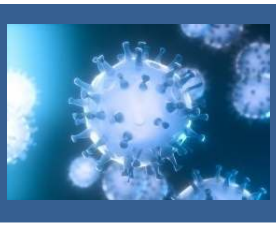
COVID-19

Jun 24 – 30, 2021



RESEARCH PUBLICATIONS

Publication Date: Jun 30 2021

SARS-CoV-2-specific T cell memory is sustained in COVID-19 convalescent patients for 10 months with successful development of stem cell-like memory T cells

Abstract

Memory T cells contribute to rapid viral clearance during re-infection, but the longevity and differentiation of SARS-CoV-2-specific memory T cells remain unclear. Here ex vivo assays were conducted to evaluate SARS-CoV-2-specific CD4+ and CD8+ T cell responses in COVID-19 convalescent patients up to 317 days post-symptom onset (DPSO), and find that memory T cell responses are maintained during the study period regardless of the severity of COVID-19. In particular, sustained polyfunctionality and proliferation capacity of SARS-CoV-2-specific T cells were observed. Among SARS-CoV-2-specific CD4+ and CD8+ T cells detected by activation-induced markers, the proportion of stem cell-like memory T (TSCM) cells is increased, peaking at approximately 120 DPSO. Development of TSCM cells is confirmed by SARS-CoV-2-specific MHC-I multimer staining. Considering the self-renewal capacity and multipotency of TSCM cells, our data suggest that SARS-CoV-2-specific T cells are long-lasting after recovery from COVID-19, thus support the feasibility of effective vaccination programs as a measure for COVID-19 control.

Reference

https://www.nature.com/articles/s41467-021-24377-1

Comparative performance of SARS-CoV-2 lateral flow antigen tests and association with detection of infectious virus in clinical specimens: A single-centre laboratory evaluation study

Abstract

Background: Lateral flow devices (LFDs) for rapid antigen testing are set to become a cornerstone of SARS-CoV-2 mass community testing, although their reduced sensitivity compared with PCR has raised questions of how well they identify infectious cases. Understanding their capabilities and limitations is, therefore, essential for successful implementation. We evaluated six commercial LFDs and assessed their correlation with infectious virus culture and PCR cycle threshold (Ct) values.

Methods: In a single-centre, laboratory evaluation study, we did a head-to-head comparison of six LFDs commercially available in the UK: Innova Rapid SARS-CoV-2 Antigen Test, Spring Healthcare SARS-CoV-2 Antigen Rapid Test Cassette, E25Bio Rapid Diagnostic Test, Encode SARS-CoV-2 Antigen Rapid Test Device, SureScreen COVID-19 Rapid Antigen Test Cassette, and SureScreen COVID-19 Rapid Fluorescence Antigen Test. We estimated the specificities and sensitivities of the LFDs using stored naso-oropharyngeal swabs collected at St Thomas' Hospital (London, UK) for routine diagnostic SARS-CoV-2 testing by real-time RT-PCR (RT-rtPCR). Swabs were from inpatients and outpatients from all departments of St Thomas' Hospital, and from health-care staff (all departments) and their household contacts. SARS-CoV-2-negative swabs from the same population (confirmed by RT-rtPCR) were used for comparative specificity determinations. All samples were collected between March 23 and Oct 27, 2020. The limit of detection (LOD) for each test was determined using viral plaque-forming units (PFUs) and viral RNA copy numbers of laboratory-grown SARS-CoV-2. Additionally, LFDs were selected to assess the correlation of antigen test result with RT-rtPCR Ct values and positive viral culture in Vero E6 cells. This analysis included longitudinal swabs from five infected inpatients with varying disease severities. Furthermore, the sensitivities of available LFDs were assessed in swabs (n=23; collected from Dec 4, 2020, to Jan 12, 2021) confirmed to be positive (RT-rtPCR and whole-genome sequencing) for the B.1.1.7 variant, which was the dominant genotype in the UK at the time of study completion.

Findings: All LFDs showed high specificity (≥98·0%), except for the E25Bio test (86·0% [95% CI 77·9–99·9]), and most tests reliably detected 50 PFU/test (equivalent SARS-CoV-2 N gene Ct value of 23·7, or RNA copy number of 3 × 106/mL). Sensitivities of the LFDs on clinical samples ranged from 65·0% (55·2–73·6) to 89·0% (81·4–93·8). These

sensitivities increased to greater than 90% for samples with Ct values of lower than 25 for all tests except the SureScreen fluorescence (SureScreen-F) test. Positive virus culture was identified in 57 (40·4%) of 141 samples; 54 (94·7%) of the positive cultures were from swabs with Ct values lower than 25. Among the three LFDs selected for detailed comparisons (the tests with highest sensitivity [Innova], highest specificity [Encode], and alternative technology [SureScreen-F]), sensitivity of the LFDs increased to at least 94·7% when only including samples with detected viral growth. Longitudinal studies of RT-rtPCR-positive samples (tested with Innova, Encode, and both SureScreen-F and the SureScreen visual [SureScreen-V] test) showed that most of the tests identified all infectious samples as positive. Test performance (assessed for Innova and SureScreen-V) was not affected when reassessed on swabs positive for the UK variant B.1.1.7.

Interpretation: In this comprehensive comparison of antigen LFDs and virus infectivity, we found a clear relationship between Ct values, quantitative culture of infectious virus, and antigen LFD positivity in clinical samples. The data support regular testing of target groups with LFDs to supplement the current PCR testing capacity, which would help to rapidly identify infected individuals in situations in which they would otherwise go undetected.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00143-9/fulltext

Publication Date: Jun 29, 2021

Structure-guided T cell vaccine design for SARS-CoV-2 variants and sarbecoviruses

Abstract

The emergence of SARS-CoV-2 variants that escape convalescent and vaccine-induced antibody responses has renewed focus on the development of broadly protective T cell-based vaccines. Here structure-based network analysis was applied and assessments of HLA class I-peptide stability to define mutationally constrained CD8+ T cell epitopes across the SARS-CoV-2 proteome. Highly networked residues are conserved temporally among circulating variants and across the Sarbecovirus

subgenus, and disproportionately impair Spike pseudotyped lentivirus infectivity when mutated. Evaluation of HLA class I stabilizing activity for 18 globally prevalent alleles identifies CD8+ T cell epitopes within highly networked regions with limited mutational frequencies in circulating SARS-CoV-2 variants and deep-sequenced primary isolates. Moreover, these epitopes elicit demonstrable CD8+ T cell reactivity in convalescent individuals but reduced recognition in mRNA-based vaccine recipients. These data thereby elucidate key mutationally constrained regions and immunogenic epitopes in the SARS-CoV-2 proteome for a global T cell-based vaccine against emerging variants and sarbecoviruses.

