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COVID-19, SARS-CoV-2 and variant

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Abstract: Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms begin 1 - 14 days after exposure to the coronavirus. At least 30% of people who are infected do not develop noticeable symptoms. Of those people who develop symptoms noticeable enough to be classed as patients, around 80% develop mild to moderate symptoms, while 14% develop severe, and 5% suffer critical symptoms. Some people continue to experience a range of effects for months after recovery, and damage to organs has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease. COVID-19 transmits when people breathe in air contaminated by droplets and small airborne particles containing the virus. People remain contagious for up to 20 days, and can spread the virus even if they do not develop symptoms. The standard diagnostic method is by detection of the virus' nucleic acid by real-time reverse transcription polymerase chain reaction (rRT-PCR), transcription-mediated amplification (TMA), or by reverse transcription loop-mediated isothermal amplification (RT-LAMP) from a nasopharyngeal swab. Several COVID-19 vaccines have been approved and distributed in various countries, which have initiated mass vaccination campaigns. Other preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. (https://en.wikipedia.org/wiki/COVID-19). Upto 12/1/2021 in USA, Total Cases are 48,377,531, Total accines Administered are 460,773,508, Total Deaths 778,489 (https://www.cdc.gov/coronavirus/2019-ncov/index.html).
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Key words: COVID-19; SARS-CoV-2; variant; life; research; literature; cell

1. Introduction

Coronavirus disease 2019 (COVID-19) is a contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The first known case was identified in December 2019. The disease has since spread worldwide, leading to an ongoing pandemic. Symptoms of COVID-19 are variable, but often include fever, cough, headache, fatigue, breathing difficulties, and loss of smell and taste. Symptoms begin 1 - 14 days after exposure to the coronavirus. At least 30% of people who are infected do not develop noticeable symptoms. Of those people who develop symptoms noticeable enough to be classed as patients, around 80% develop mild to moderate symptoms, while 14% develop severe, and 5% suffer critical symptoms. Some people continue to experience a range of effects for months after recovery, and damage to organs has been observed. Multi-year studies are underway to further investigate the long-term effects of the disease. COVID-19 transmits when people breathe in air contaminated by droplets and small airborne particles containing the virus. People remain contagious for up to 20 days, and can spread the virus even if they do not develop symptoms. The standard diagnostic method is by detection of the virus' nucleic acid by real-time reverse transcription polymerase chain reaction (rRT-PCR), transcription-mediated amplification (TMA), or by reverse transcription loop-mediated isothermal amplification (RT-LAMP) from a nasopharyngeal swab. Several COVID-19 vaccines have been approved and distributed in various countries, which have initiated mass vaccination campaigns. Other preventive measures include physical or social distancing, quarantining, ventilation of indoor spaces, covering coughs and sneezes, hand washing, and keeping unwashed hands away from the face. The use of face masks or coverings has been recommended in public settings to minimize the risk of transmissions. Management involves the treatment of symptoms, supportive care, isolation, and experimental measures. (https://en.wikipedia.org/wiki/COVID-19).

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There are many variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). Some are believed, or have been stated, to be of particular importance due to their potential for increased transmissibility,[1] increased virulence, or reduced effectiveness of vaccines against them.[2][3] These variants contribute to the continuation of the COVID-19 pandemic.

The emergence of SARS-CoV-2 may have resulted from recombination events between a bat SARS-like coronavirus and a pangolincoronavirus through cross-species transmission.[4]

The earliest available human virus genomes were collected from patients since December 2019, and Chinese researchers compared these early genomes with bat and pangolin coronavirus strains to estimate the ancestral human coronavirus type; the identified ancestral genome type was labeled "S", and its dominant derived type was labeled "L" to reflect the mutant amino acid changes. Independently, Western researchers carried out similar analyses but labeled the ancestral type "A" and the derived type "B". The B-type mutated into further types including into B.1, which is the ancestor of the major global variants of concern, labeled in 2021 by the WHO as alpha, beta, gamma, delta and omicron.[5][6][7]

Early in the pandemic, there were few mutant variant viruses because of the small number of people infected.[8] Also during the early pandemic, S protein mutations in the RBD region interacting with ACE2 were rare.[9]

As time went on, SARS-CoV-2 started evolving to become more transmissible. Notably, the Alpha variant and the Delta variant are both more transmissible than the original virus identified around Wuhan in China.[10]

SARS-CoV-2 variants of concern are able to mutate so that they can continue spreading in the face of rising population immunity while maintaining their replication fitness.[11] Some of the variants of concern show mutations in the RBD of the S-protein.[12]

The following table presents information and relative risk level[13] for variants of concern (VOC). The intervals assume a 95% confidence or credibility level, unless otherwise stated. Currently, all estimates are approximations due to the limited availability of data for studies. For Alpha, Beta, Gamma and Delta, there is no change in test accuracy,[17][23] and neutralising antibody activity is retained by some monoclonal antibodies.[15][24][25] PCR tests continue to detect the Omicron variant.[26]

SARS-CoV-2 variants are classified according to their lineage and component mutations.[11] As of July 2021, no consistent nomenclature was established for it.[60] Many organisations, including governments and news outlets, referred colloquially to concerning variants by the country in which they were first identified.[61][62][63] After months of discussions, the World Health Organization announced Greek-letter names for important strains on 31 May 2021,[64] so they could be easily referred to in a simple, easy to say, and non-stigmatising fashion.[65][66] This decision may have partially been taken because of criticism from governments on using country names to refer to variants of the virus; the WHO mentioned the potential for mentioning country names to cause stigma.[67] WHO skipped two letters of the Greek alphabet, Nu and Xi, as Nu is too easily confounded with "new" and Xi is a "common last name", particularly in China, where it is the name of President Xi Jinping.[68] In the event the WHO used the entirety of the Greek alphabet, the agency considered naming future variants after constellations.[69]

While there are many thousands of variants of SARS-CoV-2,[70]subtypes of the virus can be put into larger groupings such as lineages or clades.[c] Three main, generally used nomenclatures[60] have been proposed:

- As of January 2021, GISAID—referring to SARS-CoV-2 as hCoV-19[50]—had identified eight global clades (S, O, L, V, G, GH, GR, and GV).[71]
- In 2017, Hadfield et al. announced Nextstrain, intended "for real-time tracking of pathogen evolution".[72] Nextstrain has later been used for tracking SARS-CoV-2, identifying 13 major clades[d] (19A–B, 20A–20J and 21A) as of June 2021.[73]
- In 2020, Rambaut et al. of the Phylogenetic Assignment of Named Global Outbreak Lineages (PANGOLIN)[74] software team proposed in an article[49] "a dynamic nomenclature for SARS-CoV-2 lineages that focuses on actively circulating virus lineages and those that spread to new locations";[60] as of August 2021, 1340 lineages had been designated.[75][76]

Each national public health institute may also institute its own nomenclature system for the purposes of tracking specific variants. For example, Public Health England designated each tracked variant by year, month and number in the format [YYYY] [MM]/[NN], prefixing 'VUI' or 'VOC' for a variant under investigation or a variant of concern respectively.[16] This system has now been modified and now uses the format [YY] [MMM]-[NN], where the month is written out using a three-letter code.[16]

Classification of variants

Variants that appear to meet one or more specific criteriaconsidered during the COVID-19 pandemic may be labeled "variants of interest" or "variants under investigation" ('VUI') pending verification and validation of these properties. Once validated, variants of interest /VUI may be renamed "variants of concern" by monitoring organizations,

such as the CDC in the US.[77][78][79] A related category is "variant of high consequence", used by the CDC if there is clear evidence that the effectiveness of prevention or intervention measures for a particular variant is substantially reduced.[80]

Reference sequence

As it is currently not known when the index case or 'patient zero' occurred, the choice of reference sequence for a given study is relatively arbitrary, with different notable research studies' choices varying as follows:

- The earliest sequence, *Wuhan-1*, was collected on 24 December 2019.[81]
- One group (Sudhir Kumar et al.)[81] refers extensively to an NCBI reference genome (GenBankID:NC_045512; GISAID ID: EPI_ISL_402125),[82] this sample was collected on 26 December 2019,[83] although they also used the *WIV04* GISAID reference genome (ID: EPI_ISL_402124),[84] in their analyses.[85]
- According to another source (Zhukova et al.), the sequence *WIV04/2019*, belonging to the GISAID S clade / PANGO A lineage / Nextstrain 19B clade, is thought to most closely reflect the sequence of the original virus infecting humans—known as "sequence zero".[53] *WIV04/2019* was sampled from a symptomatic patient on 30 December 2019 and is widely used (especially by those collaborating with GISAID)[86] as a reference sequence.[53]

The variant first sampled and identified in Wuhan, China is considered by researchers to differ from the proenitor genome by three mutations.[81][87] Subsequently, many distinct lineages of SARS-CoV-2 have evolved.[75]

Notability criteria

Viruses generally acquire mutations over time, giving rise to new variants. When a new variant appears to be growing in a population, it can be labelled as an "emerging variant". In the case of SARS-CoV-2, new lineages often differ from one another by just a few nucleotides.[11]

Some of the potential consequences of emerging variants are the following:[37][88]

- Increased transmissibility
- Increased morbidity
- Increased mortality
- Ability to evade detection by diagnostic tests
- Decreased susceptibility to antiviral drugs (if and when such drugs are available)
- Decreased susceptibility to neutralising antibodies, either therapeutic (e.g., convalescent plasma or monoclonal antibodies) or in laboratory experiments
- Ability to evade natural immunity (e.g., causing reinfections)
- Ability to infect vaccinated individuals
- Increased risk of particular conditions such as multisystem inflammatory syndrome or long COVID.
- Increased affinity for particular demographic or clinical groups, such as children or immunocompromised individuals.

Variants that appear to meet one or more of these criteria may be labelled "variants under investigation" or "variants of interest" pending verification and validation of these properties. The primary characteristic of a variant of interest is that it shows evidence that demonstrates it is the cause of an increased proportion of cases or unique outbreak clusters; however, it must also have limited prevalence or expansion at national levels, or the classification would be elevated to a "variant of concern".[16][78] If there is clear evidence that the effectiveness of prevention or intervention measures for a particular variant is substantially reduced, that variant is termed a "variant of high consequence".[15]

Variants of concern (WHO)

Listed below are the Variants of Concern (VOC) recognised by the World Health Organization as of June 2021.[14] Other organisations such as the CDC in the United States have at times used a slightly different list. As of July 2021, their list matched that of the WHO.[15]

First detected in October 2020 during the COVID-19 pandemic in the United Kingdom from a sample taken the previous month in Kent,[89] lineage B.1.1.7,[90] labelled Alpha variant by the WHO, was previously known as the first Variant Under Investigation in December 2020 (VUI – 202012/01)[91] and later notated as VOC-202012/01.[16] It is also known as 20I (V1),[27] 20I/501Y.V1[92] (formerly 20B/501Y.V1),[37][93][94] or 501Y.V1.[24] From October to December 2020, its prevalence doubled every 6.5 days, the presumed generational interval.[95][96] It is correlated with a significant increase in the rate of COVID-19 infection in United Kingdom, associated partly with the N501Y mutation.[95] There was some evidence that this variant had 40–80% increased transmissibility (with most estimates lying around the middle to higher end of this range),[97][98] and early analyses suggested an increase in lethality,[99][100] though later work found no evidence of increased virulence.[101] As of May 2021, the Alpha variant had been detected in some 120 countries.[102]

B.1.1.7 with E484K

Variant of Concern 21FEB-02 (previously written as VOC-202102/02), described by Public Health England (PHE) as "B.1.1.7 with E484K"[16] is of the same lineage in the Pango nomenclature system, but has an additional E484K mutation. As of 17 March 2021, there were 39 confirmed cases of VOC-21FEB-02 in the UK.[16] On 4 March 2021, scientists reported B.1.1.7 with E484K mutations in the state of Oregon. In 13 test samples analysed, one had this combination, which appeared to have arisen

spontaneously and locally, rather than being imported.[103][104][105] Other names for this variant include B.1.1.7+E484K[106] and B.1.1.7 Lineage with S:E484K.[107]

Beta (lineage B.1.351)

On 18 December 2020, the 501.V2 variant, also known as 501.V2, 20H (V2),[27] 20H/501Y.V2[92] (formerly 20C/501Y.V2), 501Y.V2,[108] VOC-20DEC-02 (formerly VOC-202012/02), or lineage B.1.351,[37] was first detected in South Africa and reported by the country's health department.[109] It has been labelled as Beta variant by WHO. Researchers and officials reported that the prevalence of the variant was higher among young people with no underlying health conditions, and by comparison with other variants it is more frequently resulting in serious illness in those cases.[110][111] The South African health department also indicated that the variant may be driving the second wave of the COVID-19 epidemic in the country due to the variant spreading at a more rapid pace than other earlier variants of the virus.[109][110]

Scientists noted that the variant contains several mutations that allow it to attach more easily to human cells because of the following three mutations in the receptor-binding domain (RBD) in the spike glycoprotein of the virus: N501Y,[109][112] K417N, and E484K.[113][114] The N501Y mutation has also been detected in the United Kingdom.[109][115]

Gamma (lineage P.1)

The Gamma variant or lineage P.1, termed Variant of Concern 21JAN-02[16] (formerly VOC-202101/02) by Public Health England,[16] 20J (V3)[27] or 20J/501Y.V3[92] by Nextstrain, or just 501Y.V3,[24] was detected in Tokyo on 6 January 2021 by the National Institute of Infectious Diseases (NIID). It has been labelled as Gamma variant by WHO. The new variant was first identified in four people who arrived in Tokyo having travelled from the Brazilian Amazonas state on 2 January 2021.[116] On 12 January 2021, the Brazil-UK CADDE Centre confirmed 13 local cases of the new Gamma variant in the Amazon rainforest.[117] This variant of SARS-CoV-2 has been named lineage P.1 (although it is a descendant of B.1.1.28, the name B.1.1.28.1[17][118] is not permitted and thus the resultant name is P.1), and has 17 unique amino acid changes, 10 of which in its spike protein, including the three concerning mutations: N501Y, E484K and K417T.[117][118][119][120]:

The N501Y and E484K mutations favour the formation of a stable RBD-hACE2 complex, thus, enhancing the binding affinity of RBD to hACE2. However, the K417T mutation disfavours complex formation between RBD and hACE2, which has been demonstrated to reduce the binding affinity.[1]

The new variant was absent in samples collected from March to November 2020 in Manaus, Amazonas state, but it was detected for the same city in 42% of the samples from 15 to 23 December 2020, followed by 52.2% during 15–31 December and 85.4% during 1–9 January 2021.[117] A study found that infections by Gamma can produce nearly ten times more viral load compared to persons infected by one of the other lineages identified in Brazil (B.1.1.28 or B.1.195). Gamma also showed 2.2 times higher transmissibility with the same ability to infect both adults and older persons, suggesting P.1 and P.1-like lineages are more successful at infecting younger humans irrespective of sex.[121]

A study of samples collected in Manaus between November 2020 and January 2021, indicated that the Gamma variant is 1.4–2.2 times more transmissible and was shown to be capable of evading 25–61% of inherited immunity from previous coronavirus diseases, leading to the possibility of reinfection after recovery from an earlier COVID-19 infection. As for the fatality ratio, infections by Gamma were also found to be 10–80% more lethal.[122][123][124]

A study found that people fully vaccinated with Pfizer or Moderna have significantly decreased neutralisation effect against Gamma, although the actual impact on the course of the disease is uncertain. A pre-print study by the Oswaldo Cruz Foundation published in early April found that the real-world performance of people with the initial dose of the Sinovac's Coronavac Vaccine had approximately 50% efficacy rate. They expected the efficacy to be higher after the 2nd dose. As of July 2021, the study is ongoing.[125]

Preliminary data from two studies indicate that the Oxford–AstraZeneca vaccine is effective against the Gamma variant, although the exact level of efficacy has not yet been released.[126][127] Preliminary data from a study conducted by Instituto Butantan suggest that CoronaVacis effective against the Gamma variant as well, and as of July 2021 has yet to be expanded to obtain definitive data.[128]

Delta (lineage B.1.617.2)

The Delta variant, also known as B.1.617.2, G/452R.V3, 21A[27] or 21A/S:478K,[92] is a globally dominant variant that spread to at least 185 countries.[129] It was first discovered in India. Descendant of lineage B.1.617, which also includes the Kappa variant under investigation, it was first discovered in October 2020 and has since spread internationally.[130][131][132][133][134] On 6 May 2021, British scientists declared B.1.617.2 (which notably lacks mutation at E484Q) as a "variant of concern", labelling it VOC-21APR-02, after they flagged evidence that it spreads more quickly than the original version of the virus and could spread quicker or as quickly as Alpha.[135][18][136][137] It carries L452R and P681R mutations in Spike;[29] unlike Kappa it carries T478K but not E484Q.

