COVID-19 Evidence Support Team

EVIDENCE SEARCH REPORT

**Review Question:** What is the epidemiology of variants and what are the implications for healthcare?

**Context:** What is the epidemiology of variants and what are the implications for healthcare?

**Review Code:** EOC031801v014 ESR

**Complete Date:** September 24, 2021

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Librarian Notes & Comments

Hello All,

Here is the update on the COVID-19 variants from September 10, 2021 to September 24, 2021.

Sincerely,

Lukas and Brianna

Search Results: Guidelines, Summaries & Other Grey Literature

**Government**

**Public Health Ontario**


Disclaimer

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Public Health England

CDC
• Outbreak of SARS-CoV-2 B.1.617.2 (Delta) Variant Infections Among Incarcerated Persons in a Federal Prison — Texas, July–August 2021. September 24, 2021. https://www.cdc.gov/mmwr/volumes/70/wr/mm7038e3.htm?s_cid=mm7038e3_w

Agencies
European Centre for Disease Prevention and Control
  o Librarian’s Note: According to the 4th chart the Alpha variant has been “de-escalated”

Research Centres
Strategy for Patient Oriented Research (SPOR) Alliance & COVID-END & Coronavirus Variants Rapid Response Network (CoVaRR)
• Public Health Implications of SARS-CoV-2 Variants Of Concern

National Collaborating Centre for Infectious Diseases

**COVID-19 Immunity Task Force**
- Older adults likely remain at higher risk for COVID-19 – particularly infections caused by variants of concern – even after vaccination. September 14, 2021. [https://www.covid19immunitytaskforce.ca/older-adults-likely-remain-at-higher-risk-for-covid-19-%e2%88%92-particularly-infections-caused-by-variants-of-concern-%e2%88%92-even-after-vaccination/](https://www.covid19immunitytaskforce.ca/older-adults-likely-remain-at-higher-risk-for-covid-19-%e2%88%92-particularly-infections-caused-by-variants-of-concern-%e2%88%92-even-after-vaccination/)

**Search Results: News, Blogs, & Social Media**

**CBC**

**The Washington Post**

**Search Results: Journal Articles (includes preprints)**

Sorted by newest-oldest.

   DOI: 10.1001/jama.2021.15116

   DOI: 10.1001/jama.2021.15115

   **ABSTRACT:** The outbreak of SARS-CoV-2 is responsible for the COVID-19 pandemic. Despite unprecedented research and developmental efforts, SARS-CoV-2-specific antivirals are still unavailable for the treatment of COVID-19. In most instances, SARS-CoV-2 infection initiates with the binding of spike glycoprotein to the host cell ACE2 receptor. Utilizing the crystal structure of the ACE2/Spike receptor-binding domain (S-RBD) complex (PDB file 6M0J) in a computer-aided drug design (CADD) approach, we identified and validated 5 potential inhibitors of S-RBD and ACE-2 interaction. Two of the five compounds, MU-UNMC-1 and MU-UNMC-2, blocked the entry of pseudovirus particles expressing
SARS-CoV-2 Spike glycoprotein. In live SARS-CoV-2 infection assays, both the compounds showed antiviral activity with IC50 values in the micromolar range (MU-UNMC-1: IC50= 0.67 μM and MU-UNMC-2: IC50= 1.72 μM) in human bronchial epithelial cells. Furthermore, MU-UNMC-1 and MU-UNMC-2 effectively blocked the replication of rapidly transmitting variants of concern: South African variant B.1.351 (IC50= 9.27 μM & 3.00 μM) and Scotland variant B.1.222 (IC50= 2.64 μM & 1.39 μM) respectively. Following these assays, we conducted 'induced-fit (flexible docking' to understand the binding mode of MU-UNMC-1/MU-UNMC-2 at the S-RBD/ACE2 interface. Our data showed that mutation N501Y (present in B.1.351 variant) alters the binding mode of MU-UNMC-2 such that it is partially exposed to the solvent and has reduced polar contacts. Finally, MU-UNMC-2 displayed high synergy with remdesivir (RDV), the only approved drug for treating hospitalized COVID-19 patients.

IMPORTANCE The ongoing coronavirus infectious disease 2019 (COVID-19) pandemic is caused by a novel coronavirus named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). More than 207 million people have been infected globally, and 4.3 million have died due to this viral outbreak. While a few vaccines have been deployed, a SARS-CoV-2 specific antiviral for the treatment of COVID-19 is yet to be approved. As the interaction of SARS-CoV-2 spike protein with ACE2 is critical for cellular entry, using a combination of a computer-aided drug design (CADD) approach and cell-based in vitro assays, we report the identification of five potential SARS-CoV-2 entry inhibitors. Out of the five, two compounds (MU-UNMC-1 and MU-UNMC-2) have antiviral activity against ancestral SARS-CoV-2 and emerging variants from South Africa and Scotland. Furthermore, MU-UNMC-2 acts synergistically with remdesivir, suggesting that RDV and MU-UNMC-2 can be developed as a combination therapy to treat COVID-19, infected individuals.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34550770
DOI: 10.1128/JVI.01437-21


ABSTRACT: BACKGROUND: SARS-CoV-2 epidemiology implicates airborne transmission; aerosol infectiousness and impacts of masks and variants on aerosol shedding are not well understood.

METHODS: We recruited COVID-19 cases to give blood, saliva, mid-turbinate and fomite (phone) swabs, and 30-minute breath samples while vocalizing into a Gesundheit-II, with and without masks at up to two visits two days apart. We quantified and sequenced viral RNA, cultured virus, and assayed sera for infectiousness and impacts of masks and variants on aerosol shedding are not well understood.

RESULTS: We enrolled 49 seronegative cases (mean days post onset 3.8 +/- 2.1), May 2020 through April 2021. We detected SARS-CoV-2 RNA in 45% of fine (<5 microm), 31% of coarse (>5 microm) aerosols, and 65% of fomite samples overall and in all samples from four alpha-variant cases. Masks reduced viral RNA by 48% (95% confidence interval [CI], 3 to 72%) in fine and by 77% (95% CI, 51 to 89%) in coarse aerosols; cloth and surgical masks were not significantly different. The alpha variant was associated with a 43-fold (95% CI, 6.6 to 280-fold) increase in fine aerosol viral RNA, compared with earlier viruses, that remained a significant 18-fold (95% CI, 3.4 to 92-fold) increase adjusting for viral RNA in saliva, swabs, and other potential confounders. Two fine aerosol samples, collected while participants wore masks, were culture-positive. CONCLUSION: SARS-CoV-2 is evolving toward more efficient aerosol generation and loose-fitting masks provide significant but only modest source control. Therefore, until vaccination rates are very high, continued layered controls and tight-fitting masks and respirators will be necessary.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34519774
DOI: 10.1093/cid/ciab797


ABSTRACT: Introduction: As the global severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) pandemic expands, genomic epidemiology and whole genome sequencing are being constantly used to investigate its transmissions and evolution. Aims and Objectives: To ensure that best use is made of the whole genome sequencing programmes for SARS-CoV-2 results, in improving public health. Analyze and establish a correlation of demographic features and vaccination status with clinical outcome of VOC’s. Material(s) and Method(s): 478 samples (December 15, 2020- June 15, 2021) were shortlisted as per state government policy of sample selection criteria for genome sequencing, packed in triple layer according to standard transportation protocol and sent to the National Public Health Laboratory (NPHL) for whole genome sequencing. The data collected by us were analyzed and correlated with the results of whole genome sequencing, shared by the NPHL to enhance public health impact of the variant identified. Observation and Results: In our study we found 92% of B.1.617.2 (Delta) variants and 8% of B.1.1.7 (Alpha) variant. We found significantly high mortality (25%) in age group > 60 years compared to other age group (20-40 years, 40-60 years) with Delta variant (p value < .05). We also found that Delta variant is significantly more transmissible (p value < .05) than Alpha variant. Mortality was significantly higher among unvaccinated patients having co-morbid conditions rather than vaccinated patients having co-morbid conditions with delta variant (p value <0.05). Conclusion(s): B.1.617.2 (Delta) variant has emerged as a common VOC among SARS-COV-2 patients in southern Rajasthan. Vaccination has a very high level of protective role in decreasing mortality, especially old age patients with associated co-morbidities among Delta variant. Copyright © 2021 Ubiquity Press. All rights reserved.


ABSTRACT: In this paper by Ranzani and colleagues (BMJ 2021;374:n2015, doi:, published 20 August 2021), author Edlaine Faria de Moura Villela should have been shown affiliated with address 5 [not 6], the Disease Control Coordination of the Sao Paulo State Department of Health, Sao Paulo, Brazil. Copyright © 2021 BMJ Publishing Group. All rights reserved.


ABSTRACT: Background: Emerged mutations can be attributed to increased transmissibility of the B.1.617 and B.1.36 Indian delta variants of SARS-CoV-2, most notably substitutions L452R/E484Q and N440K, respectively, which occur in the receptor-binding domain (RBD) of the Spike (S) fusion glycoprotein. Objective(s): We aimed to assess the effects of mutations L452R/E484Q and N440K (as well as the previously studied mutation E484K present in variants B.1.351 and P.1) on the affinity of RBD for ACE2, SARS-CoV-2 main receptor. We also aimed to assess the ability of antibodies induced by natural infection or by immunization with BNT162b2 mRNA vaccine to recognize the mutated versions of the RBD, as well as blocking the interaction RBD-ACE2, an important surrogate readout for virus neutralization. Method(s): To this end, we produced recombinant wild-type RBD, as well as RBD containing each of the mutations L452R/E484Q, N440K, or E484K (the latest present in variants of concern B.1.351 and P.1), as well as the ectodomain of ACE2. Using Biolayer Interferometry (BLI), we
measured the binding affinity of RBD for ACE2 and the ability of sera from COVID-19 convalescent donors or subjects immunized with BNT162b2 mRNA vaccine to block this interaction. Finally, we correlated these results with total anti-RBD IgG titers measured from the same sera by direct ELISA.

Result(s): The binding assays showed L452R/E484Q double-mutant RBD to interact with ACE2 with higher affinity ($K_{D} = 4.6$ nM) than wild-type ($K_{D} = 21.3$ nM) or single mutants N440K ($K_{D} = 9.9$ nM) and E484K ($K_{D} = 19.7$ nM) RBDs. Meanwhile, the anti-RBD IgG titration resulted in lower recognition of mutants E484K and L452R/E484Q by infection-induced antibodies, whereas only mutant E484K was recognized less by antibodies induced by vaccination. More interestingly, sera from convalescent as well as immunized subjects showed reduced ability to block the interaction between ACE2 and RBD mutants E484K and L452R/E484Q, as shown by the inhibition assays.