Reference

https://www.cell.com/cell/fulltext/S0092-8674%2821%2900797-2

Role of spatial patterning of N-protein interactions in SARS-CoV-2 genome packaging

Abstract

Viruses must efficiently and specifically package their genomes while excluding cellular nucleic acids and viral subgenomic fragments. Some viruses use specific packaging signals, which are conserved sequence or structure motifs present only in the full-length genome. Recent work has shown that viral proteins important for packaging can undergo liquid-liquid phase separation (LLPS), in which one or two viral nucleic acid binding proteins condense with the genome. The compositional simplicity of viral components lends itself well to theoretical modeling compared with more complex cellular organelles. Viral LLPS can be limited to one or two viral proteins and a single genome that is enriched in LLPS-promoting features. In the previous study, it was observed that LLPS-promoting sequences of severe acute respiratory syndrome coronavirus 2 are located at the 5′ and 3′ ends of the genome, whereas the middle of the genome is predicted to consist mostly of solubilizing elements. Is this arrangement sufficient to drive single genome packaging, genome compaction, and genome cyclization? These questions were addressed using a coarse-grained polymer model, LASSI, to study the LLPS of nucleocapsid protein with RNA sequences that either promote LLPS or solubilization. With respect to genome cyclization, we find the most optimal arrangement restricts LLPS-promoting elements to the 5′ and 3′ ends of the

genome, consistent with the native spatial patterning. Genome compaction is enhanced by clustered LLPS-promoting binding sites, whereas single genome packaging is most efficient when binding sites are distributed throughout the genome. These results suggest that many and variably positioned LLPS-promoting signals can support packaging in the absence of a singular packaging signal which argues against necessity of such a feature. It was hypothesized that this model should be generalizable to multiple viruses as well as cellular organelles such as paraspeckles, which enrich specific long RNA sequences in a defined arrangement.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495%2821%2900505-1

Publication Date: Jun 28, 2021

FDA-authorized mRNA COVID-19 vaccines are effective per real-world evidence synthesized across a multi-state health system

Abstract

Background: Two FDA-authorized mRNA COVID-19 vaccines, BNT162b2 (Pfizer/BioNTech) and mRNA-1273 (Moderna), have demonstrated high efficacies in large Phase 3 randomized clinical trials. It is important to assess their effectiveness in a real-world setting.

Methods: This is a retrospective analysis of 136,532 individuals in the Mayo Clinic health system (Arizona, Florida, Iowa, Minnesota, Wisconsin) with PCR testing data between December 1, 2020 and April 20, 2021. We compared clinical outcomes for a vaccinated cohort of 68,266 individuals who received at least one dose of either vaccine (nBNT162b2 = 51,795; nmRNA-1273 = 16,471) and an unvaccinated control cohort of 68,266 individuals propensity-matched based on relevant demographic, clinical, and geographic features. We estimated real-world vaccine effectiveness by comparing incidence rates of positive SARS-CoV-2 PCR testing and COVID-19 associated hospitalization and ICU admission starting 7 days after the second vaccine dose.

Findings: The real-world vaccine effectiveness in preventing SARS-CoV-2 infection was 86.1% (95% CI: 82.4-89.1%) for BNT162b2 and 93.3% (95% CI: 85.7-97.4%) for mRNA-1273. BNT162b2 and mRNA-1273 were 88.8% (95% CI: 75.5-95.7%) and

86.0% (95% CI: 71.6-93.9%) effective in preventing COVID-19 associated hospitalization. Both vaccines were 100% effective (95% CIBNT162b2: 51.4-100%; 95% CImRNA-1273: 43.3-100%) in preventing COVID-19 associated ICU admission.

Conclusions: BNT162b2 and mRNA-1273 are both effective in a real-world setting and are associated with reduced rates of SARS-CoV-2 infection and decreased burden of COVID-19 on the healthcare system.

Reference

https://www.cell.com/med/fulltext/S2666-6340%2821%2900238-5

Real-time analysis of a mass vaccination effort confirms the safety of FDA-authorized mRNA COVID-19 vaccines

Abstract

Background: As the COVID-19 vaccination campaign unfolds, it is important to continuously assess the real world safety of FDA-authorized vaccines. Curation of large-scale electronic health records (EHRs) enables near real-time safety evaluations that were not previously possible.

Methods: In this retrospective study, deep neural networks were deployed over a large EHR system to automatically curate the adverse effects mentioned by physicians in over 1.2 million clinical notes between December 1st 2020 and April 20th 2021. We compared notes from 68,266 individuals who received at least one dose of BNT162b2 (n = 51,795) or mRNA-1273 (n = 16,471) to notes from 68,266 unvaccinated individuals who were matched by demographic, geographic, and clinical features.

Findings: Individuals vaccinated with BNT162b2 or mRNA-1273 had a higher rate of return to the clinic, but not the emergency department, after both doses compared to unvaccinated controls. The most frequently documented adverse effects within 7 days of each vaccine dose included myalgia, headache, and fatigue, but the rates of EHR documentation for each side effect were remarkably low compared to those derived from active solicitation during clinical trials. Severe events including anaphylaxis, facial paralysis, and cerebral venous sinus thrombosis were rare and occurred at similar frequencies in vaccinated and unvaccinated individuals.

Conclusions: This analysis of vaccine-related adverse effects from over 1.2 million EHR notes of more than 130,000 individuals reaffirms the safety and tolerability of the FDA-authorized mRNA COVID-19 vaccines in practice.

Reference

https://www.cell.com/med/fulltext/S2666-6340%2821%2900237-3

Prediction model for the spread of the COVID-19 outbreak in the global environment

Abstract

COVID-19 has long become a worldwide pandemic. It is responsible for the death of over two million people and posed an economic recession. This paper studies the spread pattern of COVID-19, aiming to establish a prediction model for this event. Data Mining and Machine Learning methodologies were harnessed to train regression models to predict the number of confirmed cases in a spatial-temporal space. An innovative concept was introduced – the Center of Infection Mass (CoIM) – adapted from the field of physics. The model was empirically evaluated on western European countries, based on the CoIM index and other features, and showed that a relatively high accurate prediction of the spread can be obtained. The contribution is twofold: first, a prediction methodology was introduced and proved empirically that a prediction can be made even to the range of over a month; second, promise was shown in adopting the CoIM index to prediction models, when models that adopt the CoIM yield significantly better results than those that discard it. By applying our model, and better controlling the inherent tradeoff between life-saving and economy, it was believed that decision-makers can take close to optimal measures. Thus, this methodology may contribute to public welfare.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440%2821%2901519-X

SARS-CoV-2 variant B.1.617 is resistant to Bamlanivimab and evades antibodies induced by infection and vaccination

Abstract

The emergence of SARS-CoV-2 variants threatens efforts to contain the COVID-19 pandemic. The number of COVID-19 cases and deaths in India has risen steeply and a SARS-CoV-2 variant, B.1.617, is believed to be responsible for many of these cases. The spike protein of B.1.617 harbors two mutations in the receptor binding domain, which interacts with the ACE2 receptor and constitutes the main target of neutralizing antibodies. Therefore, it was analyzed whether B.1.617 is more adept in entering cells and/or evades antibody responses. B.1.617 enters two out of eight cell lines tested with roughly 50% increased efficiency and is equally inhibited by two entry inhibitors. In contrast, B.1.617 is resistant against Bamlanivimab, an antibody used for COVID-19 treatment. B.1.617 evades antibodies induced by infection or vaccination, although less so than the B.1.351 variant. Collectively, the study reveals that antibody evasion of B.1.617 may contribute to the rapid spread of this variant.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900828-7

Distinctive features of SARS-CoV-2-specific T cells predict recovery from severe COVID-19

Abstract

Although T cells are likely players in SARS-CoV-2 immunity, little is known about the phenotypic features of SARS-CoV-2-specific T cells associated with recovery from severe COVID-19. T cells were analyzed from 34 COVID-19 patients with severities ranging from mild (outpatient) to critical culminating in death. Relative to patients that succumbed, individuals that recovered from severe COVID-19 harbor elevated and increasing numbers of SARS-CoV-2-specific T cells capable of homeostatic proliferation. In contrast, fatal COVID-19 displays elevated numbers of SARS-CoV-2-specific regulatory T cells and a time-dependent escalation in activated bystander CXCR4+ T cells as assessed by longitudinal sampling. Together with the demonstration of increased proportions of inflammatory CXCR4+ T cells in the lungs of severe COVID-19 patients, these results support a model whereby lung-homing T cells activated through bystander effects contribute to immunopathology, while a robust, non-suppressive SARS-CoV-2-specific T cell response limits pathogenesis and promotes recovery from severe COVID-19.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900827-5

