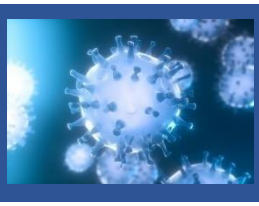

RESEARCH PUBLICATIONS

Publication Date: Nov 04, 2020

Analytical and clinical performances of five immunoassays for the detection of SARS-CoV-2 antibodies in comparison with neutralization activity

Abstract

Background: Reliable high-throughput serological assays for SARS-CoV-2 antibodies are urgently needed for the effective containment of the COVID-19 pandemic, as it is of crucial importance to understand the strength and duration of immunity after infection, and to make informed decisions concerning the activation or discontinuation of physical distancing restrictions.

Methods: In 184 serum samples from 130 COVID-19 patients and 54 SARS-CoV-2 negative subjects, the analytical and clinical performances of four commercially available chemiluminescent assays (Abbott SARS-Cov-2 IgG, Roche Elecsys anti-SARS-CoV-2, Ortho SARS-CoV-2 total and IgG) and one enzyme-linked immunosorbent assay (Diesse ENZY-WELL SARS-CoV-2 IgG) were evaluated and compared with the neutralization activity achieved using the plaque reduction neutralization test (PRNT).

Findings: Precision results ranged from 0.9% to 11.8% for all assays. Elecsys anti-SARS-CoV-2 demonstrated linearity of results at concentrations within the cut-off value. Overall, sensitivity ranged from 78.5 to 87.7%, and specificity, from 97.6 to 100%. On limiting the analysis to samples collected 12 days after onset of symptoms, the sensitivity of all assays increased, the highest value (95.2%) being obtained with VITRO Anti-SARS-CoV-2 Total and Architect SARS-CoV-2 IgG. The strongest PRNT50

correlation with antibody levels was obtained with ENZY-Well SARS-CoV-2 IgG (R2adj = 0.569).

Interpretation: The results confirmed that all immunoassays had an excellent specificity, whereas sensitivity varied across immunoassays, depending strongly on the time interval between symptoms onset and sample collection. Further studies should be conducted to achieve a stronger correlation between antibody measurement and PRNT50 in order to obtain useful information for providing a better management of COVID-19 patients, effective passive antibody therapy, and developing a vaccine against the SARS-CoV-2 virus.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30477-1/fulltext

Factors affecting the mortality of patients with COVID-19 undergoing surgery and the safety of medical staff: A systematic review and meta-analysis

Abstract

Background: The 2019 novel coronavirus disease (COVID-19) can complicate the perioperative course to increase postoperative mortality in operative patients, and also is a serious threat to medical staff. However, studies summarizing the impact of COVID-19 on the perioperative mortality of patients and on the safety of medical staff are lacking.

Methods: PubMed, Cochrane Library, Embase and Chinese database National Knowledge Infrastructure (CNKI) with the search terms “COVID-19″ or “SARS-CoV-2″ and “Surgery” or “Operation” for all published articles on COVID-19, were searched from December 1, 2019 to October 5, 2020.

Findings: A total of 269 patients from 47 studies were included in our meta-analysis. The mean age of operative patients with COVID-19 was 50.91 years, and 49% were female. A total of 28 patients were deceased, with the overall mortality of 6%. All deceased patients had postoperative complications associated with operation or COVID-19, including respiratory failure, acute respiratory distress syndrome (ARDS),

short of breath, dyspnea, fever, cough, fatigue or myalgia, cardiopulmonary system, shock/infection, acute kidney injury and severe lymphopenia. Patients who presented any or more of the symptoms of respiratory failure, ARDS, short of breath and dyspnea after operation were associated with significantly higher mortality ($r = 0.891$, $p < 0.001$), while patients whose symptoms were presented as fever, cough, fatigue or myalgia only demonstrated marginally significant association with postoperative mortality ($r = 0.675$, $p = 0.023$). Twenty studies reported the information of medical staff infection, and a total of 38 medical staff were infected, and medical staff who used biosafety level 3 (BSL-3) protective equipment did not get infected.

Interpretation: COVID-19 patients, in particular those with severe respiratory complications, may have high postoperative mortality. Medical staff in close contact with infected patients is suggested to take high level personal protective equipment (PPE).

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30356-4/fulltext

Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: A proof-of-concept study

Abstract

Background: Complement pathway inhibition may provide benefit for severe acute respiratory illnesses caused by viral infections such as COVID-19. Results were presented from a nonrandomized proof-of-concept study of complement C5 inhibitor eculizumab for treatment of severe COVID-19.

Methods: All patients (N = 80) with confirmed SARS-CoV-2 infection and severe COVID-19 admitted to our intensive care unit between March 10 and May 5, 2020 were included. Forty-five patients were treated with standard care and 35 with standard care plus eculizumab through expanded-access emergency treatment. The prespecified primary outcome was day-15 survival. Clinical laboratory values and biomarkers, complement levels, and treatment-emergent serious adverse events (TESAEs) were also assessed.

Findings: At day 15, estimated survival was 82.9% (95% CI: 70.4%–95.3%) with eculizumab and 62.2% (48.1%–76.4%) without eculizumab (log-rank test, P = 0.04). Patients treated with eculizumab experienced a significantly more rapid decrease in lactate, blood urea nitrogen, total and conjugated bilirubin levels and a significantly more rapid increase in platelet count, prothrombin time, and in the ratio of arterial oxygen tension over fraction of inspired oxygen versus patients treated without eculizumab. Eculizumab-associated changes in complement levels, laboratory values, and biomarkers were consistent with terminal complement inhibition, reduced hypoxia, and decreased inflammation. TESAEs of special interest occurring in >5% of patients treated with/without eculizumab were ventilator-associated pneumonia (51%/24%), bacteremia (11%/2%), gastroduodenal hemorrhage (14%/16%), and hemolysis (3%/18%).