Conclusion(s): Our data suggest that the newly emerged SARS-CoV-2 variant B.1.617, as well as the better-studied variants B.1.351 and P.1 (all containing a mutation at position E484) display increased transmissibility both due to their higher affinity for the cell receptor ACE2 and their ability to partially bypass immunity generated against the wild-type virus. For variant B.1.36 (with a point mutation at position N440), only increased affinity seems to play a role. Copyright © 2021 The Authors. Allergy published by European Academy of Allergy and Clinical Immunology and John Wiley & Sons Ltd.


ABSTRACT: The Delta variant of concern of severe acute respiratory syndrome coronavirus 2 is dominant worldwide. We report a case cluster caused by Delta sublineage B.1.617.2 harboring the mutation E484K in Italy during July 11-July 29, 2021. This mutation appears to affect immune response and vaccine efficacy; monitoring its appearance is urgent.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34499599
DOI: 10.3201/eid2712.211792


ABSTRACT: INTRODUCTION: The Delta variant of SARS-CoV-2 has caused a new wave of the COVID-19 epidemic in many countries. It is the most infectious variant of SARS-CoV-2 to date, and its high infectivity means that a higher proportion of the population needs to be vaccinated to reduce the disease burden, which poses a substantial public health challenge. AREAS COVERED: The evolution of the Delta variant is reviewed, including an overview of the Delta Plus variant with a K417N mutation in the RBD, which may confer an improved immune evasion ability. Decreases in serum neutralizing antibody titers after vaccination against Delta were greater than those against Alpha but less than those against Beta. The protective efficacy of existing vaccines against the Delta variant have declined and is related to the number of doses and the time since vaccination. EXPERT OPINION: The currently used vaccines are effective against hospitalization/severe disease due to the Delta variant. Accelerating the popularization of vaccination, improving the coverage rate, and the implementation of intervention measures, such as wearing masks, are effective means to control the spread of the Delta variant and other variants. However, vaccination alone against SARS-CoV-2 without intervention measures may lead to continuous spread and the emergence of new variants.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34488546
DOI: 10.1080/14760584.2021.1976153

**ABSTRACT:** We compared PCR results from SARS-CoV-2-positive patients tested in the community in France from 14 June to 30 July 2021. In asymptomatic individuals, Cq values were significantly higher in fully vaccinated than non-fully vaccinated individuals (effect size: 1.7; 95% CI: 1-2.3; p< 10-6). In symptomatic individuals and controlling for time since symptoms, the difference vanished (p= 0.26). Infections with the Delta variant had lower Cq values at symptom onset than with Alpha (effect size: -3.32; 95% CI: -4.38 to -2.25; p< 10-6).

**URL:** https://www.ncbi.nlm.nih.gov/pubmed/34533119

**DOI:** 10.2807/1560-7917.ES.2021.26.37.2100824


**ABSTRACT:** [Figure: see text].

**URL:** https://www.ncbi.nlm.nih.gov/pubmed/34516917

**DOI:** 10.1126/sciadv.abj5365


**ABSTRACT:** Hundred years after the flu pandemic of 1918, the world faces an outbreak of a new severe acute respiratory syndrome, caused by a novel coronavirus. With a high transmissibility, the pandemic spreads worldwide, creating a scenario of devastation in many countries. By middle of 2021, about 3% of the world population has been infected and more than 4 million people have died. Different from the $H_1N_1$ pandemic, which had a deadly wave and cessed, the new disease is maintained by successive waves, mainly produced by new virus variants, and the small number of vaccinated people. In the present work, we create a version of the SIR model with spatial localization of persons, their movements, and taking into account social isolation probabilities. We discuss the effects of virus variants, and the role of vaccination rate in the pandemic dynamics. We show that, unless a global vaccination is implemented, we will have continuous waves of infections.

**Competing Interest Statement**

The authors have declared no competing interest.

**Funding Statement**

This research did not receive any specific grant from funding agencies in the commercial, or non-profit sectors. SPR acknowledges grant from Conselho Nacional de Desenvolvimento Científico e Tecnológico - CNPq, through process 306572/2019-2. Author Declarations confirm all relevant ethical guidelines have been followed, and any necessary IRB and/or ethics committee approvals have been obtained. Yes, the details of the IRB/oversight body that provided approval or exemption for the research described are given below: The manuscript is a modeling paper, there was no clinical trial of any kind. All necessary patient/participant consent has been obtained and the appropriate institutional forms have been archived. Yes, I understand that all clinical trials and any other prospective interventional studies must be registered with an ICMJE-approved registry, such as ClinicalTrials.gov. I confirm that any such study reported in the manuscript has been registered and the trial registration ID is provided (note: if posting a prospective study registered retrospectively, please provide a statement in the trial ID field explaining why the study was not registered in advance). Yes, I have followed all appropriate research reporting guidelines and uploaded the relevant EQUATOR Network research reporting checklist(s) and other pertinent material as supplementary files, if applicable. Yes, the code of model is included in the manuscript files.

**URL:** http://medrxiv.org/content/early/2021/09/23/2021.09.21.21263901.abstract

**DOI:** 10.1101/2021.09.21.21263901

ABSTRACT: As the SARS-CoV-2 pandemic evolves, new variants continue to emerge. Some highly transmissible variants, such as Delta, also raised concerns about the effectiveness provided by current vaccines. Understanding immunological correlates of protection and how laboratory findings correspond to clinical effectiveness is imperative to shape future vaccination strategies.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34534444
DOI: 10.1016/j.cell.2021.09.010


ABSTRACT: The variant 20I/501Y.V1, associated to a higher risk of transmissibility, emerged in Nice city (Southeast of France, French Riviera) during January 2021. The pandemic has resumed late December 2020 in this area. A high incidence rate together with a fast turnover of the main circulating variants, provided us the opportunity to analyze modifications in clinical profile and outcome traits. We performed an observational study in the University hospital of Nice from December 2020 to February 2021. We analyzed data of sequencing of SARS-CoV-2 from the sewage collector and PCR screening from all positive samples at the hospital. Then, we described the characteristics of all COVID-19 patients admitted in the emergency department (ED) (n = 1247) and those hospitalized in the infectious diseases ward or ICU (n = 232). The UK-variant was absent in this area in December, then increasingly spread in January representing 59% of the PCR screening performed mid-February. The rate of patients over 65 years admitted to the ED decreased from 63 to 50% (p = 0.001). The mean age of hospitalized patients in the infectious diseases ward decreased from 70.7 to 59.2 (p < 0.001) while the proportion of patients without comorbidity increased from 16 to 42% (p = 0.007). Spread of the UK-variant in the Southeast of France affects younger and healthier patients.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34531412
DOI: 10.1038/s41598-021-95067-7


ABSTRACT: Introduction: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) lineage B.1.1.7 has an increased transmissibility compared to predecessor lineages. Healthcare workers (HCWs) are at an increased risk of being exposed to SARS-CoV-2 but also of being a source of transmission. Objective(s): To describe the lessons learned from a B.1.1.7 outbreak in a tertiary hospital. Method(s): An Outbreak Management Team developed a mitigation strategy. 1) The importance of the prevailing infection control measures, including social distancing, capacity limits for rooms, universal masking in case of < 1.5 m distance and the early testing and domestic quarantine of HCW with symptoms was stressed. 2) An infection control practitioner visited the ward each working day during the outbreak period, to advise and observe practice. 3) Contacts were traced and divided into high-risk and low risk contacts in the workplace and in household/social contacts. 4) Voluntary nasopharyngeal swabs were taken twice a week, to detect asymptomatic cases. 5) Potential weak links of infection control measures were discussed with nurses. Result(s): Nine nurses and two informal caregivers tested RT-PCR positive for SARS-CoV-2 in December 2020. The index nurse tested positive following the earlier infection of a household contact. The outbreak was recognized a day later when the second nurse tested positive and was confirmed by Whole Genome Sequencing. Of the remaining nine cases which tested positive in the following 11 days, one case tested positive after a documented SARS-CoV-2 infection 83 days prior. We
found a primary attack rate within the department of 18% and a secondary attack rate of 54% among contacts of positive cases. Short conversations in changing rooms without masks, short periods of lack of social distancing during breaks and the incorrect wearing of masks were mentioned as potential causes for transmission. Conclusion(s): Two keys point were taken from this outbreak with lineage B.1.1.7. First, it was controlled by adherence to guidelines in place, despite increased transmissibility of the variant. Second, reinfections with lineage B.1.1.7 can occur rapidly after primary infection. These lessons, reiterate the importance of adherence to prevailing infection prevention methods to prevent transmission among HCW.

ABSTRACT: BACKGROUND: A large cluster of 59 cases were linked to a single flight with 146 passengers from New Delhi to Hong Kong in April 2021. This outbreak coincided with early reports of exponential pandemic growth in New Delhi, which reached a peak of > 400,000 newly confirmed cases on 7 May 2021. METHODS: Epidemiological information including date of symptom onset, date of positive-sample detection, and travel and contact history for individual cases from this flight were collected. Whole genome sequencing was performed, and sequences were classified based on the dynamic Pango nomenclature system. Maximum-likelihood phylogenetic analysis compared sequences from this flight alongside other cases imported from India to Hong Kong on 26 flights between June 2020 and April 2021, as well as sequences from India or associated with India-related travel from February to April 2021, and 1217 reference sequences. RESULTS: Sequence analysis identified six lineages of SARS-CoV-2 belonging to two variants of concern (Alpha and Delta) and one variant of public health interest (Kappa) involved in this outbreak. Phylogenetic analysis confirmed at least three independent sub-lineages of Alpha with limited onward transmission, a superspreading event comprising 37 cases of Kappa, and transmission of Delta to only one passenger. Additional analysis of another 26 flights from India to Hong Kong confirmed widespread circulation of all three variants in India since early March 2021. CONCLUSIONS: The broad spectrum of disease severity and long incubation period of SARS-CoV-2 pose a challenge for surveillance and control. As illustrated by this particular outbreak, opportunistic infections of SARS-CoV-2 can occur irrespective of variant lineage, and requiring a nucleic acid test within 72 hours of departure may be insufficient to prevent importation or in-flight transmission.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34542623
DOI: 10.1093/jtm/taab149

18. Dyer O. Covid-19: Unvaccinated face 11 times risk of death from delta variant, CDC data show. BMJ. 2021;374:n2282. DOI: 10.1136/bmj.n2282
URL: https://www.ncbi.nlm.nih.gov/pubmed/34531181
DOI: 10.1136/bmj.n2282