A single intranasal or intramuscular immunization with chimpanzee adenovirus vectored SARS-CoV-2 vaccine protects against pneumonia in hamsters

Abstract

The development of an effective vaccine against SARS-CoV-2, the etiologic agent of COVID-19, is a global priority. Here, the protective capacity of intranasal and intramuscular delivery of a chimpanzee adenovirus-vectored vaccine was compared, encoding a pre-fusion stabilized spike protein (ChAd-SARS-CoV-2-S) in Golden Syrian hamsters. While immunization with ChAd-SARS-CoV-2-S induced robust spike protein specific antibodies capable of neutralizing the virus, antibody levels in serum were higher in hamsters vaccinated by an intranasal compared to intramuscular route. Accordingly, against challenge with SARS-CoV-2, ChAd-SARS-CoV-2-S immunized hamsters were protected against less weight loss and had reduced viral infection in nasal swabs and lungs, and reduced pathology and inflammatory gene expression in the lungs, compared to ChAd-Control immunized hamsters. Intranasal immunization with ChAd-SARS-CoV-2-S provided superior protection against SARS-CoV-2 infection and inflammation in the upper respiratory tract. These findings support intranasal administration of the ChAd-SARS-CoV-2-S candidate vaccine to prevent SARS-CoV-2 infection, disease, and possibly transmission.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900798-1

Transient complexes of the Nsp7, Nsp8 and Nsp12 in SARS-CoV-2 replication transcription complex

Abstract

The RNA transcription complex (RTC) from the virus, SARS-CoV-2, is responsible for recognizing and processing RNA for two principal purposes. The RTC copies viral RNA for propagation into new virus and for ribosomal transcription of viral proteins. To accomplish these activities the RTC mechanism must also conform to a large number of imperatives including RNA over DNA base recognition, base pairing, distinguishing viral and host RNA, production of mRNA that conforms to host ribosome conventions, interface with error checking machinery and evading host immune responses. In addition, the RTC will discontinuously transcribe specific sections of viral RNA to amplify certain proteins over others. Central to SARS-CoV-2 viability, the RTC is therefore dynamic and sophisticated. A systematic structural investigation of three components was conducted that make up the RTC: Nsp7, Nsp8 and Nsp12 (also known as RNA dependent RNA polymerase (RdRp)). A high resolution crystal structures of the Nsp7/8 complex was solved providing insight into the interaction between the proteins. We have used small angle X-ray and neutron solution scattering (SAXS and SANS) on each component individually as pairs and higher order complexes and with and without RNA. Using size exclusion chromatography and multi-angle light scattering coupled SAXS (SEC-MALS-SAXS), it was defined which combination of components form transient or stable complexes. A contrast matching neutron scattering was used to mask specific complex forming components to test whether components change conformation upon complexation. Altogether, we find that individual Nsp7, Nsp8 and Nsp12 structures vary based on whether other proteins in their complex are present. Combining the crystal structure, atomic coordinates reported elsewhere, SAXS, SANS and other biophysical techniques we provide greater insight into the RTC assembly, mechanism and potential avenues for disruption of the complex and its functions.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495%2821%2900491-4

Dynamics of the SARS-CoV-2 nucleoprotein N-terminal domain triggers RNA duplex destabilization

Abstract

The nucleocapsid (N) protein of betacoronaviruses is responsible for nucleocapsid assembly and other essential regulatory functions. N protein N-terminal domain (N-NTD) interacts and melts the double stranded transcriptional regulatory sequences (dsTRS), regulating the discontinuous subgenome transcription process. Here, we used molecular dynamics (MD) simulations to study the binding of SARS-CoV-2 N-NTD to non-specific (NS) and TRS dsRNAs. dsRNAs' Watson and Crick (WC) base-pairing was probed over 25 replicas of 100 ns MD simulations, showing that only one N-NTD of dimeric N is enough to destabilize dsRNAs, triggering melting initiation. dsRNA destabilization driven by N-NTD was more efficient for dsTRS than dsNS. N-NTD dynamics, especially a tweezer-like motion of β2-β3 and α2-β5 loops, seems to play a key role in WC base-pairing destabilization. Based on experimental information available in the literature, kinetics models were constructed for N-NTD-mediated dsRNA melting. The results support a 1:1 stoichiometry (N-NTD:dsRNA), matching MD simulations and raising different possibilities for N-NTD action: (i) two N-NTD arms of dimeric N would bind to two different RNA sites, either closely or spatially spaced in the viral genome, in a cooperative manner; (ii) monomeric N-NTD would be active, opening up the possibility of a regulatory dissociation event.

Reference

https://www.cell.com/biophysj/fulltext/S0006-3495%2821%2900488-4

COVID-19 mRNA vaccine induced antibody responses against three SARS-CoV-2 variants

Abstract

As SARS-CoV-2 has been circulating for over a year, dozens of vaccine candidates are under development or in clinical use. The BNT162b2 mRNA COVID-19 vaccine induces spike protein-specific neutralizing antibodies associated with protective immunity. The emergence of the B.1.1.7 and B.1.351 variants has raised concerns of reduced vaccine efficacy and increased re-infection rates. Here it was shown, that after the second dose,

the sera of BNT162b2-vaccinated health care workers (n = 180) effectively neutralize the SARS-CoV-2 variant with the D614G substitution and the B.1.1.7 variant, whereas the neutralization of the B.1.351 variant is five-fold reduced. Despite the reduction, 92% of the seronegative vaccinees have a neutralization titre of >20 for the B.1.351 variant indicating some protection. The vaccinees' neutralization titres exceeded those of recovered non-hospitalized COVID-19 patients. The work provides evidence that the second dose of the BNT162b2 vaccine induces cross-neutralization of at least some of the circulating SARS-CoV-2 variants.

Reference

https://www.nature.com/articles/s41467-021-24285-4

Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine (CoronaVac) in healthy children and adolescents: A double-blind, randomised, controlled, phase 1/2 clinical trial

Abstract

Background: A vaccine against SARS-CoV-2 for children and adolescents will play an important role in curbing the COVID-19 pandemic. Here we aimed to assess the safety, tolerability, and immunogenicity of a candidate COVID-19 vaccine, CoronaVac, containing inactivated SARS-CoV-2, in children and adolescents aged 3–17 years.

Methods: A double-blind, randomised, controlled, phase 1/2 clinical trial of CoronaVac was done in healthy children and adolescents aged 3–17 years old at Hebei Provincial Center for Disease Control and Prevention in Zanhuang (Hebei, China). Individuals with SARS-CoV-2 exposure or infection history were excluded. Vaccine (in 0·5 mL aluminum hydroxide adjuvant) or aluminum hydroxide only (alum only, control) was given by intramuscular injection in two doses (day 0 and day 28). A phase 1 trial in 72 participants was done with an age de-escalation in three groups and dose-escalation in two blocks (1·5 μg or 3·0 μg per injection). Within each block, participants were randomly assigned (3:1) by means of block randomisation to receive CoronaVac or alum only. In phase 2, participants were randomly assigned (2:2:1) by means of block randomisation to receive either CoronaVac at 1·5 μg or 3·0 μg per dose, or alum only. All participants, investigators, and laboratory staff were masked to group allocation. The primary safety endpoint was adverse reactions within 28 days after each injection in all

participants who received at least one dose. The primary immunogenicity endpoint assessed in the per-protocol population was seroconversion rate of neutralising antibody to live SARS-CoV-2 at 28 days after the second injection. This study is ongoing and is registered with ClinicalTrials.gov, NCT04551547.