Interpretation: Findings from this proof-of-concept study suggest eculizumab may improve survival and reduce hypoxia in patients with severe COVID-19. Randomized studies evaluating the efficacy and safety of this treatment approach are needed.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(20)30334-5/fulltext

Comparative sensitivity of different respiratory specimen types for molecular diagnosis and monitoring of SARS-CoV-2 shedding in COVID-19 patients

Abstract

The global pandemic of Coronavirus Disease 2019 (COVID-19) is now ongoing. Rapid and accurate detection of the causative virus SARS-CoV-2 is vital for the treatment and control of COVID-19. In this study, the comparative sensitivity of different respiratory specimens were retrospectively analyzed using 3552 clinical samples from 410 Guangdong CDC (Center for Disease Control and Prevention) confirmed COVID-19 patients. Except for BALF, the sputum possessed the highest positive rate (73.4%~87.5%), followed by nasal swabs (53.1%~85.3%) for both severe and mild cases during the first 14 days after illness onset (d.a.o). Viral RNA could be detected in all BALF from the severe group collected as early as 4 days after illness onset (d.a.o) and lasted up to 46 d.a.o., while none of BALF samples from mild group. Moreover,

although viral RNA was negative in the upper respiratory samples, it was also positive in BALF samples in most cases from severe group during treatment. Despite of typical ground-glass opacity observed via computed tomographic (CT) scans, no viral RNA was detected in the first 3 or all upper respiratory tract specimens from some COVID-19 patients. In conclusion, sputum is most sensitive for routine laboratory diagnosis of COVID-19, followed by nasal swabs. Detection of viral RNAs in BLAF improves diagnostic accuracy in severe COVID-19 patients.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758(20)30064-3

Case Study: Prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised cancer patient

Abstract

Long-term SARS-CoV-2 shedding was observed from the upper respiratory tract of a female immunocompromised patient with chronic lymphocytic leukemia and acquired hypogammaglobulinemia. Shedding of infectious SARS-CoV-2 was observed up to 70 days, and genomic and subgenomic RNA up to 105 days past initial diagnosis. The infection was not cleared after a first treatment with convalescent plasma, suggesting limited impact on SARS-CoV-2 in the upper respiratory tract within this patient. Several weeks after a second convalescent plasma transfusion, SARS-CoV-2 RNA was no longer detected. We observed marked within-host genomic evolution of SARS-CoV-2, with continuous turnover of dominant viral variants. However, replication kinetics in Vero E6 cells and primary human alveolar epithelial tissues were not affected. Our data indicate that certain immunocompromised patients may shed infectious virus for longer durations than previously recognized. Detection of subgenomic RNA is recommended in persistently SARS-CoV-2 positive individuals as a proxy for shedding of infectious virus.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31456-2?utm_medium=homepage

An artificial intelligence-based first-line defence against COVID-19: Digitally screening citizens for risks *via* a chatbot

Abstract

To combat the pandemic of the coronavirus disease 2019 (COVID-19), numerous governments have established phone hotlines to prescreen potential cases. These hotlines have struggled with the volume of callers, leading to wait times of hours or, even, an inability to contact health authorities. Symptoma is a symptom-to-disease digital health assistant that can differentiate more than 20,000 diseases with an accuracy of more than 90%. We tested the accuracy of Symptoma to identify COVID-19 using a set of diverse clinical cases combined with case reports of COVID-19. We showed that Symptoma can accurately distinguish COVID-19 in 96.32% of clinical cases. When considering only COVID-19 symptoms and risk factors, Symptoma identified 100% of those infected when presented with only three signs. Lastly, we showed that Symptoma's accuracy far exceeds that of simple "yes–no" questionnaires widely available online. In summary, Symptoma provides unparalleled accuracy in systematically identifying cases of COVID-19 while also considering over 20,000 other diseases. Furthermore, Symptoma allows free text input, furthered with disease-specific follow up questions, in 36 languages. Combined, these results and accessibility give Symptoma the potential to be a key tool in the global fight against COVID-19. The Symptoma predictor is freely available online at https://www.symptoma.com

Reference

https://www.nature.com/articles/s41598-020-75912-x

Optimized and scalable synthesis of magnetic nanoparticles for RNA extraction in response to developing countries' needs in the detection and control of SARS-CoV-2

Abstract

Ecuador is one of the most affected countries, with the coronavirus disease 2019 (COVID-19) infection, in Latin America derived from an ongoing economic crisis. One of the most important methods for COVID-19 detection is the use of techniques such as

real time RT-PCR based on a previous extraction/purification of RNA procedure from nasopharyngeal cells using functionalized magnetic nanoparticles (MNP). This technique allows the processing of ~ 10,000 tests per day in private companies and around hundreds per day at local Universities guaranteeing to reach a wide range of the population. However, the main drawback of this method is the need for specialized MNP with a strong negative charge for the viral RNA extraction to detect the existence of the SARS-CoV-2 virus. Here we present a simplified low cost method to produce 10 g of nanoparticles in 100 mL of solution that was scaled to one litter by parallelizing the process 10 times in just two days and allowing for the possibility of making ~ 50,000 COVID-19 tests. This communication helps in reducing the cost of acquiring MNP for diverse biomolecular applications supporting developing country budgets constraints and chemical availability specially during the COVID-19 International Health Emergency.

Reference

https://www.nature.com/articles/s41598-020-75798-9

Satisfaction of scientists during the COVID-19 pandemic lockdown

Abstract

The discussion of the social, political and economic consequences of the lockdown during the COVID-19 pandemic mainly revolves around negative effects. This study exploits a unique opportunity and analyses data from a survey (N = 13,316) that happened to be in the field in the months of the development and eventual manifestation of the COVID-19 pandemic. It documents slightly higher levels of average general life satisfaction as well as of satisfaction with various specific aspects of life (health, work, work-life balance and leisure) during the lockdown among scientists in Austria, Germany and Switzerland. It is argued that the lockdown can be regarded as a large-scale social experiment of a very sudden and abrupt change of work and social life, which is unique in history. Daily survey data elicited before and after the lockdown allows the construction of a quasi-experimental design for analysing how this abrupt change of social reality has affected satisfaction. For scientists, the lockdown mainly entailed the transition to work from home, leading to a reduced speed of life and

allowing for more flexibility in incorporating family and leisure into the work day. It is discussed how some of these mechanisms might apply to the general population.