ABSTRACT: Since the initial report of the severe acute respiratory syndrome (SARS CoV-2) in Wuhan, China, in 2019, the virus has constantly mutated, resulting in the appearance of novel variants. In December 2020, the B.1.617.2 (delta) variant concern (VOC) was first reported in India, and rapidly spread around the globe, is now the main brand in the United Kingdom, and it has grown dramatically. Here we present the clinical features and laboratory findings of the first case of B. 1.617.2 (delta) variant concern (VOC) in Iraq. A 6-year-old female child presented with severe abdominal pain, headache, severe vomiting, and diarrhea, runny nose, alerted mental status, loss of appetite, and fever. The patient
was diagnosed with COVID-19 delta variant B.1.617.2 by RT-PCR. The patient was treated by administration of glucose saline 4% for 3 days, ceftriaxone vial 1 mg every 12 h for 6 days, and an acetaminophen bottle on a need to prevent fever followed by a Flagyl bottle every 24 h for 3 days. Vaccination and prevention the spread of the virus and against it are important preventive approaches for delta variant. Sore throat, runny nose, headache, and vomiting, diarrhea are the major clinical features of the delta variant. This was followed by an elevation of the leukocyte WBC, and blood platelets. To reduce the impact of new delta variant B.1.617.2 infection; handwashing, wearing a double mask, avoiding crowded and closed settings, social distancing, lockdown, and ensuring good ventilation are major significant options against this variant.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34512963
DOI: 10.1016/j.amsu.2021.102814


ABSTRACT: Background: Since the end of 2020, there has been a great deal of international concern about the variants of SARS-CoV-2 B.1.1.7, identified in the United Kingdom; B.1.351 discovered in South Africa and P.1, originating from the Brazilian state of Amazonas. The three variants were associated with an increase in transmissibility and worsening of the epidemiological situation in the places where they expanded. The lineage B.1.1.7 was associated with the increase in case fatality rate in the United Kingdom. There are still no studies on the case fatality rate of the other two variants. The aim of this study was to analyze the mortality profile before and after the emergence of the P.1 strain in the Amazonas state. Methods: We analyzed data from the Influenza Epidemiological Surveillance Information System, SIVEP-Gripe (Sistema de Informacao de Vigilancia Epidemiologica da Gripe), comparing two distinct epidemiological periods: during the peak of the first wave, between April and May 2020, and in January 2021 (the second wave), the month in which the new variant came to predominate. We calculated mortality rates, overall case fatality rate and case fatality rate among hospitalized patients; all rates were calculated by age and gender and 95% confidence intervals (95% CI) were determined. Findings: We observed that in the second wave there were a higher incidence and an increase in the proportion of cases of COVID-19 in the younger age groups. There was also an increase in the proportion of women among Severe Acute Respiratory Infection (SARI) cases from 40% (2,709) in the first wave to 47% (2,898) in the second wave and in the proportion of deaths due to COVID-19 between the two periods varying from 34% (1,051) to 47% (1,724), respectively. In addition, the proportion of deaths among people between 20 and 59 years old has increased in both sexes. The case fatality rate among those hospitalized in the population between 20 and 39 years old during the second wave was 2.7 times the rate observed in the first wave (female rate ratio = 2.71; 95% CI: 1.9-3.9], p <0.0001; male rate ratio = 2.70, 95%CI:2.0-3.7), and in the general population the rate ratios were 1.15 (95% CI: 1.1-1.2) in females and 0.78 (95% CI: 0.7-0.8) in males. Interpretation: Based on this prompt analysis of the epidemiological scenario in the Amazonas state, the observed changes in the pattern of mortality due to COVID-19 between age groups and gender simultaneously with the emergence of the P.1 strain suggest changes in the pathogenicity and virulence profile of this new variant. Further studies are needed to better understanding of SARS-CoV-2 variants profile and their impact for the health population. Funding: There was no funding for this study.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34514463
DOI: 10.1016/j.lana.2021.100021

ABSTRACT: For the first time in human history, obtaining a COVID-19 vaccine has become essential for the sustainability of our species. As an amazing product of collective ideation, remarkably safe and efficient vaccines have been invented, tested, distributed, and administered to the population on a voluntary basis. The fast-mutating individual behavior of the virus is probably guided by a similar goal of the sustainability of the species. With this commentary, we analyze and compare two means of sustainability through adaptability: collective ideation in the case of humans and individual mutations in the case of viruses - two very different species whose behaviors are driven by sustainability.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34527953
DOI: 10.31579/2642-9756/058


ABSTRACT: Specific S477N, N501Y, K417N, K417T, E484K mutations in the receptor binding domain (RBD) of the spike protein in the wild type SARS-CoV-2 virus have resulted, among others, in the following variants: B.1.160 (20A or EU2, first reported in continental Europe), B1.1.7 (alpha or 20I501Y.V1, first reported in the United Kingdom), B.1.351 (beta or 20H/501Y.V2, first reported in South Africa), B.1.1.28.1 (gamma or P.1 or 20J/501Y.V3, first reported in Brazil), and B.1.1.28.2 (zeta, or P.2 or 20B/S484K, also first reported in Brazil). From the analysis of a set of bonding descriptors firmly rooted in the formalism of quantum mechanics, including Natural Bond Orbitals (NBO), Quantum Theory of Atoms In Molecules (QTAIM) and highly correlated energies within the Domain Based Local Pair Natural Orbital Coupled Cluster Method (DLPNO-CCSD(T)), and from a set of computed electronic spectral patterns with environmental effects, we show that the new variants improve their ability to recognize available sites to either hydrogen bond or to form salt bridges with residues in the ACE2 receptor of the host cells. This results in significantly improved initial virus cell molecular recognition and attachment at the microscopic level, which trigger the infectious cycle.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34529328
DOI: 10.1002/cbic.202100393


ABSTRACT: Towards the end of 2020, multiple variants of concern (VOCs) and variants of interest (VOIs) have arisen from the original SARS-CoV-2 Wuhan-Hu-1 strain. Mutations in the Spike protein are highly scrutinized for their impact on transmissibility, pathogenesis and vaccine efficacy. Here, we contribute to the growing body of literature on emerging variants by evaluating the impact of single mutations on the overall antigenicity of selected variants and their binding to the ACE2 receptor. We observe a differential contribution of single mutants to the global variants phenotype related to ACE2 interaction and antigenicity. Using biolayer interferometry, we observe that enhanced ACE2 interaction is mostly modulated by a decrease in off-rate. Finally, we made the interesting observation that the Spikes from tested emerging variants bind better to ACE2 at 37 degrees C compared to the D614G variant. Whether improved ACE2 binding at higher temperature facilitates emerging variants transmission remain to be demonstrated.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34536797
DOI: 10.1016/j.virol.2021.09.001

**ABSTRACT:** Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to an outbreak of a pandemic worldwide. The spike (S) protein of SARS-CoV-2, which plays a key role in the receptor recognition and cell membrane fusion process, is composed of two subunits, S1 and S2. The S1 subunit contains a receptor-binding domain that recognizes and binds to the host receptor angiotensin-converting enzyme 2 (ACE2), while the S2 subunit mediates viral cell membrane fusion with the cell membrane and subsequent entry into cells. Mutations in the spike protein (S) are of particular interest due to their potential for reduced susceptibility to neutralizing antibodies or increasing the viral transmissibility and infectivity. Recently, many mutations in the spike protein released new variants, including the Delta and Kappa ones (known as the Indian variants). The variants Delta and Kappa are now of most recent concern because of their well-increased infectivity, both a spin-off of the B.1.617 lineage, which was first identified in India in October 2020. This study employed homology modeling to probe the potential structural effects of the mutations. It was found that the mutations, Leu452Arg, Thr478Lys, and Glu484Gln in the spike protein increase the affinity for the hACE2 receptor, which explains the greater infectivity of the SARS-CoV-2 B.1.617 (Indian Variant).

URL: https://www.ncbi.nlm.nih.gov/pubmed/34513478
DOI: 10.7759/cureus.16905


**ABSTRACT:** We present evidence for multiple independent origins of recombinant SARS-CoV-2 viruses sampled from late 2020 and early 2021 in the United Kingdom. Their genomes carry single-nucleotide polymorphisms and deletions that are characteristic of the B.1.1.7 variant of concern but lack the full complement of lineage-defining mutations. Instead, the remainder of their genomes share contiguous genetic variation with non-B.1.1.7 viruses circulating in the same geographic area at the same time as the recombinants. In four instances, there was evidence for onward transmission of a recombinant-origin virus, including one transmission cluster of 45 sequenced cases over the course of 2 months. The inferred genomic locations of recombination breakpoints suggest that every community-transmitted recombinant virus inherited its spike region from a B.1.1.7 parental virus, consistent with a transmission advantage for B.1.1.7’s set of mutations.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34499854
DOI: 10.1016/j.cell.2021.08.014


URL: https://www.ncbi.nlm.nih.gov/pubmed/34531555
DOI: 10.1038/s41423-021-00767-9


**ABSTRACT:** SARS-CoV-2 virus during its spread in the last one and half year has picked up critical changes in its genetic code i.e. mutations, which have leads to deleterious epidemiological
characteristics. Due to critical role of spike protein in cell entry and pathogenesis, mutations in spike regions have been reported to enhance transmissibility, disease severity, possible escape from vaccine-induced immune response and reduced diagnostic sensitivity/specificity. Considering the structure-function impact of mutations, understanding the molecular details of these key mutations of newly emerged variants/lineages is of urgent concern. In this review, we have explored the literature on key spike mutations harbored by alpha, beta, gamma and delta 'variants of concern' (VOCs) and discussed their molecular consequences in the context of resultant virus biology. Commonly all these VOCs i.e. B.1.1.7, B.1.351, P.1 and B.1.617.2 lineages have decisive mutation in Receptor Binding Motif (RBM) region and/or region around Furin cleavage site (FCS) of spike protein. In general, mutation induced disruption of intra-molecular interaction enhances molecular flexibility leading to exposure of spike protein surface in these lineages to make it accessible for inter-molecular interaction with hACE2. A disruption of spike antigen-antibody inter-molecular interactions in epitope region due to the chemical nature of substituting amino acid hampers the neutralization efficacy. Simplified surveillance of mutation induced changes and their consequences at molecular level can contribute in rationalizing mutation's impact on virus biology. It is believed that molecular level dissection of these key spike mutation will assist the future investigations for a more resilient outcome against severity of COVID-19.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34541298
DOI: 10.1002/slct.202102074

