higher score on a COVID-19 conspiracy beliefs scale, lower trust in employer, lack of influenza vaccine uptake in the previous season, previous COVID-19, and pregnancy. Qualitative data from 99 participants identified the following contributors to hesitancy: lack of trust in government and employers, safety concerns due to the speed of vaccine development, lack of ethnic diversity in vaccine studies, and confusing and conflicting information. Participants felt uptake in ethnic minority communities might be improved through inclusive communication, involving HCWs in the vaccine rollout, and promoting vaccination through trusted networks.

Interpretation: Despite increased risk of COVID-19, HCWs from some ethnic minority groups are more likely to be vaccine hesitant than their White British colleagues. Strategies to build trust and dispel myths surrounding the COVID-19 vaccine in these communities are urgently required. Emphasis should be placed on the safety and benefit of SARS-CoV-2 vaccination in pregnancy and in those with previous COVID-19. Public health communications should be inclusive, non-stigmatising and utilise trusted networks.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00157-5/fulltext

Targeted metabolomics identifies high performing diagnostic and prognostic biomarkers for COVID-19

Abstract

Research exploring the development and outcome of COVID-19 infections has led to the need to find better diagnostic and prognostic biomarkers. This cross-sectional study used targeted metabolomics to identify potential COVID-19 biomarkers that predicted the course of the illness by assessing 110 endogenous plasma metabolites from individuals admitted to a local hospital for diagnosis/treatment. Patients were classified into four groups (≈ 40 each) according to standard polymerase chain reaction (PCR) COVID-19 testing and disease course: PCR−/controls (i.e., non-COVID controls), PCR+/not-hospitalized, PCR+/hospitalized, and PCR+/intubated. Blood samples were collected within 2 days of admission/PCR testing. Metabolite concentration data, demographic data and clinical data were used to propose biomarkers and develop optimal regression models for the diagnosis and prognosis of COVID-19. The area under the receiver operating characteristic curve (AUC; 95% CI) was used to assess each models' predictive value. A panel that included the kynurenine: tryptophan ratio, lysoPC a C26:0, and pyruvic acid discriminated non-COVID controls from PCR+/not-hospitalized (AUC = 0.947; 95% CI 0.931–0.962). A second panel consisting of C10:2, butyric acid, and pyruvic acid distinguished PCR+/not-hospitalized from PCR+/hospitalized and PCR+/intubated (AUC = 0.975; 95% CI 0.968–0.983). Only lysoPC a C28:0 differentiated PCR+/hospitalized from PCR+/intubated patients (AUC = 0.770; 95% CI 0.736–0.803). If additional studies with targeted metabolomics confirm the diagnostic value of these plasma biomarkers, such panels could eventually be of clinical use in medical practice.

Reference

https://www.nature.com/articles/s41598-021-94171-y

Frequency and phenotype of headache in COVID-19: A study of 2194 patients

Abstract

To estimate the frequency of headache in patients with confirmed COVID-19 and characterize the phenotype of headache attributed to COVID-19, comparing patients depending on the need of hospitalization and sex, an observational study was done. All eligible patients were systematically screened from a reference population of 261,431 between March 8 (first case) and April 11, 2020. A physician administered a survey assessing demographic and clinical data and the phenotype of the headache. During the study period, 2194 patients out of the population at risk were diagnosed with COVID-19. Headache was described by 514/2194 patients (23.4%, 95% CI 21.7–25.3%), including 383/1614 (23.7%) outpatients and 131/580 (22.6%) inpatients. The headache phenotype was studied in detail in 458 patients (mean age, 51 years; 72% female; prior history of headache, 49%). Headache was the most frequent first symptom of COVID-19. Median headache onset was within 24 h, median duration was 7 days and persisted after 1 month in 13% of patients. Pain was bilateral (80%), predominantly frontal (71%), with pressing quality (75%), of severe intensity. Systemic symptoms were present in 98% of patients. Headache frequency and phenotype was similar in patients with and without need for hospitalization and when comparing male and female patients, being more intense in females.

Reference

https://www.nature.com/articles/s41598-021-94220-6

Cardiomyocytes recruit monocytes upon SARS-CoV-2 infection by secreting CCL2

Abstract

Heart injury has been reported in up to 20% of COVID-19 patients, yet the cause of myocardial histopathology remains unknown. Here, using an established *in vivo* hamster model, it was demonstrated that SARS-CoV-2 can be detected in cardiomyocytes of infected animals. Furthermore, it was found damaged cardiomyocytes in hamsters and COVID-19 autopsy samples. To explore the mechanism, we show that both human pluripotent stem cell-derived cardiomyocytes (hPSC-derived CMs) and adult cardiomyocytes (CMs) can be productively infected by

SARS-CoV-2, leading to secretion of the monocyte chemoattractant cytokine CCL2 and subsequent monocyte recruitment. Increased CCL2 expression and monocyte infiltration was also observed in the hearts of infected hamsters. Although infected CMs suffer damage, we find that the presence of macrophages significantly reduces SARS-CoV-2 infected CMs. Overall, the study provides direct evidence that SARS-CoV-2 infects CMs *in vivo* and suggests a mechanism of immune-cell infiltration and histopathology in heart tissues of COVID-19 patients.