Reference

https://www.nature.com/articles/s41599-020-00618-4

Selection, biophysical and structural analysis of synthetic nanobodies that effectively neutralize SARS-CoV-2

Abstract

The coronavirus SARS-CoV-2 is the cause of the ongoing COVID-19 pandemic. Therapeutic neutralizing antibodies constitute a key short-to-medium term approach to tackle COVID-19. However, traditional antibody production is hampered by long development times and costly production. Here, we report the rapid isolation and characterization of nanobodies from a synthetic library, known as sybodies (Sb), that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. Several binders with low nanomolar affinities and efficient neutralization activity were identified of which Sb23 displayed high affinity and neutralized pseudovirus with an IC50 of 0.6 µg/ml. A cryo-EM structure of the spike bound to Sb23 showed that Sb23 binds competitively in the ACE2 binding site. Furthermore, the cryo-EM reconstruction revealed an unusual conformation of the spike where two RBDs are in the ‘up’ ACE2-binding conformation. The combined approach represents an alternative, fast workflow to select binders with neutralizing activity against newly emerging viruses.

Reference

https://www.nature.com/articles/s41467-020-19204-y

Heparan sulfate assists SARS-CoV-2 in cell entry and can be targeted by approved drugs *in vitro*

Abstract

The cell entry of SARS-CoV-2 has emerged as an attractive drug repurposing target for COVID-19. Here, genetics and chemical perturbation was combined to demonstrate that ACE2-mediated entry of SARS-Cov and CoV-2 requires the cell surface heparan sulfate

(HS) as an assisting cofactor: ablation of genes involved in HS biosynthesis or incubating cells with a HS mimetic both inhibit Spike-mediated viral entry. We show that heparin/HS binds to Spike directly, and facilitates the attachment of Spike-bearing viral particles to the cell surface to promote viral entry. Approved drugs were screened and identified two classes of inhibitors that act *via* distinct mechanisms to target this entry pathway. Among the drugs characterized, Mitoxantrone is a potent HS inhibitor, while Sunitinib and BNTX disrupt the actin network to indirectly abrogate HS-assisted viral entry. It was shown that drugs of the two classes can be combined to generate a synergized activity against SARS-CoV-2-induced cytopathic effect. Altogether, our study establishes HS as an attachment factor that assists SARS coronavirus cell entry and reveals drugs capable of targeting this important step in the viral life cycle.

Reference

https://www.nature.com/articles/s41421-020-00222-5

Epitope similarity cannot explain the pre-formed T-cell immunity towards structural SARS-CoV-2 proteins

Abstract

The current pandemic is caused by the SARS-CoV-2 virus and large progress in understanding the pathology of the virus has been made since its emergence in late 2019. Several reports indicate short lasting immunity against endemic coronaviruses, which contrasts studies showing that biobanked venous blood contains T cells reactive to SARS-CoV-2 S-protein even before the outbreak in Wuhan. This suggests a preformed T cell memory towards structural proteins in individuals not exposed to SARS-CoV-2. Given the similarity of SARS-CoV-2 to other members of the Coronaviridae family, the endemic coronaviruses appear likely candidates to generate this T cell memory. However, given the apparent poor immunological memory created by the endemic coronaviruses, immunity against other common pathogens might offer an alternative explanation. Here, we utilize a combination of epitope prediction and similarity to common human pathogens to identify potential sources of the SARS-CoV-2 T cell memory. Although beta-coronaviruses are the most likely candidates to explain the pre-existing SARS-CoV-2 reactive T cells in uninfected individuals, the SARS-CoV-2 epitopes with the highest similarity to those from beta-coronaviruses are confined to

replication associated proteins—not the host interacting S-protein. Thus, our study suggests that the observed SARS-CoV-2 pre-formed immunity to structural proteins is not driven by near-identical epitopes.

Reference

https://www.nature.com/articles/s41598-020-75972-z

The study of automatic machine learning base on radiomics of non-focus area in the first chest CT of different clinical types of COVID-19 pneumonia

Abstract

To explore the possibility of predicting the clinical types of Corona-Virus-Disease-2019 (COVID-19) pneumonia by analyzing the non-focus area of the lung in the first chest CT image of patients with COVID-19 by using automatic machine learning (Auto-ML). 136 moderate and 83 severe patients were selected from the patients with COVID-19 pneumonia. The clinical and laboratory data were collected for statistical analysis. The texture features of the Non-focus area of the first chest CT of patients with COVID-19 pneumonia were extracted, and then the classification model of the first chest CT of COVID-19 pneumonia was constructed by using these texture features based on the Auto-ML method of radiomics, The area under curve(AUC), true positive rate(TPR), true negative rate (TNR), positive predictive value(PPV) and negative predictive value (NPV) of the operating characteristic curve (ROC) were used to evaluate the accuracy of the first chest CT image classification model in patients with COVID-19 pneumonia. The TPR, TNR, PPV, NPV and AUC of the training cohort and test cohort of the moderate group and the control group, the severe group and the control group, the moderate group and the severe group were all greater than 95% and 0.95 respectively. The non-focus area of the first CT image of COVID-19 pneumonia has obvious difference in different clinical types. The AUTO-ML classification model of Radiomics based on this difference can be used to predict the clinical types of COVID-19 pneumonia.

Reference

https://www.nature.com/articles/s41598-020-76141-y

Persistence of viral RNA, pneumocyte syncytia and thrombosis are hallmarks of advanced COVID-19 pathology

Abstract

Background: COVID-19 is a deadly pulmonary disease with peculiar characteristics, which include variable clinical course and thrombophilia. A thorough understanding of the pathological correlates of the disease is still missing.

Methods: Here we report the systematic analysis of 41 consecutive post-mortem samples from individuals who died of COVID-19. Histological analysis is complemented by immunohistochemistry for cellular and viral antigens and the detection of viral genomes by in situ RNA hybridization.