ABSTRACT: RNA viruses (except retroviruses) replicate by the action of an RNA-dependent RNA polymerase, which lacks a proofreading exonuclease and, consequently, errors may occur in each replication giving place to viral mutants. Depending on their fitness, these mutants either become extinct or thrive, spawning variants that escape the immune system. The most important SARS-CoV-2 mutations are those that alter the amino acid sequence in the viral S protein because this protein holds the key for the virus to enter the human cell. The more viruses replicate, the more they mutate, and the more likely it is that dominant resistant variants will appear. In such cases, more stringent measures for community protection will be required. Vaccines and polyclonal antibodies, which induce a response directed towards several sites along the S protein, would maintain effective protection against SARS-CoV-2 variants. Furthermore, vaccines appear to induce an increased helper and cytotoxic T-cell response, which may also be a biomarker of protection. In densely populated areas with insufficient protection measures, the virus spreads freely, thus increasing the likelihood of generating escape mutants. India and Manaus exemplify this situation. Natural evolution selects the mutants that multiply most efficiently without eliminating the host, thus facilitating their spread. Contrastingly, the circulation of viruses of high virulence and lethality (Ebola, hantavirus) that eliminate the host remain limited to certain geographic areas, without further dissemination. Therefore, it would be expected that SARS-CoV-2 will evolve into more infectious and less virulent variants.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34137703

ABSTRACT: This is a century of corona virus. The world is still coping up with the third wave of COVID-19, while the scientists have already warned that a fourth wave is imminent. This wave is expected to be more lethal due to multiple mutated variety of the corona virus, including one of the most lethal one known as Indian variant or delta variant. Meanwhile, the health staff has to deal with those patients who survived COVID-19, but continued to have a variety of new complaints, including respiratory distress, dysautonomia, intravascular thrombosis and endocardial myocarditis etc. Anti-corona therapy,
in itself lead to multiple syndromes including acute kidney injury, bone marrow depression and deranged blood sugar levels. One of the more lethal complication is mucormycosis—a fungal disease. It has affected thousands of recovering or recovered corona patients in India. This editorial highlights the salient features of post-corona syndrome or long covid. Copyright © 2021 Faculty of Anaesthesia, Pain and Intensive Care, AFMS. All rights reserved.


ABSTRACT: The ability to predict emerging variants of SARS-CoV-2 would be of enormous value, as it would enable proactive design of vaccines in advance of such emergence. We estimated diversity of each site on a multiple sequence alignment (MSA) of the Spike (S) proteins from close relatives of SARS-CoV-2 that infected bat and pangolin before the pandemic. Then we compared the locations of high diversity sites in this MSA and those of mutations found in multiple emerging lineages of human-infecting SARS-CoV-2. This comparison revealed a significant correspondence, which suggests that a limited number of sites in this protein are repeatedly substituted in different lineages of this group of viruses. It follows, therefore, that the sites of future emerging mutations in SARS-CoV-2 can be predicted by analyzing their relatives (outgroups) that have infected non-human hosts. We discuss a possible evolutionary basis for these substitutions and provide a list of frequently substituted sites that potentially include future emerging variants in SARS-CoV-2.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34552191
DOI: 10.1038/s42003-021-02663-4


ABSTRACT: The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) outbreak in December 2019 has caused a global pandemic. The rapid mutation rate in the virus has created alarming situations worldwide and is being attributed to the false negativity in RT-PCR tests. It has also increased the chances of reinfection and immune escape. Recently various lineages namely, B.1.1.7 (Alpha), B.1.617.1 (Kappa), B.1.617.2 (Delta) and B.1.617.3 have caused rapid infection around the globe. To understand the biophysical perspective, we have performed molecular dynamic simulations of four different spikes (receptor binding domain)-hACE2 complexes, namely wildtype (WT), Alpha variant (N501Y spike mutant), Kappa (L452R, E484Q) and Delta (L452R, T478K), and compared their dynamics, binding energy and molecular interactions. Our results show that mutation has caused significant increase in the binding energy between the spike and hACE2 in Alpha and Kappa variants. In the case of Kappa and Delta variants, the mutations at L452R, T478K and E484Q increased the stability and intra-chain interactions in the spike protein, which may change the interaction ability of neutralizing antibodies to these spike variants. Further, we found that the Alpha variant had increased hydrogen interaction with Lys353 of hACE2 and more binding affinity in comparison to WT. The current study provides the biophysical basis for understanding the molecular mechanism and rationale behind the increase in the transmissivity and infectivity of the mutants compared to wild-type SARS-CoV-2.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34502041
DOI: 10.3390/ijms22179131

32. Lee BU. Why does the sars-cov-2 delta voc spread so rapidly? Universal conditions for the rapid spread of respiratory viruses, minimum viral loads for viral aerosol generation, effects of vaccination

**ABSTRACT:** This study analyzes the reasons the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Delta variant of concern (VOC) spreads so rapidly. Novel topics such as universal conditions for the rapid spread of respiratory viruses, minimum viral loads for viral aerosol generation, effects of vaccination on viral aerosol generation, and viral aerosol clouds were studied. The analyses were based on experimental results and analytic model studies. Four universal conditions, namely asymptomatic host, high viral load, stability of viruses in air, and binding affinity of viruses to human cells, need to be satisfied for the rapid spread of respiratory viruses. SARS-CoV-2 and its variants such as the Alpha VOC and Delta VOC satisfy the four fundamental conditions. In addition, there is an original principle of aerosol generation of respiratory viruses. Assuming that the aerosol-droplet cutoff particle diameter for distinguishing potential aerosols from earthbound respiratory particles is 100 microm, the minimum viral load required in respiratory fluids to generate viral aerosols is \(~10^{6}\) copies \(\text{mL}^{-1}\), which is within the range of the reported viral loads in the Alpha VOC cases and the Delta VOC cases. The daily average viral loads of the Delta VOC in hosts have been reported to be between \(~10^{9}\) and \(~10^{10}\) copies \(\text{mL}^{-1}\) during the four days after symptom onset in 1848 cases of the Delta VOC infection. Owing to the high viral load, the SARS-CoV-2 Delta VOC has the potential to effectively spread through aerosols. COVID-19 vaccination can decrease aerosol transmission of the SARS-CoV-2 Alpha VOC by reducing the viral load. The viral load can explain the conundrum of viral aerosol spreading. The SARS-CoV-2 Delta VOC aerosol clouds have been assumed to be formed in restricted environments, resulting in a massive numbers of infected people in a very short period with a high spreading speed. Strong control methods against bioaerosols should be considered in this SARS-CoV-2 Delta VOC pandemic. Large-scale environmental monitoring campaigns of SARS-CoV-2 Delta VOC aerosols in public places in many countries are necessary, and these activities could contribute to controlling the coronavirus disease pandemic. Copyright © 2021 by the author. Licensee MDPI, Basel, Switzerland.


**ABSTRACT:** New threats posed by the emerging circulating variants of SARS-CoV-2 highlight the need to find conserved neutralizing epitopes for therapeutic antibodies and efficient vaccine design. Here, we identified a receptor-binding domain (RBD)-binding antibody, XG014, which potently neutralizes beta-coronavirus lineage B (beta-CoV-B), including SARS-CoV-2, its circulating variants, SARS-CoV and bat SARSr-CoV WIV1. Interestingly, antibody family members competing with XG014 binding show reduced levels of cross-reactivity and induce antibody-dependent SARS-CoV-2 spike (S) protein-mediated cell-cell fusion, suggesting a unique mode of recognition by XG014. Structural analyses reveal that XG014 recognizes a conserved epitope outside the ACE2 binding site and completely locks RBD in the non-functional "down" conformation, while its family member XG005 directly competes with ACE2 binding and position the RBD "up". Single administration of XG014 is effective in protection against and therapy of SARS-CoV-2 infection in vivo. Our findings suggest the potential to develop XG014 as pan-beta-CoV-B therapeutics and the importance of the XG014 conserved antigenic epitope for designing broadly protective vaccines against beta-CoV-B and newly emerging SARS-CoV-2 variants of concern.

**URL:** https://www.ncbi.nlm.nih.gov/pubmed/34554412

**DOI:** 10.1007/s13238-021-00871-6
URL: https://www.ncbi.nlm.nih.gov/pubmed/34537321
DOI: 10.1016/j.jinf.2021.09.005

ABSTRACT: Emergency and establishment of variants of concern (VOC) impose significant challenges for the COVID-19 pandemic control specially when a large portion of the population has not been fully vaccinated. Here we develop a mathematical model and utilize this model to examine the impact of non pharmaceutical interventions, including the COVID-test (PCR, antigen and antibody test) and whole genome sequencing (WGS) test capacity and contact tracing and quarantine strength, on the VOC-induced epidemic wave. We point out the undesirable and unexpected effect of lukewarm tracing and quarantine that can potentially increase the VOC-cases at the outbreak peak time, and we demonstrate the significance of strain-specific interventions to either prevent a VOC-induced outbreak, or to mitigate the epidemic wave when this outbreak is unavoidable.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34547362
DOI: 10.1016/j.mbs.2021.108703

ABSTRACT: Contamination of surfaces has been implicated in transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We tested by real-time PCR for SARS-CoV-2 contamination environmental samples from three hospitals during the peak of the third pandemic wave. Overall, 19 of 463 (4.1%) samples tested positive: 12 of 173 (6.9%) samples from a COVID-19 hospital, 3 of 177 (1.7%) samples from a non-COVID-19 hospital, and 4 of 113 (3.5%) samples from a pediatric hospital with dedicated COVID-19 clinics. Most positive samples originated from emergency departments (EDs) (47.3%) and the intensive care units (ICUs) (26.3%) of the COVID-19 hospital. Positive samples belonged almost exclusively (18/19) to the highly transmissible B.1.1.7 cluster, that might explain environmental contamination at this stage of the pandemic. The frequency and efficiency of disinfection in high-risk patient areas, such as EDs and ICUs, should be reinforced, especially during this period where highly transmissible variants of concern are widespread.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34455029
DOI: 10.1016/j.ajic.2021.08.022