Findings: Between Oct 31, 2020, and Dec 2, 2020, 72 participants were enrolled in phase 1, and between Dec 12, 2020, and Dec 30, 2020, 480 participants were enrolled in phase 2. 550 participants received at least one dose of vaccine or alum only (n=71 for phase 1 and n=479 for phase 2; safety population). In the combined safety profile of phase 1 and phase 2, any adverse reactions within 28 days after injection occurred in 56 (26%) of 219 participants in the 1·5 μg group, 63 (29%) of 217 in the 3·0 μg group, and 27 (24%) of 114 in the alum-only group, without significant difference (p=0·55). Most adverse reactions were mild and moderate in severity. Injection site pain was the most frequently reported event (73 [13%] of 550 participants), occurring in 36 (16%) of 219 participants in the 1·5 μg group, 35 (16%) of 217 in the 3·0 μg group, and two (2%) in the alum-only group. As of June 12, 2021, only one serious adverse event of pneumonia has been reported in the alum-only group, which was considered unrelated to vaccination. In phase 1, seroconversion of neutralising antibody after the second dose was observed in 27 of 27 participants (100·0% [95% CI 87·2–100·0]) in the 1·5 μg group and 26 of 26 participants (100·0% [86·8-100·0]) in the 3·0 μg group, with the geometric mean titres of 55·0 (95% CI 38·9–77·9) and 117·4 (87·8–157·0). In phase 2, seroconversion was seen in 180 of 186 participants (96·8% [93·1–98·8]) in the 1·5 μg group and 180 of 180 participants (100·0% [98·0–100·0]) in the 3·0 μg group, with the geometric mean titres of 86·4 (73·9–101·0) and 142·2 (124·7–162·1). There were no detectable antibody responses in the alum-only groups.

Interpretation: CoronaVac was well tolerated and safe and induced humoral responses in children and adolescents aged 3–17 years. Neutralising antibody titres induced by the 3·0 μg dose were higher than those of the 1·5 μg dose. The results support the use of 3·0 μg dose with a two-immunisation schedule for further studies in children and adolescents.

Reference

https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00319-4/fulltext

The global prevalence of depression, anxiety, stress, and, insomnia and its changes among health professionals during COVID-19 pandemic: A rapid systematic review and meta-analysis

Abstract

Background: During the COVID-19 pandemic, the health professionals who are at the frontline of this crisis have been facing extreme psychological disorders. This research aims to provide an overall scenario of the prevalence of depression, anxiety, stress, as well as insomnia and to inspect the changes in these prevalence over time by analyzing the existing evidence during this COVID-19 pandemic.

Methods: A systematic search was performed on March 30, 2021, in PubMed, MEDLINE, Google Scholar databases, and Web of Science. To assess the heterogeneity, Q-test, I2 statistics, and Meta regression and to search for the publication bias, Eggers's test and funnel plot were used. The random-effect model and subgroup analysis were performed due to the significant heterogeneity.

Results: Among eighty-three eligible studies in the final synthesis, 69 studies (n = 144649) assessed the depression prevalence of 37.12% (95% CI: 31.80–42.43), 75 studies (n = 147435) reported the anxiety prevalence of 41.42% (95% CI: 36.17–46.54), 41 studies (n = 82783) assessed the stress prevalence of 44.86% (95% CI: 36.98–52.74), 21 studies (n = 33370) enunciated the insomnia prevalence of 43.76% (95% CI: 35.83–51.68). The severity of the mental health problems among health professionals increased over the time during January 2020 to September 2020.

Limitations: A significant level of heterogeneity was found among psychological measurement tools and across studies.

Conclusions: Therefore, it is an emergency to develop psychological interventions that can protect the mental health of vulnerable groups like health professionals.

Reference

https://www.cell.com/heliyon/fulltext/S2405-8440%2821%2901496-1

Antibody landscape against SARS-CoV-2 reveals significant differences between non-structural/accessory and structural proteins

Abstract

The immunogenicity of the SARS-CoV-2 proteome is largely unknown, especially for non-structural proteins and accessory proteins. In this study, 2,360 COVID-19 sera and 601 control sera were collected. These sera were analyzed on a protein microarray with 20 proteins of SARS-CoV-2, building an antibody response landscape for immunoglobulin (Ig)G and IgM. Non-structural proteins and accessory proteins NSP1, NSP7, NSP8, RdRp, ORF3b, and ORF9b elicit prevalent IgG responses. The IgG patterns and dynamics of non-structural/accessory proteins are different from those of the S and N proteins. The IgG responses against these six proteins are associated with disease severity and clinical outcome, and they decline sharply about 20 days after symptom onset. In non-survivors, a sharp decrease of IgG antibodies against S1 and N proteins before death is observed. The global antibody responses to non-structural/accessory proteins revealed here may facilitate a deeper understanding of SARS-CoV-2 immunology.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900789-0

Clinical performance evaluation of SARS-CoV-2 rapid antigen testing in point of care usage in comparison to RT-qPCR

Abstract

Background: Antigen rapid diagnostic tests (RDT) for SARS-CoV-2 are fast, broadly available, and inexpensive. Despite this, reliable clinical performance data from large field studies is sparse.

Methods: In a prospective performance evaluation study, RDT from three manufacturers (NADAL®, Panbio™, MEDsan®, conducted on different samples) were compared to quantitative reverse transcription polymerase chain reaction (RT-qPCR) in 5 068 oropharyngeal swabs for detection of SARS-CoV-2 in a hospital setting. Viral load was derived from standardised RT-qPCR Cycle threshold (Ct) values. The data collection period ranged from November 12, 2020 to February 28, 2021.

Findings: The sensitivity of RDT compared to RT-qPCR was 42·57% (95% CI 33·38%–52·31%). The specificity was 99·68% (95% CI 99·48%–99·80%). Sensitivity declined with decreasing viral load from 100% in samples with a deduced viral load of ≥108 SARS-CoV-2 RNA copies per ml to 8·82% in samples with a viral load lower than 104 SARS-CoV-2 RNA copies per ml. No significant differences in sensitivity or specificity could be observed between samples with and without spike protein variant B.1.1.7. The NPV in the study cohort was 98·84%; the PPV in persons with typical COVID-19 symptoms was 97·37%, and 28·57% in persons without or with atypical symptoms.

Interpretation: RDT are a reliable method to diagnose SARS-CoV-2 infection in persons with high viral load. RDT are a valuable addition to RT-qPCR testing, as they reliably detect infectious persons with high viral loads before RT-qPCR results are available.

Reference

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00248-6/fulltext

Centenarians and extremely old people living with frailty can elicit durable SARS-CoV-2 spike specific IgG antibodies with virus neutralization functions following virus infection as determined by serological study

Abstract

Background: The SARS-CoV-2 (Severe Acute Respiratory Syndrome coronavirus 2) has led to more than 165 million COVID-19 cases and >3.4 million deaths worldwide. Epidemiological analysis has revealed that the risk of developing severe COVID-19 increases with age. Despite a disproportionate number of older individuals and long-term care facilities being affected by SARS-CoV-2 and COVID-19, very little is understood about the immune responses and development of humoral immunity in the extremely old person after SARS-CoV-2 infection. Here a serological study was conducted to investigate the development of humoral immunity in centenarians following a SARS-CoV-2 outbreak in a long-term care facility.