On 3 June 2021, Public Health England reported that twelve of the 42 deaths from the Delta variant in England were among the fully vaccinated,

and that it was spreading almost twice as fast as the Alpha variant.[138] Also on 11 June, Foothills Medical Centre in Calgary, Canada reported that half of their 22 cases of the Delta variant occurred among the fully vaccinated.[139]

In June 2021, reports began to appear of a variant of Delta with the K417N mutation.[140] The mutation, also present in the Beta and Gamma variants, raised concerns about the possibility of reduced effectiveness of vaccines and antibody treatments and increased risk of reinfection.[141] The variant, called "Delta with K417N" by Public Health England, includes two clades corresponding to the Pango lineages AY.1 and AY.2.[142] It has been nicknamed "Delta plus"[143] from "Delta plus K417N".[144] The name of the mutation, K417N, refers to an exchange whereby lysine (K) is replaced by asparagine (N) at position 417.[145] On 22 June, India's Ministry of Health and Family Welfare declared the "Delta plus" variant of COVID-19 a Variant of Concern after 22 cases of the variant were reported in India.[146] After the announcement, leading virologists said there was insufficient data to support labelling the variant as a distinct variant of concern, pointing to the small number of patients studied.[147] In the UK in July 2021, AY.4.2 was identified. Alongside those previously mentioned it also gained the nickname 'Delta Plus', on the strength of its extra mutations, Y145H and A222V. These are not unique to it, but distinguish it from the original Delta variant.[148]

Omicron (lineage B.1.1.529)

The Omicron variant, known as lineage B.1.1.529, was declared a variant of concern by the World Health Organization on 26 November 2021.[149]

The variant has a large number of mutations, of which some are concerning. The number of cases in the B.1.1.529 lineage is increasing in all areas of South Africa. Some evidence shows that this variant has an increased risk of reinfection. Studies are underway to evaluate the exact impact on transmissibility, mortality, and other factors.[150]

Variants of interest (WHO)

Listed below are the Variants of Interest (VOI) which are, as of August 2021, recognised by the World Health Organization.[14] Other organisations such as the CDC in the United States may at times use a slightly different list.[15]

Lambda (lineage C.37)

The Lambda variant, also known as lineage C.37, was first detected in Peru in August 2020 and was designated by the WHO as a variant of interest on 14 June 2021.[14] It spread to at least 30 countries[151] around the world and, as of July 2021, it is unknown whether it is more infectious and resistant to vaccines than other strains.[152][153]

Mu (lineage B.1.621)

The Mu variant, also known as lineage B.1.621, was first detected in Colombia in January 2021 and was designated by the WHO as a variant of interest on 30 August 2021.[14] There have been outbreaks in South America and Europe.[154][155]

Former variants of interest

Epsilon (lineages B.1.429, B.1.427, CAL.20C)

The Epsilon variant or lineage B.1.429, also known as CAL.20C[156] or CA VUI1,[157] 21C[27] or 20C/S:452R,[92] is defined by five distinct mutations (I4205V and D1183Y in the ORF1ab gene, and S13I, W152C, L452R in the spike protein's S-gene), of which the L452R (previously also detected in other unrelated lineages) was of particular concern.[55][158] From 17 March to 29 June 2021, the CDC listed B.1.429 and the related B.1.427 as "variants of concern".[29][159][160][161] As of July 2021, Epsilon is no longer considered a variant of interest by the WHO,[14] as it was overtaken by Alpha.[162]

From September 2020 to January 2021, it was 19% to 24% more transmissible than earlier variants in California. Neutralisation against it by antibodies from natural infections and vaccinations was moderately reduced,[163] but it remained detectable in most diagnostic tests.[164]

Epsilon (CAL.20C) was first observed in July 2020 by researchers at the Cedars-Sinai Medical Center, California, in one of 1,230 virus samples collected in Los Angeles County since the start of the COVID-19 epidemic.[165] It was not detected again until September when it reappeared among samples in California, but numbers remained very low until November.[166][167] In November 2020, the Epsilon variant accounted for 36 per cent of samples collected at Cedars-Sinai Medical Center, and by January 2021, the Epsilon variant accounted for 50 per cent of samples.[158] In a joint press release by University of California, San Francisco, California Department of Public Health, and Santa Clara County Public Health Department,[168] the variant was also detected in multiple counties in Northern California. From November to December 2020, the frequency of the variant in sequenced cases from Northern California rose from 3% to 25%.[169] In a preprint, CAL.20C is described as belonging to clade 20C and contributing approximately 36% of samples, while an emerging variant from the 20G clade accounts for some 24% of the samples in a study focused on Southern California. Note, however, that in the US as a whole, the 20G clade predominates, as of January 2021.[55] Following the increasing numbers of Epsilon in California, the variant has been detected at varying frequencies in most US states. Small numbers have been detected in other countries in North America, and in Europe, Asia and Australia.[166][167] After an initial increase, its frequency rapidly dropped from February 2021 as it was being outcompeted by the more transmissible Alpha. In April, Epsilon remained relatively frequent in parts of northern California, but it had virtually

disappeared from the south of the state and had never been able to establish a foothold elsewhere; only 3.2% of all cases in the United States were Epsilon, whereas more than two-thirds were Alpha.[162]

Zeta (lineage P.2)

Zeta variant or lineage P.2, a sub-lineage of B.1.1.28 like Gamma (P.1), was first detected in circulation in the state of Rio de Janeiro; it harbours the E484K mutation, but not the N501Y and K417T mutations.[120] It evolved independently in Rio de Janeiro without being directly related to the Gamma variant from Manaus.[117] Though previously Zeta was labeled a variant of interest, as of July 2021, it is no longer considered as such by the WHO.[14]

Eta (lineage B.1.525)

The Eta variant or lineage B.1.525, also called VUI-21FEB-03[16] (previously VUI-202102/03) by Public Health England (PHE) and formerly known as UK1188,[16] 21D[27] or 20A/S:484K,[92] does not carry the same N501Y mutation found in Alpha, Beta and Gamma, but carries the same E484K-mutation as found in the Gamma, Zeta, and Beta variants, and also carries the same ΔH69/ΔV70 deletion (a deletion of the amino acids histidine and valine in positions 69 and 70) as found in Alpha, N439K variant (B.1.141 and B.1.258) and Y453F variant (Cluster 5).[170] Eta differs from all other variants by having both the E484K-mutation and a new F888L mutation (a substitution of phenylalanine (F) with leucine (L) in the S2 domain of the spike protein). As of 5 March 2021, it had been detected in 23 countries.[171][172][173] It has also been reported in Mayotte, the overseas department/region of France.[171] The first cases were detected in December 2020 in the UK and Nigeria, and as of 15 February 2021, it had occurred in the highest frequency among samples in the latter country.[173] As of 24 February 56 cases were found in the UK.[16] Denmark, which sequences all its COVID-19 cases, found 113 cases of this variant from 14 January to 21 February 2021, of which seven were directly related to foreign travel to Nigeria.[172]

As of July 2021, UK experts are studying it to ascertain how much of a risk it could be. It is currently regarded as a "variant under investigation", but pending further study, it may become a "variant of concern". Ravi Gupta, from the University of Cambridge said in a BBCinterview that lineage B.1.525 appeared to have "significant mutations" already seen in some of the other newer variants, which means their likely effect is to some extent more predictable.[174]

Theta (lineage P.3)

On 18 February 2021, the Department of Health of the Philippines confirmed the detection of two mutations of COVID-19 in Central Visayas after samples from patients were sent to undergo genome sequencing. The mutations were later named as E484K and N501Y, which were detected in 37 out of 50 samples, with both mutations co-occurrent in 29 out of these.[175]

On 13 March, the Department of Health confirmed the mutations constitutes a variant which was designated as lineage P.3.[176] On the same day, it also confirmed the first COVID-19 case caused by the Gamma variant in the country. The Philippines had 98 cases of the Theta variant on 13 March.[177] On 12 March it was announced that Theta had also been detected in Japan.[178][179] On 17 March, the United Kingdom confirmed its first two cases,[180] where PHE termed it VUI-21MAR-02.[16] On 30 April 2021, Malaysia detected 8 cases of the Theta variant in Sarawak.[181]

As of July 2021, Theta is no longer considered a variant of interest by the WHO.[14]

Iota (lineage B.1.526)

In November 2020, a mutant variant was discovered in New York City, which was named lineage B.1.526.[182] As of 11 April 2021, the variant has been detected in at least 48 U.S. states and 18 countries. In a pattern mirroring Epsilon, Iota was initially able to reach relatively high levels in some states, but by May 2021 it was outcompeted by the more transmissible Delta and Alpha.[162]

Kappa (lineage B.1.617.1)

The Kappa variant[14] is one of the three sublineages of lineage B.1.617. It is also known as lineage B.1.617.1, 21B[27] or 21A/S:154K,[92]and was first detected in India in December 2020.[183] By the end of March 2021, Kappa accounted for more than half of the sequences being submitted from India.[184] On 1 April 2021, it was designated a variant under investigation (VUI-21APR-01) by Public Health England.[28] It has the notable mutations L452R, E484Q, P681R.[185]

Alerts for further monitoring (WHO)

Defined as variants with genetic changes suspected to affect virus characteristics and some indication of posing a future risk, but with unclear evidence of phenotypic or epidemiological impact, requiring enhanced monitoring and repeat assessment after new evidence.[14]Some former variants of interest are monitored as well.

Other notable variants

Lineage B.1.1.207 was first sequenced in August 2020 in Nigeria;[209] the implications for transmission and virulence are unclear but it has been listed as an emerging variant by the US Centers for Disease Control.[37] Sequenced by the African Centre of Excellence for Genomics of Infectious Diseases in Nigeria, this variant has a P681H mutation, shared in common with the Alpha variant. It shares no other mutations with the Alpha variant and as of late December 2020 this variant accounts for around 1% of viral genomes sequenced in Nigeria, though this may rise.[209] As of May 2021, lineage B.1.1.207 has been detected in 10 countries.[210]

Lineage B.1.1.317, while not considered a variant of concern, is noteworthy in that Queensland

Health forced 2 people undertaking hotel quarantine in Brisbane, Australia to undergo an additional 5 days' quarantine on top of the mandatory 14 days after it was confirmed they were infected with this variant.[211]

Lineage B.1.616, being identified in Western France in early January 2021 and designated by WHO as "Variant under investigation" in March 2021, was reported to be difficult to detect from nasopharyngeal swab sampling method of coronavirus detection, and detection of the virus need to rely on samples from lower respiratory tract.

Lineage B.1.618 was first isolated in October 2020. It has the E484K mutation in common with several other variants, and showed significant spread in April 2021 in West Bengal, India.[212][213] As of 23 April 2021, the PANGOLIN database showed 135 sequences detected in India, with single-figure numbers in each of eight other countries worldwide.[214]

Notable missense mutations

There have been a number of missense mutations observed of SARS-CoV-2.

del 69-70

The name of the mutation, del 69-70, or 69-70 del, or other similar notations, refers to the deletion of amino acid at position 69 to 70. The mutation is found in the Alpha variant, and could lead to "spike gene target failure" and result in false negative result in PCR virus test.[215]

RSYLTPGD246-253N

Otherwise referred to as del 246-252, or other various similar expression, refer to the deletion of amino acid from the position of 246 to 252, in the N-terminal domain of spike protein, accompanied with a replacement of the aspartic acid (D) at the position 253 for asparagine(N).[216][217]

The 7 amino acid deletion mutation is currently described as unique in the Lambda variant, and have been attributed to as one of the cause of the strain's increased capability to escape from neutralizing antibodies according to preprint paper.[218]

N440K

The name of the mutation, N440K, refers to an exchange whereby the asparagine (N) is replaced by lysine (K) at position 440.[219]

This mutation has been observed in cell cultures to be 10 times more infective compared to the previously widespread A2a strain (A97V substitution in RdRP sequence) and 1000 times more in the lesser widespread A3i strain (D614G substitution in Spike and a and P323L substitution in RdRP).[220] It was involved in rapid surges of Covid cases in India in May 2021.[221] India has the largest proportion of N440K mutated variants followed by the US and Germany.[222]

G446V

The name of the mutation, G446V, refers to an exchange whereby the glycine (G) is replaced by valine (V) at position 446.[219]

The mutation, identified in Japan among inbound travelers starting from May, and among 33 samples from individuals related to 2020 Tokyo Olympic Games and 2020 Tokyo Paralympic Games, are said to be possible to impact affinity of multiple monoclonal antibody, although its clinical impact against the use of antibody medicine is still yet to be known.[223]

L452R

The name of the mutation, L452R, refers to an exchange whereby the leucine (L) is replaced by arginine (R) at position 452.[219]

L452R is found in both the Delta and Kappa variants which first circulated in India, but have since spread around the world. L452R is a relevant mutation in this strain that enhances ACE2 receptor binding ability and can reduce vaccine-stimulated antibodies from attaching to this altered spike protein.

L452R, some studies show, could even make the coronavirus resistant to T cells, that are class of cells necessary to target and destroy virus-infected cells. They are different from antibodies that are useful in blocking coronavirus particles and preventing it from proliferating.[131]

Y453F

The name of the mutation, Y453F, refers to an exchange whereby the tyrosine (Y) is replaced by phenylalanine (F) at position 453. The mutation have been found potentially linked to the spread of SARS-CoV-2 among minks in the Netherlands in 2020.[224]

S477G/N

A highly flexible region in the receptor binding domain (RBD) of SARS-CoV-2, starting from residue 475 and continuing up to residue 485, was identified using bioinformatics and statistical methods in several studies. The University of Graz[225] and the Biotech Company Innophore[226] have shown in a recent publication that structurally, the position S477 shows the highest flexibility among them.[227]

At the same time, S477 is hitherto the most frequently exchanged amino acid residue in the RBDs of SARS-CoV-2 mutants. By using molecular dynamics simulations of RBD during the binding process to hACE2, it has been shown that both S477G and S477N strengthen the binding of the SARS-COV-2 spike with the hACE2 receptor. The vaccine developer BioNTech[228] referenced this amino acid exchange as relevant regarding future vaccine design in a preprint published in February 2021.[229]

E484Q

The name of the mutation, E484Q, refers to an exchange whereby the glutamic acid (E) is replaced by glutamine (Q) at position 484.[219]

The Kappa variant circulating in India has E484Q. These variants were initially (but misleadingly) referred to as a "double mutant".[230] E484Q may enhance ACE2 receptor binding ability, and may reduce vaccine-stimulated antibodies' ability to attach to this altered spike protein.[131]

E484K

The name of the mutation, E484K, refers to an exchange whereby the glutamic acid (E) is replaced by lysine (K) at position 484.[219] It is nicknamed "Eeek".[231]

E484K has been reported to be an escape mutation (i.e., a mutation that improves a virus's ability to evade the host's immune system[232][233]) from at least one form of monoclonal antibody against SARS-CoV-2, indicating there may be a "possible change in antigenicity".[234] The Gamma variant (lineage P.1),[117] the Zeta variant (lineage P.2, also known as lineage B.1.1.28.2)[120] and the Beta variant (501.V2) exhibit this mutation.[234] A limited number of lineage B.1.1.7 genomes with E484K mutation have also been detected.[40] Monoclonal and serum-derived antibodies are reported to be from 10 to 60 times less effective in neutralising virus bearing the E484K mutation.[235][236] On 2 February 2021, medical scientists in the United Kingdom reported the detection of E484K in 11 samples (out of 214,000 samples), a mutation that may compromise current vaccine effectiveness.[237][238]

F490S

F490S denotes a change from phenylalanine (F) to serine (S) in amino-acid position 490.[239]

It is one of the mutation found in Lambda, and have been associated with reduced susceptibility to antibody generated by those who were infected with other strains, meaning antibody treatment against people infected with strains carrying such mutation would be less effective.[240]

N501Y

N501Y denotes a change from asparagine (N) to tyrosine (Y) in amino-acid position 501.[241] N501Y has been nicknamed "Nelly".[231]

This change is believed by PHE to increase binding affinity because of its position inside the spike glycoprotein's receptor-binding domain, which binds ACE2 in human cells; data also support the hypothesis of increased binding affinity from this change.[38] Molecular interaction modelling and the free energy of binding calculations has demonstrated that the mutation N501Y has the highest binding affinity in variants of concern RBD to hACE2.[1] Variants with N501Y include Gamma,[234][117] Alpha (VOC 20DEC-01), Beta, and COH.20G/501Y (identified in Columbus, Ohio).[1] This last became the dominant form of the virus in Columbus in late December 2020 and January and appears to have evolved independently of other variants.[242][243]

N501S

N501S denotes a change from asparagine (N) to serine (S) in amino-acid position 501.[244]

As of September 2021, there are 8 cases of patients around the world infected with Delta variant which feature this N501S mutation. As it is considered a mutation similar to N501Y, it is suspected to have similar characteristics as N501Y mutation, which is believed to increase the infectivity of the virus, however the exact effect is unknown yet.[245]

D614G

D614G is a missense mutation that affects the spike protein of SARS-CoV-2. From early appearances in Eastern China early in 2020, the frequency of this mutation in the global viral population has increased during the pandemic.[247] G (glycine) has replaced D (aspartic acid) at position 614 in many countries, especially in Europe though more slowly in China and the rest of East Asia, supporting the hypothesis that G increases the transmission rate, which is consistent with higher viral titres and infectivity in vitro.[53] Researchers with the PANGOLIN tool nicknamed this mutation "Doug".[231]

In July 2020, it was reported that the more infectious D614G SARS-CoV-2 variant had become the dominant form in the pandemic.[248][249][250][251] PHE confirmed that the D614G mutation had a "moderate effect on transmissibility" and was being tracked internationally.[241][252]

The global prevalence of D614G correlates with the prevalence of loss of smell (anosmia) as a symptom of COVID-19, possibly mediated by higher binding of the RBD to the ACE2 receptor or higher protein stability and hence higher infectivity of the olfactory epithelium.[253]

Variants containing the D614G mutation are found in the G clade by GISAID[53] and the B.1 clade by the PANGOLIN tool.[53]

Q677P/H

The name of the mutation, Q677P/H, refers to an exchange whereby the glutamine (Q) is replaced by proline (P) or histidine (H) at position 677.[219] There are several sub-lineages containing the Q677P mutation; six of these, which also contain various different combinations of other mutations, are referred to by names of birds. One of the earlier ones noticed for example is known as "Pelican," while the most common of these as of early 2021 was provisionally named "Robin 1."[254]

The mutation has been reported in multiple lineages circulating inside the United States as of late 2020 and also some lineages outside the country. 'Pelican' was first detected in Oregon, and as of early 2021 'Robin 1' was found often in the Midwestern United States, while another Q667H sub-lineage, 'Robin 2', was found mostly in the southeastern United States.[254] The frequency of such mutation being recorded has increased from late 2020 to early 2021.[255]

P681H

The name of the mutation, P681H, refers to an exchange whereby the proline (P) is replaced by histidine (H) at position 681.[246]

In January 2021, scientists reported in a preprint that the mutation P681H, a characteristic feature of the Alpha variant and lineage B.1.1.207 (identified in Nigeria), is showing a significant exponential increase in worldwide frequency, thus following a trend to be expected in the lower limb of the logistics curve. This may be compared with the trend of the now globally prevalent D614G.[246][256]

P681R

The name of the mutation, P681R, refers to an exchange whereby the proline (P) is replaced by arginine (R) at position 681.[219]

Indian SARS-CoV-2 Genomics Consortium (INSACOG) found that other than the two mutations E484Q and L452R, there is also a third significant mutation, P681R in lineage B.1.617. All three concerning mutations are on the spike protein, the operative part of the coronavirus that binds to receptor cells of the body.[131]

A701V

According to initial media reports, the Malaysian Ministry of Health announced on 23 December 2020 that it had discovered a mutation in the SARS-CoV-2 genome which they designated as A701B(sic), among 60 samples collected from the Benteng Lahad Datu cluster in Sabah. The mutation was characterised as being similar to the one found recently at that time in South Africa, Australia, and the Netherlands, although it was uncertain if this mutation was more infectious or aggressive than before.[257] The provincial government of Sulu in neighbouring Philippines temporarily suspended travel to Sabah in response to the discovery of 'A701B' due to uncertainty over the nature of the mutation.[258]

On 25 December 2020, the Malaysian Ministry of Health described a mutation A701V as circulating and present in 85% of cases (D614G was present in 100% of cases) in Malaysia.[259][260] These reports also referred to samples collected from the Benteng Lahad Datu cluster.[259][260] The text of the announcement was mirrored verbatim on the Facebook page of Noor Hisham Abdullah, Malay Director-General of Health, who was quoted in some of the news articles.[260]

The A701V mutation has the amino acid alanine (A) substituted by valine (V) at position 701 in the spike protein. Globally, South Africa, Australia, Netherlands and England also reported A701V at about the same time as Malaysia.[259] In GISAID, the prevalence of this mutation is found to be about 0.18%. of cases.[259]

On 14 April 2021, the Malaysian Ministry of Health reported that the third wave, which had started in Sabah, has involved the introduction of variants with D614G and A701V mutations.[261]

Differential vaccine effectiveness

Data and methods

Modern DNA sequencing, where available, may permit rapid detection (sometimes known as 'real-time detection') of genetic variants that appear in pathogens during disease outbreaks.[262] Through use of phylogenetic tree visualisation software, records of genome sequences can be clustered into groups of identical genomes all containing the same set of mutations. Each group represents a 'variant', 'clade', or 'lineage', and comparison of the sequences allows the evolutionary path of a virus to be deduced. For SARS-CoV-2, over 330,000 viral genomic sequences have been generated by molecular epidemiology studies across the world.[263]

New variant detection and assessment

On 26 January 2021, the British government said it would share its genomic sequencing capabilities with other countries in order to increase the genomic sequencing rate and trace new variants, and announced a "New Variant Assessment Platform".[264] As of January 2021, more than half of all genomic sequencing of COVID-19 was carried out in the UK.[265]