ABSTRACT: Multiple effective vaccines are currently being deployed to combat the COVID-19 pandemic, and are viewed as the major factor in marked reductions of disease burden in regions with moderate to high vaccination coverage. The effectiveness of COVID-19 vaccination programs is, however, significantly threatened by the emergence of new SARS-CoV-2 variants that, in addition to being more transmissible than the wild-type (original) strain, may at least partially evade existing vaccines. A two-strain (one wild-type, one variant) and two-group (vaccinated or otherwise) mechanistic mathematical model is designed and used to assess the impact of the vaccine-induced cross-protective efficacy on the spread the COVID-19 pandemic in the United States. Rigorous analysis of the model shows that, in the absence of any co-circulating SARS-CoV-2 variant, the vaccine-derived herd immunity threshold needed to eliminate the
wild-type strain can be achieved if 59% of the US population is fully-vaccinated with either the Pfizer or Moderna vaccine. This threshold increases to 76% if the wild-type strain is co-circulating with the Alpha variant (a SARS-CoV-2 variant that is 56% more transmissible than the wild-type strain). If the wild-type strain is co-circulating with the Delta variant (which is estimated to be 100% more transmissible than the wild-type strain), up to 82% of the US population needs to be vaccinated with either of the aforementioned vaccines to achieve the vaccine-derived herd immunity. Global sensitivity analysis of the model reveal the following four parameters as the most influential in driving the value of the reproduction number of the variant strain (hence, COVID-19 dynamics) in the US: (a) the infectiousness of the co-circulating SARS-CoV-2 variant, (b) the proportion of individuals fully vaccinated (using Pfizer or Moderna vaccine) against the wild-type strain, (c) the cross-protective efficacy the vaccines offer against the variant strain and (d) the modification parameter accounting for the reduced infectiousness of fully-vaccinated individuals experiencing breakthrough infection. Specifically, numerical simulations of the model show that future waves or surges of the COVID-19 pandemic can be prevented in the US if the two vaccines offer moderate level of cross-protection against the variant (at least 67%). This study further suggests that a new SARS-CoV-2 variant can cause a significant disease surge in the US if (i) the vaccine coverage against the wild-type strain is low (roughly <66%) (ii) the variant is much more transmissible (e.g., 100% more transmissible), than the wild-type strain, or (iii) the level of cross-protection offered by the vaccine is relatively low (e.g., less than 50%). A new SARS-CoV-2 variant will not cause such surge in the US if it is only moderately more transmissible (e.g., the Alpha variant, which is 56% more transmissible) than the wild-type strain, at least 66% of the population of the US is fully vaccinated, and the three vaccines being deployed in the US (Pfizer, Moderna, and Johnson & Johnson) offer a moderate level of cross-protection against the variant.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34518808
DOI: 10.1016/j.idm.2021.08.008


ABSTRACT: Mass mapping using high-resolution mass spectrometry has been applied to identify and rapidly distinguish SARS-CoV-2 coronavirus strains across five major variants of concern. Deletions or mutations within the surface spike protein across these variants, which originated in the UK, South Africa, Brazil and India (known as the alpha, beta, gamma and delta variants respectively), lead to associated mass differences in the mass maps. Peptides of unique mass have thus been determined that can be used to identify and distinguish the variants. The same mass map profiles are also utilized to construct phylogenetic trees, without the need for protein (or gene) sequences or their alignment, in order to chart and study viral evolution. The combined strategy offers advantages over conventional PCR-based gene-based approaches exploiting the ease with which protein mass maps can be generated and the speed and sensitivity of mass spectrometric analysis.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34532764
DOI: 10.1007/s00216-021-03649-1


ABSTRACT: The independent emergence late in 2020 of the B.1.1.7, B.1.351, and P.1 lineages of SARS-CoV-2 prompted renewed concerns about the evolutionary capacity of this virus to overcome public health interventions and rising population immunity. Here, by examining patterns of synonymous and non-synonymous mutations that have accumulated in SARS-CoV-2 genomes since the pandemic began, we find that the emergence of these three "501Y lineages" coincided with a major global shift in the selective forces acting on various SARS-CoV-2 genes. Following their emergence, the adaptive evolution...
of 501Y lineage viruses has involved repeated selectively favored convergent mutations at 35 genome sites, mutations we refer to as the 501Y meta-signature. The ongoing convergence of viruses in many other lineages on this meta-signature suggests that it includes multiple mutation combinations capable of promoting the persistence of diverse SARS-CoV-2 lineages in the face of mounting host immune recognition.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34537136
DOI: 10.1016/j.cell.2021.09.003

URL: https://www.ncbi.nlm.nih.gov/pubmed/34555339
DOI: 10.1016/j.jamda.2021.08.032

ABSTRACT: Many countries in the world are experiencing a recent surge in COVID-19 cases. This is mainly attributed to the emergence of new SARS-CoV-2 variants. Genome sequencing is the only means to detect the evolving virus mutants and emerging variants. Cycle threshold values have an inverse relationship with viral load and lower Ct values are also found to be associated with increased infectivity. In this study, we propose to use Ct values as an early indicator for upcoming COVID-19 waves. A retrospective cross-sectional study was carried out to analyze the Ct values of positive samples reported during the first wave and second wave (April 2020-May 2021). Median Ct values of confirmatory genes were taken into consideration for comparison. Ct values below 25, >25-30, and >30 were categorized as high, moderate, and low viral load respectively. Our study found a significantly higher proportion of positive samples with a low Ct value (<25) across age groups and gender during the second wave of the COVID-19 pandemic. A higher proportion of positive samples with a low Ct value (high viral load) may act as an early indicator of an upcoming surge. Copyright © 2021 Wiley Periodicals LLC

ABSTRACT: The SARS-CoV-2 B.1.617.2 (Delta) variant was first identified in the state of Maharashtra in late 2020 and spread throughout India, outcompeting pre-existing lineages including B.1.617.1 (Kappa) and B.1.1.7 (Alpha)(1). In vitro, B.1.617.2 is 6-fold less sensitive to serum neutralising antibodies from recovered individuals, and 8-fold less sensitive to vaccine-elicited antibodies as compared to wild type (WT) Wuhan-1 bearing D614G. Serum neutralising titres against B.1.617.2 were lower in ChAdOx-1 versus BNT162b2 vaccinees. B.1.617.2 spike pseudotyped viruses exhibited compromised sensitivity to monoclonal antibodies against the receptor binding domain (RBD) and N-terminal domain (NTD). B.1.617.2 demonstrated higher replication efficiency in both airway organoid and human airway epithelial systems compared to B.1.1.7, associated with B.1.617.2 spike in a predominantly cleaved state compared to B.1.1.7. The B.1.617.2 spike protein was able to mediate highly efficient syncytium formation that was less sensitive to inhibition by neutralising antibody as compared to WT spike. Additionally we observed that B.1.617.2 had higher replication and spike mediated entry as compared to B.1.617.1, potentially explaining B.1.617.2 dominance. In an analysis of over 130 SARS-CoV-2 infected healthcare workers across three centres in India during a period of mixed lineage circulation, we observed reduced ChAdOx-1 vaccine effectiveness against B.1.617.2 relative to non- B.1.617.2, with the caveat of possible residual confounding. Compromised vaccine efficacy against the highly fit and
immune evasive B.1.617.2 Delta variant warrants continued infection control measures in the post-vaccination era.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34488225
DOI: 10.1038/s41586-021-03944-y


ABSTRACT: To better understand the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variant lineage distribution in a college campus population, we carried out viral genome surveillance over a 7-week period from January to March 2021. Among the sequences were three novel viral variants: BV-1 with a B.1.1.7/20I genetic background and an additional spike mutation Q493R, associated with a mild but longer-than-usual COVID-19 case in a college-age person, BV-2 with a T478K mutation on a 20B genetic background, and BV-3, an apparent recombinant lineage. This work highlights the potential of an undervaccinated younger population as a reservoir for the spread and generation of novel variants. This also demonstrates the value of whole genome sequencing as a routine disease surveillance tool.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34544043
DOI: 10.4269/ajtmh.21-0542


ABSTRACT: SARS-CoV-2, the virus that causes COVID-19, has had a major impact on human health globally; infecting a large number of people and resulting in increased mortality. The WHO has received many reports of SARS-CoV-2 mutations and variants. The best-known variants are the British, South African, and Brazilian variants, which differ in the genetic record but share the N501Y mutation, which exists in the receptor-binding domain, and is critical for binding to the human ACE2 receptor (angiotensin-converting enzyme 2). So far, mRNA (Pfizer, Moderna) and vector (Astra Zeneca, Johnson & Johnson) vaccines have been used against the SARS-CoV-2 virus. Others are undergoing diagnostic tests. However, further research is needed to show how the respective vaccines deal with the identified mutations and the whole range of SARS-CoV-2 variants. A systematic review including the current evidence related to different variants of SARS-CoV-2 and COVID-19 vaccines was conducted through a systemic search utilizing the keywords in the online databases including Scopus, PubMed, and Web of Science; we retrieved all related papers and reports published in English from 2019 to 2021. Copyright © 2021 by Polish Pharmaceutical Society. This is an open-access article under the CC BY NC license (http://creativecommons.org/licenses/BY/4.0/).


ABSTRACT: Certain genetic variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are of substantial concern because they may be more transmissible or detrimentally alter the pandemic course and disease features in individual patients. SARS-CoV-2 genome sequences from 12,476 patients in the Houston Methodist health care system diagnosed from January 1 through May 31, 2021 are reported here. Prevalence of the B.1.1.7 (Alpha) variant increased rapidly and caused 63% to 90% of new cases in the latter half of May. Eleven B.1.1.7 genomes had an E484K replacement in spike protein, a change also identified in other SARS-CoV-2 lineages. Compared with non-B.1.1.7-infected patients,
individuals with B.1.1.7 had a significantly lower cycle threshold (a proxy for higher virus load) and significantly higher hospitalization rate. Other variants [eg, B.1.429 and B.1.427 (Epsilon), P.1 (Gamma), P.2 (Zeta), and R.1] also increased rapidly, although the magnitude was less than that in B.1.1.7. Twenty-two patients infected with B.1.617.1 (Kappa) or B.1.617.2 (Delta) variants had a high rate of hospitalization. Breakthrough cases (n = 207) in fully vaccinated patients were caused by a heterogeneous array of virus genotypes, including many not currently designated variants of interest or concern. In the aggregate, this study delineates the trajectory of SARS-CoV-2 variants circulating in a major metropolitan area, documents B.1.1.7 as the major cause of new cases in Houston, TX, and heralds the arrival of B.1.617 variants in the metroplex. Copyright © 2021 American Society for Investigative Pathology

ABSTRACT: Potent neutralizing SARS-CoV-2 antibodies often target the spike protein receptor-binding site (RBS), but the variability of RBS epitopes hampers broad neutralization of multiple sarbecoviruses and drifted viruses. Here, using humanized mice, we identified an RBS antibody with a germline VH gene that potently neutralized SARS-related coronaviruses, including SARS-CoV and SARS-CoV-2 variants. X-ray crystallography revealed coordinated recognition by the heavy chain of non-RBS conserved sites and the light chain of RBS with a binding angle mimicking the angiotensin-converting enzyme 2 (ACE2) receptor. The minimum footprints in the hypervariable region of RBS contributed to the breadth of neutralization, which was enhanced by immunoglobulin G3 (IgG3) class switching. The coordinated binding resulted in broad neutralization of SARS-CoV and emerging SARS-CoV-2 variants of concern. Low-dose therapeutic antibody treatment in hamsters reduced the virus titers and morbidity during SARS-CoV-2 challenge. The structural basis for broad neutralizing activity may inform the design of a broad spectrum of therapeutics and vaccines.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34508662
DOI: 10.1016/j.immuni.2021.08.025

