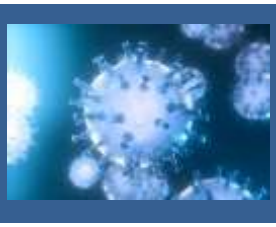
# COVID-19

*Sep 23-29, 2021*



# RESEARCH PUBLICATIONS

**Publication Date: Sep 29, 2021**

## Genomic sequencing of SARS-CoV-2 in Rwanda reveals the importance of incoming travelers on lineage diversity


### Abstract

COVID-19 transmission rates are often linked to locally circulating strains of SARS-CoV-2. Here 203 SARS-CoV-2 whole genome sequences were described and analyzed from strains circulating in Rwanda from May 2020 to February 2021. In particular, a shift was reported in variant distribution towards the emerging sub-lineage A.23.1 that is currently dominating. Furthermore, it was reported that detection of the first Rwandan cases of the B.1.1.7 and B.1.351 variants of concern among incoming travelers tested at Kigali International Airport. To assess the importance of viral introductions from neighboring countries and local transmission, available individual travel history metadata was exploited to inform spatio-temporal phylogeographic inference, enabling us to take into account infections from unsampled locations. An important role of neighboring countries in seeding introductions into Rwanda was uncovered, including those from which no genomic sequences were available. These results highlight the importance of systematic genomic surveillance and regional collaborations for a durable response towards combating COVID-19.


### Reference


https://www.nature.com/articles/s41467-021-25985-7

## Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection


### Abstract

The global supply of COVID-19 vaccines remains limited. An understanding of the immune response that is predictive of protection could facilitate rapid licensure of new vaccines. Data from a randomized efficacy trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine in the United Kingdom was analyzed to determine the antibody levels associated with protection against SARS-CoV-2. Binding and neutralizing antibodies at 28 days after the second dose were measured in infected and noninfected vaccine recipients. Higher levels of all immune markers were correlated with a reduced risk of symptomatic infection. A vaccine efficacy of 80% against symptomatic infection with majority Alpha (B.1.1.7) variant of SARS-CoV-2 was achieved with 264 (95% CI: 108, 806) binding antibody units (BAU)/ml: and 506 (95% CI: 135, not computed (beyond data range) (NC)) BAU/ml for anti-spike and anti-RBD antibodies, and 26 (95% CI: NC, NC) international unit (IU)/ml and 247 (95% CI: 101, NC) normalized neutralization titers (NF50) for pseudovirus and live-virus neutralization, respectively. Immune markers were not correlated with asymptomatic infections at the 5% significance level. These data can be used to bridge to new populations using validated assays, and allow extrapolation of efficacy estimates to new COVID-19 vaccines.


### Reference


https://www.nature.com/articles/s41591-021-01540-1


## Prospective postmortem evaluation of 735 consecutive SARS-CoV-2-associated death cases


### Abstract

Coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become a global pandemic with significant mortality. Accurate information on the specific circumstances of death and whether patients died from or with SARS-CoV-2 is scarce. To distinguish COVID-19 from non-COVID-19 deaths, we performed a systematic review of 735 SARS-CoV-2-associated deaths in Hamburg, Germany, from March to December 2020, using conventional autopsy,

ultrasound-guided minimally invasive autopsy, postmortem computed tomography and medical records. Statistical analyses including multiple logistic regression were used to compare both cohorts. 84.1% (n = 618) were classified as COVID-19 deaths, 6.4% (n = 47) as non-COVID-19 deaths, 9.5% (n = 70) remained unclear. Median age of COVID-19 deaths was 83.0 years, 54.4% were male. In the autopsy group (n = 283), the majority died of pneumonia and/or diffuse alveolar damage (73.6%; n = 187). Thromboses were found in 39.2% (n = 62/158 cases), pulmonary embolism in 22.1% (n = 56/253 cases). In 2020, annual mortality in Hamburg was about 5.5% higher than in the previous 20 years, of which 3.4% (n = 618) represented COVID-19 deaths. Our study highlights the need for mortality surveillance and postmortem examinations. The vast majority of individuals who died directly from SARS-CoV-2 infection were of advanced age and had multiple comorbidities.

**Reference**

https://www.nature.com/articles/s41598-021-98499-3

## COVID-19 hospital admissions and deaths after BNT162b2 and ChAdOx1 nCoV-19 vaccinations in 2·57 million people in Scotland (EAVE II): A prospective cohort study

**Abstract**

*Background*: The UK COVID-19 vaccination programme has prioritised vaccination of those at the highest risk of COVID-19 mortality and hospitalisation. The programme was rolled out in Scotland during winter 2020–21, when SARS-CoV-2 infection rates were at their highest since the pandemic started, despite social distancing measures being in place. We aimed to estimate the frequency of COVID-19 hospitalisation or death in people who received at least one vaccine dose and characterise these individuals.