Reference

https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00378-7

Development of safe and highly protective live-attenuated SARS-CoV-2 vaccine candidates by genome recoding

Abstract

Safe and effective vaccines are urgently needed to stop the pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). A series of live attenuated vaccine candidates were constructed by large-scale recoding of the SARS-CoV-2 genome and assess their safety and efficacy in Syrian hamsters. Animals were vaccinated with a single dose of the respective recoded virus and challenged 21 days later. Two of the tested viruses do not cause clinical symptoms but are highly immunogenic and induce strong protective immunity. Attenuated viruses replicate efficiently in the upper but not in the lower airways, causing only mild pulmonary histopathology. After challenge, hamsters develop no signs of disease and rapidly clear challenge virus: at no time could infectious virus be recovered from the lungs of infected animals. The ease with which attenuated virus candidates can be produced and administered favors their further development as vaccines to combat the ongoing pandemic.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00920-7

Inhibitors of VPS34 and fatty-acid metabolism suppress SARS-CoV-2 replication

Abstract

Coronaviruses rely on host membranes for entry, establishment of replication centers, and egress. Compounds targeting cellular membrane biology and lipid biosynthetic pathways have previously shown promise as antivirals and are actively being pursued as treatments for other conditions. Here, small molecule inhibitors were tested that target the PI3 kinase VPS34 or fatty acid metabolism for anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) activity. The studies determine that compounds targeting VPS34 are potent SARS-CoV-2 inhibitors. Mechanistic studies with compounds targeting multiple steps up- and downstream of fatty acid synthase (FASN) identify the importance of triacylglycerol production and protein palmitoylation as requirements for efficient viral RNA synthesis and infectious virus production. Further, FASN knockout results in significantly impaired SARS-CoV-2 replication that can be rescued with fatty acid supplementation. Together, these studies clarify roles for VPS34 and fatty acid metabolism in SARS-CoV-2 replication and identify promising avenues for the development of countermeasures against SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00906-2

Publication Date: Jul 18, 2021

Mask use in community settings in the context of COVID-19: A systematic review of ecological data

Abstract

Background: The wearing of medical and non-medical masks by the general public in community settings is one intervention that is important for the reduction of SARS-CoV-2 transmission, and has been the subject of considerable research, policy, advocacy and debate. Several observational studies have used ecological (population-level) data to assess the effect of masks on transmission, hospitalization, and mortality at the region or community level.

Methods: This systematic review was undertaken to summarize the study designs, outcomes, and key quality indicators of using ecological data to evaluate the association between mask wearing and COVID-19 outcomes. The World Health Organization (WHO) COVID-19 global literature database was searched up to 5 March 2021 for studies reporting the impact of mask use in community settings on outcomes related to SARS-CoV-2 transmission using ecological data.

Findings: Twenty one articles were identified that analysed ecological data to assess the protective effect of policies mandating community mask wearing. All studies reported SARS-CoV-2 benefits in terms of reductions in either the incidence, hospitalization, or mortality, or a combination of these outcomes. Few studies assessed compliance to mask wearing policies or controlled for the possible influence of other preventive measures such as hand hygiene and physical distancing, and information about compliance to these policies was lacking.

Interpretation: Ecological studies have been cited as evidence to advocate for the adoption of universal masking policies. The studies summarized by this review suggest that community mask policies may reduce the population-level burden of SARS-CoV-2. Methodological limitations, in particular controlling for the actual practice of mask wearing and other preventive policies make it difficult to determine causality. There are several important limitations to consider for improving the validity of ecological data.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00304-7/fulltext

Publication Date: Jul 17, 2021

Implementation of a pooled surveillance testing program for asymptomatic SARS-CoV-2 infections in K-12 schools and universities

Abstract

Background: The negative impact of continued school closures during the height of the COVID-19 pandemic warrants the establishment of cost-effective strategies for surveillance and screening to safely reopen and monitor for potential in-school transmission. Here, a novel approach was presented to increase the availability of

repetitive and routine COVID-19 testing that may ultimately reduce the overall viral burden in the community.

Methods: A testing program was implemented using the SalivaClear pooled surveillance method that included students, faculty and staff from K-12 schools (student age range 5–18 years) and universities (student age range >18 years) across the country (Mirimus Clinical Labs, Brooklyn, NY). The data analysis was performed using descriptive statistics, kappa agreement, and outlier detection analysis.

Findings: From August 27, 2020 until January 13, 2021, 253,406 saliva specimens were self-collected from students, faculty and staff from 93 K-12 schools and 18 universities. Pool sizes of up to 24 samples were tested over a 20-week period. Pooled testing did not significantly alter the sensitivity of the molecular assay in terms of both qualitative (100% detection rate on both pooled and individual samples) and quantitative (comparable cycle threshold (Ct) values between pooled and individual samples) measures. The detection of SARS-CoV-2 in saliva was comparable to the nasopharyngeal swab. Pooling samples substantially reduced the costs associated with PCR testing and allowed schools to rapidly assess transmission and adjust prevention protocols as necessary. In one instance, in-school transmission of the virus was determined within the main office and led to review and revision of heating, ventilating and air-conditioning systems.

Interpretation: By establishing low-cost, weekly testing of students and faculty, pooled saliva analysis for the presence of SARS-CoV-2 enabled schools to determine whether transmission had occurred, make data-driven decisions, and adjust safety protocols. A strong evidence was provided that pooled testing may be a fundamental component to the reopening of schools by minimizing the risk of in-school transmission among students and faculty.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00308-4/fulltext

Characterisation of in-hospital complications associated with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol UK: A prospective, multicentre cohort study

Abstract

Background: COVID-19 is a multisystem disease and patients who survive might have in-hospital complications. These complications are likely to have important short-term and long-term consequences for patients, health-care utilisation, health-care system preparedness, and society amidst the ongoing COVID-19 pandemic. Our aim was to characterise the extent and effect of COVID-19 complications, particularly in those who survive, using the International Severe Acute Respiratory and Emerging Infections Consortium WHO Clinical Characterisation Protocol UK.