ABSTRACT: New variants of SARS-CoV-2 Alpha (B.1.1.7); Beta (B.1.351) Gamma (P.1) and Delta (B.1.617.2) quickly spread in the UK, South Africa, Brazil and India, respectively. To address whether mutations in SARS-CoV-2 RBD spike protein could affect virus infectivity, peptides containing RBD amino acids mutations have been constructed and interacted with human ACE2 by computational methods. Our results suggest that mutations in RBD amino acids K417, E484, L452, T478 and N501 are expressively increasing the affinity of this protein with human angiotensin-converting enzyme 2 (ACE2), consequently, variants Alpha (B.1.1.7), Beta (B1.351), Gamma (P.1) and Delta (B.1.617.2) could be more infective in human cells compared with SARS-CoV-2 isolated in Wuhan-2019 and the Gamma and Delta variants could be the most infective among them.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34548928
DOI: 10.1016/j.jve.2021.100054

ABSTRACT: Middle East respiratory syndrome coronavirus (MERS-CoV) is enzootic in dromedary camels across the Middle East and Africa. Virus-induced pneumonia in humans results from animal contact, with a potential for limited onward transmission. Phenotypic changes have been suspected after a novel recombinant clade (lineage 5) caused large nosocomial outbreaks in Saudi Arabia and South Korea in 2016. However, there has been no functional assessment. Here we perform a comprehensive in vitro and ex vivo comparison of viruses from parental and recombinant virus lineages (lineage 3, n = 7; lineage 4, n = 8; lineage 5, n = 9 viruses) from Saudi Arabia, isolated immediately before and after the shift toward lineage 5. Replication of lineage 5 viruses is significantly increased. Transcriptional profiling finds reduced induction of immune genes IFNB1, CCL5, and IFNL1 in lung cells infected with lineage 5 strains. Phenotypic differences may be determined by IFN antagonism based on experiments using IFN receptor knock out and signaling inhibition. Additionally, lineage 5 is more resilient against IFN pre-treatment of Calu-3 cells (ca. 10-fold difference in replication). This phenotypic change associated with lineage 5 has remained undiscovered by viral sequence surveillance, but may be a relevant indicator of pandemic potential.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34493730
DOI: 10.1038/s41467-021-25519-1

ABSTRACT: Genomic surveillance can provide early insights into new circulating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants. While conducting genomic surveillance (1,663 cases) from December 2020-April 2021 in Arizona, USA, we detected an emergent E484K-harboring variant, B.1.243.1. This finding demonstrates the importance of real-time SARS-CoV-2 surveillance to better inform public health responses.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34545803
DOI: 10.3201/eid2710.211189

URL: https://www.ncbi.nlm.nih.gov/pubmed/34474059
DOI: 10.1016/j.jinf.2021.08.041

URL: https://www.ncbi.nlm.nih.gov/pubmed/34491353
DOI: 10.1001/jamanetworkopen.2021.24343

ABSTRACT: BACKGROUND: SARS-CoV-2 lineage B.1.1.7 has been associated with an increased rate of transmission and disease severity among subjects testing positive in the community. Its impact on hospitalised patients is less well documented. METHODS: We collected viral sequences and clinical data of patients admitted with SARS-CoV-2 and hospital-onset COVID-19 infections (HOCIs), sampled 16 November 2020 to 10 January 2021, from eight hospitals participating in the COG-UK-HOCI study. Associations between the variant and the outcomes of all-cause mortality and intensive therapy unit (ITU) admission were evaluated using mixed effects Cox models adjusted by age, sex, comorbidities, care
home residence, pregnancy and ethnicity. FINDINGS: Sequences were obtained from 2341 inpatients (HOCI cases=786) and analysis of clinical outcomes was carried out in 2147 inpatients with all data available. The HR for mortality of B.1.1.7 compared with other lineages was 1.01 (95% CI 0.79 to 1.28, p=0.94) and for ITU admission was 1.01 (95% CI 0.75 to 1.37, p=0.96). Analysis of sex-specific effects of B.1.1.7 identified increased risk of mortality (HR 1.30, 95% CI 0.95 to 1.78, p=0.096) and ITU admission (HR 1.82, 95% CI 1.15 to 2.90, p=0.011) in females infected with the variant but not males (mortality HR 0.82, 95% CI 0.61 to 1.10, p=0.177; ITU HR 0.74, 95% CI 0.52 to 1.04, p=0.086). INTERPRETATION: In common with smaller studies of patients hospitalised with SARS-CoV-2, we did not find an overall increase in mortality or ITU admission associated with B.1.1.7 compared with other lineages. However, women with B.1.1.7 may be at an increased risk of admission to intensive care and at modestly increased risk of mortality.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34544733
DOI: 10.1136/bmjresp-2021-001029


ABSTRACT: The increasing prevalence of SARS-CoV-2 variants with the ability to escape existing humoral protection conferred by previous infection and/or immunization necessitates the discovery of broadly-reactive neutralizing antibodies (nAbs). Utilizing mRNA display, we identified a set of antibodies against SARS-CoV-2 spike (S) proteins and characterized the structures of nAbs that recognized epitopes in the S1 subunit of the S glycoprotein. These structural studies revealed distinct binding modes for several antibodies, including targeting of rare cryptic epitopes in the receptor-binding domain (RBD) of S that interacts with angiotensin-converting enzyme 2 (ACE2) to initiate infection, as well as the S1 subdomain 1. A potent ACE2-blocking nAb was further engineered to sustain binding to S RBD with the E484K and L452R substitutions found in multiple SARS-CoV-2 variants. We demonstrate that mRNA display is a promising approach for the rapid identification of nAbs that can be used in combination to combat emerging SARS-CoV-2 variants.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34545362


ABSTRACT: The past several months have witnessed the emergence of SARS-CoV-2 variants with novel spike protein mutations that are influencing the epidemiological and clinical aspects of the COVID-19 pandemic. These variants can increase rates of virus transmission and/or increase the risk of reinfection and reduce the protection afforded by neutralizing monoclonal antibodies and vaccination. These variants can therefore enable SARS-CoV-2 to continue its spread in the face of rising population immunity while maintaining or increasing its replication fitness. The identification of four rapidly expanding virus lineages since December 2020, designated variants of concern, has ushered in a new stage of the pandemic. The four variants of concern, the Alpha variant (originally identified in the UK), the Beta variant (originally identified in South Africa), the Gamma variant (originally identified in Brazil) and the Delta variant (originally identified in India), share several mutations with one another as well as with an increasing number of other recently identified SARS-CoV-2 variants. Collectively, these SARS-CoV-2 variants complicate the COVID-19 research agenda and necessitate additional avenues of laboratory, epidemiological and clinical research.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34535792
DOI: 10.1038/s41576-021-00408-x
URL: https://www.ncbi.nlm.nih.gov/pubmed/34473593
DOI: 10.1080/21645515.2021.1963601


**ABSTRACT:** mRNA-based vaccines effectively induce protective neutralizing antibodies against SARS-CoV-2, the etiological agent of COVID-19. Yet, the kinetics and compositional patterns of vaccine-induced antibody responses to the original strain and emerging variants of concern remain largely unknown. Here we characterized serum antibody classes and subclasses targeting the spike receptor-binding domain of SARS-CoV-2 wild type and alpha, beta, gamma and delta variants in a longitudinal cohort of SARS-CoV-2 naive and COVID-19 recovered individuals receiving the mRNA-1273 vaccine. We found that mRNA-1273 vaccine recipients developed a SARS-CoV-2-specific antibody response with a subclass profile comparable to that induced by natural infection. Importantly, these antibody responses targeted both wild type SARS-CoV-2 as well as its alpha, beta, gamma and delta variants. Following primary vaccination, individuals with pre-existing immunity showed higher induction of all antibodies but IgG3 compared to SARS-CoV-2-naive individuals. Unlike naive individuals, COVID-19 recovered subjects did not mount a recall antibody response upon the second vaccine dose. In these individuals, secondary immunization resulted in a slight reduction of IgG1 against the receptor-binding domain of beta and gamma variants. Despite the lack of recall humoral response, vaccinees with pre-existing immunity still showed higher titers of IgG1 and IgA to all variants analyzed compared to fully vaccinated naive individuals. Our findings indicate that mRNA-1273 vaccine triggered cross-variant antibody responses with distinct profiles in vaccinees with or without pre-existing immunity and suggest that individuals with prior history of SARS-CoV-2 infection may not benefit from the second mRNA vaccine dose with the current standard regimen.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34539673
DOI: 10.3389/fimmu.2021.737083


**ABSTRACT:** Antivirals are urgently needed to combat the global SARS-CoV-2/COVID-19 pandemic, supplement existing vaccine efforts, and target emerging SARS-CoV-2 variants of concern. Small molecules that interfere with binding of the viral spike receptor binding domain (RBD) to the host ACE2 receptor may be effective inhibitors of SARS-CoV-2 cell entry. Here we screened 512 pure compounds derived from natural products using a high-throughput RBD/ACE2 binding assay and identified (-)-hopeaphenol, a resveratrol tetramer, in addition to vatalbinside A and vaticanol B, as potent and selective inhibitors of RBD/ACE2 binding and viral entry. For example, (-)-hopeaphenol disrupted RBD/ACE2 binding with a 50% inhibitory concentration (IC50) of 0.11 μM in contrast to an IC50 of 28.3 μM against the unrelated host ligand/receptor binding pair PD-1/PD-L1 (selectivity index = 257.3). When assessed against the USA-WA1/2020 variant, (-)-hopeaphenol also inhibited entry of a VSVDeltaG-GFP reporter pseudovirus expressing SARS-CoV-2 spike into ACE2-expressing Vero-E6 cells and in vitro replication of infectious virus in cytopathic effect and yield reduction assays (50% effective concentrations (EC50s) = 10.2 - 23.4 μM) without cytotoxicity and approaching the activities of the control antiviral remdesivir (EC50s = 1.0 - 7.3 μM). Notably, (-)-hopeaphenol also inhibited two
emerging variants of concern including B.1.1.7/"Alpha" and B.1.351/"Beta" in both viral and spike-containing pseudovirus assays with similar or improved activities over the USA-WA1/2020 variant. These results identify (-)-hopeapheanol and related stilbenoid analogues as potent and selective inhibitors of viral entry across multiple SARS-CoV-2 variants of concern.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34543092
DOI: 10.1128/AAC.00772-21