Testing

On 11 June 2021, Public Health England introduced a rules-based decision algorithm to distinguish between variants in RT-PCR results. The system is reviewed weekly. In particular, the rules require that specific mutations in the S gene[266] be present for each variant (P681R for Delta, K417N for Beta and K417T for Gamma); the confirmation status of the test is dependent also on other requirements for the detection or non-detection of presence or absence of these mutations and the mutations N501Y and E484K. Where the result is 'undetermined', two categories are possible: with or without E484K..[267]

Incubation theory for multiple mutated variants

Researchers have suggested that multiple mutations can arise in the course of the persistent infection of an immunocompromised patient, particularly when the virus develops escape mutations under the selection pressure of antibody or convalescent plasma treatment,[268][269] with the same deletions in surface antigens repeatedly recurring in different patients.[270]

Cross-species transmission

Cluster 5

In early November 2020, Cluster 5, also referred to as ΔFVI-spike by the Danish State Serum Institute (SSI),[271] was discovered in Northern Jutland, Denmark, and is believed to have been spread from minks to humans via mink farms. On 4 November 2020, it was announced that the mink population in Denmark would be culled to prevent the possible spread of this mutation and reduce the risk of new mutations happening. A lockdown and travel restrictions were introduced in seven

municipalities of Northern Jutland to prevent the mutation from spreading, which could compromise national or international responses to the COVID-19 pandemic. By 5 November 2020, some 214 mink-related human cases had been detected.[272]

The WHO has stated that cluster 5 has a "moderately decreased sensitivity to neutralising antibodies".[273] SSI warned that the mutation could reduce the effect of COVID-19 vaccines under development, although it was unlikely to render them useless. Following the lockdown and mass-testing, SSI announced on 19 November 2020 that cluster 5 in all probability had become extinct.[274] As of 1 February 2021, authors to a peer-reviewed paper, all of whom were from the SSI, assessed that cluster 5 was not in circulation in the human population.[275]

There is a risk that COVID-19 could transfer from humans to other animal populations and could combine with other animal viruses to create yet more variants that are dangerous to humans.[276]

Omicron is a variant of SARS-CoV-2, the virus that causes COVID-19. The variant was first reported to the World Health Organization (WHO) from South Africa on 11/24/2021. On 11/26/2021, the WHO designated it as a variant of concern and named it after omicron, the `5th letter in the Greek alphabet. The variant has an unusually large number of mutations, several of which are novel and several of which affect the spike protein used for most vaccine targeting at the time of its discovery. This level of variation has led to concerns regarding transmissibility, immune system evasion, and vaccine resistance. As a result, the variant was quickly designated as being "of concern", and travel restrictions were introduced by several countries to limit or slow its international spread. The variant has a large number of mutations, of which some are concerning. 32 mutations affect the spike protein, the main antigenic target of antibodies generated by infections and of many vaccines widely administered. Many of those mutations had not been observed in other strains. The variant is characterised by 30 amino acid changes, 3 small deletions and 1 small insertion in the spike protein compared with the original virus, of which 15 are located in the receptor binding domain (residues 319-541). It also carries a number of changes and deletions in other genomic regions. Additionally, the variant has three mutations at the furin cleavage site. The furin cleavage site increases SARS-CoV-2 infectivity. The mutations by genomic region are the following. Spike protein: A67V, Δ69-70, T95I, G142D, Δ143-145, Δ211, L212I, ins214EPE, G339D, S371L, S373P, S375F, K417N, N440K, G446S, S477N, T478K, E484A, Q493R, G496S, Q498R, N501Y, Y505H, T547K, D614G, H655Y, N679K, P681H, N764K, D796Y, N856K, Q954H, N969K, L981F (Half (15) of these 30 changes are located in the receptor binding domain-RBD (residues 319-541). ORF1ab: nsp3: K38R, V1069I, Δ1265, L1266I, A1892T; nsp4: T492I; nsp5: P132H; nsp6: Δ105-107, A189V; nsp12: P323L; nsp14: I42V. Envelope protein: T9I. Membrane protein: D3G, Q19E, A63T. Nucleocapsid protein: P13L, Δ31-33, R203K, G204R. (https://en.wikipedia.org/wiki/SARS-CoV-2_Omicron_variant).

The following introduces recent reports as references in the related studies.

Abdel Sater, F., et al. (2021). "A rapid and low-cost protocol for the detection of B.1.1.7 lineage of SARS-CoV-2 by using SYBR Green-based RT-qPCR." Mol Biol Rep **48**(11): 7243-7249.

BACKGROUND: The new SARS-CoV-2 variant VOC (202012/01), identified recently in the United Kingdom (UK), exhibits a higher transmissibility rate compared to other variants, and a reproductive number 0.4 higher. In the UK, scientists were able to identify the increase of this new variant through the rise of false negative results for the spike (S) target using a three-target RT-PCR assay (TaqPath kit). METHODS: To control and study the current coronavirus pandemic, it is important to develop a rapid and low-cost molecular test to identify the aforementioned variant. In this work, we designed primer sets specific to the VOC (202012/01) to be used by SYBR Green-based RT-PCR. These primers were specifically designed to confirm the deletion mutations Delta69/Delta70 in the spike and the Delta106/Delta107/Delta108 in the NSP6 gene. We studied 20 samples from positive patients, detected by using the Applied Biosystems TaqPath RT-PCR COVID-19 kit (Thermo Fisher Scientific, Waltham, USA) that included the ORF1ab, S, and N gene targets. 16 samples displayed an S-negative profile (negative for S target and positive for N and ORF1ab targets) and four samples with S, N and ORF1ab positive profile. RESULTS: Our results emphasized that all S-negative samples harbored the mutations Delta69/Delta70 and Delta106/Delta107/Delta108. This protocol could be used as a second test to confirm the diagnosis in patients who were already positive to COVID-19 but showed false negative results for S-gene. CONCLUSIONS: This technique may allow to identify patients carrying the VOC (202012/01) or a closely related variant, in case of shortage in sequencing.

Ai, Y., et al. (2021). "Wastewater SARS-CoV-2 monitoring as a community-level COVID-19 trend tracker and variants in Ohio, United States." Sci Total Environ **801**: 149757.

The global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has resulted in more than 129 million confirm cases. Many health authorities around the world have implemented wastewater-based epidemiology as a rapid and complementary tool for the COVID-19 surveillance system and more recently for variants of

concern emergence tracking. In this study, three SARS-CoV-2 target genes (N1 and N2 gene regions, and E gene) were quantified from wastewater influent samples (n = 250) obtained from the capital city and 7 other cities in various size in central Ohio from July 2020 to January 2021. To determine human-specific fecal strength in wastewater samples more accurately, two human fecal viruses (PMMoV and crAssphage) were quantified to normalize the SARS-CoV-2 gene concentrations in wastewater. To estimate the trend of new case numbers from SARS-CoV-2 gene levels, different statistical models were built and evaluated. From the longitudinal data, SARS-CoV-2 gene concentrations in wastewater strongly correlated with daily new confirmed COVID-19 cases (average Spearman's $r = 0.70$, $p < 0.05$), with the N2 gene region being the best predictor of the trend of confirmed cases. Moreover, average daily case numbers can help reduce the noise and variation from the clinical data. Among the models tested, the quadratic polynomial model performed best in correlating and predicting COVID-19 cases from the wastewater surveillance data, which can be used to track the effectiveness of vaccination in the later stage of the pandemic. Interestingly, neither of the normalization methods using PMMoV or crAssphage significantly enhanced the correlation with new case numbers, nor improved the estimation models. Viral sequencing showed that shifts in strain-defining variants of SARS-CoV-2 in wastewater samples matched those in clinical isolates from the same time periods. The findings from this study support that wastewater surveillance is effective in COVID-19 trend tracking and provide sentinel warning of variant emergence and transmission within various types of communities.

Annavajhala, M. K., et al. (2021). "Emergence and expansion of SARS-CoV-2 B.1.526 after identification in New York." Nature **597**(7878): 703-708.

SARS-CoV-2 infections have surged across the globe in recent months, concomitant with considerable viral evolution(1-3). Extensive mutations in the spike protein may threaten the efficacy of vaccines and therapeutic monoclonal antibodies(4). Two signature spike mutations of concern are E484K, which has a crucial role in the loss of neutralizing activity of antibodies, and N501Y, a driver of rapid worldwide transmission of the B.1.1.7 lineage. Here we report the emergence of the variant lineage B.1.526 (also known as the Iota variant(5)), which contains E484K, and its rise to dominance in New York City in early 2021. This variant is partially or completely resistant to two therapeutic monoclonal antibodies that are in clinical use and is less susceptible to neutralization by plasma from individuals who had recovered from SARS-CoV-2 infection or serum from vaccinated individuals, posing a modest antigenic challenge. The presence of the B.1.526 lineage has now been reported in all 50 states in the United States and in many other countries. B.1.526 rapidly replaced earlier lineages in New York, with an estimated transmission advantage of 35%. These transmission dynamics, together with the relative antibody resistance of its E484K sub-lineage, are likely to have contributed to the sharp rise and rapid spread of B.1.526. Although SARS-CoV-2 B.1.526 initially outpaced B.1.1.7 in the region, its growth subsequently slowed concurrently with the rise of B.1.1.7 and ensuing variants.

Atyeo, C., et al. (2021). "Dissecting strategies to tune the therapeutic potential of SARS-CoV-2-specific monoclonal antibody CR3022." JCI Insight **6**(1).

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), coupled with a lack of therapeutics, has paralyzed the globe. Although significant effort has been invested in identifying antibodies that block infection, the ability of antibodies to target infected cells through Fc interactions may be vital to eliminate the virus. To explore the role of Fc activity in SARS-CoV-2 immunity, the functional potential of a cross-SARS-reactive antibody, CR3022, was assessed. CR3022 was able to broadly drive antibody effector functions, providing critical immune clearance at entry and upon egress. Using selectively engineered Fc variants, no protection was observed after administration of WT IgG1 in mice or hamsters. Conversely, the functionally enhanced Fc variant resulted in increased pathology in both the mouse and hamster models, causing weight loss in mice and enhanced viral replication and weight loss in the more susceptible hamster model, highlighting the pathological functions of Fc-enhancing mutations. These data point to the critical need for strategic Fc engineering for the treatment of SARS-CoV-2 infection.

Babiker, A., et al. (2021). "Single-Amplicon Multiplex Real-Time Reverse Transcription-PCR with Tiled Probes To Detect SARS-CoV-2 spike Mutations Associated with Variants of Concern." J Clin Microbiol **59**(12): e0144621.

To provide an accessible and inexpensive method to surveil for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mutations, we developed a multiplex real-time reverse transcription-PCR (rRT-PCR) assay, the Spike single-nucleotide polymorphism (SNP) assay, to detect specific mutations in the spike receptor binding domain. A single primer pair was designed to amplify a 348-bp region of spike, and probes were initially designed to detect K417, E484K, and N501Y. The assay was evaluated using characterized variant sample pools and residual nasopharyngeal samples. Variant calls were confirmed by SARS-CoV-2 genome sequencing in a subset of samples. Subsequently, a fourth probe was designed to detect L452R. The lower limit of 95% detection was 2.46 to

2.48 log10 genome equivalents (GE)/ml for the three initial targets (approximately 1 to 2 GE/reaction). Among 253 residual nasopharyngeal swabs with detectable SARS-CoV-2 RNA, the Spike SNP assay was positive in 238 (94.1%) samples. All 220 samples with threshold cycle (CT) values of <30 for the SARS-CoV-2 N2 target were detected, whereas 18/33 samples with N2 CT values of >/=30 were detected. Spike SNP results were confirmed by sequencing in 50/50 samples (100%). Addition of the 452R probe did not affect performance for the original targets. The Spike SNP assay accurately identifies SARS-CoV-2 mutations in the receptor binding domain, and it can be quickly modified to detect new mutations that emerge.

Badr, H., et al. (2020). "Psychosocial and health behavioural impacts of COVID-19 pandemic on adults in the USA: protocol for a longitudinal cohort study." BMJ Open **10**(12): e044642.

INTRODUCTION: Although social distancing may help contain the spread of COVID-19, the social isolation and loneliness it causes can heighten stress, contribute to unhealthy lifestyle behaviours and have deleterious effects on social relationships. This ongoing longitudinal cohort study aims to (1) characterise the psychological, social and health behavioural impacts of the COVID-19 pandemic over a 12-month period in the USA; (2) determine whether these impacts differ for certain subgroups based on sociodemographics and other individual-level factors; and (3) explore whether there are modifiable factors (eg, coping, social support) that moderate the effects of the pandemic over time. METHODS AND ANALYSIS: Adults (aged >/=18 years) who were fluent in either English or Spanish were recruited via social media and invited to complete an online survey during the 8-week period from 13 April to 8 June 2020 (baseline). Follow-up surveys will be conducted 6 and 12 months after baseline. Data transformations, non-parametric tests or other alternative methods will be used when appropriate. Descriptive statistics and cross-sectional analyses will be performed. Longitudinal associations will be analysed using multilevel modelling with time-variant and time-invariant predictors of change in trajectory over the study period. ETHICS AND DISSEMINATION: Research ethics approval was received from the Baylor College of Medicine Institutional Review Board (H-47505). Overall, this study will provide timely information that can be used to inform public health messaging strategies and guide development of assessment tools and interventions to support vulnerable individuals dealing with the long-term impacts of the COVID-19 pandemic.

Baker, F. L., et al. (2021). "Acute exercise increases immune responses to SARS CoV-2 in a previously infected man." Brain Behav Immun Health **18**: 100343.

Evidence is emerging that exercise and physical activity provides protection against severe COVID-19 disease in patients infected with SARS-CoV-2, but it is not known how exercise affects immune responses to the virus. A healthy man completed a graded cycling ergometer test prior to and after SARS-CoV-2 infection, then again after receiving an adenovirus vector-based COVID-19 vaccine. Using whole blood SARS-CoV-2 peptide stimulation assays, IFN-gamma ELISPOT assays, flow cytometry, ex vivo viral-specific T-cell expansion assays and deep T-cell receptor (TCR) beta sequencing, we found that exercise robustly mobilized highly functional SARS-CoV-2 specific T-cells to the blood compartment that recognized spike protein, membrane protein, nucleocapsid antigen and the B.1.1.7 alpha-variant, and consisted mostly of CD3+/CD8+ T-cells and double-negative (CD4-/CD8-) CD3(+) T-cells. The magnitude of SARS-CoV-2 T-cell mobilization with exercise was intensity dependent and robust when compared to T-cells recognizing other viruses (e.g. CMV, EBV, influenza). Vaccination enhanced the number of exercise-mobilized SARS-CoV-2 T-cells recognizing spike protein and the alpha-variant only. Exercise-mobilized SARS-CoV-2 specific T-cells proliferated more vigorously to ex vivo peptide stimulation and maintained broad TCR-beta diversity against SARS-CoV-2 antigens both before and after ex vivo expansion. Neutralizing antibodies to SARS-CoV-2 were transiently elevated during exercise after both infection and vaccination. Finally, infection was associated with an increased metabolic demand to defined exercise workloads, which was restored to pre-infection levels after vaccination. This case study provides impetus for larger studies to determine if these immune responses to exercise can facilitate viral clearance, ameliorate symptoms of long COVID syndrome, and/or restore functional exercise capacity following SARS-CoV-2 infection.

Beltran-Pavez, C., et al. (2021). "Insights into neutralizing antibody responses in individuals exposed to SARS-CoV-2 in Chile." Sci Adv **7**(7).

Chile has one of the worst numbers worldwide in terms of SARS-CoV-2 positive cases and COVID-19-related deaths per million inhabitants; thus, characterization of neutralizing antibody (NAb) responses in the general population is critical to understanding of immunity at the local level. Given our inability to perform massive classical neutralization assays due to the scarce availability of BSL-3 facilities in the country, we developed and fully characterized an HIV-based SARS-CoV-2 pseudotype, which was used in a 96-well plate format to investigate NAb responses in samples from individuals exposed to SARS-CoV-2 or treated with convalescent plasma. We also identified samples with decreased or enhanced neutralization activity against the D614G spike

variant compared with the wild type, indicating the relevance of this variant in host immunity. The data presented here represent the first insights into NAb responses in individuals from Chile, serving as a guide for future studies in the country.

Bourassa, L., et al. (2021). "A SARS-CoV-2 Nucleocapsid Variant that Affects Antigen Test Performance." J Clin Virol **141**: 104900.

More than one year into a global pandemic, SARS-CoV-2 is now defined by a variety of rapidly evolving variant lineages. Several FDA authorized molecular diagnostic tests have been impacted by viral variation, while no reports of viral variation affecting antigen test performance have occurred to date. While determining the analytical sensitivity of the Quidel Sofia SARS Antigen FIA test (Sofia 2), we uncovered a high viral load specimen that repeatedly tested negative by this antigen test. Whole genome sequencing of the specimen uncovered two mutations, T205I and D399N, present in the nucleocapsid protein of the isolate. All six SARS-CoV-2 positive clinical specimens available in our laboratory with a D399N nucleocapsid mutation and CT < 31 were not detected by the Sofia 2 but detected by the Abbott BinaxNOW COVID-19 Ag Card, while clinical specimens with the T205I mutation were detected by both assays. Testing of recombinant SARS-CoV-2 nucleocapsid with these variants demonstrated an approximate 1000-fold loss in sensitivity for the Quidel Sofia SARS Antigen FIA test associated with the D399N mutation, while the BinaxNOW and Quidel Quickvue SARS Antigen tests were unaffected by the mutation. The D399N nucleocapsid mutation has been relatively uncommon to date, appearing in only 0.02% of genomes worldwide at time of writing. Our results demonstrate how routine pathogen genomics can be integrated into the clinical microbiology laboratory to investigate diagnostic edge cases, as well as the importance of profiling antigenic diversity outside of the spike protein for SARS-CoV-2 diagnostics.

Cedro-Tanda, A., et al. (2021). "The Evolutionary Landscape of SARS-CoV-2 Variant B.1.1.519 and Its Clinical Impact in Mexico City." Viruses **13**(11).

The SARS-CoV-2 pandemic is one of the most concerning health problems around the globe. We reported the emergence of SARS-CoV-2 variant B.1.1.519 in Mexico City. We reported the effective reproduction number (Rt) of B.1.1.519 and presented evidence of its geographical origin based on phylogenetic analysis. We also studied its evolution via haplotype analysis and identified the most recurrent haplotypes. Finally, we studied the clinical impact of B.1.1.519. The B.1.1.519 variant was predominant between November 2020 and May 2021, reaching 90% of all cases sequenced in February 2021. It is characterized by three amino acid changes in the spike protein: T478K, P681H, and T732A. Its Rt varies between 0.5 and 2.9. Its geographical origin remain to be investigated. Patients infected with variant B.1.1.519 showed a highly significant adjusted odds ratio (aOR) increase of 1.85 over non-B.1.1.519 patients for developing a severe/critical outcome (p = 0.000296, 1.33-2.6 95% CI) and a 2.35-fold increase for hospitalization (p = 0.005, 1.32-4.34 95% CI). The continuous monitoring of this and other variants will be required to control the ongoing pandemic as it evolves.

Chen, H. H., et al. (2021). "Host genetic effects in pneumonia." Am J Hum Genet **108**(1): 194-201.