Methods: We did a prospective, multicentre cohort study in 302 UK health-care facilities. Adult patients aged 19 years or older, with confirmed or highly suspected SARS-CoV-2 infection leading to COVID-19 were included in the study. The primary outcome of this study was the incidence of in-hospital complications, defined as organ-specific diagnoses occurring alone or in addition to any hallmarks of COVID-19 illness. We used multilevel logistic regression and survival models to explore associations between these outcomes and in-hospital complications, age, and pre-existing comorbidities.

Findings: Between Jan 17 and Aug 4, 2020, 80 388 patients were included in the study. Of the patients admitted to hospital for management of COVID-19, 49·7% (36 367 of 73 197) had at least one complication. The mean age of our cohort was 71·1 years (SD 18·7), with 56·0% (41 025 of 73 197) being male and 81·0% (59 289 of 73 197) having at least one comorbidity. Males and those aged older than 60 years were most likely to have a complication (aged ≥60 years: 54·5% [16 579 of 30 416] in males and 48·2% [11 707 of 24 288] in females; aged <60 years: 48·8% [5179 of 10 609] in males and 36·6% [2814 of 7689] in females). Renal (24·3%, 17 752 of 73 197), complex respiratory (18·4%, 13 486 of 73 197), and systemic (16·3%, 11 895 of 73 197) complications were the most frequent. Cardiovascular (12·3%, 8973 of 73 197), neurological (4·3%, 3115 of 73 197), and gastrointestinal or liver (10·8%, 7901 of 73 197) complications were also reported.

Interpretation: Complications and worse functional outcomes in patients admitted to hospital with COVID-19 are high, even in young, previously healthy individuals. Acute complications are associated with reduced ability to self-care at discharge, with neurological complications being associated with the worst functional outcomes. COVID-19 complications are likely to cause a substantial strain on health and social care in the coming years. These data will help in the design and provision of services aimed at the post-hospitalisation care of patients with COVID-19.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00799-6/fulltext

Publication Date: Jul 16, 2021

Safety and Immunogenicity of a DNA SARS-CoV-2 vaccine (ZyCoV-D): Results of an open-label, non-randomized phase I part of phase I/II clinical study by intradermal route in healthy subjects in India

Abstract

Background: ZyCoV-D is a DNA vaccine candidate, which comprises a plasmid DNA carrying spike-S gene of SARS-CoV-2 virus along with gene coding for signal peptide. The spike(S) region includes the receptor-binding domain (RBD), which binds to the human angiotensin converting Enzyme (ACE)-2 receptor and mediates the entry of virus inside the cell.

Methods: A single-center, open-label, non-randomized, Phase 1 trial was conducted in India between July 2020 and October 2020. Healthy adults aged between 18 and 55 years were sequentially enrolled and allocated to one of four treatment arms in a dose escalation manner. Three doses of vaccine were administered 28 days apart and each subject was followed up for 28 days post third dose to evaluate safety and immunogenicity.

Findings: Out of 126 individuals screened for eligibility. Forty-eight subjects (mean age 34·9 years) were enrolled and vaccinated in the Phase 1 study Overall, 12/48 (25%) subjects reported at least one AE (i.e. combined solicited and unsolicited) during the study. There were no deaths or serious adverse events reported in Phase 1 of the study. The proportion of subjects who seroconverted based on IgG titers on day 84 was

4/11 (36·36%), 4/12 (33·33%), 10/10 (100·00%) and 8/10 (80·00%) in the treatment Arm 1 (1 mg: Needle), Arm 2 (1 mg: NFIS), Arm 3 (2 mg: Needle) and Arm 4 (2 mg: NFIS), respectively.

Interpretation: ZyCoV-D vaccine is found to be safe, well-tolerated and immunogenic in the Phase 1 trial. These findings suggested that the DNA vaccine warranted further investigation.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00300-X/fulltext

In vitro efficacy of artemisinin-based treatments against SARS-CoV-2

Abstract

Effective and affordable treatments for patients suffering from coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), are needed. *In vitro* efficacy of Artemisia annua extracts as well as artemisinin, artesunate, and artemether against SARS-CoV-2, were reported. The latter two are approved active pharmaceutical ingredients of anti-malarial drugs. Concentration–response antiviral treatment assays, based on immunostaining of SARS-CoV-2 spike glycoprotein, revealed that treatment with all studied extracts and compounds inhibited SARS-CoV-2 infection of VeroE6 cells, human hepatoma Huh7.5 cells and human lung cancer A549-hACE2 cells, without obvious influence of the cell type on antiviral efficacy. In treatment assays, artesunate proved most potent (range of 50% effective concentrations (EC50) in different cell types: 7–12 µg/mL), followed by artemether (53–98 µg/mL), A. annua extracts (83–260 µg/mL) and artemisinin (151 to at least 208 µg/mL). The selectivity indices (SI), calculated based on treatment and cell viability assays, were mostly below 10 (range 2 to 54), suggesting a small therapeutic window. Time-of-addition experiments in A549-hACE2 cells revealed that artesunate targeted SARS-CoV-2 at the post-entry level. Peak plasma concentrations of artesunate exceeding EC50 values can be achieved. Clinical studies are required to further evaluate the utility of these compounds as COVID-19 treatment.

Reference

https://www.nature.com/articles/s41598-021-93361-y

The impact of the COVID-19 pandemic on influenza, respiratory syncytial virus, and other seasonal respiratory virus circulation in Canada: A population-based study

Abstract

Background: The ongoing coronavirus disease 2019 (COVID-19) pandemic has resulted in implementation of public health measures worldwide to mitigate disease spread, including; travel restrictions, lockdowns, messaging on handwashing, use of face coverings and physical distancing. As the pandemic progresses, exceptional decreases in seasonal respiratory viruses are increasingly reported. We aimed to evaluate the impact of the pandemic on laboratory confirmed detection of seasonal non-SARS-CoV-2 respiratory viruses in Canada.