Methods: Extreme aged individuals and centenarians who were residents in a long-term care facility and infected with or exposed to SARS-CoV-2 were investigated between April and June 2020 for the development of antibodies to SARS-CoV-2. Blood samples were collected from positive and bystander individuals 30 and 60 days after original

diagnosis of SARS-CoV-2 infection. Plasma was used to quantify IgG, IgA, and IgM isotypes and subsequent subclasses of antibodies specific for SARS-CoV-2 spike protein. The function of anti-spike was then assessed by virus neutralization assays against the native SARS-CoV-2 virus.

Findings: Fifteen long-term care residents were investigated for SARS-CoV-2 infection. All individuals had a Clinical Frailty scale score ≥5 and were of extreme older age or were centenarians. Six women with a median age of 98.8 years tested positive for SARS-CoV-2. Anti-spike IgG antibody titers were the highest titers observed in the cohort with all IgG positive individuals having virus neutralization ability. Additionally, 5 out of the 6 positive participants had a robust IgA anti-SARS-CoV-2 response. In all 5, antibodies were detected after 60 days from initial diagnosis.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00255-8/fulltext

Nitazoxanide superiority to placebo to treat moderate COVID-19 – A Pilot prove of concept randomized double-blind clinical trial

Abstract

Background: The absence of specific antivirals to treat COVID-19 leads to the repositioning of candidates' drugs. Nitazoxanide (NTZ) has a broad antiviral effect.

Methods: This was a randomized, double-blind pilot clinical trial comparing NTZ 600 mg BID versus Placebo for seven days among 50 individuals (25 each arm) with SARS-COV-2 RT-PCR+ (PCR) that were hospitalized with mild respiratory insufficiency from May 20th, 2020, to September 21st, 2020 (ClinicalTrials.gov NCT04348409). Clinical and virologic endpoints and inflammatory biomarkers were evaluated. A five-point scale for disease severity (SSD) was used.

Findings: Two patients died in the NTZ arm compared to 6 in the placebo arm ($p = 0.564$). NTZ was superior to placebo when considering SSD ($p < 0001$), the mean time for hospital discharge (6.6 vs. 14 days, $p = 0.021$), and negative PCR at day 21 ($p = 0.035$), whereas the placebo group presented more adverse events ($p = 0.04$). Among adverse events likely related to the study drug, 14 were detected in the NTZ group and 22 in placebo ($p = 0.24$). Among the 30 adverse events unlikely related, 21 occurred in

the placebo group (p = 0.04). A decrease from baseline was higher in the NTZ group for d-Dimer (p = 0.001), US-RCP (p < 0.002), TNF (p < 0.038), IL-6 (p < 0.001), IL-8 (p = 0.014), HLA DR. on CD4+ T lymphocytes (p < 0.05), CD38 in CD4+ and CD8+ T (both p < 0.05), and CD38 and HLA-DR. on CD4+ (p < 0.01)

Interpretation: Compared to placebo in clinical and virologic outcomes and improvement of inflammatory outcomes, the superiority of NTZ warrants further investigation of this drug for moderate COVID-19 in larger clinical trials. A higher incidence of adverse events in the placebo arm might be attributed to COVID-19 related symptoms.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00261-3/fulltext

Effect of Tenofovir Disoproxil Fumarate and Emtricitabine on nasopharyngeal SARS-CoV-2 viral load burden amongst outpatients with COVID-19: A pilot, randomized, open-label phase 2 trial

Abstract

Background: Tenofovir and emtricitabine interfere with the SARS CoV-2 ribonucleic acid (RNA)-dependent RNA polymerase (RdRp). Several cohorts reported that people treated by tenofovir disoproxil fumarate and emtricitabine are less likely to develop SARS CoV-2 infection and related severe COVID-19.

Methods: a pilot randomized, open-label, controlled, phase 2 trial was conducted at two hospitals in France. Eligible patients were consecutive outpatients (aged ≥18 years) with RT-PCR-confirmed SARS-CoV-2 infection and an interval from symptom onset to enrolment of 7 days or less. Patients were randomly assigned in a 1:1 ratio to receive oral tenofovir disoproxil fumarate and emtricitabine (2 pills on day 1 followed by 1 pill per day on days 2–7) or the standard of care. The primary and secondary endpoints were SARS-CoV-2 viral clearance from baseline assessed by cycle threshold (Ct) RT-PCR on nasopharyngeal swab collected at day 4 and day 7, respectively. A higher Ct corresponds to a lower SARS CoV-2 viral burden. Other endpoints were the time to recovery and the number of adverse events. This trial is registered with ClinicalTrials.gov, NCT04685512.

Findings: From November, 20th 2020 to March, 19th 2021, 60 patients were enrolled and randomly assigned to a treatment group (30 to tenofovir disoproxil fumarate and emtricitabine and 30 to standard of care). The median number of days from symptom onset to inclusion was 4 days (IQR 3–5) in both groups. Amongst patients who received tenofovir disoproxil fumarate, the difference from standard of care in the increase in Ct RT-PCR from baseline was 2.3 (95% confidence interval [-0.6 to 5.2], p = 0.13) at day 4 and 2.9 (95% CI [0.1 to 5.2], p = 0.044) at day 7. At day 7, 6/30 in the tenofovir disoproxil fumarate and emtricitabine group and 3/30 in the standard of care group reported no COVID-related symptoms. Adverse events included 11 cases of gastrointestinal side effects (grade ≤ 2), three of which leaded to drug discontinuation. Three patients had COVID-19 related hospitalisation, no participant died.

Interpretation: In this pilot study of outpatients adult with recent non-severe COVID-19, tenofovir disoproxil fumarate plus emtricitabine appeared to accelerate the natural clearance of nasopharyngeal SARS-CoV-2 viral burden. These findings support the conduct of larger trials of tenofovir-based therapies for the prevention and early treatment of COVID-19.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00273-X/fulltext

Different spreading dynamics throughout Germany during the second wave of the COVID-19 pandemic: A time series study based on national surveillance data

Abstract

Background: The second wave of the COVID-19 pandemic led to substantial differences in incidence rates across Germany.

Methods: Assumption-free k-nearest neighbour clustering from the principal component analysis of weekly incidence rates of German counties groups similar spreading behaviour. Different spreading dynamics was analysed by the derivative plots of the temporal evolution of tuples [x(t),x'(t)] of weekly incidence rates and their derivatives. The effectiveness of the different shutdown measures in Germany during the second wave is assessed by the difference of weekly incidences before and after the respective time periods.

Findings: The implementation of non-pharmaceutical interventions of different extents resulted in four distinct time periods of complex, spatially diverse, and age-related spreading patterns during the second wave of the COVID-19 pandemic in Germany. Clustering gave three regions of coincident spreading characteristics. October 2020 showed a nationwide exponential growth of weekly incidence rates with a doubling time of 10 days. A partial shutdown during November 2020 decreased the overall infection rates by 20–40% with a plateau-like behaviour in northern and southwestern Germany. The eastern parts exhibited a further near-linear growth by 30–80%. All over the incidence rates among people above 60 years still increased by 15–35% during partial shutdown measures. Only an extended shutdown led to a substantial decrease in incidence rates. These measures decreased the numbers among all age groups and in all regions by 15–45%. This decline until January 2021 was about -1•25 times the October 2020 growth rates with a strong correlation of -0•96.