Findings: COVID-19 is characterized by extensive alveolar damage (41/41 of patients) and thrombosis of the lung micro- and macro-vasculature (29/41, 71%). Thrombi were in different stages of organization, consistent with their local origin. Pneumocytes and endothelial cells contained viral RNA even at the later stages of the disease. An additional feature was the common presence of a large number of dysmorphic pneumocytes, often forming syncytial elements (36/41, 87%). Despite occasional detection of virus-positive cells, no overt signs of viral infection were detected in other organs, which showed non-specific alterations.

Interpretation: COVID-19 is a unique disease characterized by extensive lung thrombosis, long-term persistence of viral RNA in pneumocytes and endothelial cells, along with the presence of infected cell syncytia. Several of COVID-19 features might be consequent to the persistence of virus-infected cells for the duration of the disease.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(20)30480-1/fulltext

Compromised humoral functional evolution tracks with SARS-CoV-2 mortality

Abstract

The urgent need for an effective SARS-CoV-2 vaccine has forced development to progress in the absence of well-defined correlates of immunity. While, neutralization has been linked to protection against other pathogens, whether neutralization alone will be sufficient to drive protection against SARS-CoV-2 in the broader population remains unclear. Therefore, to fully define protective humoral immunity we dissected the early evolution of the humoral response in 193 hospitalized individuals ranging from moderate-to severe. Although robust IgM and IgA responses evolved in both survivors and non-survivors with severe disease, non-survivors showed attenuated IgG responses, accompanied by compromised Fcɣ-receptor binding and Fc-effector activity, pointing to deficient humoral development rather than disease-enhancing humoral immunity. In contrast, individuals with moderate disease exhibited delayed responses that ultimately matured. These data highlight distinct humoral trajectories associated with resolution of SARS-CoV-2 infection and the need for early functional humoral immunity.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31459-8

Quick COVID-19 healers sustain anti-SARS-CoV-2 antibody production

Abstract

Antibodies are key immune effectors that confer protection against pathogenic threats. The nature and longevity of the antibody response to SARS-CoV-2 infection is not well defined. We charted longitudinal antibody responses to SARS-CoV-2 in 92 subjects after symptomatic COVID-19. Antibody responses to SARS-CoV-2 are unimodally distributed over a broad range, with symptom severity correlating directly with virus-specific antibody magnitude. Seventy-six subjects followed longitudinally to ~100 days demonstrated marked heterogeneity in antibody duration dynamics. Virus-specific IgG decayed substantially in most individuals, whereas a distinct subset had stable or increasing antibody levels in the same time frame despite similar initial antibody

magnitudes. These individuals with increasing responses recovered rapidly from symptomatic COVID-19 disease, harbored increased somatic mutations in virus-specific memory B cell antibody genes, and had persistent higher frequencies of previously activated CD4+ T cells. These findings illuminate an efficient immune phenotype that connects symptom clearance speed to differential antibody durability dynamics.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31458-6

Neighbourhood income and physical distancing during the COVID-19 pandemic in the United States

Abstract

Physical distancing has been the primary strategy to control COVID-19 in the United States. Mobility data was used from a large, anonymized sample of smartphone users to assess the relationship between neighbourhood income and physical distancing during the pandemic. A strong gradient was found between neighbourhood income and physical distancing. Individuals in high-income neighbourhoods increased their days at home substantially more than individuals in low-income neighbourhoods did. Residents of low-income neighbourhoods were more likely to work outside the home, compared to residents in higher-income neighbourhoods, but were not more likely to visit locations such as supermarkets, parks and hospitals. Finally, it was found that state orders were only associated with small increases in staying home in low-income neighbourhoods. Our findings indicate that people in lower-income neighbourhoods have faced barriers to physical distancing, particularly needing to work outside the home, and that state physical distancing policies have not mitigated these disparities.

Reference

https://www.nature.com/articles/s41562-020-00998-2

SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: A retrospective cohort study

Abstract

Background: The proportion of asymptomatic carriers and transmission risk factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among household and non-household contacts remains unclear. In Singapore, extensive contact tracing by the Ministry of Health for every diagnosed COVID-19 case, and legally enforced quarantine and intensive health surveillance of close contacts provided a rare opportunity to determine asymptomatic attack rates and SARS-CoV-2 transmission risk factors among community close contacts of patients with COVID-19.

Methods: This retrospective cohort study involved all close contacts of confirmed COVID-19 cases in Singapore, identified between Jan 23 and April 3, 2020. Household contacts were defined as individuals who shared a residence with the index COVID-19 case. Non-household close contacts were defined as those who had contact for at least 30 min within 2 m of the index case. All patients with COVID-19 in Singapore received inpatient treatment, with access restricted to health-care staff. All close contacts were quarantined for 14 days with thrice-daily symptom monitoring *via* telephone. Symptomatic contacts underwent PCR testing for SARS-CoV-2. Secondary clinical attack rates were derived from the prevalence of PCR-confirmed SARS-CoV-2 among close contacts. Consenting contacts underwent serology testing and detailed exposure risk assessment. Bayesian modelling was used to estimate the prevalence of missed diagnoses and asymptomatic SARS-CoV-2-positive cases. Univariable and multivariable logistic regression models were used to determine SARS-CoV-2 transmission risk factors.

Findings: Between Jan 23 and April 3, 2020, 7770 close contacts (1863 household contacts, 2319 work contacts, and 3588 social contacts) linked to 1114 PCR-confirmed index cases were identified. Symptom-based PCR testing detected 188 COVID-19 cases, and 7582 close contacts completed quarantine without a positive SARS-CoV-2

PCR test. Among 7518 (96·8%) of the 7770 close contacts with complete data, the secondary clinical attack rate was 5·9% (95% CI 4·9–7·1) for 1779 household contacts, 1·3% (0·9–1·9) for 2231 work contacts, and 1·3% (1·0–1·7) for 3508 social contacts. Bayesian analysis of serology and symptom data obtained from 1150 close contacts (524 household contacts, 207 work contacts, and 419 social contacts) estimated that a symptom-based PCR-testing strategy missed 62% (95% credible interval 55–69) of COVID-19 diagnoses, and 36% (27–45) of individuals with SARS-CoV-2 infection were asymptomatic. Sharing a bedroom (multivariable odds ratio [OR] 5·38 [95% CI 1·82–15·84]; p=0·0023) and being spoken to by an index case for 30 min or longer (7·86 [3·86–16·02]; p<0·0001) were associated with SARS-CoV-2 transmission among household contacts. Among non-household contacts, exposure to more than one case (multivariable OR 3·92 [95% CI 2·07–7·40], p<0·0001), being spoken to by an index case for 30 min or longer (2·67 [1·21–5·88]; p=0·015), and sharing a vehicle with an index case (3·07 [1·55–6·08]; p=0·0013) were associated with SARS-CoV-2 transmission. Among both household and non-household contacts, indirect contact, meal sharing, and lavatory co-usage were not independently associated with SARS-CoV-2 transmission.