Methods: Epidemiologic data were obtained from the Canadian Respiratory Virus Detection Surveillance System. Weekly data from the week ending 30th August 2014 until the week ending the 13th March 2021 were analysed. Trends were compared in laboratory detection and test volumes during the 2020/2021 season with pre-pandemic seasons from 2014 to 2019.

Findings: A dramatically lower percentage of tests positive was observed for all seasonal respiratory viruses during 2020-2021, compared to pre-pandemic seasons. For influenza A and B the percent positive decreased to 0•0015 and 0•0028 times that of pre-pandemic levels respectively and for RSV, the percent positive dropped to 0•0169 times that of pre-pandemic levels. Ongoing detection of enterovirus/rhinovirus occurred, with regional variation in the epidemic patterns and intensity.

Interpretation: An effective absence of the annual seasonal epidemic of most seasonal respiratory viruses in 2020/2021 was reported. This dramatic decrease is likely related to implementation of multi-layered public health measures during the pandemic. The impact of such measures may have relevance for public health practice in mitigating seasonal respiratory virus epidemics and for informing responses to future respiratory virus pandemics.

Reference

https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(21)00007-7/fulltext

SARS-CoV-2 infection induces the dedifferentiation of multiciliated cells and impairs mucociliary clearance

Abstract

Understanding how SARS-CoV-2 spreads within the respiratory tract is important to define the parameters controlling the severity of COVID-19. Here the functional and structural consequences of SARS-CoV-2 infection were examined in a reconstructed human bronchial epithelium model. SARS-CoV-2 replication causes a transient decrease in epithelial barrier function and disruption of tight junctions, though viral particle crossing remains limited. Rather, SARS-CoV-2 replication leads to a rapid loss of the ciliary layer, characterized at the ultrastructural level by axoneme loss and misorientation of remaining basal bodies. Downregulation of the master regulator of ciliogenesis Foxj1 occurs prior to extensive cilia loss, implicating this transcription factor in the dedifferentiation of ciliated cells. Motile cilia function is compromised by SARS-CoV-2 infection, as measured in a mucociliary clearance assay. Epithelial defense mechanisms, including basal cell mobilization and interferon-lambda induction, ramp up only after the initiation of cilia damage. Analysis of SARS-CoV-2 infection in Syrian hamsters further demonstrates the loss of motile cilia in vivo. This study identifies cilia damage as a pathogenic mechanism that could facilitate SARS-CoV-2 spread to the deeper lung parenchyma.

Reference

https://www.nature.com/articles/s41467-021-24521-x

Multidisciplinary assessment of the Abbott BinaxNOW SARS-CoV-2 point-of-care antigen test in the context of emerging viral variants and self-administration

Abstract

While there has been significant progress in the development of rapid COVID-19 diagnostics, as the pandemic unfolds, new challenges have emerged, including whether these technologies can reliably detect the more infectious variants of concern and be viably deployed in non-clinical settings as “self-tests”. Multidisciplinary evaluation of the Abbott BinaxNOW COVID-19 Ag Card (BinaxNOW, a widely used rapid antigen test, included limit of detection, variant detection, test performance across different age-

groups, and usability with self/caregiver-administration. While BinaxNOW detected the highly infectious variants, B.1.1.7 (Alpha) first identified in the UK, B.1.351 (Beta) first identified in South Africa, P.1 (Gamma) first identified in Brazil, B.1.617.2 (Delta) first identified in India and B.1.2, a non-VOC, test sensitivity decreased with decreasing viral loads. Moreover, BinaxNOW sensitivity trended lower when devices were performed by patients/caregivers themselves compared to trained clinical staff, despite universally high usability assessments following self/caregiver-administration among different age groups. Overall, these data indicate that while BinaxNOW accurately detects the new viral variants, as rapid COVID-19 tests enter the home, their already lower sensitivities compared to RT-PCR may decrease even more due to user error.

Reference

https://www.nature.com/articles/s41598-021-94055-1

Proteomics and metabonomics analyses of Covid-19 complications in patients with pulmonary fibrosis

Abstract

Pulmonary fibrosis is a devastating disease, and the pathogenesis of this disease is not completely clear. Here, the medical records of 85 Covid-19 cases were collected, among which fibrosis and progression of fibrosis were analyzed in detail. Next, data independent acquisition (DIA) quantification proteomics and untargeted metabolomics were used to screen disease-related signaling pathways through clustering and enrichment analysis of the differential expression of proteins and metabolites. The main imaging features were lesions located in the bilateral lower lobes and involvement in five lobes. The closed association pathways were FcγR-mediated phagocytosis, PPAR signaling, TRP-inflammatory pathways, and the urea cycle. Our results provide evidence for the detection of serum biomarkers and targeted therapy in patients with Covid-19.

Reference

https://www.nature.com/articles/s41598-021-94256-8

High coverage COVID-19 mRNA vaccination rapidly controls SARS-CoV-2 transmission in long-term care facilities

Abstract

Background: Residents of Long-Term Care Facilities (LTCFs) represent a major share of COVID-19 deaths worldwide. Measuring the vaccine effectiveness among the most vulnerable in these settings is essential to monitor and improve mitigation strategies.