Interpretation: Three regional groups with different dynamics and different degrees of effectiveness of the applied measures were identified. The partial shutdown was moderately effective and at most stopped the exponential growth, but the spread remained partly plateau-like and regionally continued to grow in a nearly linear fashion. Only the extended shutdown reversed the linear growth.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00128-9/fulltext

Publication Date: Jun 25, 2021

Graphene nanoplatelet and graphene oxide functionalization of face mask materials inhibits infectivity of trapped SARS-CoV-2

Abstract

Recent advancements in bidimensional nanoparticles production such as graphene (G) and graphene oxide (GO) have the potential to meet the need for highly functional personal protective equipment (PPE) against SARS-CoV-2 infection. The ability of G and GO to interact with microorganisms provides an opportunity to develop engineered textiles for use in PPE and limit the spread of COVID-19. PPE in current use in high-risk settings for COVID transmission provides only a physical barrier that decreases

infection likelihood and does not inactivate the virus. Here, it was shown that virus pre-incubation with soluble GO inhibits SARS-CoV-2 infection of VERO cells. Furthermore, when G/GO-functionalized polyurethane or cotton was in contact SARS-CoV-2, the infectivity of the fabric was nearly completely inhibited. The findings presented here constitute an important innovative nanomaterial-based strategy to significantly increase PPE efficacy in protection against the SARS-CoV-2 virus that may implement water filtration, air purification, and diagnostics methods.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900756-2

An automatic pipeline for the design of irreversible derivatives identifies a potent SARS-CoV-2 Mpro inhibitor

Abstract

Designing covalent inhibitors is increasingly important, although it remains challenging. Here, covalentizer was presented, a computational pipeline for identifying irreversible inhibitors based on structures of targets with non-covalent binders. Through covalent docking of tailored focused libraries, we identify candidates that can bind covalently to a nearby cysteine while preserving the interactions of the original molecule. ∼11,000 cysteines were found, proximal to a ligand across 8,386 complexes in the PDB. Of these, the protocol identified 1,553 structures with covalent predictions. In a prospective evaluation, five out of nine predicted covalent kinase inhibitors showed half-maximal inhibitory concentration (IC50) values between 155 nM and 4.5 μM. Application against an existing SARS-CoV Mpro reversible inhibitor led to an acrylamide inhibitor series with low micromolar IC50 values against SARS-CoV-2 Mpro. The docking was validated by 12 co-crystal structures. Together these examples hint at the vast number of covalent inhibitors accessible through our protocol.

Reference

https://www.cell.com/cell-chemical-biology/fulltext/S2451-9456%2821%2900263-4

Temporal trends of SARS-CoV-2 seroprevalence during the first wave of the COVID-19 epidemic in Kenya

Abstract

Observed SARS-CoV-2 infections and deaths are low in tropical Africa raising questions about the extent of transmission. SARS-CoV-2 IgG were measured by ELISA in 9,922 blood donors across Kenya and adjusted for sampling bias and test performance. By 1st September 2020, 577 COVID-19 deaths were observed nationwide and seroprevalence was 9.1% (95%CI 7.6-10.8%). Seroprevalence in Nairobi was 22.7% (18.0-27.7%). Although most people remained susceptible, SARS-CoV-2 had spread widely in Kenya with apparently low associated mortality.

Reference

https://www.nature.com/articles/s41467-021-24062-3

Immunogenicity and reactogenicity of BNT162b2 booster in ChAdOx1-S-primed participants (CombiVacS): A multicentre, open-label, randomised, controlled, phase 2 trial

Abstract

Background: To date, no immunological data on COVID-19 heterologous vaccination schedules in humans have been reported. The immunogenicity and reactogenicity of BNT162b2 (Comirnaty, BioNTech, Mainz, Germany) administered as second dose in participants, was assessed, primed with ChAdOx1-S (Vaxzevria, AstraZeneca, Oxford, UK).

Methods: We did a phase 2, open-label, randomised, controlled trial on adults aged 18–60 years, vaccinated with a single dose of ChAdOx1-S 8–12 weeks before screening, and no history of SARS-CoV-2 infection. Participants were randomly assigned (2:1) to receive either BNT162b2 (0·3 mL) via a single intramuscular injection (intervention group) or continue observation (control group). The primary outcome was 14-day immunogenicity, measured by immunoassays for SARS-CoV-2 trimeric spike protein and receptor binding domain (RBD). Antibody functionality was assessed using a pseudovirus neutralisation assay, and cellular immune response using an interferon-γ immunoassay. The safety outcome was 7-day reactogenicity, measured as solicited

local and systemic adverse events. The primary analysis included all participants who received at least one dose of BNT162b2 and who had at least one efficacy evaluation after baseline. The safety analysis included all participants who received BNT162b2. This study is registered with EudraCT (2021-001978-37) and ClinicalTrials.gov (NCT04860739), and is ongoing.

Findings: Between April 24 and 30, 2021, 676 individuals were enrolled and randomly assigned to either the intervention group (n=450) or control group (n=226) at five university hospitals in Spain (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men). 663 (98%) participants (n=441 intervention, n=222 control) completed the study up to day 14. In the intervention group, geometric mean titres of RBD antibodies increased from 71·46 BAU/mL (95% CI 59·84–85·33) at baseline to 7756·68 BAU/mL (7371·53–8161·96) at day 14 (p<0·0001). IgG against trimeric spike protein increased from 98·40 BAU/mL (95% CI 85·69–112·99) to 3684·87 BAU/mL (3429·87–3958·83). The interventional:control ratio was 77·69 (95% CI 59·57–101·32) for RBD protein and 36·41 (29·31–45·23) for trimeric spike protein IgG. Reactions were mild (n=1210 [68%]) or moderate (n=530 [30%]), with injection site pain (n=395 [88%]), induration (n=159 [35%]), headache (n=199 [44%]), and myalgia (n=194 [43%]) the most commonly reported adverse events. No serious adverse events were reported.

Interpretation: BNT162b2 given as a second dose in individuals prime vaccinated with ChAdOx1-S induced a robust immune response, with an acceptable and manageable reactogenicity profile.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01420-3/fulltext

Safety and immunogenicity of a Recombinant Stabilized Prefusion SARS-CoV-2 Spike Protein Vaccine (MVCCOV1901) Adjuvanted with CpG 1018 and Aluminum Hydroxide in healthy adults: A Phase 1, dose-escalation study

Abstract

Background: This was a phase 1, dose-escalation open-label trial to evaluate the safety and immunogenicity of MVC COV1901, a SARS-CoV-2 S-2P protein vaccine adjuvanted with aluminum hydroxide and CpG 1018.

Methods: Between September 28 and November 13 2020, 77 participants were screened. Of these, 45 healthy adults from 20 to 49 years of age were to be administered two doses of MVC COV1901 in doses of 5 µg, 15 µg, or 25 µg of spike protein at 28 days apart. There were 15 participants in each dose group; all were followed for 28 days after the second dose at the time of the interim analysis. Adverse events and laboratory data were recorded for the safety evaluation. Blood samples were collected for humoral, and cellular immune response at various time points. Trial Registration: ClinicalTrials.gov NCT 04487210.

Findings: Solicited adverse events were mostly mild and similar. No subject experienced fever. After the second dose, the geometric mean titers (GMTs) for SARS-CoV-2 spike-specific immunoglobulin G were 7178.2, 7746.1, 11,220.6 in the 5 µg, 15 µg, and 25 µg dose groups, respectively. The neutralizing activity was detected in both methods. (Day 43 GMTs, 538.5, 993.1, and 1905.8 for pseudovirus; and 33.3, 76.3, and 167.4 for wild-type virus). The cellular immune response induced by MVC COV1901 demonstrated substantially higher numbers of IFN-γ- producing cells, suggesting a Th1-skewed immune response.