Interpretation: Targeted community measures should include physical distancing and minimising verbal interactions. Testing of all household contacts, including asymptomatic individuals, is warranted.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30833-1/fulltext

Publication Date: Oct 31, 2020

Aptamer BC 007 - Efficient binder of spreading-crucial SARS-CoV-2 proteins

Abstract

Corona virus disease 2019 (COVID-19) is a respiratory disease caused by a new coronavirus (SARS-CoV-2) which causes significant morbidity and mortality. The emergence of this novel and highly pathogenic SARS-CoV-2 and its rapid international

spread poses a serious global public health emergency. To date 32,174,627 cases, of which 962,613 (2.99%) have died, have been reported (https://www.who.int/westernpacific/health-topics/coronavirus, accessed 23 Sep 2020). The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. There are still not many SARS-CoV-2-specific and effective treatments or vaccines available. A second round of infection is obviously unavoidable.

Aptamers had already been at the centre of interest in the fight against viruses before now. The selection and development of a new aptamer is, however, a time-consuming process. It was, therefore, checked whether a clinically developed aptamer, BC 007, which is currently in phase 2 of clinical testing for a different indication, would also be able to efficiently bind DNA-susceptible peptide structures from SARS-CoV-2-spreading crucial proteins, such as the receptor binding domain (RBD) of the spike protein and the RNA dependent RNA polymerase of SARS-CoV-2 (re-purposing). Indeed, several such sequence-sections have been identified. In particular for two of these sequences, BC 007 showed specific binding in a therapy-relevant concentration range, as shown in Nuclear magnetic resonance (NMR)- and Circular dicroism (CD)-spectroscopy and isothermal titration calorimetry (ITC). The excellent clinical toxicity and tolerability profile of this substance opens up an opportunity for rapid clinical testing of its COVID-19 effectiveness.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440(20)32264-7

Publication Date: Oct 30, 2020

The emergence of SARS-CoV-2 in Europe and North America

Abstract

Accurate understanding of the global spread of emerging viruses is critical for public health responses and for anticipating and preventing future outbreaks. Here we elucidate when, where, and how the earliest sustained severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission networks became established in Europe and North America. Our results suggest that rapid early interventions

successfully prevented early introductions of the virus from taking hold in Germany and the United States. Other, later introductions of the virus from China to both Italy and Washington state, United States, founded the earliest sustained European and North America transmission networks. Our analyses demonstrate the effectiveness of public health measures in preventing onward transmission and show that intensive testing and contact tracing could have prevented SARS-CoV-2 outbreaks from becoming established in these regions.

Reference

https://science.sciencemag.org/content/370/6516/564

Elicitation of potent neutralizing antibody responses by designed protein nanoparticle vaccines for SARS-CoV-2

Abstract

A safe, effective, and scalable vaccine is needed to halt the ongoing SARS-CoV-2 pandemic. We describe the structure-based design of self-assembling protein nanoparticle immunogens that elicit potent and protective antibody responses against SARS-CoV-2 in mice. The nanoparticle vaccines display 60 SARS-CoV-2 spike receptor-binding domains (RBDs) in a highly immunogenic array and induce neutralizing antibody titers 10-fold higher than the prefusion-stabilized spike despite a 5-fold lower dose. Antibodies elicited by the RBD nanoparticles target multiple distinct epitopes, suggesting they may not be easily susceptible to escape mutations, and exhibit a lower binding:neutralizing ratio than convalescent human sera, which may minimize the risk of vaccine-associated enhanced respiratory disease. The high yield and stability of the assembled nanoparticles suggest that manufacture of the nanoparticle vaccines will be highly scalable. These results highlight the utility of robust antigen display platforms and have launched cGMP manufacturing efforts to advance the SARS-CoV-2-RBD nanoparticle vaccine into the clinic.

Reference

https://www.cell.com/cell/fulltext/S0092-8674(20)31450-1

Nonstructural protein 1 of SARS-CoV-2 is a potent pathogenicity factor redirecting host protein synthesis machinery toward viral RNA.

Abstract

The causative virus of the COVID-19 pandemic, SARS-CoV-2, uses its nonstructural protein 1 (Nsp1) to suppress cellular, but not viral, protein synthesis through yet unknown mechanisms. We show here that among all viral proteins, Nsp1 has the largest impact on host viability in the cells of human lung origin. Differential expression analysis of mRNA-seq data revealed that Nsp1 broadly alters the cellular transcriptome. Our cryo-EM structure of the Nsp1-40S ribosome complex shows that Nsp1 inhibits translation by plugging the mRNA-entry channel of the 40S. We also determined the structure of the 48S preinitiation complex formed by Nsp1, 40S, and the cricket paralysis virus internal ribosome entry site (IRES) RNA, which shows that it is nonfunctional due to the incorrect position of the mRNA 3' region. Our results elucidate the mechanism of host translation inhibition by SARS-CoV-2 and advances the understanding of the impacts from a major pathogenicity factor of SARS-CoV-2.