Methods: The early effect of the administration of BNT162b2-mRNA vaccine were evaluated to individuals older than 64 years residing in LTCFs in Catalonia, Spain. All the SARS-CoV-2 documented infections and deaths were monitored among LTCFs residents once more than 70% of them were fully vaccinated (February–March 2021). A modeling framework was developed based on the relationship between community and LTCFs transmission during the pre-vaccination period (July–December 2020). The total reduction in SARS-CoV-2 documented infections and deaths were computed among residents of LTCFs over time, as well as the reduction in the detected transmission for all the LTCFs. The true observations were compared with the counterfactual predictions.

Results: It was estimated that once more than 70% of the LTCFs population are fully vaccinated, 74% (58–81%, 90% CI) of COVID-19 deaths and 75% (36–86%, 90% CI) of all expected documented infections among LTCFs residents are prevented. Further, detectable transmission among LTCFs residents is reduced up to 90% (76–93%, 90% CI) relative to that expected given transmission in the community.

Conclusions: The findings provide evidence that high-coverage vaccination is the most effective intervention to prevent SARS-CoV-2 transmission and death among LTCFs residents. Widespread vaccination could be a feasible avenue to control the COVID-19 pandemic conditional on key factors such as vaccine escape, roll out and coverage.

Reference

https://www.nature.com/articles/s43856-021-00015-1

Compartmentalization-aided interaction screening reveals extensive high-order complexes within the SARS-CoV-2 proteome

Abstract

Bearing a relatively large single-stranded RNA genome in nature, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) utilizes sophisticated replication/transcription complexes (RTCs), mainly composed of a network of nonstructural proteins and nucleocapsid protein, to establish efficient infection. In this study, we develop an innovative interaction screening strategy based on phase separation in cellulo, namely compartmentalization of protein-protein interactions in cells (CoPIC). Utilizing CoPIC screening, we map the interaction network among RTC-related viral proteins. We identify a total of 47 binary interactions among 14 proteins governing replication, discontinuous transcription, and translation of coronaviruses. Further exploration via CoPIC leads to the discovery of extensive ternary complexes composed of these components, which infer potential higher-order complexes. Taken together, our results present an efficient and robust interaction screening strategy, and they indicate the existence of a complex interaction network among RTC-related factors, thus opening up opportunities to understand SARS-CoV-2 biology and develop therapeutic interventions for COVID-19.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00909-8

Publication Date: Jul 15, 2021

Mental disorders and risk of COVID-19-related mortality, hospitalisation, and intensive care unit admission: A systematic review and meta-analysis

Abstract

Background: Mental disorders might be a risk factor for severe COVID-19. We aimed to assess the specific risks of COVID-19-related mortality, hospitalisation, and intensive care unit (ICU) admission associated with any pre-existing mental disorder, and specific diagnostic categories of mental disorders, and exposure to psychopharmacological drug classes.

Methods: In this systematic review and meta-analysis, Web of Science, Cochrane, PubMed, and PsycINFO databases were searched between Jan 1, 2020, and March 5, 2021, for original studies reporting data on COVID-19 outcomes in patients with psychiatric disorders compared with controls. Studies were excluded with overlapping samples, studies that were not peer-reviewed, and studies written in languages other than English, Danish, Dutch, French, German, Italian, and Portuguese. Random-effects meta-analyses were modeled to estimate crude odds ratios (OR) for mortality after SARS-CoV-2 infection as the primary outcome, and hospitalisation and ICU admission as secondary outcomes. Adjusted ORs for available data were calculated. Heterogeneity was assessed using the I2 statistic, and publication bias was tested with Egger regression and visual inspection of funnel plots. The GRADE approach was used to assess the overall strength of the evidence and the Newcastle Ottawa Scale to assess study quality. Subgroup analyses and meta-regressions were also done to assess the effects of baseline COVID-19 treatment setting, patient age, country, pandemic phase, quality assessment score, sample sizes, and adjustment for confounders. This study is registered with PROSPERO, CRD42021233984.

Findings: 841 Studies were identified by the systematic search, of which 33 studies were included in the systematic review and 23 studies in the meta-analysis, comprising 1 469 731 patients with COVID-19, of whom 43 938 had mental disorders. The sample included 130 807 females (8·9% of the whole sample) and 130 373 males (8·8%). Nine studies provided data on patient race and ethnicity, and 22 studies were rated as high quality. The presence of any mental disorder was associated with an increased risk of COVID-19 mortality (OR 2·00 [95% CI 1·58–2·54]; I2=92·66%). This association was also observed for psychotic disorders (2·05 [1·37–3·06]; I2=80·81%), mood disorders (1·99 [1·46–2·71]; I2=68·32%), substance use disorders (1·76 [1·27–2·44]; I2=47·90%), and intellectual disabilities and developmental disorders (1·73 [1·29–2·31]; I2=90·15%) but not for anxiety disorders (1·07 [0·73–1·56]; I2=11·05%). COVID-19 mortality was associated with exposure to antipsychotics (3·71 [1·74–7·91]; I2=90·31%), anxiolytics (2·58 [1·22–5·44]; I2=96·42%), and antidepressants (2·23 [1·06–4·71]; I2=95·45%). For psychotic disorders, mood disorders, antipsychotics, and anxiolytics, the association remained significant after adjustment for age, sex, and other confounders. Mental disorders were associated with increased risk of hospitalisation (2·24 [1·70–2·94]; I2=88·80%). No significant associations with mortality were identified for ICU admission.

Subgroup analyses and meta-regressions showed significant associations of baseline COVID-19 treatment setting (p=0·013) and country (p<0·0001) with mortality. No significant associations with mortality were identified for other covariates. No evidence of publication bias was found. GRADE assessment indicated high certainty for crude mortality and hospitalisation, and moderate certainty for crude ICU admission.