Interpretation: The MVC COV1901 vaccine was well tolerated and elicited robust immune responses and is suitable for further development.

Reference

https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00269-8/fulltext

Publication Date: Jun 24, 2021

COVID-19 and obesity: Fighting two pandemics with intermittent fasting

Abstract

Obesity is strongly and independently associated with an increased risk of severe illness and death from coronavirus disease (COVID-19). The pathophysiological changes that result from elevated body weight lead to metabolic dysfunction, chronic inflammation, impaired immunological responses and multi-system disorders which increase vulnerability to severe illness from COVID-19. While vaccination strategies are underway across the world, the second and third waves of the pandemic, along with the emergence of novel SARS-CoV-2 strains, continue to threaten the stability of medical

systems worldwide. Furthermore, evidence from previous pandemics suggests that vaccines are less effective in obese individuals than in their healthy-weight counterparts over the long-term. Therefore, a consideration of lifestyle changes that can boost metabolic health and immunity is critical to reduce the risk of complications and severe illness from viral infection. In this review we discuss the potential mechanisms linking excess body weight with COVID-19 morbidity. We also present evidence that intermittent fasting, a dietary program that has gained popularity in recent years, may be an effective strategy to improve metabolic health and immunity and thus reduce the impact of obesity on COVID-19 morbidity and mortality.

Reference

https://www.cell.com/trends/endocrinology-metabolism/fulltext/S1043-2760%2821%2900134-X

Anemia during SARS-CoV-2 infection is associated with rehospitalization after viral clearance

Abstract

Patients with COVID-19 can experience symptoms and complications after viral clearance. It is important to identify clinical features of patients who are likely to experience these prolonged effects. We conducted a retrospective study to compare longitudinal laboratory test measurements (hemoglobin, hematocrit, estimated glomerular filtration rate, serum creatinine, and blood urea nitrogen) in patients rehospitalized after PCR-confirmed SARS-CoV-2 clearance (n = 104) versus patients not rehospitalized after viral clearance (n = 278). Rehospitalized patients had lower median hemoglobin levels in the year prior to COVID-19 diagnosis (Cohen's D = −0.50; p = 1.2 × 10−3) and during their active SARS-CoV-2 infection (Cohen's D = −0.71; p = 4.6 × 10−8). Rehospitalized patients were also more likely to be diagnosed with moderate or severe anemia during their active infection (Odds Ratio = 4.07; p = 4.99 × 10−9). These findings suggest that anemia-related laboratory tests should be considered in risk stratification algorithms for patients with COVID-19.

Reference

https://www.cell.com/iscience/fulltext/S2589-0042%2821%2900748-3

Directed evolution of potent neutralizing nanobodies against SARS-CoV-2 using CDR-swapping mutagenesis

Abstract

There is widespread interest in facile methods for generating potent neutralizing antibodies, nanobodies, and other affinity proteins against SARS-CoV-2 and related viruses to address current and future pandemics. While isolating antibodies from animals and humans are proven approaches, these methods are limited to the affinities, specificities, and functional activities of antibodies generated by the immune system. Here we report a surprisingly simple directed evolution method for generating nanobodies with high affinities and neutralization activities against SARS-CoV-2. We demonstrate that complementarity-determining region swapping between low-affinity lead nanobodies, which we discovered unintentionally but find is simple to implement systematically, results in matured nanobodies with unusually large increases in affinity. Importantly, the matured nanobodies potently neutralize both SARS-CoV-2 pseudovirus and live virus, and possess drug-like biophysical properties. We expect that our methods will improve in vitro nanobody discovery and accelerate the generation of potent neutralizing nanobodies against diverse coronaviruses.

Reference

https://www.cell.com/cell-chemical-biology/fulltext/S2451-9456%2821%2900264-6

Effect of natural mutations of SARS-CoV-2 on spike structure, conformation, and antigenicity

Abstract

SARS-CoV-2 variants with multiple spike mutations enable increased transmission and antibody resistance. Here, cryo-EM, binding and computational analyses were combined to study variant spikes, including one that was involved in transmission between minks and humans, and others that originated and spread in human populations. All variants showed increased ACE2 receptor binding and increased propensity for RBD up states. While adaptation to mink resulted in spike destabilization, the B.1.1.7 (UK) spike balanced stabilizing and destabilizing mutations. A local destabilizing effect of the RBD E484K mutation was implicated in resistance of the

B.1.1.28/P.1 (Brazil) and B.1.351 (South Africa) variants to neutralizing antibodies. The studies revealed allosteric effects of mutations and mechanistic differences that drive either inter-species transmission or escape from antibody neutralization.

Reference

https://science.sciencemag.org/content/early/2021/06/23/science.abi6226

CORRESPONDANCE

Publication Date: Jun 28, 2021

AZD1222-induced neutralising antibody activity against SARS-CoV-2 Delta VOC

The SARS-CoV-2 B.1.617.2 Delta variant of concern (VOC) continues to drive a sharp increase in COVID-19 cases in the UK, with a current doubling time of 3·5–16 days, consistent with previous pandemic waves during 2020–21, and a sustained increase in the reproduction number (R) to 1·2–1·4. Daily hospital admissions and the number of patients requiring mechanical ventilation are now increasing in both England and Scotland, despite the ongoing roll-out of widespread vaccination in the UK.

The ChAdOx1 nCoV-19 (AZD1222, Oxford–AstraZeneca) vaccine forms the core of the UK's vaccination programme and the global COVAXX programme. To determine B.1.617.2 sensitivity to AZD1222-induced neutralising antibodies (NAbs) and to compare this to our previous measurements of NAbs induced by BNT162b2 (Pfizer–BioNTech), we carried out a second initial analysis of Legacy study participants vaccinated with AZD1222. Legacy was initiated in early 2021 by University College London Hospitals and the Francis Crick Institute in London, UK, to track serological responses to vaccination during the national COVID-19 vaccination programme in prospectively recruited healthy staff volunteers. A description of the methods and clinical cohort are available in the appendix. The Legacy study was approved by the London Camden and Kings Cross Health Research Authority Research and Ethics committee (IRAS number 286469) and is sponsored by University College London Hospitals. For more details, read the link given below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01462-8/fulltext

COMMENT

Publication Date: Jun 28, 2021

Paucity and discordance of neutralising antibody responses to SARS-CoV-2 VOCs in vaccinated immunodeficient patients and health-care workers in the UK

As of June, 2021, the UK population is only partly vaccinated against COVID-19, with many people having received just one vaccination dose (either BNT162b2 [Pfizer–BioNTech]) or ChAdOx1 nCoV-19 [AZD1222; Oxford–AstraZeneca]). Tracking the spread of SARS-CoV-2 Variants of Concern (VOCs) remains important for understanding the levels of vaccine-induced immunity and for identifying the emergence of vaccine escape variants. The immune correlates of protection to SARS-CoV-2 and COVID-19 established in phase 3 clinical trials following two doses of vaccine was the titre of neutralising antibodies (NAbs) to SARS-CoV-2 in study groups, before the VOCs emerged. Vaccination programmes are leading to promising reductions in disease severity and mortality in vaccinated populations. However, the combined situation of ongoing transmission within communities, including in some vaccine recipients, alongside newly arising VOCs, continues to pose a serious threat to public health and the efficacy of these vaccines. As of Jan 11, 2021, in the UK, the interval between the first and second dose of vaccination was extended to 12 weeks. This extension achieved the aim of maximising population coverage by immunising the greatest possible number of individuals to prevent disease and hospital admissions. Encouragingly, a growing number of studies have reported a marked reduction in the number of individuals with moderate-to-severe clinical symptoms and a substantial decline in the number of hospitalised patients with COVID-19 in the UK, underscoring the success of this strategy.