Reference

https://www.cell.com/molecular-cell/fulltext/S1097-2765(20)30741-3

Summary of evidence to reduce the two-dose infant priming schedule to a single dose of the 13-valent pneumococcal conjugate vaccine in the national immunisation programme in the UK

Abstract

Pneumococcal conjugate vaccines (PCVs) are highly effective in preventing invasive and non-invasive pneumococcal infections in all age groups through a combination of direct and indirect protection. In many industrialised countries with established PCV programmes, the maximum benefit of the PCV programme has already been achieved, with most cases now due to non-PCV serotypes. On Jan 1, 2020, the UK changed its childhood pneumococcal immunisation programme from a two-dose infant priming

schedule with the 13-valent PCV at 8 and 16 weeks after birth, to a single priming dose at 12 weeks after birth, while retaining the 12-month booster. This decision was made after reviewing the evidence from surveillance data, clinical trials, epidemiological analyses, vaccine effectiveness estimates, and modelling studies to support the reduced schedule. In this Review, we summarise the epidemiology of pneumococcal disease in the UK, the evidence supporting the decision to implement a reduced schedule, and the national and global implications of the proposed schedule.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30492-8/fulltext

CORRESPONDANCE

Publication Date: Nov 03, 2020

Widespread smell testing for COVID-19 has limited application

Abstract

Having campaigned to achieve recognition that anosmia (loss of smell) is a highly prevalent symptom of COVID-19, it was delighted that Public Health England changed the case definition on May 18, 2020. We agree with Cristina Menni and colleagues, that the added sensitivity attributed to adding anosmia to the case definition (less than 2%) is very likely to be a gross underestimate. Indeed, even the additional 15·9% of cases who are identified when including anosmia might still fail to capture the full benefit because access to testing in the UK has been so restricted for patients with mild disease. Data from elsewhere suggest that anosmia will have most value as a marker in mild cases that, until recently, were excluded from testing.

However, caution was urged about a call to introduce smell tests as a screening tool in some settings, such as airports and shopping centres, with the intention of denying access to those identified as having lost their sense of smell. Although new-onset and sudden-onset anosmia has a high likelihood of predicting a positive test for COVID-19 when the prevalence of disease is high, population estimates suggest that 19·1% of adults suffer from pre-existing diminished sense of smell, a figure that rises to 80% in patients older than 75·5 years. These data closely reflect the 21·7% of patients who tested negative for COVID-19 in the COVID Symptom Study who reported a loss of sense of smell. Furthermore, in patients who have developed anosmia as a result of COVID-19, chemosensory loss persists for 8 weeks in approximately 10% of cases (unpublished), but this does not reflect how infectious these individuals are to others and when they have viral clearance. The self-reported median recovery rate of 5 days, as reported by Menni and colleagues, will not be matched by the results of psychophysical smell tests. To deny access to airports or retail parks to approximately one fifth of the population on this basis risks introducing a form of discrimination and

would be an intervention that goes beyond the public health benefits of reducing transmission.

It was strongly advised that all people who experience new-onset loss of sense of smell to self-isolate and seek confirmatory testing. However, it must not impose punitive measures on those patients who have lived without a sense of smell for many years. It was encouraged that extreme caution in how this new finding is incorporated into policy and would suggest that clinicians and researchers working in this field be called upon to ensure that such policies are rigorously and appropriately defined.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32317-5/fulltext

Publication Date: Nov 02, 2020

Co-infections: Testing macrolides for added benefit in patients with COVID-19

Co-infections and pulmonary inflammation are potentially life-threatening consequences of COVID-19. It was believed that for the management of co-infections, macrolide antibiotics are particularly useful. Although azithromycin is actively being pursued, we would also like to suggest josamycin as a worthwhile alternative. Both macrolides are indicated for the treatment of a variety of respiratory infections including pharyngolaryngitis, acute bronchitis, and pneumonia, and the minimum inhibitory concentration of these drugs for the treatment of these infections are rapidly reached in the lungs. With regards to COVID-19, macrolides are well known for their anti-inflammatory and immunomodulatory effects, observed in pulmonary inflammatory disorders such as diffuse panbronchiolitis, asthma, and cystic fibrosis.

Recently, we have been particularly interested in josamycin, and we have assembled further evidence (appendix pp 1–7) of its antifibrotic and anti-inflammatory effects. On the basis of this evidence, we therefore consider that josamycin could be a good choice for patients with COVID-19, as these patients often develop fibrosis-related comorbidities and serious inflammatory symptoms. The UK National Institute for Health and Care Excellence (NICE) treatment guidance for pneumonia is the broad-spectrum antibiotic amoxicillin–clavulanic acid (co-amoxiclav) plus a macrolide. It was concurred

with the opinion expressed by Michael Cox and colleagues that further longitudinal surveillance data would improve antimicrobial stewardship throughout the course of the COVID-19 pandemic. Furthermore, however, it was suggested that the choice of the supplemental macrolide antibiotic should be evaluated through interventional clinical trials and the choice of candidates be guided by their antifibrotic and anti-inflammatory secondary effects. The primary endpoint of such studies should be patient survival and the secondary endpoint the duration of stay in the intensive-care unit. Assessments of morbidity specifically due to lung function deterioration would also be important. For research on predictors of such adverse effects, specific biomarker sampling procedures have been suggested.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(20)30170-1/fulltext

Limitations of using mobile phone data to model COVID-19 transmission in the USA

Mobile phone data provide a unique means to capture individual-level and population-level movement patterns, which have become heavily relied upon to inform COVID-19 responses—specifically, for evaluating the impact of, and compliance with, non-pharmaceutical interventions (NPIs), as well as modelling the spatiotemporal variability of transmission dynamics. In the Article by Hamada S Badr and colleagues, the strong correlation was revealed between population-level mobility patterns and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission patterns for the 25 most affected counties in the USA in the early stages of the COVID-19 pandemic. The analysis was since extended to include all affected counties in the USA, and a longer time period spanning from March 16 to September 16, during which mobility and local outbreaks exhibited much more complex growth and decline patterns. Furthermore, the analysis was applied to subgroups of counties clustered spatially and temporally according to both the magnitude of their outbreaks and growth (or decline) rates during specified periods, in efforts to distinguish the role of mobility patterns in SARS-CoV-2 transmission as a function of these characteristic outbreak dynamics. Critically, results from our more comprehensive analysis reveal that the strong linear association between mobility and case growth rates previously observed is absent after April.