Interpretation: Pre-existing mental disorders, in particular psychotic and mood disorders, and exposure to antipsychotics and anxiolytics were associated with COVID-19 mortality in both crude and adjusted models. Although further research is required to determine the underlying mechanisms, the findings highlight the need for targeted approaches to manage and prevent COVID-19 in at-risk patient groups identified in this study.

Reference

https://www.thelancet.com/journals/lanpsy/article/PIIS2215-0366(21)00232-7/fulltext

Interferon-armed RBD dimer enhances the immunogenicity of RBD for sterilizing immunity against SARS-CoV-2

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global crisis, urgently necessitating the development of safe, efficacious, convenient-to-store, and low-cost vaccine options. A major challenge is that the receptor-binding domain (RBD)-only vaccine fails to trigger long-lasting protective immunity if used alone for vaccination. To enhance antigen processing and cross-presentation in draining lymph nodes (DLNs), we developed an interferon (IFN)-armed RBD dimerized by an immunoglobulin fragment (I-R-F). I-R-F efficiently directs immunity against RBD to DLNs. A low dose of I-R-F induces not only high titers of long-lasting neutralizing antibodies (NAbs) but also more comprehensive T cell responses than RBD. Notably, I-R-F provides comprehensive protection in the form of a one-dose vaccine without an adjuvant. Our study shows that the pan-epitope modified human I-R-F (I-P-R-F) vaccine provides rapid and complete protection throughout the upper and lower respiratory tracts against a high-dose SARS-CoV-2 challenge in rhesus macaques. Based on these promising results, we have initiated a randomized, placebo-controlled, phase I/II trial of the human I-P-R-F vaccine (V-01) in 180 healthy adults, and the vaccine appears safe

and elicits strong antiviral immune responses. Due to its potency and safety, this engineered vaccine may become a next-generation vaccine candidate in the global effort to overcome COVID-19.

Reference

https://www.nature.com/articles/s41422-021-00531-8

Sex and age bias viral burden and interferon responses during SARS-CoV-2 infection in ferrets

Abstract

SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) hospitalizations and deaths disportionally affect males and older ages. Here the impact of male sex and age comparing sex-matched or age-matched ferrets infected with SARS-CoV-2, was investigated. Differences in temperature regulation were identified for male ferrets, which was accompanied by prolonged viral replication in the upper respiratory tract after infection. Gene expression analysis of the nasal turbinates indicated that 1-year-old female ferrets had significant increases in interferon response genes post infection which were delayed in males. These results provide insight into COVID-19 and suggested that older males may play a role in viral transmission due to decreased antiviral responses.

Reference

https://www.nature.com/articles/s41598-021-93855-9

Danshensu alleviates pseudo-typed SARS-CoV-2 induced mouse acute lung inflammation

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can induce acute inflammatory response like acute lung inflammation (ALI) or acute respiratory distress syndrome, leading to severe progression and mortality. Therapeutics for treatment of SARS-CoV-2-triggered respiratory inflammation are urgent to be discovered. The previous study shows that Salvianolic acid C potently inhibits SARS-CoV-2 infection. In this study, we investigated the antiviral effects of a Salvia miltiorrhiza compound,

Danshensu, *in vitro* and *in vivo*, including the mechanism of S protein-mediated virus attachment and entry into target cells. In authentic and pseudo-typed virus assays *in vitro*, Danshensu displayed a potent antiviral activity against SARS-CoV-2 with EC50 of 0.97 μM, and potently inhibited the entry of SARS-CoV-2 S protein-pseudo-typed virus (SARS-CoV-2 S) into ACE2-overexpressed HEK-293T cells (IC50 = 0.31 μM) and Vero-E6 cell (IC50 = 4.97 μM). Mice received SARS-CoV-2 S via trachea to induce ALI, while the VSV-G treated mice served as controls. The mice were administered Danshensu (25, 50, 100 mg/kg, i.v., once) or Danshensu (25, 50, 100 mg·kg-1·d-1, oral administration, for 7 days) before SARS-CoV-2 S infection. It was showed that SARS-CoV-2 S infection induced severe inflammatory cell infiltration, severely damaged lung tissue structure, highly expressed levels of inflammatory cytokines, and activated TLR4 and hyperphosphorylation of the NF-κB p65; the high expression of angiotensinogen (AGT) and low expression of ACE2 at the mRNA level in the lung tissue were also observed. Both oral and intravenous pretreatment with Danshensu dose-dependently alleviated the pathological alterations in mice infected with SARS-CoV-2 S. This study not only establishes a mouse model of pseudo-typed SARS-CoV-2 (SARS-CoV-2 S) induced ALI, but also demonstrates that Danshensu is a potential treatment for COVID-19 patients to inhibit the lung inflammatory response.

Reference

https://www.nature.com/articles/s41401-021-00714-4

A hybrid computational framework for intelligent inter-continent SARS-CoV-2 sub-strains characterization and prediction

Abstract

Whereas accelerated attention beclouded early stages of the coronavirus spread, knowledge of actual pathogenicity and origin of possible sub-strains remained unclear. By harvesting the Global initiative on Sharing All Influenza Data (GISAID) database (https://www.gisaid.org/), between December 2019 and January 15, 2021, a total of 8864 human SARS-CoV-2 complete genome sequences processed by gender, across 6 continents (88 countries) of the world, Antarctica exempt, were analyzed. It was hypothesized that data speak for itself and can discern true and explainable patterns of the disease. Identical genome diversity and pattern correlates analysis performed using

a hybrid of biotechnology and machine learning methods corroborate the emergence of inter- and intra- SARS-CoV-2 sub-strains transmission and sustain an increase in sub-strains within the various continents, with nucleotide mutations dynamically varying between individuals in close association with the virus as it adapts to its host/environment. Interestingly, some viral sub-strain patterns progressively transformed into new sub-strain clusters indicating varying amino acid, and strong nucleotide association derived from same lineage. A novel cognitive approach to knowledge mining helped the discovery of transmission routes and seamless contact tracing protocol. The classification results were better than state-of-the-art methods, indicating a more robust system for predicting emerging or new viral sub-strain(s). The results therefore offer explanations for the growing concerns about the virus and its next wave(s). A future direction of this work is a defuzzification of confusable pattern clusters for precise intra-country SARS-CoV-2 sub-strains analytics.