Given the coronavirus disease 2019 (COVID-19) pandemic, investigations into host susceptibility to infectious diseases and downstream sequelae have never been more relevant. Pneumonia is a lung disease that can cause respiratory failure and hypoxia and is a common complication of infectious diseases, including COVID-19. Few genome-wide association studies (GWASs) of host susceptibility and severity of pneumonia have been conducted. We performed GWASs of pneumonia susceptibility and severity in the Vanderbilt University biobank (BioVU) with linked electronic health records (EHRs), including Illumina Expanded Multi-Ethnic Global Array (MEGA(EX))-genotyped European ancestry (EA, n= 69,819) and African ancestry (AA, n = 15,603) individuals. Two regions of large effect were identified: the CFTR locus in EA (rs113827944; OR = 1.84, p value = 1.2 x 10(-36)) and HBB in AA (rs334 [p.Glu7Val]; OR = 1.63, p value = 3.5 x 10(-13)). Mutations in these genes cause cystic fibrosis (CF) and sickle cell disease (SCD), respectively. After removing individuals diagnosed with CF and SCD, we assessed heterozygosity effects at our lead variants. Further GWASs after removing individuals with CF uncovered an additional association in R3HCC1L (rs10786398; OR = 1.22, p value = 3.5 x 10(-8)), which was replicated in two independent datasets: UK Biobank (n = 459,741) and 7,985 non-overlapping BioVU subjects, who are genotyped on arrays other than MEGA(EX). This variant was also validated in GWASs of COVID-19 hospitalization and lung function. Our results highlight the importance of the host genome in infectious disease susceptibility and severity and offer crucial insight into genetic effects that could potentially influence severity of COVID-19 sequelae.

Chen, T., et al. (2021). "A Low-Producing Haplotype of Interleukin-6 Disrupting CTCF Binding Is Protective against Severe COVID-19." mBio **12**(5): e0137221.

Interleukin6 (IL-6) is a key driver of hyperinflammation in COVID-19, and its level strongly correlates with disease progression. To investigate whether variability in COVID-19 severity partially results from differential IL-6 expression, functional single-nucleotide polymorphisms (SNPs) of IL-6 were determined in Chinese COVID-19 patients with mild or severe illness. An Asian-common IL-6 haplotype defined by promoter SNP

rs1800796 and intronic SNPs rs1524107 and rs2066992 correlated with COVID-19 severity. Homozygote carriers of C-T-T variant haplotype were at lower risk of developing severe symptoms (odds ratio, 0.256; 95% confidence interval, 0.088 to 0.739; P = 0.007). This protective haplotype was associated with lower levels of IL-6 and its antisense long noncoding RNA IL-6-AS1 by cis-expression quantitative trait loci analysis. The differences in expression resulted from the disturbance of stimulus-dependent bidirectional transcription of the IL-6/IL-6-AS1 locus by the polymorphisms. The protective rs2066992-T allele disrupted a conserved CTCF-binding locus at the enhancer elements of IL-6-AS1, which transcribed antisense to IL-6 and induces IL-6 expression in inflammatory responses. As a result, carriers of the protective allele had significantly reduced IL-6-AS1 expression and attenuated IL-6 induction in response to acute inflammatory stimuli and viral infection. Intriguingly, this low-producing variant that is endemic to present-day Asia was found in early humans who had inhabited mainland Asia since approximately 40,000 years ago but not in other ancient humans, such as Neanderthals and Denisovans. The present study suggests that an individual's IL-6 genotype underlies COVID-19 outcome and may be used to guide IL-6 blockade therapy in Asian patients. IMPORTANCE Overproduction of cytokine interleukin-6 (IL-6) is a hallmark of severe COVID-19 and is believed to play a critical role in exacerbating the excessive inflammatory response. Polymorphisms in IL-6 account for the variability of IL-6 expression and disparities in infectious diseases, but its contribution to the clinical presentation of COVID-19 has not been reported. Here, we investigated IL-6 polymorphisms in severe and mild cases of COVID-19 in a Chinese population. The variant haplotype C-T-T, represented by rs1800796, rs1524107, and rs2066992 at the IL-6 locus, was reduced in patients with severe illness; in contrast, carriers of the wild-type haplotype G-C-G had higher risk of severe illness. Mechanistically, the protective variant haplotype lost CTCF binding at the IL-6 intron and responded poorly to inflammatory stimuli, which may protect the carriers from hyperinflammation in response to acute SARS-CoV-2 infection. These results point out the possibility that IL-6 genotypes underlie the differential viral virulence during the outbreak of COVID-19. The risk loci we identified may serve as a genetic marker to screen high-risk COVID-19 patients.

Costagliola, A., et al. (2020). "Do Animals Play a Role in the Transmission of Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2)? A Commentary." Animals (Basel) **11**(1).

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) belongs to the Beta-coronavirus genus. It is 96.2% homologous to bat CoV RaTG13 and 88% homologous to two bat SARS-like coronaviruses. SARS-CoV-2 is the infectious agent responsible for the coronavirus disease (COVID-19), which was first reported in the Hubei province of Wuhan, China, at the beginning of December 2019. Human transmission from COVID-19 patients or incubation carriers occurs via coughing, sneezing, speaking, discharge from the nose, or fecal contamination. Various strains of the virus have been reported around the world, with different virulence and behavior. In addition, SARS-CoV-2 shares certain epitopes with some taxonomically related viruses, with tropism for the most common synanthropic animals. By elucidating the immunological properties of the circulating SARS-CoV-2, a partial protection due to human-animal interactions could be supposed in some situations. In addition, differential epitopes could be used for the differential diagnosis of SARS-CoV-2 infection. There have been cases of transmission from people with COVID-19 to pets such as cats and dogs. In addition, wild felines were infected. All These animals were either asymptomatic or mildly symptomatic and recovered spontaneously. Experimental studies showed cats and ferrets to be more susceptible to COVID-19. COVID-19 positive dogs and felines do not transmit the infection to humans. In contrast, minks at farms were severely infected from people with COVID-19. A SARS-Cov-2 variant in the Danish farmed mink that had been previously infected by COVID-19 positive workers, spread to mink workers causing the first case of animal-to-human infection transmission that causes a moderate decreased sensitivity to neutralizing antibodies. Thus, more investigations are necessary. It remains important to understand the risk that people with COVID-19 pose to their pets, as well as wild or farm animals so effective recommendations and risk management measures against COVID-19 can be made. A One Health unit that facilitates collaboration between public health and veterinary services is recommended.

da Rocha, J. E. B., et al. (2021). "G6PD distribution in sub-Saharan Africa and potential risks of using chloroquine/hydroxychloroquine based treatments for COVID-19." Pharmacogenomics J **21**(6): 649-656.

Chloroquine/hydroxychloroquine have been proposed as potential treatments for COVID-19. These drugs have warning labels for use in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Analysis of whole genome sequence data of 458 individuals from sub-Saharan Africa showed significant G6PD variation across the continent. We identified nine variants, of which four are potentially deleterious to G6PD function, and one (rs1050828) that is known to cause G6PD deficiency. We supplemented data for the rs1050828 variant with genotype array data from over 11,000 Africans. Although this variant is common in Africans overall, large allele frequency differences exist between sub-

populations. African sub-populations in the same country can show significant differences in allele frequency (e.g. 16.0% in Tsonga vs 0.8% in Xhosa, both in South Africa, p = 2.4 x 10(-3)). The high prevalence of variants in the G6PD gene found in this analysis suggests that it may be a significant interaction factor in clinical trials of chloroquine and hydroxychloroquine for treatment of COVID-19 in Africans.

Dalvie, N. C., et al. (2021). "Engineered SARS-CoV-2 receptor binding domain improves immunogenicity in mice and elicits protective immunity in hamsters." bioRxiv.

Global containment of COVID-19 still requires accessible and affordable vaccines for low- and middle-income countries (LMICs). (1) Recently approved vaccines provide needed interventions, albeit at prices that may limit their global access. (2) Subunit vaccines based on recombinant proteins are suited for large-volume microbial manufacturing to yield billions of doses annually, minimizing their manufacturing costs. (3) These types of vaccines are well-established, proven interventions with multiple safe and efficacious commercial examples. (4-6) Many vaccine candidates of this type for SARS-CoV-2 rely on sequences containing the receptor-binding domain (RBD), which mediates viral entry to cells via ACE2. (7,8) Here we report an engineered sequence variant of RBD that exhibits high-yield manufacturability, high-affinity binding to ACE2, and enhanced immunogenicity after a single dose in mice compared to the Wuhan-Hu-1 variant used in current vaccines. Antibodies raised against the engineered protein exhibited heterotypic binding to the RBD from two recently reported SARS-CoV-2 variants of concern (501Y.V1/V2). Presentation of the engineered RBD on a designed virus-like particle (VLP) also reduced weight loss in hamsters upon viral challenge.

Dalvie, N. C., et al. (2021). "Engineered SARS-CoV-2 receptor binding domain improves manufacturability in yeast and immunogenicity in mice." Proc Natl Acad Sci U S A **118**(38).

Global containment of COVID-19 still requires accessible and affordable vaccines for low- and middle-income countries (LMICs). Recently approved vaccines provide needed interventions, albeit at prices that may limit their global access. Subunit vaccines based on recombinant proteins are suited for large-volume microbial manufacturing to yield billions of doses annually, minimizing their manufacturing cost. These types of vaccines are well-established, proven interventions with multiple safe and efficacious commercial examples. Many vaccine candidates of this type for SARS-CoV-2 rely on sequences containing the receptor-binding domain (RBD), which mediates viral entry to cells via ACE2. Here we report an engineered sequence variant of RBD that exhibits high-yield manufacturability, high-affinity binding to ACE2, and enhanced immunogenicity after a single dose in mice compared to the Wuhan-Hu-1 variant used in current vaccines. Antibodies raised against the engineered protein exhibited heterotypic binding to the RBD from two recently reported SARS-CoV-2 variants of concern (501Y.V1/V2). Presentation of the engineered RBD on a designed virus-like particle (VLP) also reduced weight loss in hamsters upon viral challenge.

Daniels, R. S., et al. (2021). "A Sanger sequencing protocol for SARS-CoV-2 S-gene." Influenza Other Respir Viruses **15**(6): 707-710.

We describe a Sanger sequencing protocol for SARS-CoV-2 S-gene the Spike (S)-glycoprotein product of which, composed of receptor-binding (S1) and membrane fusion (S2) segments, is the target of vaccines used to combat COVID-19. The protocol can be used in laboratories with basic Sanger sequencing capabilities and allows rapid "at source" screening for SARS-CoV-2 variants, notably those of concern. The protocol has been applied for surveillance, with clinical specimens collected in either nucleic acid preservation lysis-mix or virus transport medium, and research involving cultured viruses, and can yield data of public health importance in a timely manner.

Das, A., et al. (2021). "Understanding the immunological aspects of SARS-CoV-2 causing COVID-19 pandemic: A therapeutic approach." Clin Immunol **231**: 108804.

In December 2019, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), a novel variant of coronavirus has emerged from Wuhan in China and has created havoc impulses across the world with a larger number of fatalities. At the same time, studies are on roll to discover potent vaccine against it or repurposing of approved drugs which are widely adopted are under trial to eradicate the SARS-CoV-2 causing COVID-19 pandemic. Reports have also shown that there are asymptomatic carriers of COVID-19 disease who can transmit the disease to others too. However, the first line defense of the viral attack is body's strong and well-coordinated immune response producing excessive inflammatory innate reaction, thus impaired adaptive host immune defense which lead to death upon the malfunctioning. Considerable works are going on to establish the relation between immune parameters and viral replication that, might alter both the innate and adaptive immune system of COVID-19 patient by up riding a massive cytokines and chemokines secretion. This review mainly gives an account on how SARS-CoV-2 interacts with our immune system and how does our immune system responds to it, along with that drugs which are being used or can be used in fighting COVID-19 disease. The curative therapies as treatment for it have also been addressed in the perspective of adaptive immunity of the patients.

Desai, S., et al. (2021). "IPD 2.0: To derive insights from an evolving SARS-CoV-2 genome." BMC Bioinformatics **22**(1): 247.

BACKGROUND: Rapid analysis of SARS-CoV-2 genomic data plays a crucial role in surveillance and adoption of measures in controlling spread of Covid-19. Fast, inclusive and adaptive methods are required for the heterogenous SARS-CoV-2 sequence data generated at an unprecedented rate. RESULTS: We present an updated version of the SARS-CoV-2 analysis module of our automated computational pipeline, Infectious Pathogen Detector (IPD) 2.0, to perform genomic analysis to understand the variability and dynamics of the virus. It adopts the recent clade nomenclature and demonstrates the clade prediction accuracy of 92.8%. IPD 2.0 also contains a SARS-CoV-2 updater module, allowing automatic upgrading of the variant database using genome sequences from GISAID. As a proof of principle, analyzing 208,911 SARS-CoV-2 genome sequences, we generate an extensive database of 2.58 million sample-wise variants. A comparative account of lineage-specific mutations in the newer SARS-CoV-2 strains emerging in the UK, South Africa and Brazil and data reported from India identify overlapping and lineages specific acquired mutations suggesting a repetitive convergent and adaptive evolution. CONCLUSIONS: A novel and dynamic feature of the SARS-CoV-2 module of IPD 2.0 makes it a contemporary tool to analyze the diverse and growing genomic strains of the virus and serve as a vital tool to help facilitate rapid genomic surveillance in a population to identify variants involved in breakthrough infections. IPD 2.0 is freely available from http://www.actrec.gov.in/pi-webpages/AmitDutt/IPD/IPD.html and the web-application is available at http://ipd.actrec.gov.in/ipdweb/.

Desai, S., et al. (2021). "An integrated approach to determine the abundance, mutation rate and phylogeny of the SARS-CoV-2 genome." Brief Bioinform **22**(2): 1065-1075.

The analysis of the SARS-CoV-2 genome datasets has significantly advanced our understanding of the biology and genomic adaptability of the virus. However, the plurality of advanced sequencing datasets-such as short and long reads-presents a formidable computational challenge to uniformly perform quantitative, variant or phylogenetic analysis, thus limiting its application in public health laboratories engaged in studying epidemic outbreaks. We present a computational tool, Infectious Pathogen Detector (IPD), to perform integrated analysis of diverse genomic datasets, with a customized analytical module for the SARS-CoV-2 virus. The IPD pipeline quantitates individual occurrences of 1060 pathogens and performs mutation and phylogenetic analysis from heterogeneous sequencing datasets. Using IPD, we demonstrate a varying burden (5.055-999655.7 fragments per million) of SARS-CoV-2 transcripts across 1500 short- and long-read sequencing SARS-CoV-2 datasets and identify 4634 SARS-CoV-2 variants (~3.05 variants per sample), including 449 novel variants, across the genome with distinct hotspot mutations in the ORF1ab and S genes along with their phylogenetic relationships establishing the utility of IPD in tracing the genome isolates from the genomic data (as accessed on 11 June 2020). The IPD predicts the occurrence and dynamics of variability among infectious pathogens-with a potential for direct utility in the COVID-19 pandemic and beyond to help automate the sequencing-based pathogen analysis and in responding to public health threats, efficaciously. A graphical user interface (GUI)-enabled desktop application is freely available for download for the academic users at http://www.actrec.gov.in/pi-webpages/AmitDutt/IPD/IPD.html and for web-based processing at http://ipd.actrec.gov.in/ipdweb/ to generate an automated report without any prior computational know-how.

Dong, J., et al. (2021). "Genetic and structural basis for SARS-CoV-2 variant neutralization by a two-antibody cocktail." Nat Microbiol **6**(10): 1233-1244.

Understanding the molecular basis for immune recognition of SARS-CoV-2 spike glycoprotein antigenic sites will inform the development of improved therapeutics. We determined the structures of two human monoclonal antibodies-AZD8895 and AZD1061-which form the basis of the investigational antibody cocktail AZD7442, in complex with the receptor-binding domain (RBD) of SARS-CoV-2 to define the genetic and structural basis of neutralization. AZD8895 forms an 'aromatic cage' at the heavy/light chain interface using germ line-encoded residues in complementarity-determining regions (CDRs) 2 and 3 of the heavy chain and CDRs 1 and 3 of the light chain. These structural features explain why highly similar antibodies (public clonotypes) have been isolated from multiple individuals. AZD1061 has an unusually long LCDR1; the HCDR3 makes interactions with the opposite face of the RBD from that of AZD8895. Using deep mutational scanning and neutralization escape selection experiments, we comprehensively mapped the crucial binding residues of both antibodies and identified positions of concern with regards to virus escape from antibody-mediated neutralization. Both AZD8895 and AZD1061 have strong neutralizing activity against SARS-CoV-2 and variants of concern with antigenic substitutions in the RBD. We conclude that germ line-encoded antibody features enable recognition of the SARS-CoV-2 spike RBD and demonstrate the utility of the cocktail AZD7442 in neutralizing emerging variant viruses.

Esper, F. P., et al. (2021). "Genomic Epidemiology of SARS-CoV-2 Infection During the Initial

Pandemic Wave and Association With Disease Severity." JAMA Netw Open **4**(4): e217746.

Importance: Understanding of SARS-CoV-2 variants that alter disease outcomes are important for clinical risk stratification and may provide important clues to the complex virus-host relationship. Objective: To examine the association of identified SARS-CoV-2 variants, virus clades, and clade groups with disease severity and patient outcomes. Design, Setting, and Participants: In this cross-sectional study, viral genome analysis of clinical specimens obtained from patients at the Cleveland Clinic infected with SARS-CoV-2 during the initial wave of infection (March 11 to April 22, 2020) was performed. Identified variants were matched with clinical outcomes. Data analysis was performed from April to July 2020. Main Outcomes and Measures: Hospitalization, intensive care unit (ICU) admission, mortality, and laboratory outcomes were matched with SARS-CoV-2 variants. Results: Specimens sent for viral genome sequencing originated from 302 patients with SARS-CoV-2 infection (median [interquartile range] age, 52.6 [22.8 to 82.5] years), of whom 126 (41.7%) were male, 195 (64.6%) were White, 91 (30.1%) required hospitalization, 35 (11.6%) needed ICU admission, and 17 (5.6%) died. From these specimens, 2531 variants (484 of which were unique) were identified. Six different SARS-CoV-2 clades initially circulated followed by a rapid reduction in clade diversity. Several variants were associated with lower hospitalization rate, and those containing 23403A>G (D614G Spike) were associated with increased survival when the patient was hospitalized (64 of 74 patients [86.5%] vs 10 of 17 patients [58.8%]; chi21 = 6.907; P = .009). Hospitalization and ICU admission were similar regardless of clade. Infection with Clade V variants demonstrated higher creatinine levels (median [interquartile range], 2.6 [-0.4 to 5.5] mg/dL vs 1.0 [0.2 to 2.2] mg/dL; mean creatinine difference, 2.9 mg/dL [95% CI, 0.8 to 5.0 mg/dL]; Kruskal-Wallis P = .005) and higher overall mortality rates (3 of 14 patients [21.4%] vs 17 of 302 patients [5.6%]; chi21 = 5.640; P = .02) compared with other variants. Infection by strains lacking the 23403A>G variant showed higher mortality in multivariable analysis (odds ratio [OR], 22.4; 95% CI, 0.6 to 5.6; P = .01). Increased variants of open reading frame (ORF) 3a were associated with decreased hospitalization frequency (OR, 0.4; 95% CI, 0.2 to 0.96; P = .04), whereas increased variants of Spike (OR, 0.01; 95% CI, <0.01 to 0.3; P = .01) and ORF8 (OR, 0.03; 95% CI, <0.01 to 0.6; P = .03) were associated with increased survival. Conclusions and Relevance: Within weeks of SARS-CoV-2 circulation, a profound shift toward 23403A>G (D614G) specific genotypes occurred. Replaced clades were associated with worse clinical outcomes, including mortality. These findings help explain persistent hospitalization yet decreasing mortality as the pandemic progresses. SARS-CoV-2 clade assignment is an important factor that may aid in estimating patient outcomes.