County-level epidemiological data was used from the Johns Hopkins University Center for Systems Science and Engineering to compute the COVID-19 growth rate ratio and aggregated anonymised location data from *SafeGraph* to estimate the time-varying mobility ratio. The methodology from Badr and colleagues was used to compute each metric and the lagged correlations. The correlation distribution for all counties over different time periods is illustrated in the appendix, with counties grouped by outbreak magnitude (low, medium, or high) or outbreak phase (growth rate ratio is increasing, decreasing, or neither increasing or decreasing). Both sets of analysis confirm a uniquely strong association between mobility patterns and SARS-CoV-2 transmission in March–April, whereas the clustering analysis reveals the relationship is strongest for those counties with larger outbreaks that were experiencing a decline in case growth (which aligns with the 25 counties evaluated in our previous study). However, after April, there is no consistent, generalisable relationship between mobility patterns and SARS-CoV-2 transmission across counties, or for any subgroups.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30861-6/fulltext

Publication Date: Oct 30, 2020

Specificity and cross-reactivity of a test for anti-SARS-CoV-2 antibodies

In their Article on the risk of COVID-19 in health-care workers in Denmark, Kasper Iversen and colleagues used a point-of-care test for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) IgG and IgM antibodies developed by Livzon Diagnostics (Zhuhai, Guangdong, China). That particular diagnostic kit for IgM and IgG antibodies is listed on the US Food and Drug Administration (FDA)'s removed test list. According to the FDA, a test is listed on the removed test list if an Emergency Use Authorization has not been submitted by a commercial manufacturer of a serology test within a reasonable period of time or significant problems have been identified that cannot be, or have not been, addressed in a timely manner.

In evaluating the point-of-care assay specificity, Iversen and colleagues do not appear to have tested sera positive for IgM or IgG antibodies against seasonal coronavirus

infections and other acute infections. In addition, the authors did not assess the potential for assay cross-reactivity with autoantibodies present in the sera of patients with autoimmune disease. Cross-reaction of severe acute respiratory syndrome coronavirus antigen with autoantibodies in autoimmune diseases was previously reported. As immunodeficiency can lead to false-negative serology results, the measurements of total IgG and total IgM should be considered, along with any history of immunodeficiency.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30787-8/fulltext

Publication Date: Oct 29, 2020

Specificity and cross-reactivity of a test for anti-SARS-CoV-2 antibodies

Matthieu Schmidt and colleagues aimed to establish the clinical characteristics and outcomes of patients with COVID-19 and respiratory failure treated with extracorporeal membrane oxygenation (ECMO). Among 83 patients, 30 (36%) died, 35 (42%) had major bleeding events, and four (5%) had a haemorrhagic stroke. When discussing the effectiveness of ECMO, an essential aspect is assessing whether the associated bleeding events are adverse incidents, or events resulting from abnormal coagulation.
Bleeding symptoms generally tend to be interpreted as adverse events related to heparin dissolved in the ECMO circuit. However, the amount of anticoagulant therapy used in their cases seemed to be appropriate and is unlikely to be the main cause of bleeding. Therefore, other mechanisms should be considered as reasons for bleeding under ECMO use in patients with COVID-19. Firstly, excessive fibrinolytic activation could occur. A report by Tang and colleagues showed that in the severe cases of COVID-19 leading to death, elevated fibrinogen dropped sharply to 1·0 g/L, and mildly elevated fibrin degradation products increased to 100 μg/mL in just 3 days (day 7 to 10 after admission). During this period, elevations in D-dimer were relatively gradual, leading to a large discrepancy between fibrin degradation product and D-dimer concentrations. These data suggest disseminated intravascular coagulation with enhanced fibrinolysis, indicating the development of coagulation disorders in COVID-19 that could cause major clinical bleeding. Another plausible mechanism is vascular

endotheliitis, given that severe COVID-19 reportedly causes severe vascular endothelial injury and vascular vulnerability. Acquired von Willebrand syndrome is also a possibility. During extracorporeal circulation, such as ECMO, high shear stress is known to destroy large multimers of von Willebrand factor.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30467-7/fulltext

PERSPECTIVE

Publication Date: Oct 30, 2020

Will SARS-CoV-2 become endemic?

Reinfection, in which an individual is subject to multiple, distinct infections from the same virus species throughout their lifetime, is a salient feature of many respiratory viruses. Indeed, the persistence and ubiquity in human society of common respiratory viruses—including influenza viruses, respiratory syncytial virus (RSV), rhinovirus, and the endemic coronaviruses—are largely due to their ability to produce repeat infection. Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for the ongoing coronavirus disease 2019 (COVID-19) pandemic, a critical concern has been whether humans will experience reinfections with this pathogen, which might enable it to become endemic.

Typically, following an initial infection, the human adaptive immune system develops a suite of defenses, including memory B lymphocytes capable of producing neutralizing antibodies targeted to bind to that particular pathogen, and memory T lymphocytes that help regulate immune responses and induce death of infected cells. These adaptive immune components, particularly B cells, can produce sterilizing immunity in which the pathogen, if reintroduced to the host, is prevented from replicating within the body.

However, for many viruses, a number of processes, particularly insufficient adaptive immune response, waning immunity, and immune escape, can undermine or circumvent the sterilizing character of immunity and allow subsequent reinfection. In the first instance, an initial infection with a particular agent may not engender an adaptive immune response sufficient to confer sterilizing immunity. Serological studies indicate that most SARS-CoV-2 infections, regardless of severity, induce development of some specific antibodies; however, despite encouraging results from the experimental vaccination of primates, it remains unclear whether those antibodies are sufficient to provide long-term effective protection or if other adaptive immune components are present and functional. Furthermore, immune response to SARS-CoV-2 infection is heterogeneous, with individuals who experience asymptomatic infections manifesting a

weaker immune response than those experiencing more severe disease. It is possible that some individuals never develop sterilizing immunity following infection with SARS-CoV-2, or that multiple exposures will be needed for affinity maturation and development of long-lasting protection. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/370/6516/527

FORUM

Publication Date: Oct 31, 2020

A potential role of interleukin-10 in COVID-19 pathogenesis

A unique feature of the cytokine storm in COVID-19 is the dramatic elevation of IL-10. Its significance was thought as a negative-feedback mechanism for suppressing inflammation. However, several lines of clinical evidence suggest that dramatic early pro-inflammatory IL-10 elevation might play a pathological role in COVID-19 severity. For more details, read the link given below.