Reference

https://www.nature.com/articles/s41598-021-93757-w

Age-dependent appearance of SARS-CoV-2 entry sites in mouse chemosensory systems reflects COVID-19 anosmia-ageusia symptoms

Abstract

COVID-19 pandemic has given rise to a collective scientific effort to study its viral causing agent SARS-CoV-2. Research is focusing in particular on its infection mechanisms and on the associated-disease symptoms. Interestingly, this environmental pathogen directly affects the human chemosensory systems leading to anosmia and ageusia. Evidence for the presence of the cellular entry sites of the virus, the ACE2/TMPRSS2 proteins, has been reported in non-chemosensory cells in the rodent's nose and mouth, missing a direct correlation between the symptoms reported in patients and the observed direct viral infection in human sensory cells. Here, mapping the gene and protein expression of ACE2/TMPRSS2 in the mouse olfactory and gustatory cells, we precisely identify the virus target cells to be of basal and sensory origin and reveal the age-dependent appearance of viral entry-sites. The results propose an alternative interpretation of the human viral-induced sensory symptoms and give investigative perspectives on animal models.

Reference

https://www.nature.com/articles/s42003-021-02410-9

Predictability of COVID-19-related morbidity and mortality based on model estimations to establish proactive protocols of countermeasures

Abstract

The COVID-19 pandemic (SARS-CoV-2) has revealed the need for proactive protocols to react and act, imposing preventive and restrictive countermeasures on time in any society. The extent to which confirmed cases can predict the morbidity and mortality in a society remains an unresolved issue. The research objective is therefore to test a generic model's predictability through time, based on percentage of confirmed cases on hospitalized patients, ICU patients and deceased. This study reports the explanatory and predictive ability of COVID-19-related healthcare data, such as whether there is a spread of a contagious and virulent virus in a society, and if so, whether the morbidity and mortality can be estimated in advance in the population. The model estimations stress the implementation of a pandemic strategy containing a proactive protocol entailing what, when, where, who and how countermeasures should be in place when a virulent virus (e.g. SARS-CoV-1, SARS-CoV-2 and MERS) or pandemic strikes next time. Several lessons for the future can be learnt from the reported model estimations. One lesson is that COVID-19-related morbidity and mortality in a population is indeed predictable. Another lesson is to have a proactive protocol of countermeasures in place.

Reference

https://www.nature.com/articles/s41598-021-93932-z

Safety and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population aged 18 years or older: Two single-center, randomised, double-blind, placebo-controlled, phase 1 and phase 2 trials

Abstract

COVID-19 vaccines from multiple manufacturers are needed to cope with the problem of insufficient supply. Two single-center, randomised, double-blind, placebo-controlled phase 1 and phase 2 trials were done to assess the safety, tolerability and immunogenicity of a recombinant COVID-19 vaccine (Sf9 cells) in healthy population

aged 18 years or older in China. Eligible participants were enrolled, the ratio of candidate vaccine and placebo within each dose group was 3:1 (phase 1) or 5:1 (phase 2). From August 28, 2020, 168 participants were sequentially enrolled and randomly assigned to receive the low dose vaccine, high dose vaccine or placebo with the schedule of 0, 28 days or 0, 14, 28 days in phase 1 trial. From November 18, 2020, 960 participants were randomly assigned to receive the low dose vaccine, high dose vaccine or placebo with the schedule of 0, 21 days or 0, 14, 28 days in phase 2 trial. The most common solicited injection site adverse reaction within 7 days in both trials was pain. The most common solicited systematic adverse reactions within 7 days were fatigue, cough, sore throat, fever and headache. ELISA antibodies and neutralising antibodies increased at 14 days, and peaked at 28 days (phase 1) or 30 days (phase 2) after the last dose vaccination. The GMTs of neutralising antibody against live SARS-CoV-2 at 28 days or 30 days after the last dose vaccination were highest in the adult high dose group (0, 14, 28 days), with 102.9 (95% CI 61.9–171.2) and 102.6 (95% CI 75.2–140.1) in phase 1 and phase 2 trials, respectively. Specific T-cell response peaked at 14 days after the last dose vaccination in phase 1 trial. This vaccine is safe, and induced significant immune responses after three doses of vaccination.

Reference

https://www.nature.com/articles/s41392-021-00692-3

COVID-19 vaccine mRNA-1273 elicits a protective immune profile in mice that is not associated with vaccine-enhanced disease upon SARS-CoV-2 challenge

Abstract

Vaccine-associated enhanced respiratory disease (VAERD) was previously observed in some preclinical models of severe acute respiratory syndrome (SARS) and MERS coronavirus vaccines. We used the SARS coronavirus 2 (SARS-CoV-2) mouse-adapted, passage 10, lethal challenge virus (MA10) mouse model of acute lung injury to evaluate the immune response and potential for immunopathology in animals vaccinated with research-grade mRNA-1273. Whole-inactivated virus or heat-denatured spike protein subunit vaccines with alum designed to elicit low-potency antibodies and Th2-skewed CD4+ T cells resulted in reduced viral titers and weight loss post challenge but more severe pathological changes in the lung compared to saline-immunized

animals. In contrast, a protective dose of mRNA-1273 induced favorable humoral and cellular immune responses that protected from viral replication in the upper and lower respiratory tract upon challenge. A subprotective dose of mRNA-1273 reduced viral replication and limited histopathological manifestations compared to animals given saline. Overall, our findings demonstrate an immunological signature associated with antiviral protection without disease enhancement following vaccination with mRNA-1273.