ABSTRACT: Emergence of new SARS-CoV-2 variants has raised concerns related to the effectiveness of vaccines and antibody therapeutics developed against the unmutated wild-type virus. Here we examined the effect of the 12 most commonly occurring mutations in the receptor binding domain of the Spike protein on its expression, stability, activity, and antibody escape potential. Stability was measured using thermal denaturation, and the activity and antibody escape potential were measured using isothermal titration calorimetry in terms of binding to the human angiotensin-converting enzyme 2 (ACE2) and to neutralizing human antibody CC12.1, respectively. Our results show that mutants differ in their expression levels. Of the 8 best-expressed mutants, 2 (N501Y and K417T/E484K/N501Y) showed stronger affinity to ACE2 compared to the wild-type, while 4 (Y453F, S477N, T478I and S494P) had similar affinity and 2 (K417N and E484K) had weaker affinity than the wild-type. Compared to the wild-type, 4 mutants (K417N, Y453F, N501Y and K417T/E484K/N501Y) had weaker affinity for the CC12.1 antibody, whereas 2 (S477N and S494P) had similar affinity, and 2 (T478I and E484K) had stronger affinity than the wild-type. Mutants also differ in their thermal stability, with the two least stable mutants showing reduced expression. Taken together, these results indicate that multiple factors contribute towards the natural selection of variants, and all these factors need to be considered to understand the evolution of the virus. In addition, since not all variants can escape a given neutralizing antibody, antibodies to treat new variants can be chosen based on the specific mutations in that variant.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34543625
DOI: 10.1016/j.jbc.2021.101208

URL: https://www.ncbi.nlm.nih.gov/pubmed/34528522
DOI: 10.4103/ijmr.ijmr_2061_21


ABSTRACT: The prevalence of chemosensory dysfunction in patients with COVID-19 varies greatly between populations. It is unclear whether such differences are due to factors at the level of the human host, or at the level of the coronavirus, or both. At the host level, the entry proteins which allow virus binding and entry have variants with distinct properties, and the frequency of such variants differs between ethnicities. At the level of the virus, the D614G mutation enhances virus entry to the host cell. Since the two virus strains (D614 and G614) coexisted in the first six months of the pandemic in most populations, it has been difficult to distinguish between contributions of the virus and contributions of the host for anosmia. To answer this question, we conducted a systematic review and meta-analysis of studies in South Asian populations when either the D614 or the G614 virus was dominant. We show that populations infected predominantly with the G614 virus had a much higher prevalence of anosmia.
Evidence Search Report: EOC031801v014 ESR

25

(pooled prevalence of 31.8%) compared with the same ethnic populations infected mostly with the D614 virus strain (pooled anosmia prevalence of 5.3%). We conclude that the D614G mutation is a major contributing factor that increases the prevalence of anosmia in COVID-19, and that this enhanced effect on olfaction constitutes a previously unrecognized phenotype of the D614G mutation. The new virus strains that have additional mutations on the background of the D614G mutation can be expected to cause a similarly increased prevalence of chemosensory dysfunctions.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34533304
DOI: 10.1021/acschemneuro.1c00542


ABSTRACT: The recent global surge in COVID-19 infections has been fueled by new SARS-CoV-2 variants, namely Alpha, Beta, Gamma, Delta, etc. The molecular mechanism underlying such surge is elusive due to 4,653 non-degenerate mutations on the spike protein, which is the target of most COVID-19 vaccines. The understanding of the molecular mechanism of transmission and evolution is a prerequisite to foresee the trend of emerging vaccine-breakthrough variants and the design of mutation-proof vaccines and monoclonal antibodies. We integrate the genotyping of 1,489,884 SARS-CoV-2 genomes isolates, 130 human antibodies, tens of thousands of mutational data points, topological data analysis, and deep learning to reveal SARS-CoV-2 evolution mechanism and forecast emerging vaccine-escape variants. We show that infectivity-strengthening and antibody-disruptive co-mutations on the S protein RBD can quantitatively explain the infectivity and virulence of all prevailing variants. We demonstrate that Lambda is as infectious as Delta but is more vaccine-resistant. We analyze emerging vaccine-breakthrough co-mutations in 20 countries, including the United Kingdom, the United States, Denmark, Brazil, and Germany, etc. We envision that natural selection through infectivity will continue to be the main mechanism for viral evolution among unvaccinated populations, while antibody disruptive co-mutations will fuel the future growth of vaccine-escape variants among fully vaccinated populations. Finally, we have identified the co-mutations that have the great likelihood of becoming dominant: [A411S, L452R, T478K], [L452R, T478K, N501Y], [V401L, L452R, T478K], [K417N, L452R, T478K], [L452R, T478K, E484K, N501Y], and [P384L, K417N, E484K, N501Y]. We predict they, particularly the last four, will break through existing vaccines. We foresee an urgent need to develop new vaccines that target these co-mutations.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34518803

ABSTRACT: COVID-19 is seriously threatening human health all over the world. A comprehensive understanding of the genetic mechanisms driving the rapid evolution of its pathogen (SARS-CoV-2) is the key to controlling this pandemic. In this study, by comparing the entire genome sequences of SARS-CoV-2 isolates from Asia, Europe and America, and analyzing their phyllogenetic histories, we found a lineage derived from a recombination event that likely occurred before March 2020. More importantly, the recombinant offspring has become the dominant strain responsible for more than one-third of the
Evidence Search Report: EOC031801v014 ESR

global cases in the pandemic. These results indicated that the recombination might have played a key role in the pandemic of the virus. Copyright © 2021

ABSTRACT: Background: A novel variant of SARS-CoV-2, the Delta variant of concern (VOC, also known as lineage B.1.617.2), is fast becoming the dominant strain globally. We reported the epidemiological, viral, and clinical characteristics of hospitalized patients infected with the Delta VOC during the local outbreak in Guangzhou, China. Methods: We extracted the epidemiological and clinical information pertaining to the 159 cases infected with the Delta VOC across seven transmission generations between May 21 and June 18, 2021. The whole chain of the Delta VOC transmission was described. Kinetics of viral load and clinical characteristics were compared with a cohort of wild-type infection in 2020 admitted to the Guangzhou Eighth People's Hospital. Findings: There were four transmission generations within the first ten days. The Delta VOC yielded a significantly shorter incubation period (4.0 vs. 6.0 days), higher viral load (20.6 vs. 34.0, cycle threshold of the ORF1a/b gene), and a longer duration of viral shedding in pharyngeal swab samples (14.0 vs. 8.0 days) compared with the wild-type strain. In cases with critical illness, the proportion of patients over the age of 60 was higher in the Delta VOC group than in the wild-type strain (100.0% vs. 69.2%, p = 0.03). The Delta VOC had a higher risk than wild-type infection in deterioration to critical status (hazards ratio 2.98 [95%CI 1.29-6.86]; p = 0.01). Interpretation: Infection with the Delta VOC is characterized by markedly increased transmissibility, viral loads and risk of disease progression compared with the wild-type strain, calling for more intensive prevention and control measures to contain future outbreaks. Funding: National Grand Program, National Natural Science Foundation of China, Guangdong Provincial Department of Science and Technology, Guangzhou Laboratory.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34541481
DOI: 10.1016/j.eclinm.2021.101129

ABSTRACT: The recent emergence of multiple SARS-CoV-2 variants has caused considerable concern due to reduced vaccine efficacy and escape from neutralizing antibody therapeutics. It is therefore paramount to develop therapeutic strategies that inhibit all known and future SARS-CoV-2 variants. Here we report that all SARS-CoV-2 variants analyzed, including variants of concern (VOC) Alpha, Beta, Gamma, and Delta, exhibit enhanced binding affinity to clinical grade and phase 2 tested recombinant human soluble ACE2 (APN01). Importantly, soluble ACE2 neutralized infection of VeroE6 cells and human lung epithelial cells by multiple VOC strains with markedly enhanced potency when compared to reference SARS-CoV-2 isolates. Effective inhibition of infections with SARS-CoV-2 variants was validated and confirmed in two independent laboratories. These data show that SARS-CoV-2 variants that have emerged around the world, including current VOC and several variants of interest, can be inhibited by soluble ACE2, providing proof of principle of a pan-SARS-CoV-2 therapeutic.
URL: https://www.ncbi.nlm.nih.gov/pubmed/34545368
DOI: 10.1101/2021.09.10.459744

ABSTRACT: Although the current coronavirus disease 2019 (COVID-19) vaccines have been used worldwide to halt spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the
emergence of new SARS-CoV-2 variants with E484K mutation shows significant resistance to the neutralization of vaccine sera. To better understand the resistant mechanism, we calculated the binding affinities of 26 antibodies to wild-type (WT) spike protein and to the protein harboring E484K mutation, respectively. The results showed that most antibodies (~85%) have weaker binding affinities to the E484K mutated spike protein than to the WT, indicating the high risk of immune evasion of the mutated virus from most of current antibodies. Binding free energy decomposition revealed that the residue E484 forms attraction with most antibodies, while the K484 has repulsion from most antibodies, which should be the main reason of the weaker binding affinities of E484K mutant to most antibodies. Impressively, a monoclonal antibody (mAb) combination was found to have much stronger binding affinity with E484K mutant than WT, which may work well against the mutated virus. Based on binding free energy decomposition, we predicted that the mutation of four more residues on receptor-binding domain (RBD) of spike protein, viz., F490, V483, G485 and S494, may have high risk of immune evasion, which we should pay close attention on during the development of new mAb therapeutics.


ABSTRACT: The mutants resulted from the ongoing SARS-CoV-2 epidemic have showed resistance to antibody neutralization and vaccine-induced immune response. The present study isolated and identified two novel SARS-CoV-2 neutralizing antibodies (nAbs) from convalescent COVID-19 patients. These two nAbs (XG81 and XG83) were then systemically compared with nine nAbs that were reconstructed by using published data, and revealed that, even though these two nAbs shared targeting epitopes on spike protein, they were different from any of the nine nAbs. Compared with XG81, XG83 exhibited a higher RBD binding affinity and neutralization potency against wild-typed pseudovirus, variant pseudoviruses with mutated spike proteins, such as D614G, E484Q, and A475V, as well as the authentic SARS-CoV-2 virus. To explore potential broadly neutralizing antibodies, heavy and light chains from all 18 nAbs (16 published nAbs, XG81 and XG83) were cross-recombined, and some of the functional antibodies were screened and studied for RBD binding affinity, and neutralizing activity against pseudovirus and the authentic SARS-CoV-2 virus. The results demonstrated that several recombed antibodies had a more potent neutralization activity against variant pseudoviruses compared with the originally paired Abs. Taken together, the novel neutralizing antibodies identified in this study are a likely valuable addition to candidate antibody drugs for the development of clinical therapeutic agents against SARS-CoV-2 to minimize mutational escape.