Reference

https://www.cell.com/trends/immunology/fulltext/S1471-4906(20)30256-8

Publication Date: Oct 29, 2020

PET imaging as a tool for assessing COVID-19 brain changes

A substantial fraction of coronavirus disease 2019 (COVID-19) patients experience neurological manifestations. Nevertheless, brain changes caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain largely unknown. Here, we provide a brief overview of positron emission tomography (PET) applications that could advance current understanding of CNS pathophysiological alterations associated with SARS-CoV-2 infection.

Reference

https://www.cell.com/trends/neurosciences/fulltext/S0166-2236(20)30243-5

REPORT

Publication Date: Nov 03, 2020

HSV-1 and Zika Virus but not SARS-CoV-2 replicate in the human cornea and are restricted by corneal type iii interferon

Here, studies of immune-mediated regulation of Zika virus (ZIKV), herpes simplex virus 1 (HSV-1), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in the human cornea was reported. It was found that ZIKV can be transmitted via corneal transplantation in mice. However, in human corneal explants, we report that ZIKV does not replicate efficiently and that SARS-CoV-2 does not replicate at all. Additionally, we demonstrate that type III interferon (IFN-λ) and its receptor (IFNλR1) are expressed in the corneal epithelium. Treatment of human corneal explants with IFN-λ, and treatment of mice with IFN-λ eye drops, upregulates antiviral interferon-stimulated genes. In human corneal explants, blockade of IFNλR1 enhances replication of ZIKV and HSV-1 but not SARS-CoV-2. In addition to an antiviral role for IFNλR1 in the cornea, our results suggest that the human cornea does not support SARS-CoV-2 infection despite expression of ACE2, a SARS-CoV-2 receptor, in the human corneal epithelium.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247(20)31328-0

Publication Date: Oct 30, 2020

Cryptic transmission of SARS-CoV-2 in Washington state

After its emergence in Wuhan, China, in late November or early December 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus rapidly spread globally. Genome sequencing of SARS-CoV-2 allows the reconstruction of its transmission history, although this is contingent on sampling. We analyzed 453 SARS-CoV-2 genomes collected between 20 February and 15 March 2020 from infected patients in Washington state in the United States. We find that most SARS-CoV-2 infections sampled during this time derive from a single introduction in late January or

early February 2020, which subsequently spread locally before active community surveillance was implemented.

Reference

https://science.sciencemag.org/content/370/6516/571

COMMENT

Publication Date: Nov 04, 2020

Recovery of four COVID-19 patients *via* ozonated autohemotherapy

Abstract

A case series of ozonated autohemotherapy of four COVID-19 patients was reported, classified as critically ill (1 patient), severe (1 patient), and moderate (2 patients). Each ozonated autohemotherapy treatment was performed at a concentration of 40 μg/ml of ozone per 100 ml of blood. The number of treatments varied from 1 to 9 depending on the disease severity. All 4 patients, including 1 critically ill patient with severe acute respiratory distress syndrome (ARDS) and life-threatening refractory hypoxemia, recovered uneventfully and were discharged from the hospital after viral clearance. The younger sibling of the critically ill patient was also diagnosed with COVID-19 and developed ARDS with hypoxemia, who received mechanical ventilation through an endotracheal tube and extracorporeal membrane oxygenation (ECMO) support. The overall medical cost for 18 days spent in the intensive care unit (ICU) and 56 days of hospitalization was $139,935 USD. On the other hand, our critically ill patient underwent 9 ozonated autohemotherapy treatments and spent 10 days in the ICU and was discharged on hospital day 30; his hospitalization cost amounted to $15,466.50 USD. This case series suggests that ozonated autohemotherapy may be an alternative noninvasive medical treatment for COVID-19 patients.

Reference

https://www.cell.com/the-innovation/fulltext/S2666-6758(20)30063-1

Dexamethasone in hospitalised patients with COVID-19: Addressing uncertainties

The impressive results of the RECOVERY trial established that a moderate dose of dexamethasone (6 mg daily for 10 days) reduced mortality in hospitalised patients with COVID-19 and respiratory failure who required therapy with supplemental oxygen or mechanical ventilation. The data also indicated that dexamethasone might increase

mortality in hospitalised patients who were not receiving oxygen. This landmark trial and the subsequent practice guidelines from several academic and health organisations recommending dexamethasone use in patients with severe COVID-19 have changed clinical practice for hospitalised patients on supplemental oxygen or mechanical ventilation. These favourable findings are supported by three other trials of glucocorticoids for COVID-19, which stopped enrolment in early June, 2020, when the RECOVERY trial results were released. Each of these trials showed some evidence of benefit, although none had completed enrolment. A prospective meta-analysis of these and other trials, totalling 1703 participants (1007 [59%] from the RECOVERY trial), confirmed a reduction in 28-day mortality (summary odds ratio [OR] 0·66, 95% CI 0·53–0·82; p<0·001), with minimal heterogeneity across studies. While confirming beneficial effects of corticosteroids for critically ill hospitalised patients with COVID-19, some unanswered questions and issues remain that deserve discussion and should be addressed in future research.

Because the design of the largest trial, RECOVERY, was pragmatic, data were scarce in some domains. For example, physicians were able to exclude patients from the trial whom they determined should not be a candidate for treatment with dexamethasone, but reasons for exclusion were not recorded. Thus, we do not know why 1707 patients were unsuitable for randomisation. Patients might have been excluded because of perceived contraindications, including uncontrolled diabetes, acute delirium, underlying malignancy, immunosuppression, or other conditions in which corticosteroids might have harmful effects. Therefore, the benefit–risk profile of corticosteroids across the full spectrum of patients with critical COVID-19 and a range of comorbidities remains uncertain.

Reference

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30503-8/fulltext