Fareh, M., et al. (2021). "Reprogrammed CRISPR-Cas13b suppresses SARS-CoV-2 replication and circumvents its mutational escape through mismatch tolerance." Nat Commun **12**(1): 4270.

The recent dramatic appearance of variants of concern of SARS-coronavirus-2 (SARS-CoV-2) highlights the need for innovative approaches that simultaneously suppress viral replication and circumvent viral escape from host immunity and antiviral therapeutics. Here, we employ genome-wide computational prediction and single-nucleotide resolution screening to reprogram CRISPR-Cas13b against SARS-CoV-2 genomic and subgenomic RNAs. Reprogrammed Cas13b effectors targeting accessible regions of Spike and Nucleocapsid transcripts achieved >98% silencing efficiency in virus-free models. Further, optimized and multiplexed Cas13b CRISPR RNAs (crRNAs) suppress viral replication in mammalian cells infected with replication-competent SARS-CoV-2, including the recently emerging dominant variant of concern B.1.1.7. The comprehensive mutagenesis of guide-target interaction demonstrated that single-nucleotide mismatches does not impair the capacity of a potent single crRNA to simultaneously suppress ancestral and mutated SARS-CoV-2 strains in infected mammalian cells, including the Spike D614G mutant. The specificity, efficiency and rapid deployment properties of reprogrammed Cas13b described here provide a molecular blueprint for antiviral drug development to suppress and prevent a wide range of SARS-CoV-2 mutants, and is readily adaptable to other emerging pathogenic viruses.

Faulkner, N., et al. (2021). "Reduced antibody cross-reactivity following infection with B.1.1.7 than with parental SARS-CoV-2 strains." Elife **10**.

Background: The degree of heterotypic immunity induced by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strains is a major determinant of the spread of emerging variants and the success of vaccination campaigns, but remains incompletely understood. Methods: We examined the immunogenicity of SARS-CoV-2 variant B.1.1.7 (Alpha) that arose in the United Kingdom and spread globally. We determined titres of spike glycoprotein-binding antibodies and authentic virus neutralising antibodies induced by B.1.1.7 infection to infer homotypic and heterotypic immunity. Results: Antibodies elicited by B.1.1.7 infection exhibited significantly reduced recognition and neutralisation of parental strains or of the South Africa variant B.1.351 (Beta) than of the infecting variant. The drop in cross-reactivity was significantly more pronounced following B.1.1.7 than parental strain infection. Conclusions: The results indicate that heterotypic immunity induced by SARS-CoV-2 variants is asymmetric. Funding: This work was supported by the Francis Crick Institute and the Max

Planck Institute for Dynamics of Complex Technical Systems, Magdeburg.
Fontenele, R. S., et al. (2021). "High-throughput sequencing of SARS-CoV-2 in wastewater provides insights into circulating variants." Water Res **205**: 117710.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) likely emerged from a zoonotic spill-over event and has led to a global pandemic. The public health response has been predominantly informed by surveillance of symptomatic individuals and contact tracing, with quarantine, and other preventive measures have then been applied to mitigate further spread. Non-traditional methods of surveillance such as genomic epidemiology and wastewater-based epidemiology (WBE) have also been leveraged during this pandemic. Genomic epidemiology uses high-throughput sequencing of SARS-CoV-2 genomes to inform local and international transmission events, as well as the diversity of circulating variants. WBE uses wastewater to analyse community spread, as it is known that SARS-CoV-2 is shed through bodily excretions. Since both symptomatic and asymptomatic individuals contribute to wastewater inputs, we hypothesized that the resultant pooled sample of population-wide excreta can provide a more comprehensive picture of SARS-CoV-2 genomic diversity circulating in a community than clinical testing and sequencing alone. In this study, we analysed 91 wastewater samples from 11 states in the USA, where the majority of samples represent Maricopa County, Arizona (USA). With the objective of assessing the viral diversity at a population scale, we undertook a single-nucleotide variant (SNV) analysis on data from 52 samples with >90% SARS-CoV-2 genome coverage of sequence reads, and compared these SNVs with those detected in genomes sequenced from clinical patients. We identified 7973 SNVs, of which 548 were "novel" SNVs that had not yet been identified in the global clinical-derived data as of 17(th) June 2020 (the day after our last wastewater sampling date). However, between 17(th) of June 2020 and 20(th) November 2020, almost half of the novel SNVs have since been detected in clinical-derived data. Using the combination of SNVs present in each sample, we identified the more probable lineages present in that sample and compared them to lineages observed in North America prior to our sampling dates. The wastewater-derived SARS-CoV-2 sequence data indicates there were more lineages circulating across the sampled communities than represented in the clinical-derived data. Principal coordinate analyses identified patterns in population structure based on genetic variation within the sequenced samples, with clear trends associated with increased diversity likely due to a higher number of infected individuals relative to the sampling dates. We demonstrate that genetic correlation analysis combined with SNVs analysis using wastewater sampling can provide a comprehensive snapshot of the SARS-CoV-2 genetic population structure circulating within a community, which might not be observed if relying solely on clinical cases.

Frediani, J. K., et al. (2021). "Multidisciplinary assessment of the Abbott BinaxNOW SARS-CoV-2 point-of-care antigen test in the context of emerging viral variants and self-administration." Sci Rep **11**(1): 14604.

While there has been significant progress in the development of rapid COVID-19 diagnostics, as the pandemic unfolds, new challenges have emerged, including whether these technologies can reliably detect the more infectious variants of concern and be viably deployed in non-clinical settings as "self-tests". Multidisciplinary evaluation of the Abbott BinaxNOW COVID-19 Ag Card (BinaxNOW, a widely used rapid antigen test, included limit of detection, variant detection, test performance across different age-groups, and usability with self/caregiver-administration. While BinaxNOW detected the highly infectious variants, B.1.1.7 (Alpha) first identified in the UK, B.1.351 (Beta) first identified in South Africa, P.1 (Gamma) first identified in Brazil, B.1.617.2 (Delta) first identified in India and B.1.2, a non-VOC, test sensitivity decreased with decreasing viral loads. Moreover, BinaxNOW sensitivity trended lower when devices were performed by patients/caregivers themselves compared to trained clinical staff, despite universally high usability assessments following self/caregiver-administration among different age groups. Overall, these data indicate that while BinaxNOW accurately detects the new viral variants, as rapid COVID-19 tests enter the home, their already lower sensitivities compared to RT-PCR may decrease even more due to user error.

Goel, R. R., et al. (2021). "Distinct antibody and memory B cell responses in SARS-CoV-2 naive and recovered individuals following mRNA vaccination." Sci Immunol **6**(58).

Novel mRNA vaccines for SARS-CoV-2 have been authorized for emergency use. Despite their efficacy in clinical trials, data on mRNA vaccine-induced immune responses are mostly limited to serological analyses. Here, we interrogated antibody and antigen-specific memory B cells over time in 33 SARS-CoV-2 naive and 11 SARS-CoV-2 recovered subjects. SARS-CoV-2 naive individuals required both vaccine doses for optimal increases in antibodies, particularly for neutralizing titers against the B.1.351 variant. Memory B cells specific for full-length spike protein and the spike receptor binding domain (RBD) were also efficiently primed by mRNA vaccination and detectable in all SARS-CoV-2 naive subjects after the second vaccine dose, though the memory B cell response declined slightly with age. In SARS-CoV-2 recovered individuals, antibody and memory B cell responses were

significantly boosted after the first vaccine dose; however, there was no increase in circulating antibodies, neutralizing titers, or antigen-specific memory B cells after the second dose. This robust boosting after the first vaccine dose strongly correlated with levels of pre-existing memory B cells in recovered individuals, identifying a key role for memory B cells in mounting recall responses to SARS-CoV-2 antigens. Together, our data demonstrated robust serological and cellular priming by mRNA vaccines and revealed distinct responses based on prior SARS-CoV-2 exposure, whereby COVID-19 recovered subjects may only require a single vaccine dose to achieve peak antibody and memory B cell responses. These findings also highlight the utility of defining cellular responses in addition to serologies and may inform SARS-CoV-2 vaccine distribution in a resource-limited setting.

Goel, R. R., et al. (2021). "mRNA Vaccination Induces Durable Immune Memory to SARS-CoV-2 with Continued Evolution to Variants of Concern." bioRxiv.

SARS-CoV-2 mRNA vaccines have shown remarkable efficacy, especially in preventing severe illness and hospitalization. However, the emergence of several variants of concern and reports of declining antibody levels have raised uncertainty about the durability of immune memory following vaccination. In this study, we longitudinally profiled both antibody and cellular immune responses in SARS-CoV-2 naive and recovered individuals from pre-vaccine baseline to 6 months post-mRNA vaccination. Antibody and neutralizing titers decayed from peak levels but remained detectable in all subjects at 6 months post-vaccination. Functional memory B cell responses, including those specific for the receptor binding domain (RBD) of the Alpha (B.1.1.7), Beta (B.1.351), and Delta (B.1.617.2) variants, were also efficiently generated by mRNA vaccination and continued to increase in frequency between 3 and 6 months post-vaccination. Notably, most memory B cells induced by mRNA vaccines were capable of cross-binding variants of concern, and B cell receptor sequencing revealed significantly more hypermutation in these RBD variant-binding clones compared to clones that exclusively bound wild-type RBD. Moreover, the percent of variant cross-binding memory B cells was higher in vaccinees than individuals who recovered from mild COVID-19. mRNA vaccination also generated antigen-specific CD8+ T cells and durable memory CD4+ T cells in most individuals, with early CD4+ T cell responses correlating with humoral immunity at later timepoints. These findings demonstrate robust, multi-component humoral and cellular immune memory to SARS-CoV-2 and current variants of concern for at least 6 months after mRNA vaccination. Finally, we observed that boosting of pre-existing immunity with mRNA vaccination in SARS-CoV-2 recovered individuals primarily increased antibody responses in the short-term without significantly altering antibody decay rates or long-term B and T cell memory. Together, this study provides insights into the generation and evolution of vaccine-induced immunity to SARS-CoV-2, including variants of concern, and has implications for future booster strategies. GRAPHICAL ABSTRACT:

Hajj-Hassan, H., et al. (2021). "Probing the Increased Virulence of Severe Acute Respiratory Syndrome Coronavirus 2 B.1.617 (Indian Variant) From Predicted Spike Protein Structure." Cureus **13**(8): e16905.

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).

Hasan, M. M., et al. (2021). "Global and local mutations in Bangladeshi SARS-CoV-2 genomes." Virus Res **297**: 198390.

Coronavirus Disease 2019 (COVID-19) warrants comprehensive investigations of publicly available Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) genomes to gain new insight about their epidemiology, mutations, and pathogenesis. Nearly 0.4 million mutations have been identified so far among the approximately 60,000 SARS-CoV-2 genomic sequences. In this study, we compared a total of 371 SARS-CoV-2 published whole genomes reported from different parts of Bangladesh with 467 sequences reported globally to understand the origin of viruses, possible patterns of mutations, and availability of unique mutations. Phylogenetic analyses indicated that SARS-CoV-2

viruses might have transmitted through infected travelers from European countries, and the GR clade was found as predominant in Bangladesh. Our analyses revealed 4604 mutations at the RNA level including 2862 missense mutations, 1192 synonymous mutations, 25 insertions and deletions and 525 other types of mutation. In line with the global trend, D614G mutation in spike glycoprotein was predominantly high (98 %) in Bangladeshi isolates. Interestingly, we found the average number of mutations in ORF1ab, S, ORF3a, M, and N were significantly higher ($p < 0.001$) for sequences containing the G614 variant compared to those having D614. Previously reported frequent mutations, such as R203K, D614G, G204R, P4715L and I300F at protein levels were also prevalent in Bangladeshi isolates. Additionally, 34 unique amino acid changes were revealed and categorized as originating from different cities. These analyses may increase our understanding of variations in SARS-CoV-2 virus genomes, circulating in Bangladesh and elsewhere.

He, C., et al. (2021). "A bivalent recombinant vaccine targeting the S1 protein induces neutralizing antibodies against both SARS-CoV-2 variants and wild-type of the virus." MedComm (2020).

The emerging variants of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in pandemic call for the urgent development of universal corona virus disease 2019 (COVID-19) vaccines which could be effective for both wild-type SARS-CoV-2 and mutant strains. In the current study, we formulated protein subunit vaccines with AS03 adjuvant and recombinant proteins of S1 subunit of SARS-CoV-2 (S1-WT) and S1 variant (K417N, E484K, N501Y, and D614G) subunit (S1-Mut), and immunized transgenic mice that express human angiotensin-converting enzyme 2 (hACE2). The S1 protein-specific antibody production and the neutralization capability for SARS-CoV-2 and B.1.351 variant were measured after immunization in mice. The results revealed that the S1-Mut antigens were more effective in inhibiting the receptor-binding domain and ACE2 binding in B.1.351 variant than in wild-type SARS-CoV-2. Furthermore, the development of a bivalent vaccine exhibited the ideal neutralization properties against wild-type and B.1.351 variant, as well as other variants. Our findings may provide a rationale for the development of a bivalent recombinant vaccine targeting the S1 protein that can induce the neutralizing antibodies against both SARS-CoV-2 variants and wild-type of the virus and may be of importance to explore the potential clinical use of bivalent recombinant vaccine in the future.

Hoang, V. T., et al. (2021). "Clinical outcomes in patients infected with different SARS-CoV-2 variants at one hospital during three phases of the COVID-19 epidemic in Marseille, France." Infect Genet Evol **95**: 105092.

OBJECTIVES: To compare the demographics, clinical characteristics and severity of patients infected with nine different SARS-CoV-2 variants, during three phases of the COVID-19 epidemic in Marseille. METHODS: A single centre retrospective cohort study was conducted in 1760 patients infected with SARS-CoV-2 of Nextstrain clades 20A, 20B, and 20C (first phase, February-May 2020), Pangolin lineages B.1.177 (we named Marseille-2) and B.1.160 (Marseille-4) variants (second phase, June-December 2020), and B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma) and A.27 (Marseille-501) variants (third phase, January 2021-today). Outcomes were the occurrence of clinical failures, including hospitalisation, transfer to the intensive-care unit, and death. RESULTS: During each phase, no major differences were observed with regards to age and gender distribution, the prevalence of chronic diseases, and clinical symptoms between variants circulating in a given phase. The B.1.177 and B.1.160 variants were associated with more severe outcomes. Infections occurring during the second phase were associated with a higher rate of death as compared to infections during the first and third phases. Patients in the second phase were more likely to be hospitalised than those in the third phase. Patients infected during the third phase were more frequently obese than others. CONCLUSION: A large cohort study is recommended to evaluate the transmissibility and to better characterise the clinical severity of emerging variants.

Hodcroft, E. B., et al. (2021). "Spread of a SARS-CoV-2 variant through Europe in the summer of 2020." Nature **595**(7869): 707-712.

Following its emergence in late 2019, the spread of SARS-CoV-2(1,2) has been tracked by phylogenetic analysis of viral genome sequences in unprecedented detail(3-5). Although the virus spread globally in early 2020 before borders closed, intercontinental travel has since been greatly reduced. However, travel within Europe resumed in the summer of 2020. Here we report on a SARS-CoV-2 variant, 20E (EU1), that was identified in Spain in early summer 2020 and subsequently spread across Europe. We find no evidence that this variant has increased transmissibility, but instead demonstrate how rising incidence in Spain, resumption of travel, and lack of effective screening and containment may explain the variant's success. Despite travel restrictions, we estimate that 20E (EU1) was introduced hundreds of times to European countries by summertime travellers, which is likely to have undermined local efforts to minimize infection with SARS-CoV-2. Our results illustrate how a variant can rapidly become dominant even in the absence of a substantial transmission advantage in favourable epidemiological settings. Genomic surveillance is critical for understanding how travel can affect transmission of SARS-CoV-2, and thus for

informing future containment strategies as travel resumes.

Hu, W., et al. (2021). "Mechanical activation of spike fosters SARS-CoV-2 viral infection." Cell Res **31**(10): 1047-1060.

The outbreak of SARS-CoV-2 (SARS2) has caused a global COVID-19 pandemic. The spike protein of SARS2 (SARS2-S) recognizes host receptors, including ACE2, to initiate viral entry in a complex biomechanical environment. Here, we reveal that tensile force, generated by bending of the host cell membrane, strengthens spike recognition of ACE2 and accelerates the detachment of spike's S1 subunit from the S2 subunit to rapidly prime the viral fusion machinery. Mechanistically, such mechano-activation is fulfilled by force-induced opening and rotation of spike's receptor-binding domain to prolong the bond lifetime of spike/ACE2 binding, up to 4 times longer than that of SARS-S binding with ACE2 under 10 pN force application, and subsequently by force-accelerated S1/S2 detachment which is up to ~10(3) times faster than that in the no-force condition. Interestingly, the SARS2-S D614G mutant, a more infectious variant, shows 3-time stronger force-dependent ACE2 binding and 35-time faster force-induced S1/S2 detachment. We also reveal that an anti-S1/S2 non-RBD-blocking antibody that was derived from convalescent COVID-19 patients with potent neutralizing capability can reduce S1/S2 detachment by 3 x 10(6) times under force. Our study sheds light on the mechano-chemistry of spike activation and on developing a non-RBD-blocking but S1/S2-locking therapeutic strategy to prevent SARS2 invasion.

Huang, H. C., et al. (2021). "Targeting conserved N-glycosylation blocks SARS-CoV-2 variant infection in vitro." EBioMedicine **74**: 103712.

BACKGROUND: Despite clinical success with anti-spike vaccines, the effectiveness of neutralizing antibodies and vaccines has been compromised by rapidly spreading SARS-CoV-2 variants. Viruses can hijack the glycosylation machinery of host cells to shield themselves from the host's immune response and attenuate antibody efficiency. However, it remains unclear if targeting glycosylation on viral spike protein can impair infectivity of SARS-CoV-2 and its variants. METHODS: We adopted flow cytometry, ELISA, and BioLayer interferometry approaches to assess binding of glycosylated or deglycosylated spike with ACE2. Viral entry was determined by luciferase, immunoblotting, and immunofluorescence assays. Genome-wide association study (GWAS) revealed a significant relationship between STT3A and COVID-19 severity. NF-kappaB/STT3A-regulated N-glycosylation was investigated by gene knockdown, chromatin immunoprecipitation, and promoter assay. We developed an antibody-drug conjugate (ADC) that couples non-neutralization anti-spike antibody with NGI-1 (4G10-ADC) to specifically target SARS-CoV-2-infected cells. FINDINGS: The receptor binding domain and three distinct SARS-CoV-2 surface N-glycosylation sites among 57,311 spike proteins retrieved from the NCBI-Virus-database are highly evolutionarily conserved (99.67%) and are involved in ACE2 interaction. STT3A is a key glycosyltransferase catalyzing spike glycosylation and is positively correlated with COVID-19 severity. We found that inhibiting STT3A using N-linked glycosylation inhibitor-1 (NGI-1) impaired SARS-CoV-2 infectivity and that of its variants [Alpha (B.1.1.7) and Beta (B.1.351)]. Most importantly, 4G10-ADC enters SARS-CoV-2-infected cells and NGI-1 is subsequently released to deglycosylate spike protein, thereby reinforcing the neutralizing abilities of antibodies, vaccines, or convalescent sera and reducing SARS-CoV-2 variant infectivity. INTERPRETATION: Our results indicate that targeting evolutionarily-conserved STT3A-mediated glycosylation via an ADC can exert profound impacts on SARS-CoV-2 variant infectivity. Thus, we have identified a novel deglycosylation method suitable for eradicating SARS-CoV-2 variant infection in vitro. FUNDING: A full list of funding bodies that contributed to this study can be found in the Acknowledgements section.