ABSTRACT: To support COVID-19 pandemic planning, we develop a model-inference system to estimate epidemiological properties of new SARS-CoV-2 variants of concern using case and mortality data while accounting for under-ascertainment, disease seasonality, non-pharmaceutical interventions, and mass-vaccination. Applying this system to study three variants of concern, we estimate that B.1.1.7 has a 46.6% (95% CI: 32.3-54.6%) transmissibility increase but nominal immune escape from protection induced by prior wild-type infection; B.1.351 has a 32.4% (95% CI: 14.6-48.0%) transmissibility increase and 61.3% (95% CI: 42.6-85.8%) immune escape; and P.1 has a 43.3% (95% CI: 30.3-65.3%) transmissibility increase and 52.5% (95% CI: 0-75.8%) immune escape. Model simulations indicate that
B.1.351 and P.1 could outcompete B.1.1.7 and lead to increased infections. Our findings highlight the importance of preventing the spread of variants of concern, via continued preventive measures, prompt mass-vaccination, continued vaccine efficacy monitoring, and possible updating of vaccine formulations to ensure high efficacy.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34552095
DOI: 10.1038/s41467-021-25913-9


ABSTRACT: Since the outbreak of SARS-CoV-2, the etiologic agent of the COVID-19 pandemic, the viral genome has acquired numerous mutations with the potential to alter the viral infectivity and antigenicity. Part of mutations in SARS-CoV-2 spike protein has conferred virus the ability to spread more quickly and escape from the immune response caused by the monoclonal neutralizing antibody or vaccination. Herein, we summarize the spatiotemporal distribution of mutations in spike protein, and present recent efforts and progress in investigating the impacts of those mutations on viral infectivity and antigenicity. As mutations continue to emerge in SARS-CoV-2, we strive to provide systematic evaluation of mutations in spike protein, which is vitally important for the subsequent improvement of vaccine and therapeutic neutralizing antibody strategies.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34518867
DOI: 10.1093/bib/bbab375


ABSTRACT: The COVID-19 pandemic continues to be a severe threat to human health, especially due to current and emerging SARS-CoV-2 variants with potential to escape humoral immunity developed after vaccination or infection. The development of broadly neutralizing antibodies that engage evolutionarily conserved epitopes on coronavirus spike proteins represents a promising strategy to improve therapy and prophylaxis against SARS-CoV-2 and variants thereof. Herein, a facile multivalent engineering approach is employed to achieve large synergistic improvements in the neutralizing activity of a SARS-CoV-2 cross-reactive nanobody (VHH-72) initially generated against SARS-CoV. This synergy is epitope specific and is not observed for a second high-affinity nanobody against a non-conserved epitope in the receptor-binding domain. Importantly, a hexavalent VHH-72 nanobody retains binding to spike proteins from multiple highly transmissible SARS-CoV-2 variants (B.1.1.7 and B.1.351) and potently neutralizes them. Multivalent VHH-72 nanobodies also display drug-like biophysical properties, including high stability, high solubility, and low levels of non-specific binding. The unique neutralizing and biophysical properties of VHH-72 multivalent nanobodies make them attractive as therapeutics against SARS-CoV-2 variants.

URL: https://www.ncbi.nlm.nih.gov/pubmed/34514086
DOI: 10.1002/adtp.202100099

Appendix 1: Evidence Search Details

| Filters, Limits & Exclusions: | English only
| September 10, 2021 – September 24, 2021 |
Evidence Search Report: EOC031801v014 ESR

Sources Searched:

- Agency for Clinical Innovation and New South Wales Government
- CanCOVID
- CBC
- CDC
- Center for Infectious Disease Research and Policy (CIDRAP)
- COVID-19 Best Evidence Front Door, University of Michigan
- COVID-19 Immunity Task Force
- COVID-END
- EBM Reviews - ACP Journal Club, Cochrane Central Register of Controlled Trials [CENTRAL], Cochrane Database of Systematic Reviews, Cochrane Clinical Answers, EBM Reviews Full Text
- Embase
- European Centres for Disease Prevention and Control (ECDC)
- Google
- Library and Knowledge Services (NHS, England)
- McMaster Plus
- Medline
- National Collaborating Centre for Infectious Diseases
- National Collaborating Centre for Methods and Tools
- National Health Library & Knowledge Service (Ireland)
- Newfoundland and Labrador Centre for Applied Health Research
- Ontario Science Table
- Prevent Epidemics
- Public Health England
- Public Health Ontario
- Strategy for Patient-Orient Research (SPOR) Evidence Alliance
- Usher Network for COVID-19 Evidence Reviews (UNCOVER), Usher Institute, University of Edinburgh
- Veterans Affairs Evidence Synthesis Program

Librarian(s):

- Lukas Miller, Clinical Librarian, Saskatchewan Health Authority
- Brianna Howell-Spooner, Clinical Librarian, Saskatchewan Health Authority

Appendix 2: Search Strategies

Ovid MEDLINE(R) ALL <1946 to September 23, 2021>

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<tr>
<td>7  6 and (WHO adj2 (alpha or beta or gamma or delta or lambda)).ti,kw. [WHO VOC]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8  ((british or UK or united kingdom or england or english or south african or south africa or brazil or Brazilian or brasil or brasilian or california? or new york or india?) adj2 (strain? or mutation? or variant?)).ti,kw.</td>
<td></td>
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<tr>
<td>9  ((variant? or mutation? or strain? or lineage?) adj2 (virus* or viral* or coronavirus* or COVID-19 or SARS-COV-2 or COVID19 or nCoV* or &quot;of concern&quot; or &quot;of interest&quot;).ti,kw.</td>
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<tr>
<td>10  ((genetic or new or newer or newest or novel) adj1 (variant or mutation? or lineage? or strain?)).ti,kw.</td>
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<tr>
<td>11  (&quot;20I/S:501Y.V1&quot; or &quot;20I/501Y.V1&quot; or &quot;B.1.1.7&quot; or &quot;B117&quot; or &quot;501YV1&quot; or &quot;GR/501Y.V1&quot; or &quot;GRY&quot; or (alpha adj1 variant))).ti,kw. [WHO Alpha]</td>
<td></td>
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</tr>
<tr>
<td>12  (&quot;B.1.351&quot; or &quot;B1351&quot; or &quot;20H/501Y.V2&quot; or &quot;GH/501Y.V2&quot; or &quot;20H/S:501Y.V2&quot; or &quot;501YV2&quot; or (beta adj1 variant?)).ti,kw. [WHO Beta]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13  (&quot;P.1&quot; or &quot;P1&quot; or &quot;20J/501Y.V3&quot; or &quot;501YV3&quot; or &quot;GR/501Y.V3&quot; or &quot;20J/S:501Y.V3&quot; or (gamma adj1 variant?)).ti,kw. [WHO Gamma]</td>
<td></td>
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<tr>
<td>14  (&quot;B.1.617.2&quot; or &quot;B16172&quot; or &quot;G/452R.V3&quot; or &quot;G/452RV3&quot; or &quot;G452RV3&quot; or &quot;G452.R.V3&quot; or &quot;21A/S:478K&quot; or (delta adj1 variant?)).ti,kw. [WHO Delta]</td>
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<td>15  (&quot;lambda adj1 variant?&quot; or &quot;GR/452Q.V1&quot;).ti,kw.</td>
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<tr>
<td>16  7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 [All WHO Variants of Concern]</td>
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<tr>
<td>17  (WHO adj2 (epsilon or zeta or eta or theta or iota or kappa)).ti,kw. [WHO VOI]</td>
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</tr>
<tr>
<td>18  (&quot;B.1.427&quot; or &quot;B.1.429&quot; or &quot;B.1.427/B.1.429&quot; or &quot;GH/452R.V1&quot; or &quot;20C/S.452R&quot; or (epsilon adj1 variant?)).ti,kw. [WHO Epsilon]</td>
<td></td>
<td></td>
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<tr>
<td>19  (&quot;P.2&quot; or &quot;P2&quot; or &quot;GR&quot; or &quot;20B/S.484K&quot; or (zeta adj1 variant?)).ti,kw. [WHO Zeta]</td>
<td></td>
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<tr>
<td>20  (&quot;B.1.525&quot; or &quot;B1525&quot; or &quot;G/484K.V3&quot; or &quot;20A/S:484K&quot; or (eta adj1 variant?)).ti,kw. [WHO Eta]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21  (&quot;P.3&quot; or &quot;P3&quot; or &quot;GR&quot; or &quot;20B/S:265C&quot; or (theta adj1 variant?)).ti,kw. [WHO Theta]</td>
<td></td>
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<tr>
<td>22  (&quot;B.1.526&quot; or &quot;B1526&quot; or &quot;GH&quot; or &quot;20C/S:484K&quot; or (iota adj1 variant?)).ti,kw. [WHO Iota]</td>
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<tr>
<td>23  (&quot;B.1.617.1&quot; or &quot;B16171&quot; or &quot;G/452R.V3&quot; or &quot;21A/S:154K&quot; or (kappa adj1 variant?)).ti,kw.</td>
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<tr>
<td>24  (or/17-23) and (variant? or lineage? or clade? or mutation?).ti,kw. [All WHO Variants of Interest]</td>
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<tr>
<td>25  16 or 24 [All VOC/VOI]</td>
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176256
49904
11234
401
187800
1
1034
7373
17140
317
160
4519
83
5
30141
30490
1
18
5552
3
4308
8684
4
387
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<th>#</th>
<th>Searches</th>
<th>Results</th>
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<tbody>
<tr>
<td>1</td>
<td>(nCoV* or 2019nCoV or 19nCoV or COVID19* or COVID or SARS-COV-2 or SARS-CoV-2 or SARS-CoV2 or SARS coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2 or Severe Acute Respiratory Syndrome Coronavirus 2).ti,kw,sh,hw,ot.</td>
<td>6392</td>
</tr>
<tr>
<td>2</td>
<td>((new or novel or &quot;19&quot; or &quot;2019&quot; or Wuhan or Hubei or China or Chinese) adj3 (coronavirus* or corona virus* or betacoronavirus* or CoV or HCoV)).ti,kw,sh,hw,ot.</td>
<td>2464</td>
</tr>
<tr>
<td>3</td>
<td>(longCOVID* or postCOVID* or postcoronavirus* or postSARS*).ti,kw,sh,hw,ot.</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>((coronavirus* or corona virus* or betacoronavirus*) adj3 (pandemic* or epidemic* or outbreak* or crisis)).ti,kw,sh,hw,ot.</td>
<td>173</td>
</tr>
<tr>
<td>5</td>
<td>((Wuhan or Hubei) adj5 pneumonia).ti,kw,sh,hw,ot.</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>or/1-5</td>
<td>6811</td>
</tr>
<tr>
<td>7</td>
<td>(variant? or lineage? or mutat* or strain?).ti,kw,sh,hw,ot.</td>
<td>17612</td>
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<tr>
<td>8</td>
<td>6 and 7</td>
<td>27</td>
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<tr>
<td>9</td>
<td>limit 8 to yr=&quot;2021 -Current&quot; [Limit not valid in DARE; records were retained]</td>
<td>19</td>
</tr>
</tbody>
</table>

**Other Sources**

COVID AND [variant* OR delta OR alpha OR beta OR lambda OR mu OR gamma]

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