Many countries, both in the early and advanced stages of their vaccination campaigns, are facing new cases of infection with VOCs that have acquired mutations facilitating increased transmission and evasion of pre-existing immunity. These VOCs might cause increased morbidity and mortality. The B.1.1.7 (also known as Alpha) VOC has been reported in more than 114 countries, the B.1.351 (also known as Beta) VOC in more than 68 countries, and the P.1 (also known as Gamma) VOC in more than 37 countries,

and new cases continue to be reported worldwide. Additional VOCs, such as B.1.617.2, are likely to continue to emerge and threaten our ongoing COVID-19 vaccination programmes. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00157-9/fulltext

Publication Date: Jun 26, 2021

Effects of non-pharmaceutical interventions against COVID-19 on the incidence of other diseases

The COVID-19 pandemic has resulted in unprecedented challenges to health systems globally. Most countries – including Germany – have implemented mitigation strategies, comprising non-pharmaceutical interventions (NPIs) (*e.g*. face masking, physical distancing, restrictions of movement and social gatherings). They were combined with testing, contact tracing and isolation/quarantine interventions as well as repeated lockdowns with varying intensity and resolve.

Besides their benefit for pandemic control, NPIs can also have harmful direct and indirect effects. These include interrupted or delayed access to health care, which has consequences for prevention and treatment of acute and chronic diseases, even more so in low- and middle-income countries with weak health systems than in high-income countries. Hospital admissions for heart diseases, for example, decreased sharply during the pandemic waves in Europe and the USA, while it is feared that the burden of major infectious diseases such as HIV/AIDS, tuberculosis and malaria may dramatically increase in endemic countries. The psycho-social effects of prolonged NPIs leads to an increase in mental diseases and of domestic violence. Negative effects on the economy are associated with increasing unemployment, inequity, poverty and social disruption, all determinants of poor health. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(21)00116-2/fulltext

Heterologous vaccine regimens against COVID-19

The rapid development of vaccines against COVID-19 is the biggest achievement of science in the fight against the pandemic. Although the efficacy and safety of all approved vaccines have been demonstrated in large clinical trials, recent safety signals have been reported, highlighting the importance of post-marketing surveillance with study populations larger than those of the trials, and representative of populations receiving vaccines as part of routine clinical practice. Safety concerns regarding the ChAdOx1-S vaccine have led some European countries (eg, Denmark) to minimise its use, with other countries recommending the switch from the trial-tested homologous booster to a heterologous booster, such as with BNT162b2. This recommendation has come as a surprise to some, because abundant data on more than 9 million people suggested a much reduced risk of thrombotic events with the second dose of ChAdOx1-S. In contrast, the evidence for the effectiveness and safety of heterologous vaccination regimens remains limited, and based on small phase 2 trials and cohort studies including fewer than 500 participants.

In *The Lancet*, Alberto Borobia and colleagues report the first results of a phase 2 trial in five university hospitals across Spain assessing the immunogenicity and reactogenicity of the BNT162b2 vaccine administered as second dose in people primed with ChAdOx1-S. The study included 676 adults aged 18–60 years (mean age 44 years [SD 9]; 382 [57%] women and 294 [43%] men) followed up for 14 days, and showed that BNT162b2, given as a second dose 8–12 weeks after a first dose of ChAdOx1-S, induced a robust immune response and mild reactogenicity. This trial compared this heterologous vaccine regimen to no booster vaccination, and the lack of a homologous vaccination comparator is a limitation of the study, because it does not allow for a direct comparison of the vaccination schedules used in current clinical practice. As in most phase 2 trials, the study has limited representativeness with strict eligibility criteria, including the exclusion of vulnerable and elderly people. This decision is in discord with the global prioritisation of these groups for vaccination. For more details, read the given link below.

Reference

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01442-2/fulltext

REPORT

Publication Date: Jun 24, 2021

Resistance of SARS-CoV-2 variants to neutralization by antibodies induced in convalescent patients with COVID-19

Administration of convalescent plasma or neutralizing monoclonal antibodies (mAbs) is a potent therapeutic option for coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, SARS-CoV-2 variants with mutations in the spike protein have emerged in many countries. To evaluate the efficacy of neutralizing antibodies induced in convalescent patients against emerging variants, we isolate anti-spike mAbs from two convalescent COVID-19 patients infected with prototypic SARS-CoV-2 by single-cell sorting of immunoglobulin-G-positive (IgG+) memory B cells. Anti-spike antibody induction is robust in these patients, and five mAbs have potent neutralizing activities. The efficacy of most neutralizing mAbs and convalescent plasma samples is maintained against B.1.1.7 and mink cluster 5 variants but is significantly decreased against variants B.1.351 from South Africa and P.1 from Brazil. However, mAbs with a high affinity for the receptor-binding domain remain effective against these neutralization-resistant variants. Rapid spread of these variants significantly impacts antibody-based therapies and vaccine strategies against SARS-CoV-2.

Reference

https://www.cell.com/cell-reports/fulltext/S2211-1247%2821%2900783-X

PERSPECTIVE

Publication Date: Jun 25, 2021

Hybrid immunity

Immunological memory is the source of protective immunity. Natural immunity and vaccine-generated immunity to SARS-CoV-2 are two different paths to protection. The adaptive immune system consists of three major branches: B cells (the source of antibodies), CD4+ T cells, and CD8+ T cells. For natural immunity, immunological memory to SARS-CoV-2 has been observed for more than 8 months for CD4+ T cells, CD8+ T cells, memory B cells, and antibodies, with a relatively gradual decline that appears to partially stabilize within a year. Levels of immunity can be placed on a spectrum, and natural immunity against symptomatic infection (COVID-19) has been found to be between 93 and 100% over 7 to 8 months in large studies, including locations where the SARS-CoV-2 variant of concern (VOC) B.1.1.7 (alpha) was widespread.

Natural immunity against variants with changes that substantially reduce antibody recognition [e.g., B.1.351 (beta), P.1 (gamma), B.1.526 (iota), and B.1.617] is less clear; there is evidence of more reinfections with such variants. Neutralizing antibody activity against most VOCs is reduced for natural immunity and vaccine-generated immunity. That most VOCs have mutations engendering partial antibody escape is evidence of selection pressure to evade natural immunity. The biological relevance of the reductions in neutralizing antibody potency against variants is most clearly evident from vaccine clinical trials and observational studies. Among current COVID-19 vaccines in use, ChAdOx1 nCoV-19 (AstraZeneca) vaccine efficacy against symptomatic cases dropped from 75% to 11% against B.1.351. By contrast, BNT162b2 (Pfizer/BioNTech) vaccine efficacy against symptomatic cases dropped from ~95% to 75% against B.1.351, and protection against severe disease remained at 97%. Initial reports suggest that both vaccines retain most of their efficacy against B.1.617.2 (delta). What happens when previously infected individuals are vaccinated? The observations in several studies, including those by Stamatatos et al. and Reynolds et al., are that an impressive synergy occurs—a “hybrid vigor immunity” resulting from a combination of natural immunity and

vaccine-generated immunity (see the figure). When natural immunity to SARS-CoV-2 is combined with vaccine-generated immunity, a larger-than-expected immune response arises. For more details, read the link given below.

Reference

https://science.sciencemag.org/content/372/6549/1392