Huang, S. W., et al. (2020). "Impact of Genetic Variability in ACE2 Expression on the Evolutionary Dynamics of SARS-CoV-2 Spike D614G Mutation." Genes (Basel) **12**(1).

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) glycoprotein D614G mutation became the predominant globally circulating variant after its emergence in the early coronavirus disease 2019 (COVID-19) pandemic. Studies showed that this mutation results in an open conformation of the S glycoprotein receptor-binding domain (RBD), and increased angiotensin 1-converting enzyme 2 (ACE2) binding and fusion, which result in an increase in SARS-CoV-2 transmissibility and infectivity. Dynamic tracking of SARS-CoV-2 showed that the D614G variant became predominant after emergence in Europe and North America, but not in China. The current absence of selective pressures from antiviral treatment suggests that the driving force for viral evolution could be variations in human population genetics. Results show that ACE2 expression is higher in Asian populations than that in European, North American, and African populations. This supports the idea that lower ACE2 expression is a driving force in the positive selection for the D614G mutation. This study suggests that the dynamics of the SARS-CoV-2 D614G mutation during the early-to-mid pandemic is associated with enhanced transmission efficiency in populations with lower ACE2 expression. Understanding the role that human genetic diversity plays in the adaptive evolution of

SARS-CoV-2 may have an important impact on public health and measures to control the pandemic.

Imai, M., et al. (2021). "Characterization of a new SARS-CoV-2 variant that emerged in Brazil." Proc Natl Acad Sci U S A **118**(27).

The spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) plays a key role in viral infectivity. It is also the major antigen stimulating the host's protective immune response, specifically, the production of neutralizing antibodies. Recently, a new variant of SARS-CoV-2 possessing multiple mutations in the S protein, designated P.1, emerged in Brazil. Here, we characterized a P.1 variant isolated in Japan by using Syrian hamsters, a well-established small animal model for the study of SARS-CoV-2 disease (COVID-19). In hamsters, the variant showed replicative abilities and pathogenicity similar to those of early and contemporary strains (i.e., SARS-CoV-2 bearing aspartic acid [D] or glycine [G] at position 614 of the S protein). Sera and/or plasma from convalescent patients and BNT162b2 messenger RNA vaccinees showed comparable neutralization titers across the P.1 variant, S-614D, and S-614G strains. In contrast, the S-614D and S-614G strains were less well recognized than the P.1 variant by serum from a P.1-infected patient. Prior infection with S-614D or S-614G strains efficiently prevented the replication of the P.1 variant in the lower respiratory tract of hamsters upon reinfection. In addition, passive transfer of neutralizing antibodies to hamsters infected with the P.1 variant or the S-614G strain led to reduced virus replication in the lower respiratory tract. However, the effect was less pronounced against the P.1 variant than the S-614G strain. These findings suggest that the P.1 variant may be somewhat antigenically different from the early and contemporary strains of SARS-CoV-2.

Kant, R., et al. (2021). "Common Laboratory Mice Are Susceptible to Infection with the SARS-CoV-2 Beta Variant." Viruses **13**(11).

Small animal models are of crucial importance for assessing COVID-19 countermeasures. Common laboratory mice would be well-suited for this purpose but are not susceptible to infection with wild-type SARS-CoV-2. However, the development of mouse-adapted virus strains has revealed key mutations in the SARS-CoV-2 spike protein that increase infectivity, and interestingly, many of these mutations are also present in naturally occurring SARS-CoV-2 variants of concern. This suggests that these variants might have the ability to infect common laboratory mice. Herein we show that the SARS-CoV-2 beta variant attains infectibility to BALB/c mice and causes pulmonary changes within 2-3 days post infection, consistent with results seen in other murine models of COVID-19, at a reasonable virus dose (2 x 10(5) PFU). The findings suggest that common laboratory mice can serve as the animal model of choice for testing the effectiveness of antiviral drugs and vaccines against SARS-CoV-2.

Karakasiliotis, I., et al. (2021). "Cellular senescence as a source of SARS-CoV-2 quasispecies." FEBS J.

In-depth analysis of SARS-CoV-2 biology and pathogenesis is rapidly unraveling the mechanisms through which the virus induces all aspects of COVID-19 pathology. Emergence of hundreds of variants and several important variants of concern has focused research on the mechanistic elucidation of virus mutagenesis. RNA viruses evolve quickly either through the error-prone polymerase or the RNA-editing machinery of the cell. In this review, we are discussing the links between cellular senescence, a natural aging process that has been recently linked to SARS-CoV-2 infection, and virus mutagenesis through the RNA-editing enzymes APOBEC. The action of APOBEC, enhanced by cellular senescence, is hypothesized to assist the emergence of novel variants, called quasispecies, within a cell or organism. These variants when introduced to the community may lead to the generation of a variant of concern, depending on fitness and transmissibility of the new genome. Such a mechanism of virus evolution may highlight the importance of inhibitors of cellular senescence during SARS-CoV-2 clinical treatment.

Kidd, M., et al. (2021). "S-Variant SARS-CoV-2 Lineage B1.1.7 Is Associated With Significantly Higher Viral Load in Samples Tested by TaqPath Polymerase Chain Reaction." J Infect Dis **223**(10): 1666-1670.

A SARS-CoV-2 variant B1.1.7 containing mutation Delta69/70 has spread rapidly in the United Kingdom and shows an identifiable profile in ThermoFisher TaqPath RT-qPCR, S gene target failure (SGTF). We analyzed recent test data for trends and significance. Linked cycle threshold (Ct) values for respiratory samples showed that a low Ct for ORF1ab and N were clearly associated with SGTF. Significantly more SGTF samples had higher inferred viral loads between 1x107 and 1x108. Our conclusion is that patients whose samples exhibit the SGTF profile are more likely to have high viral loads, which may explain higher infectivity and rapidity of spread.

Kim, S., et al. (2021). "Real-time ultra-sensitive detection of SARS-CoV-2 by quasi-freestanding epitaxial graphene-based biosensor." Biosens Bioelectron **197**: 113803.

We report the rapid detection of SARS-CoV-2 in infected patients (mid-turbinate swabs and exhaled breath aerosol samples) in concentrations as low as 60 copies/mL of the virus in seconds by electrical transduction of the SARS-CoV-2 S1 spike protein antigen via SARS-CoV-2 S1 spike protein antibodies immobilized on bilayer quasi-freestanding epitaxial graphene without gate or signal amplification. The sensor demonstrates the spike protein antigen detection in a concentration as low as

1 ag/mL. The heterostructure of the SARS-CoV-2 antibody/graphene-based sensor is developed through a simple and low-cost fabrication technique. Furthermore, sensors integrated into a portable testing unit distinguished B.1.1.7 variant positive samples from infected patients (mid-turbinate swabs and saliva samples, 4000-8000 copies/mL) with a response time of as fast as 0.6 s. The sensor is reusable, allowing for reimmobilization of the crosslinker and antibodies on the biosensor after desorption of biomarkers by NaCl solution or heat treatment above 40 degrees C.

King, H. A. D., et al. (2021). "Efficacy and breadth of adjuvanted SARS-CoV-2 receptor-binding domain nanoparticle vaccine in macaques." Proc Natl Acad Sci U S A **118**(38).

Emergence of novel variants of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) underscores the need for next-generation vaccines able to elicit broad and durable immunity. Here we report the evaluation of a ferritin nanoparticle vaccine displaying the receptor-binding domain of the SARS-CoV-2 spike protein (RFN) adjuvanted with Army Liposomal Formulation QS-21 (ALFQ). RFN vaccination of macaques using a two-dose regimen resulted in robust, predominantly Th1 CD4+ T cell responses and reciprocal peak mean serum neutralizing antibody titers of 14,000 to 21,000. Rapid control of viral replication was achieved in the upper and lower airways of animals after high-dose SARS-CoV-2 respiratory challenge, with undetectable replication within 4 d in seven of eight animals receiving 50 microg of RFN. Cross-neutralization activity against SARS-CoV-2 variant B.1.351 decreased only approximately twofold relative to WA1/2020. In addition, neutralizing, effector antibody and cellular responses targeted the heterotypic SARS-CoV-1, highlighting the broad immunogenicity of RFN-ALFQ for SARS-CoV-like Sarbecovirus vaccine development.

Laslett, N., et al. (2021). "Glucose-6-Phosphate Dehydrogenase Deficiency-Associated Hemolytic Anemia and Methemoglobinemia in a Patient Treated With Hydroxychloroquine in the Era of COVID-19." Cureus **13**(5): e15232.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common enzymatic disorder of red blood cells worldwide. The severity of hemolytic anemia varies among individuals with G6PD deficiency, depending on the genetic variant in the G6PD gene; this makes the diagnosis of the condition more challenging in some cases. In this report, we present a case of severe hemolytic anemia and methemoglobinemia in a patient with G6PD deficiency who had been exposed to hydroxychloroquine prescribed for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. To the best of our knowledge and based on a literature search, this is one of the first case reports in the literature about hemolytic crisis and methemoglobinemia in a patient with critical illness due to severe coronavirus disease 2019 (COVID-19) who was exposed to hydroxychloroquine. It is critical for physicians and caregivers to recognize the effects of oxidative stressors such as hydroxychloroquine, particularly in this era of the COVID-19 pandemic and in regions with a high prevalence of G6PD deficiency, for the appropriate management of this unique subset of patients.

Leach, A., et al. (2021). "A tetrameric ACE2 protein broadly neutralizes SARS-CoV-2 spike variants of concern with elevated potency." Antiviral Res **194**: 105147.

The SARS-CoV-2 receptor angiotensin converting enzyme 2 (ACE2) was previously engineered into a high affinity tetravalent format (ACE2-Fc-TD) that is a potential decoy protein in SARS-CoV-2 infection.We report that this protein shows greatly enhanced binding to SARS-CoV-2 spike proteins of the SARS-CoV-2 variants of concern B.1.1.7 (alpha variant, originally isolated in the United Kingdom) and B.1.351 (beta variant, originally isolated in South Africa) with picomolar compared with nanomolar Kd values. In addition, ACE2-Fc-TD displays greater neutralization of SARS-CoV-2 pseudotype viruses compared to a dimeric ACE2-Fc, with enhanced activity on variant B.1.351. This tetrameric decoy protein would be a valuable addition to SARS-CoV-2 therapeutic approaches, especially where vaccination cannot be used but also should there be any future coronavirus pandemics.

Leach, A., et al. (2021). "Implementing a method for engineering multivalency to substantially enhance binding of clinical trial anti-SARS-CoV-2 antibodies to wildtype spike and variants of concern proteins." Sci Rep **11**(1): 10475.

Infection by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes COVID-19 disease. Therapeutic antibodies are being developed that interact with the viral spike proteins to limit viral infection of epithelium. We have applied a method to dramatically improve the performance of anti-SARS-CoV-2 antibodies by enhancing avidity through multimerization using simple engineering to yield tetrameric antibodies. We have re-engineered six anti-SARS-CoV-2 antibodies using the human p53 tetramerization domain, including three clinical trials antibodies casirivimab, imdevimab and etesevimab. The method yields tetrameric antibodies, termed quads, that retain efficient binding to the SARS-CoV-2 spike protein, show up to two orders of magnitude enhancement in neutralization of pseudovirus infection and retain potent interaction with virus variant of concern spike proteins. The tetramerization method is simple, general and its application is a powerful methodological development for SARS-CoV-2 antibodies that are currently in pre-clinical and clinical investigation.

Lista, M. J., et al. (2021). "Resilient SARS-CoV-2 diagnostics workflows including viral heat inactivation." PLoS One **16**(9): e0256813.

There is a worldwide need for reagents to perform SARS-CoV-2 detection. Some laboratories have implemented kit-free protocols, but many others do not have the capacity to develop these and/or perform manual processing. We provide multiple workflows for SARS-CoV-2 nucleic acid detection in clinical samples by comparing several commercially available RNA extraction methods: QIAamp Viral RNA Mini Kit (QIAgen), RNAdvance Blood/Viral (Beckman) and Mag-Bind Viral DNA/RNA 96 Kit (Omega Bio-tek). We also compared One-step RT-qPCR reagents: TaqMan Fast Virus 1-Step Master Mix (FastVirus, ThermoFisher Scientific), qPCRBIO Probe 1-Step Go Lo-ROX (PCR Biosystems) and Luna(R) Universal Probe One-Step RT-qPCR Kit (Luna, NEB). We used primer-probes that detect viral N (EUA CDC) and RdRP. RNA extraction methods provided similar results, with Beckman performing better with our primer-probe combinations. Luna proved most sensitive although overall the three reagents did not show significant differences. N detection was more reliable than that of RdRP, particularly in samples with low viral titres. Importantly, we demonstrated that heat treatment of nasopharyngeal swabs at 70 degrees C for 10 or 30 min, or 90 degrees C for 10 or 30 min (both original variant and B 1.1.7) inactivated SARS-CoV-2 employing plaque assays, and had minimal impact on the sensitivity of the qPCR in clinical samples. These findings make SARS-CoV-2 testing portable in settings that do not have CL-3 facilities. In summary, we provide several testing pipelines that can be easily implemented in other laboratories and have made all our protocols and SOPs freely available at https://osf.io/uebvj/.

Madewell, Z. J., et al. (2021). "Factors Associated With Household Transmission of SARS-CoV-2: An Updated Systematic Review and Meta-analysis." JAMA Netw Open **4**(8): e2122240.

Importance: A previous systematic review and meta-analysis of household transmission of SARS-CoV-2 that summarized 54 published studies through October 19, 2020, found an overall secondary attack rate (SAR) of 16.6% (95% CI, 14.0%-19.3%). However, the understanding of household secondary attack rates for SARS-CoV-2 is still evolving, and updated analysis is needed. Objective: To use newly published data to further the understanding of SARS-CoV-2 transmission in the household. Data Sources: PubMed and reference lists of eligible articles were used to search for records published between October 20, 2020, and June 17, 2021. No restrictions on language, study design, time, or place of publication were applied. Studies published as preprints were included. Study Selection: Articles with original data that reported at least 2 of the following factors were included: number of household contacts with infection, total number of household contacts, and secondary attack rates among household contacts. Studies that reported household infection prevalence (which includes index cases), that tested contacts using antibody tests only, and that included populations overlapping with another included study were excluded. Search terms were SARS-CoV-2 or COVID-19 with secondary attack rate, household, close contacts, contact transmission, contact attack rate, or family transmission. Data Extraction and Synthesis: Meta-analyses were performed using generalized linear mixed models to obtain SAR estimates and 95% CIs. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline was followed. Main Outcomes and Measures: Overall household SAR for SARS-CoV-2, SAR by covariates (contact age, sex, ethnicity, comorbidities, and relationship; index case age, sex, symptom status, presence of fever, and presence of cough; number of contacts; study location; and variant), and SAR by index case identification period. Results: A total of 2722 records (2710 records from database searches and 12 records from the reference lists of eligible articles) published between October 20, 2020, and June 17, 2021, were identified. Of those, 93 full-text articles reporting household transmission of SARS-CoV-2 were assessed for eligibility, and 37 studies were included. These 37 new studies were combined with 50 of the 54 studies (published through October 19, 2020) from our previous review (4 studies from Wuhan, China, were excluded because their study populations overlapped with another recent study), resulting in a total of 87 studies representing 1249163 household contacts from 30 countries. The estimated household SAR for all 87 studies was 18.9% (95% CI, 16.2%-22.0%). Compared with studies from January to February 2020, the SAR for studies from July 2020 to March 2021 was higher (13.4% [95% CI, 10.7%-16.7%] vs 31.1% [95% CI, 22.6%-41.1%], respectively). Results from subgroup analyses were similar to those reported in a previous systematic review and meta-analysis; however, the SAR was higher to contacts with comorbidities (3 studies; 50.0% [95% CI, 41.4%-58.6%]) compared with previous findings, and the estimated household SAR for the B.1.1.7 (alpha) variant was 24.5% (3 studies; 95% CI, 10.9%-46.2%). Conclusions and Relevance: The findings of this study suggest that the household remains an important site of SARS-CoV-2 transmission, and recent studies have higher household SAR estimates compared with the earliest reports. More transmissible variants and vaccines may be associated with further changes.

Miersch, S., et al. (2021). "Tetravalent SARS-CoV-2 Neutralizing Antibodies Show Enhanced Potency and Resistance to Escape Mutations." J Mol Biol **433**(19): 167177.

Neutralizing antibodies (nAbs) hold promise as therapeutics against COVID-19. Here, we describe protein engineering and modular design principles that have led to the development of synthetic bivalent and tetravalent nAbs against SARS-CoV-2. The best nAb targets the host receptor binding site of the viral S-protein and tetravalent versions block entry with a potency exceeding bivalent nAbs by an order of magnitude. Structural studies show that both the bivalent and tetravalent nAbs can make multivalent interactions with a single S-protein trimer, consistent with the avidity and potency of these molecules. Significantly, we show that the tetravalent nAbs show increased tolerance to potential virus escape mutants and an emerging variant of concern. Bivalent and tetravalent nAbs can be produced at large-scale and are as stable and specific as approved antibody drugs. Our results provide a general framework for enhancing antiviral therapies against COVID-19 and related viral threats, and our strategy can be applied to virtually any antibody drug.

Miller, A., et al. (2021). "A super-potent tetramerized ACE2 protein displays enhanced neutralization of SARS-CoV-2 virus infection." Sci Rep **11**(1): 10617.

Approaches are needed for therapy of the severe acute respiratory syndrome from SARS-CoV-2 coronavirus (COVID-19). Interfering with the interaction of viral antigens with the angiotensin converting enzyme 2 (ACE-2) receptor is a promising strategy by blocking the infection of the coronaviruses into human cells. We have implemented a novel protein engineering technology to produce a super-potent tetravalent form of ACE2, coupled to the human immunoglobulin gamma1 Fc region, using a self-assembling, tetramerization domain from p53 protein. This high molecular weight Quad protein (ACE2-Fc-TD) retains binding to the SARS-CoV-2 receptor binding spike protein and can form a complex with the spike protein plus anti-viral antibodies. The ACE2-Fc-TD acts as a powerful decoy protein that out-performs soluble monomeric and dimeric ACE2 proteins and blocks both SARS-CoV-2 pseudovirus and SARS-CoV-2 virus infection with greatly enhanced efficacy. The ACE2 tetrameric protein complex promise to be important for development as decoy therapeutic proteins against COVID-19. In contrast to monoclonal antibodies, ACE2 decoy is unlikely to be affected by mutations in SARS-CoV-2 that are beginning to appear in variant forms. In addition, ACE2 multimeric proteins will be available as therapeutic proteins should new coronaviruses appear in the future because these are likely to interact with ACE2 receptor.

Miller, N. L., et al. (2021). "An Antigenic Space Framework for Understanding Antibody Escape of SARS-CoV-2 Variants." Viruses **13**(10).