Reference

https://www.cell.com/immunity/fulltext/S1074-7613(21)00262-4

Generation of glucocorticoid-resistant SARS-CoV-2 T cells for adoptive cell therapy

Abstract

Adoptive cell therapy with virus-specific T cells has been used successfully to treat life-threatening viral infections, supporting application of this approach to coronavirus disease 2019 (COVID-19). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) T cells were expanded from the peripheral blood of COVID-19-recovered donors and non-exposed controls using different culture conditions. It was observed that the choice of cytokines modulates the expansion, phenotype, and hierarchy of antigenic recognition by SARS-CoV-2 T cells. Culture with interleukin (IL)-2/4/7, but not under other cytokine-driven conditions, results in more than 1,000-fold expansion in SARS-CoV-2 T cells with a retained phenotype, function, and hierarchy of antigenic recognition compared with baseline (pre-expansion) samples. Expanded cytotoxic T lymphocytes (CTLs) are directed against structural SARS-CoV-2 proteins, including the receptor-binding domain of Spike. SARS-CoV-2 T cells cannot be expanded efficiently from the peripheral blood of non-exposed controls. Because corticosteroids are used for management of severe COVID-19, we propose an efficient strategy to inactivate the glucocorticoid receptor gene (NR3C1) in SARS-CoV-2 CTLs using CRISPR-Cas9 gene editing.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00849-4

CORRESPONDANCE

Publication Date: Jul 15, 2021

Spike-antibody waning after second dose of BNT162b2 or ChAdOx1

Vaccines based on the spike glycoprotein of SARS-CoV-2 are being rolled out globally to control transmission and limit morbidity and mortality due to COVID-19. Current evidence indicates strong immunogenicity and high short-term efficacy for BNT162b2 (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (Oxford–AstraZeneca). Both vaccines are delivered through a prime-boost strategy, and many countries, including the UK, have used dose intervals longer than 3–4 weeks, expecting to maximise first-dose coverage and immunogenicity. With continued high global incidence, and potential for more transmissible SARS-CoV-2 variants, data on longer-term vaccine efficacy and antibody dynamics in infection-naive individuals are essential for clarifying the need for further booster doses.

To identify early indications of waning antibody levels to the spike protein (S-antibody) after complete two-dose vaccination, we did a cross-sectional analysis of fully vaccinated adults (aged ≥18 years) who submitted capillary blood samples for Virus Watch, a longitudinal community cohort study in England and Wales. The study received ethical approval from the Hampstead NHS Health Research Authority Ethics Committee (20/HRA/2320). Sera were tested using Elecsys Anti-SARS-CoV-2 S and N electro-chemiluminescent immunoassays (Roche Diagnostics, Basel, Switzerland); the S assay targets total antibodies to the S1 subunit of the spike protein (range 0·4–25 000 units per mL [U/mL]), whereas the N assay targets total antibodies to the full-length nucleocapsid protein, which we took as a proxy for previous SARS-CoV-2 infection (specificity 99·8% [99·3–100]). Serological results were linked with demographic and clinical information collected at enrolment and with weekly self-reported vaccination status. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01642-1/fulltext

COMMENT

Publication Date: Jul 15, 2021

Protecting the vulnerable: SARS-CoV-2 vaccination in immunosuppressed patients with interstitial lung disease

Interstitial lung diseases (ILDs) comprise a vast array of conditions that can be responsive or non-responsive to immunosuppression. When immunosuppression is used, most commonly in connective tissue disease-associated ILD, hypersensitivity pneumonitis, and sarcoidosis, the clinician and patient have to navigate carefully between too much and too little modulation of the immune system. The COVID-19 pandemic is a threat to this equilibrium, with uncertainty about the risks of SARS-CoV-2 infection for these patients and concerns around vaccine efficacy and safety.

In the largest analysis to date, the presence of various ILDs conferred an approximately 50% increase in the risk of death from COVID-19. Individuals with fibrotic and more advanced disease are at a higher risk of severe illness and mortality from COVID-19 than are controls matched for age, sex, and comorbidities. However, there are few data relating to COVID-19 specifically in people with ILDs using immunosuppression. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00326-X/fulltext

REPORT

Publication Date: Jul 20, 2021

Masitinib is a broad coronavirus 3CL inhibitor that blocks replication of SARS-CoV-2

There is an urgent need for antiviral agents that treat SARS-CoV-2 infection. A library of 1,900 clinically safe drugs were screened against OC43, a human beta-coronavirus that causes the common cold and evaluated the top hits against SARS-CoV-2. Twenty drugs significantly inhibited replication of both viruses *in vitro*. Eight of these drugs inhibited the activity of the SARS-CoV-2 main protease, 3CLpro, with the most potent being masitinib, an orally bioavailable tyrosine kinase inhibitor. X-ray crystallography and biochemistry show that masitinib acts as a competitive inhibitor of 3CLpro. Mice infected with SARS-CoV-2 and then treated with masitinib showed >200-fold reduction in viral titers in the lungs and nose, as well as reduced lung inflammation. Masitinib was also effective *in vitro* against all tested variants of concern (B.1.1.7, B.1.351 and P.1). For more details, read the link given below.

Reference

https://science.sciencemag.org/content/early/2021/07/19/science.abg5827