The evolution of mutations in SARS-CoV-2 at antigenic sites that impact neutralizing antibody responses in humans poses a risk to immunity developed through vaccination and natural infection. The highly successful RNA-based vaccines have enabled rapid vaccine updates that incorporate mutations from current variants of concern (VOCs). It is therefore important to anticipate future antigenic mutations as the virus navigates the heterogeneous global landscape of host immunity. Toward this goal, we survey epitope-paratope interfaces of anti-SARS-CoV-2 antibodies to map an antigenic space that captures the role of each spike protein residue within the polyclonal antibody response directed against the ACE2-receptor binding domain (RBD) or the N-terminal domain (NTD). In particular, the antigenic space map builds on recently published epitope definitions by annotating epitope overlap and orthogonality at the residue level. We employ the antigenic space map as a framework to understand how mutations on nine major variants contribute to each variant's evasion of neutralizing antibodies. Further, we identify constellations of mutations that span the orthogonal epitope regions of the RBD and NTD on the variants with the greatest antibody escape. Finally, we apply the antigenic space map to predict which regions of antigenic space-should they mutate-may be most likely to complementarily augment antibody evasion for the most evasive and transmissible VOCs.

Motozono, C., et al. (2021). "SARS-CoV-2 spike L452R variant evades cellular immunity and increases infectivity." Cell Host Microbe **29**(7): 1124-1136 e1111.

Many SARS-CoV-2 variants with naturally acquired mutations have emerged. These mutations can affect viral properties such as infectivity and immune resistance. Although the sensitivity of naturally occurring SARS-CoV-2 variants to humoral immunity has been investigated, sensitivity to human leukocyte antigen (HLA)-restricted cellular immunity remains largely unexplored. Here, we demonstrate that two recently emerging mutations in the receptor-binding domain of the SARS-CoV-2 spike protein, L452R (in B.1.427/429 and B.1.617) and Y453F (in B.1.1.298), confer escape from HLA-A24-restricted cellular immunity. These mutations reinforce affinity toward the host entry receptor ACE2. Notably, the L452R mutation increases spike stability, viral infectivity, viral fusogenicity, and thereby promotes viral replication. These data suggest that HLA-restricted cellular immunity potentially affects the evolution of viral phenotypes and that a further threat of the SARS-CoV-2 pandemic is escape from cellular immunity.

Muller, N. F., et al. (2021). "Viral genomes reveal patterns of the SARS-CoV-2 outbreak in Washington State." Sci Transl Med **13**(595).

The rapid spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has gravely affected societies around the world. Outbreaks in different parts of the globe have been shaped by

repeated introductions of new viral lineages and subsequent local transmission of those lineages. Here, we sequenced 3940 SARS-CoV-2 viral genomes from Washington State (USA) to characterize how the spread of SARS-CoV-2 in Washington State in early 2020 was shaped by differences in timing of mitigation strategies across counties and by repeated introductions of viral lineages into the state. In addition, we show that the increase in frequency of a potentially more transmissible viral variant (614G) over time can potentially be explained by regional mobility differences and multiple introductions of 614G but not the other variant (614D) into the state. At an individual level, we observed evidence of higher viral loads in patients infected with the 614G variant. However, using clinical records data, we did not find any evidence that the 614G variant affects clinical severity or patient outcomes. Overall, this suggests that with regard to D614G, the behavior of individuals has been more important in shaping the course of the pandemic in Washington State than this variant of the virus.

Norman, S., et al. (2021). "Impact of the COVID-19 pandemic on neuro-oncology outcomes." J Neurooncol **154**(3): 375-381.

INTRODUCTION: The Coronavirus disease 2019 (COVID-19) pandemic has uprooted healthcare systems worldwide, disrupting care and increasing dependence on alternative forms of health care delivery. It is yet to be determined how the pandemic affected neuro-oncology patient outcomes, given that the majority of even "elective" neurosurgical oncology procedures are time-sensitive. This study quantifies changes in neuro-oncological care during the height of the pandemic and investigates patient outcomes in 2020 compared to a historical control. METHODS: We performed a retrospective review of patients with malignant brain tumor diagnoses who were seen at our institution between March 13 and May 1 of 2020 and 2019. Alterations in care, including shift from in-person to telehealth, delays in evaluation and intervention, and treatment modifications were evaluated. These variables were analyzed with respect to brain tumor control and mortality. RESULTS: 112 patients from 2020 to 166 patients from 2019 were included. There was no significant difference in outcomes between the cohorts, despite significantly more treatment delays ($p = 0.0160$) and use of telehealth ($p < 0.0001$) in 2020. Patients in 2020 who utilized telehealth visits had significantly more stable tumor control than those who had office visits ($p = 0.0124$), consistent with appropriate use of in-person visits for patients with progression. CONCLUSIONS: Our study showed that use of telehealth and selective alterations in neuro-oncological care during the COVID-19 pandemic did not lead to adverse patient outcomes. This suggests that adaptive physician-led changes were successful and may inform management during the ongoing pandemic, especially with the emergence of the Delta variant.

Omer, S. B., et al. (2021). "Promoting COVID-19 vaccine acceptance: recommendations from the Lancet Commission on Vaccine Refusal, Acceptance, and Demand in the USA." Lancet.

Since the first case of COVID-19 was identified in the USA in January, 2020, over 46 million people in the country have tested positive for SARS-CoV-2 infection. Several COVID-19 vaccines have received emergency use authorisations from the US Food and Drug Administration, with the Pfizer-BioNTech vaccine receiving full approval on Aug 23, 2021. When paired with masking, physical distancing, and ventilation, COVID-19 vaccines are the best intervention to sustainably control the pandemic. However, surveys have consistently found that a sizeable minority of US residents do not plan to get a COVID-19 vaccine. The most severe consequence of an inadequate uptake of COVID-19 vaccines has been sustained community transmission (including of the delta [B.1.617.2] variant, a surge of which began in July, 2021). Exacerbating the direct impact of the virus, a low uptake of COVID-19 vaccines will prolong the social and economic repercussions of the pandemic on families and communities, especially low-income and minority ethnic groups, into 2022, or even longer. The scale and challenges of the COVID-19 vaccination campaign are unprecedented. Therefore, through a series of recommendations, we present a coordinated, evidence-based education, communication, and behavioural intervention strategy that is likely to improve the success of COVID-19 vaccine programmes across the USA.

Patone, M., et al. (2021). "Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study." Lancet Infect Dis **21**(11): 1518-1528.

BACKGROUND: A more transmissible variant of SARS-CoV-2, the variant of concern 202012/01 or lineage B.1.1.7, has emerged in the UK. We aimed to estimate the risk of critical care admission, mortality in patients who are critically ill, and overall mortality associated with lineage B.1.1.7 compared with non-B.1.1.7. We also compared clinical outcomes between these two groups. METHODS: For this observational cohort study, we linked large primary care (QResearch), national critical care (Intensive Care National Audit & Research Centre Case Mix Programme), and national COVID-19 testing (Public Health England) databases. We used SARS-CoV-2 positive samples with S-gene molecular diagnostic assay failure (SGTF) as a proxy for the presence of lineage B.1.1.7. We extracted two cohorts from the data: the primary care cohort, comprising patients in primary care with a positive community COVID-19 test reported between Nov 1, 2020, and Jan 26, 2021, and known SGTF status; and the critical care cohort,

comprising patients admitted for critical care with a positive community COVID-19 test reported between Nov 1, 2020, and Jan 27, 2021, and known SGTF status. We explored the associations between SARS-CoV-2 infection with and without lineage B.1.1.7 and admission to a critical care unit (CCU), 28-day mortality, and 28-day mortality following CCU admission. We used Royston-Parmar models adjusted for age, sex, geographical region, other sociodemographic factors (deprivation index, ethnicity, household housing category, and smoking status for the primary care cohort; and ethnicity, body-mass index, deprivation index, and dependency before admission to acute hospital for the CCU cohort), and comorbidities (asthma, chronic obstructive pulmonary disease, type 1 and 2 diabetes, and hypertension for the primary care cohort; and cardiovascular disease, respiratory disease, metastatic disease, and immunocompromised conditions for the CCU cohort). We reported information on types and duration of organ support for the B.1.1.7 and non-B.1.1.7 groups. FINDINGS: The primary care cohort included 198 420 patients with SARS-CoV-2 infection. Of these, 117 926 (59.4%) had lineage B.1.1.7, 836 (0.4%) were admitted to CCU, and 899 (0.4%) died within 28 days. The critical care cohort included 4272 patients admitted to CCU. Of these, 2685 (62.8%) had lineage B.1.1.7 and 662 (15.5%) died at the end of critical care. In the primary care cohort, we estimated adjusted hazard ratios (HRs) of 2.15 (95% CI 1.75-2.65) for CCU admission and 1.65 (1.36-2.01) for 28-day mortality for patients with lineage B.1.1.7 compared with the non-B.1.1.7 group. The adjusted HR for mortality in critical care, estimated with the critical care cohort, was 0.91 (0.76-1.09) for patients with lineage B.1.1.7 compared with those with non-B.1.1.7 infection. INTERPRETATION: Patients with lineage B.1.1.7 were at increased risk of CCU admission and 28-day mortality compared with patients with non-B.1.1.7 SARS-CoV-2. For patients receiving critical care, mortality appeared to be independent of virus strain. Our findings emphasise the importance of measures to control exposure to and infection with COVID-19. FUNDING: Wellcome Trust, National Institute for Health Research Oxford Biomedical Research Centre, and the Medical Sciences Division of the University of Oxford.

Puray-Chavez, M., et al. (2021). "Systematic analysis of SARS-CoV-2 infection of an ACE2-negative human airway cell." Cell Rep **36**(2): 109364.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike (S) variants govern transmissibility, responsiveness to vaccination, and disease severity. In a screen for new models of SARS-CoV-2 infection, we identify human H522 lung adenocarcinoma cells as naturally permissive to SARS-CoV-2 infection despite complete absence of angiotensin-converting enzyme 2 (ACE2) expression. Remarkably, H522 infection requires the E484D S variant; viruses expressing wild-type S are not infectious. Anti-S monoclonal antibodies differentially neutralize SARS-CoV-2 E484D S in H522 cells as compared to ACE2-expressing cells. Sera from vaccinated individuals block this alternative entry mechanism, whereas convalescent sera are less effective. Although the H522 receptor remains unknown, depletion of surface heparan sulfates block H522 infection. Temporally resolved transcriptomic and proteomic profiling reveal alterations in cell cycle and the antiviral host cell response, including MDA5-dependent activation of type I interferon signaling. These findings establish an alternative SARS-CoV-2 host cell receptor for the E484D SARS-CoV-2 variant, which may impact tropism of SARS-CoV-2 and consequently human disease pathogenesis.

Rao, V. U. S., et al. (2021). "COVID-19 associated mucormycosis (CAM) in India: a formidable challenge." Br J Oral Maxillofac Surg **59**(9): 1095-1098.

Together with the ongoing serious COVID-19 second wave in India, a serious fungal infection, mucormycosis has been increasingly found in COVID-19-recovered patients. Colloquially known as 'black fungus', mucormycosis commonly causes necrosis in the head and neck including the nose, paranasal sinuses, orbits, and facial bones, with possible intracranial spread. The disease causes high morbidity and mortality given that it progresses rapidly and diagnosis is often delayed. Given the sheer magnitude of the outbreak, the Indian Health Ministry has advised all states to declare mucormycosis an epidemic. Typically, the disease has been found to be linked to COVID-19 infections caused by the B.1.617.2 (Delta) variant, which has spread rapidly throughout the country. This variant has already become a cause for global concern, having spread to at least 40 countries, including the USA and UK. We present the findings of a study conducted on COVID-19 associated mucormycosis (CAM) patients, and discuss the associated risk factors to raise awareness for OMFS colleagues.

Reuschl, A. K., et al. (2021). "Host-directed therapies against early-lineage SARS-CoV-2 retain efficacy against B.1.1.7 variant." bioRxiv.

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has resulted in millions of deaths worldwide and massive societal and economic burden. Recently, a new variant of SARS-CoV-2, known as B.1.1.7, was first detected in the United Kingdom and is spreading in several other countries, heightening public health concern and raising questions as to the resulting effectiveness of vaccines and therapeutic interventions. We and others previously identified host-directed therapies with antiviral efficacy against SARS-CoV-2 infection. Less prone to the development of therapy resistance, host-directed drugs represent promising

therapeutic options to combat emerging viral variants as host genes possess a lower propensity to mutate compared to viral genes. Here, in the first study of the full-length B.1.1.7 variant virus , we find two host-directed drugs, plitidepsin (aplidin; inhibits translation elongation factor eEF1A) and ralimetinib (inhibits p38 MAP kinase cascade), as well as remdesivir, to possess similar antiviral activity against both the early-lineage SARS-CoV-2 and the B.1.1.7 variant, evaluated in both human gastrointestinal and lung epithelial cell lines. We find that plitidepsin is over an order of magnitude more potent than remdesivir against both viruses. These results highlight the importance of continued development of host-directed therapeutics to combat current and future coronavirus variant outbreaks.

Richter, J., et al. (2021). "Molecular epidemiology of SARS-CoV-2 in Cyprus." PLoS One **16**(7): e0248792.

Whole genome sequencing of viral specimens following molecular diagnosis is a powerful analytical tool of molecular epidemiology that can critically assist in resolving chains of transmission, identifying of new variants or assessing pathogen evolution and allows a real-time view into the dynamics of a pandemic. In Cyprus, the first two cases of COVID-19 were identified on March 9, 2020 and since then 33,567 confirmed cases and 230 deaths were documented. In this study, viral whole genome sequencing was performed on 133 SARS-CoV-2 positive samples collected between March 2020 and January 2021. Phylogenetic analysis was conducted to evaluate the genomic diversity of circulating SARS-CoV-2 lineages in Cyprus. 15 different lineages were identified that clustered into three groups associated with the spring, summer and autumn/winter wave of SARS-CoV-2 incidence in Cyprus, respectively. The majority of the Cypriot samples belonged to the B.1.258 lineage first detected in September that spread rapidly and largely dominated the autumn/winter wave with a peak prevalence of 86% during the months of November and December. The B.1.1.7 UK variant (VOC-202012/01) was identified for the first time at the end of December and spread rapidly reaching 37% prevalence within one month. Overall, we describe the changing pattern of circulating SARS-CoV-2 lineages in Cyprus since the beginning of the pandemic until the end of January 2021. These findings highlight the role of importation of new variants through travel towards the emergence of successive waves of incidence in Cyprus and demonstrate the importance of genomic surveillance in determining viral genetic diversity and the timely identification of new variants for guiding public health intervention measures.

Sadoff, J., et al. (2021). "Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19." N Engl J Med **384**(23): 2187-2201.

BACKGROUND: The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion-stabilized conformation. METHODS: In an international, randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5x10(10) viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe-critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed. RESULTS: The per-protocol population included 19,630 SARS-CoV-2-negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe-critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe-critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at >/=14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at >/=28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe-critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe-critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19-related), and 16 in the placebo group (5 were Covid-19-related). CONCLUSIONS: A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe-critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of Covid-19 vaccines. (Funded by Janssen Research and Development and others; ENSEMBLE ClinicalTrials.gov number, NCT04505722.).

Saito, A., et al. (2021). "Enhanced fusogenicity and pathogenicity of SARS-CoV-2 Delta P681R mutation." Nature.

During the current SARS-CoV-2 pandemic, a variety of mutations have accumulated in the viral genome, and currently, four variants of concern (VOCs) are considered potentially hazardous to human society(1). The recently emerged

B.1.617.2/Delta VOC is closely associated with the COVID-19 surge that occurred in India in the spring of 2021(2). However, its virological properties remain unclear. Here, we show that the B.1.617.2/Delta variant is highly fusogenic and notably more pathogenic than prototypic SARS-CoV-2 in infected hamsters. The P681R mutation in the spike protein, which is highly conserved in this lineage, facilitates spike protein cleavage and enhances viral fusogenicity. Moreover, we demonstrate that the P681R-bearing virus exhibits higher pathogenicity than its parental virus. Our data suggest that the P681R mutation is a hallmark of the virological phenotype of the B.1.617.2/Delta variant and is associated with enhanced pathogenicity.

Secolin, R., et al. (2021). "Genetic variability in COVID-19-related genes in the Brazilian population." Hum Genome Var **8**: 15.

SARS-CoV-2 utilizes the angiotensin-converting enzyme 2 (ACE2) receptor and transmembrane serine protease (TMPRSS2) to infect human lung cells. Previous studies have suggested that different host ACE2 and TMPRSS2 genetic backgrounds might contribute to differences in the rate of SARS-CoV-2 infection or COVID-19 severity. Recent studies have also shown that variants in 15 genes related to type I interferon immunity to influenza virus might predispose patients toward life-threatening COVID-19 pneumonia. Other genes (SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6, XCR1, IL6, CTSL, ABO, and FURIN) and HLA alleles have also been implicated in the response to infection with SARS-CoV-2. Currently, Brazil has recorded the third-highest number of COVID-19 cases worldwide. We aimed to investigate the genetic variation present in COVID-19-related genes in the Brazilian population. We analyzed 27 candidate genes and HLA alleles in 954 admixed Brazilian exomes. We used the information available in two public databases (http://www.bipmed.org and http://abraom.ib.usp.br/) and additional exomes from individuals born in southeast Brazil, the region of the country with the highest number of COVID-19 patients. Variant allele frequencies were compared with the 1000 Genomes Project phase 3 (1KGP) and gnomAD databases. We detected 395 nonsynonymous variants; of these, 325 were also found in the 1KGP and/or gnomAD. Six of these variants were previously reported to influence the rate of infection or clinical prognosis of COVID-19. The remaining 70 variants were identified exclusively in the Brazilian sample, with a mean allele frequency of 0.0025. In silico analysis revealed that seven of these variants are predicted to affect protein function. Furthermore, we identified HLA alleles previously associated with the COVID-19 response at loci DQB1 and DRB1. Our results showed genetic variability common to other populations and rare and ultrarare variants exclusively found in the Brazilian population. These findings might lead to differences in the rate of infection or response to infection by SARS-CoV-2 and should be further investigated in patients with this disease.

Shoemaker, R. H., et al. (2021). "Development of a novel, pan-variant aerosol intervention for COVID-19." bioRxiv.

To develop a universal strategy to block SARS-CoV-2 cellular entry and infection represents a central aim for effective COVID-19 therapy. The growing impact of emerging variants of concern increases the urgency for development of effective interventions. Since ACE2 is the critical SARS-CoV-2 receptor and all tested variants bind to ACE2, some even at much increased affinity (see accompanying paper), we hypothesized that aerosol administration of clinical grade soluble human recombinant ACE2 (APN01) will neutralize SARS-CoV-2 in the airways, limit spread of infection in the lung and mitigate lung damage caused by deregulated signaling in the renin-angiotensin (RAS) and Kinin pathways. Here we show that intranasal administration of APN01 in a mouse model of SARS-CoV-2 infection dramatically reduced weight loss and prevented animal death. As a prerequisite to a clinical trial, we evaluated both virus binding activity and enzymatic activity for cleavage of Ang II following aerosolization. We report successful aerosolization for APN01, retaining viral binding as well as catalytic RAS activity. Dose range-finding and IND-enabling repeat-dose aerosol toxicology testing were conducted in dogs. Twice daily aerosol administration for two weeks at the maximum feasible concentration revealed no notable toxicities. Based on these results, a Phase I clinical trial in healthy volunteers can now be initiated, with subsequent Phase II testing in individuals with SARS-CoV-2 infection. This strategy could be used to develop a viable and rapidly actionable therapy to prevent and treat COVID-19, against all current and future SARS-CoV-2 variants.

Solanich, X., et al. (2021). "Genetic Screening for TLR7 Variants in Young and Previously Healthy Men With Severe COVID-19." Front Immunol **12**: 719115.

Introduction: Loss-of-function TLR7 variants have been recently reported in a small number of males to underlie strong predisposition to severe COVID-19. We aimed to determine the presence of these rare variants in young men with severe COVID-19. Methods: We prospectively studied males between 18 and 50 years-old without predisposing comorbidities that required at least high-flow nasal oxygen to treat COVID-19. The coding region of TLR7 was sequenced to assess the presence of potentially deleterious variants. Results: TLR7 missense variants were identified in two out of 14 patients (14.3%). Overall, the median age was 38 (IQR 30-45) years. Both variants were not previously reported in population control databases and were

predicted to be damaging by in silico predictors. In a 30-year-old patient a maternally inherited variant [c.644A>G; p.(Asn215Ser)] was identified, co-segregating in his 27-year-old brother who also contracted severe COVID-19. A second variant [c.2797T>C; p.(Trp933Arg)] was found in a 28-year-old patient, co-segregating in his 24-year-old brother who developed mild COVID-19. Functional testing of this variant revealed decreased type I and II interferon responses in peripheral mononuclear blood cells upon stimulation with the TLR7 agonist imiquimod, confirming a loss-of-function effect. Conclusions: This study supports a rationale for the genetic screening for TLR7 variants in young men with severe COVID-19 in the absence of other relevant risk factors. A diagnosis of TLR7 deficiency could not only inform on treatment options for the patient, but also enables pre-symptomatic testing of at-risk male relatives with the possibility of instituting early preventive and therapeutic interventions.

Swan, D. A., et al. (2021). "Mathematical Modeling of Vaccines That Prevent SARS-CoV-2 Transmission." Viruses **13**(10).

SARS-CoV-2 vaccine clinical trials assess efficacy against disease (VEDIS), the ability to block symptomatic COVID-19. They only partially discriminate whether VEDIS is mediated by preventing infection completely, which is defined as detection of virus in the airways (VESUSC), or by preventing symptoms despite infection (VESYMP). Vaccine efficacy against transmissibility given infection (VEINF), the decrease in secondary transmissions from infected vaccine recipients, is also not measured. Using mathematical modeling of data from King County Washington, we demonstrate that if the Moderna (mRNA-1273QS) and Pfizer-BioNTech (BNT162b2) vaccines, which demonstrated VEDIS > 90% in clinical trials, mediate VEDIS by VESUSC, then a limited fourth epidemic wave of infections with the highly infectious B.1.1.7 variant would have been predicted in spring 2021 assuming rapid vaccine roll out. If high VEDIS is explained by VESYMP, then high VEINF would have also been necessary to limit the extent of this fourth wave. Vaccines which completely protect against infection or secondary transmission also substantially lower the number of people who must be vaccinated before the herd immunity threshold is reached. The limited extent of the fourth wave suggests that the vaccines have either high VESUSC or both high VESYMP and high VEINF against B.1.1.7. Finally, using a separate intra-host mathematical model of viral kinetics, we demonstrate that a 0.6 log vaccine-mediated reduction in average peak viral load might be sufficient to achieve 50% VEINF, which suggests that human challenge studies with a relatively low number of infected participants could be employed to estimate all three vaccine efficacy metrics.

Tasakis, R. N., et al. (2021). "SARS-CoV-2 variant evolution in the United States: High accumulation of viral mutations over time likely through serial Founder Events and mutational bursts." PLoS One **16**(7): e0255169.

Since the first case of COVID-19 in December 2019 in Wuhan, China, SARS-CoV-2 has spread worldwide and within a year and a half has caused 3.56 million deaths globally. With dramatically increasing infection numbers, and the arrival of new variants with increased infectivity, tracking the evolution of its genome is crucial for effectively controlling the pandemic and informing vaccine platform development. Our study explores evolution of SARS-CoV-2 in a representative cohort of sequences covering the entire genome in the United States, through all of 2020 and early 2021. Strikingly, we detected many accumulating Single Nucleotide Variations (SNVs) encoding amino acid changes in the SARS-CoV-2 genome, with a pattern indicative of RNA editing enzymes as major mutators of SARS-CoV-2 genomes. We report three major variants through October of 2020. These revealed 14 key mutations that were found in various combinations among 14 distinct predominant signatures. These signatures likely represent evolutionary lineages of SARS-CoV-2 in the U.S. and reveal clues to its evolution such as a mutational burst in the summer of 2020 likely leading to a homegrown new variant, and a trend towards higher mutational load among viral isolates, but with occasional mutation loss. The last quartile of 2020 revealed a concerning accumulation of mostly novel low frequency replacement mutations in the Spike protein, and a hypermutable glutamine residue near the putative furin cleavage site. Finally, end of the year data and 2021 revealed the gradual increase to prevalence of known variants of concern, particularly B.1.1.7, that have acquired additional Spike mutations. Overall, our results suggest that predominant viral genomes are dynamically evolving over time, with periods of mutational bursts and unabated mutation accumulation. This high level of existing variation, even at low frequencies and especially in the Spike-encoding region may become problematic when super-spreader events, akin to serial Founder Events in evolution, drive these rare mutations to prominence.

Thomson, E. C., et al. (2021). "Circulating SARS-CoV-2 spike N439K variants maintain fitness while evading antibody-mediated immunity." Cell **184**(5): 1171-1187 e1120.

SARS-CoV-2 can mutate and evade immunity, with consequences for efficacy of emerging vaccines and antibody therapeutics. Here, we demonstrate that the immunodominant SARS-CoV-2 spike (S) receptor binding motif (RBM) is a highly variable region of S and provide epidemiological, clinical, and molecular characterization of a prevalent, sentinel RBM

mutation, N439K. We demonstrate N439K S protein has enhanced binding affinity to the hACE2 receptor, and N439K viruses have similar in vitro replication fitness and cause infections with similar clinical outcomes as compared to wild type. We show the N439K mutation confers resistance against several neutralizing monoclonal antibodies, including one authorized for emergency use by the US Food and Drug Administration (FDA), and reduces the activity of some polyclonal sera from persons recovered from infection. Immune evasion mutations that maintain virulence and fitness such as N439K can emerge within SARS-CoV-2 S, highlighting the need for ongoing molecular surveillance to guide development and usage of vaccines and therapeutics.

Tortorici, M. A., et al. (2021). "Broad sarbecovirus neutralization by a human monoclonal antibody." Nature **597**(7874): 103-108.

The recent emergence of SARS-CoV-2 variants of concern(1-10) and the recurrent spillovers of coronaviruses(11,12) into the human population highlight the need for broadly neutralizing antibodies that are not affected by the ongoing antigenic drift and that can prevent or treat future zoonotic infections. Here we describe a human monoclonal antibody designated S2X259, which recognizes a highly conserved cryptic epitope of the receptor-binding domain and cross-reacts with spikes from all clades of sarbecovirus. S2X259 broadly neutralizes spike-mediated cell entry of SARS-CoV-2, including variants of concern (B.1.1.7, B.1.351, P.1, and B.1.427/B.1.429), as well as a wide spectrum of human and potentially zoonotic sarbecoviruses through inhibition of angiotensin-converting enzyme 2 (ACE2) binding to the receptor-binding domain. Furthermore, deep-mutational scanning and in vitro escape selection experiments demonstrate that S2X259 possesses an escape profile that is limited to a single substitution, G504D. We show that prophylactic and therapeutic administration of S2X259 protects Syrian hamsters (Mesocricetus auratus) against challenge with the prototypic SARS-CoV-2 and the B.1.351 variant of concern, which suggests that this monoclonal antibody is a promising candidate for the prevention and treatment of emergent variants and zoonotic infections. Our data reveal a key antigenic site that is targeted by broadly neutralizing antibodies and will guide the design of vaccines that are effective against all sarbecoviruses.

Van Egeren, D., et al. (2021). "Controlling long-term SARS-CoV-2 infections can slow viral evolution and reduce the risk of treatment failure." Sci Rep **11**(1): 22630.

The rapid emergence and expansion of novel SARS-CoV-2 variants threatens our ability to achieve herd immunity for COVID-19. These novel SARS-CoV-2 variants often harbor multiple point mutations, conferring one or more evolutionarily advantageous traits, such as increased transmissibility, immune evasion and longer infection duration. In a number of cases, variant emergence has been linked to long-term infections in individuals who were either immunocompromised or treated with convalescent plasma. In this paper, we used a stochastic evolutionary modeling framework to explore the emergence of fitter variants of SARS-CoV-2 during long-term infections. We found that increased viral load and infection duration favor emergence of such variants. While the overall probability of emergence and subsequent transmission from any given infection is low, on a population level these events occur fairly frequently. Targeting these low-probability stochastic events that lead to the establishment of novel advantageous viral variants might allow us to slow the rate at which they emerge in the patient population, and prevent them from spreading deterministically due to natural selection. Our work thus suggests practical ways to achieve control of long-term SARS-CoV-2 infections, which will be critical for slowing the rate of viral evolution.

Vesper, N., et al. (2021). "A Barcoded Flow Cytometric Assay to Explore the Antibody Responses Against SARS-CoV-2 Spike and Its Variants." Front Immunol **12**: 730766.

The SARS-CoV-2 pandemic has spread to all parts of the world and can cause life-threatening pneumonia and other severe disease manifestations known as COVID-19. This health crisis has resulted in a significant effort to stop the spread of this new coronavirus. However, while propagating itself in the human population, the virus accumulates mutations and generates new variants with increased fitness and the ability to escape the human immune response. Here we describe a color-based barcoded spike flow cytometric assay (BSFA) that is particularly useful to evaluate and directly compare the humoral immune response directed against either wild type (WT) or mutant spike (S) proteins or the receptor-binding domains (RBD) of SARS-CoV-2. This assay employs the human B lymphoma cell line Ramos, transfected for stable expression of WT or mutant S proteins or a chimeric RBD-CD8 fusion protein. We find that the alpha and beta mutants are more stably expressed than the WT S protein on the Ramos B cell surface and/or bind with higher affinity to the viral entry receptor ACE2. However, we find a reduce expression of the chimeric RBD-CD8 carrying the point mutation N501Y and E484K characteristic for the alpha and beta variant, respectively. The comparison of the humoral immune response of 12 vaccinated probands with 12 COVID-19 patients shows that after the boost, the S-specific IgG class immune response in the vaccinated group is similar to that of the patient group. However, in comparison to WT the specific IgG serum antibodies bind less well to the alpha variant and only poorly to the beta variant S protein. This is in line with the notion that the beta variant is an immune escape variant of SARS-CoV-2. The IgA class immune response was

more variable than the IgG response and higher in the COVID-19 patients than in the vaccinated group. In summary, we think that our BSFA represents a useful tool to evaluate the humoral immunity against emerging variants of SARS-CoV-2 and to analyze new vaccination protocols against these variants.

Vidal, S. J., et al. (2021). "Correlates of Neutralization against SARS-CoV-2 Variants of Concern by Early Pandemic Sera." J Virol **95**(14): e0040421.

Emerging SARS-CoV-2 variants of concern that overcome natural and vaccine-induced immunity threaten to exacerbate the COVID-19 pandemic. Increasing evidence suggests that neutralizing antibody (NAb) responses are a primary mechanism of protection against infection. However, little is known about the extent and mechanisms by which natural immunity acquired during the early COVID-19 pandemic confers cross-neutralization of emerging variants. In this study, we investigated cross-neutralization of the B.1.1.7 and B.1.351 SARS-CoV-2 variants in a well-characterized cohort of early pandemic convalescent subjects. We observed modestly decreased cross-neutralization of B.1.1.7 but a substantial 4.8-fold reduction in cross-neutralization of B.1.351. Correlates of cross-neutralization included receptor binding domain (RBD) and N-terminal domain (NTD) binding antibodies, homologous NAb titers, and membrane-directed T cell responses. These data shed light on the cross-neutralization of emerging variants by early pandemic convalescent immune responses. IMPORTANCE Widespread immunity to SARS-CoV-2 will be necessary to end the COVID-19 pandemic. NAb responses are a critical component of immunity that can be stimulated by natural infection as well as vaccines. However, SARS-CoV-2 variants are emerging that contain mutations in the spike gene that promote evasion from NAb responses. These variants may therefore delay control of the COVID-19 pandemic. We studied whether NAb responses from early COVID-19 convalescent patients are effective against the two SARS-CoV-2 variants, B.1.1.7 and B.1.351. We observed that the B.1.351 variant demonstrates significantly reduced susceptibility to early pandemic NAb responses. We additionally characterized virological, immunological, and clinical features that correlate with cross-neutralization. These studies increase our understanding of emerging SARS-CoV-2 variants.

Winkler, E. S., et al. (2021). "SARS-CoV-2 causes lung infection without severe disease in human ACE2 knock-in mice." J Virol: JVI0151121.

The development of mouse models for COVID-19 has enabled testing of vaccines and therapeutics and defining aspects of SARS-CoV-2 pathogenesis. SARS-CoV-2 disease is severe in K18 transgenic mice (K18-hACE2-Tg) expressing human ACE2 (hACE2), the SARS-CoV-2 receptor, under an ectopic cytokeratin promoter, with high levels of infection measured in the lung and brain. Here, we evaluated SARS-CoV-2 infection in hACE2 KI mice that express hACE2 under an endogenous promoter in place of murine ACE2 (mACE2). Intranasal inoculation of hACE2 KI mice with SARS-CoV-2 WA1/2020 resulted in substantial viral replication within the upper and lower respiratory tracts with limited spread to extra-pulmonary organs. However, SARS-CoV-2-infected hACE2 KI mice did not lose weight and developed limited pathology. Moreover, no significant differences in viral burden were observed in hACE2 KI mice infected with B.1.1.7 or B.1.351 variants compared to WA1/2020 strain. Because the entry mechanisms of SARS-CoV-2 in mice remains uncertain, we evaluated the impact of the naturally-occurring, mouse-adapting N501Y mutation by comparing infection of hACE2 KI, K18-hACE2-Tg, ACE2-deficient, and wild-type C57BL/6 mice. The N501Y mutation minimally affected SARS-CoV-2 infection in hACE2 KI mice but was required for viral replication in wild-type C57BL/6 mice in a mACE2-dependent manner and augmented pathogenesis in the K18-hACE2 Tg mice. Thus, the N501Y mutation likely enhances interactions with mACE2 or hACE2 in vivo. Overall, our study highlights the hACE2 KI mice as a model of mild SARS-CoV-2 infection and disease and clarifies the requirement of the N501Y mutation in mice. IMPORTANCE Mouse models of SARS-CoV-2 pathogenesis have facilitated the rapid evaluation of countermeasures. While the first generation of models developed pneumonia and severe disease after SARS-CoV-2 infection, they relied on ectopic expression of supraphysiological levels of human ACE2 (hACE2). This has raised issues with their relevance to humans as the hACE2 receptor shows a more restricted expression pattern in the respiratory tract. Here we evaluated SARS-CoV-2 infection and disease with viruses containing or lacking a key mouse-adapting mutation in the spike gene in hACE2 KI mice, which express hACE2 under an endogenous promoter in place of murine ACE2. While infection of hACE2 KI mice with multiple strains of SARS-CoV-2 including variants of concern resulted in viral replication within the upper and lower respiratory tracts, the animals did not sustain severe lung injury. Thus, hACE2 KI mice serve as a model of mild infection with both ancestral and emerging SARS-CoV-2 variant strains.

Yang, J., et al. (2021). "Exposing structural variations in SARS-CoV-2 evolution." Sci Rep **11**(1): 22042.

The mutation of SARS-CoV-2 influences viral function as residue replacements affect both physiochemical properties and folding conformations. Although a large amount of data on SARS-CoV-2 is available, the investigation of how viral functions change in response to mutations is hampered by a lack of effective structural analysis. Here, we exploit the advances of protein structure

fingerprint technology to study the folding conformational changes induced by mutations. With integration of both protein sequences and folding conformations, the structures are aligned for SARS-CoV to SARS-CoV-2, including Alpha variant (lineage B.1.1.7) and Delta variant (lineage B.1.617.2). The results showed that the virus evolution with change in mutational positions and physicochemical properties increased the affinity between spike protein and ACE2, which plays a critical role in coronavirus entry into human cells. Additionally, these structural variations impact vaccine effectiveness and drug function over the course of SARS-CoV-2 evolution. The analysis of structural variations revealed how the coronavirus has gradually evolved in both structure and function and how the SARS-CoV-2 variants have contributed to more severe acute disease worldwide.

Zekri, A. N., et al. (2021). "Genome sequencing of SARS-CoV-2 in a cohort of Egyptian patients revealed mutation hotspots that are related to clinical outcomes." Biochim Biophys Acta Mol Basis Dis **1867**(8): 166154.

BACKGROUND: Severe acute respiratory syndrome-2 (SARS-CoV-2) exhibits a broad spectrum of clinical manifestations. Despite the fact that SARS-CoV-2 has slower evolutionary rate than other coronaviruses, different mutational hotspots have been identified along the SARS-CoV-2 genome. METHODS: We performed whole-genome high throughput sequencing on isolates from 50 Egyptian patients to see if the variation in clinical symptoms was related to mutations in the SARS-CoV-2 genome. Then, we investigated the relationship between the observed mutations and the clinical characteristics of the patients. RESULTS: Among the 36 most common mutations, we found two frameshift deletions linked to an increased risk of shortness of breath, a V6 deletion in the spike glycoprotein's signal peptide region linked to an increased risk of fever, longer fever duration and nasal congestion, and L3606-nsp6 deletion linked to a higher prevalence of cough and conjunctival congestion. S5398L nsp13-helicase was linked to an increased risk of fever duration and progression. The most common mutations (241, 3037, 14,408, and 23,403) were not linked to clinical variability. However, the E3909G-nsp7 variant was more common in children (2-13 years old) and was associated with a shorter duration of symptoms. The duration of fever was significantly reduced with E1363D-nsp3 and E3073A-nsp4. CONCLUSIONS: The most common mutations, D614G/spike-glycoprotein and P4715L/RNA-dependent-RNA-polymerase, were linked to transmissibility regardless of symptom variability. E3909G-nsp7 could explain why children recover so quickly. Nsp6-L3606fs, spike-glycoprotein-V6fs, and nsp13-S5398L variants may be linked to clinical symptom worsening. These variations related to host-virus interactions might open new therapeutic avenues for symptom relief and disease containment.

Zhang, Y. N., et al. (2021). "Mechanism of a COVID-19 nanoparticle vaccine candidate that elicits a broadly neutralizing antibody response to SARS-CoV-2 variants." bioRxiv.

Vaccines that induce potent neutralizing antibody (NAb) responses against emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are essential for combating the coronavirus disease 2019 (COVID-19) pandemic. We demonstrated that mouse plasma induced by self-assembling protein nanoparticles (SApNPs) that present 20 rationally designed S2GDeltaHR2 spikes of the ancestral Wuhan-Hu-1 strain can neutralize the B.1.1.7, B.1.351, P.1, and B.1.617 variants with the same potency. The adjuvant effect on vaccine-induced immunity was investigated by testing 16 formulations for the multilayered I3-01v9 SApNP. Using single-cell sorting, monoclonal antibodies (mAbs) with diverse neutralization breadth and potency were isolated from mice immunized with the receptor binding domain (RBD), S2GDeltaHR2 spike, and SApNP vaccines. The mechanism of vaccine-induced immunity was examined in mice. Compared with the soluble spike, the I3-01v9 SApNP showed 6-fold longer retention, 4-fold greater presentation on follicular dendritic cell dendrites, and 5-fold stronger germinal center reactions in lymph node follicles.

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