*Methods*: A prospective cohort study was conducted using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19 (EAVE II) national surveillance platform, which contained linked vaccination, primary care, RT-PCR testing, hospitalisation, and mortality records for 5·4 million people (around 99% of the population) in Scotland. Individuals were followed up from receiving their first dose of the BNT162b2 (Pfizer–BioNTech) or ChAdOx1 nCoV-19 (Oxford–AstraZeneca) COVID-19 vaccines until admission to hospital for COVID-19, death, or the end of the study

period on April 18, 2021. A time-dependent Poisson regression model was used to estimate rate ratios (RRs) for demographic and clinical factors associated with COVID-19 hospitalisation or death 14 days or more after the first vaccine dose, stratified by vaccine type.

*Findings*: Between Dec 8, 2020, and April 18, 2021, 2 572 008 individuals received their first dose of vaccine—841 090 (32·7%) received BNT162b2 and 1 730 918 (67·3%) received ChAdOx1. 1196 (<0·1%) individuals were admitted to hospital or died due to COVID-19 illness (883 hospitalised, of whom 228 died, and 313 who died due to COVID-19 without hospitalisation) 14 days or more after their first vaccine dose. These severe COVID-19 outcomes were associated with older age (≥80 years vs 18–64 years adjusted RR 4·75, 95% CI 3·85–5·87), comorbidities (five or more risk groups vs less than five risk groups 4·24, 3·34–5·39), hospitalisation in the previous 4 weeks (3·00, 2·47–3·65), high-risk occupations (ten or more previous COVID-19 tests vs less than ten previous COVID-19 tests 2·14, 1·62–2·81), care home residence (1·63, 1·32–2·02), socioeconomic deprivation (most deprived quintile vs least deprived quintile 1·57, 1·30–1·90), being male (1·27, 1·13–1·43), and being an ex-smoker (ex-smoker vs non-smoker 1·18, 1·01–1·38). A history of COVID-19 before vaccination was protective (0·40, 0·29–0·54).

*Interpretation*: COVID-19 hospitalisations and deaths were uncommon 14 days or more after the first vaccine dose in this national analysis in the context of a high background incidence of SARS-CoV-2 infection and with extensive social distancing measures in place. Sociodemographic and clinical features known to increase the risk of severe disease in unvaccinated populations were also associated with severe outcomes in people receiving their first dose of vaccine and could help inform case management and future vaccine policy formulation.

**Reference**

https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00380-5/fulltext

## *In vivo* structure and dynamics of the SARS-CoV-2 RNA genome

**Abstract**

The dynamics of SARS-CoV-2 RNA structure and their functional relevance are largely unknown. Here we develop a simplified SPLASH assay and comprehensively map the in vivo RNA-RNA interactome of SARS-CoV-2 genome across viral life cycle. We report canonical and alternative structures including 5′-UTR and 3′-UTR, frameshifting element (FSE) pseudoknot and genome cyclization in both cells and virions. We provide direct evidence of interactions between Transcription Regulating Sequences, which facilitate discontinuous transcription. In addition, we reveal alternative short and long distance arches around FSE. More importantly, we find that within virions, while SARS-CoV-2 genome RNA undergoes intensive compaction, genome domains remain stable but with strengthened demarcation of local domains and weakened global cyclization. Taken together, our analysis reveals the structural basis for the regulation of replication, discontinuous transcription and translational frameshifting, the alternative conformations and the maintenance of global genome organization during the whole life cycle of SARS-CoV-2, which we anticipate will help develop better antiviral strategies.

**Reference**

https://www.nature.com/articles/s41467-021-25999-1

## Is glucose-6-phosphatase dehydrogenase deficiency associated with severe outcomes in hospitalized COVID-19 patients?

**Abstract**

Glucose-6-phosphate dehydrogenase deficiency (G6PDd) is known to suppress the antioxidant system and is likely to aggravate severity of COVID-19, which results in a pro-oxidant response. This possible association has not been explored adequately in human studies. In this research, we report that the occurrence of non-invasive ventilation, intubation or death—all of which are indicative of severe COVID-19, are not significantly different in hospitalized COVID-19 patients with and without G6PDd (4.6 vs. 6.4%, $p = 0.33$). The likelihood of developing any of these severe outcomes were slightly lower in patients with G6PDd after accounting for age, nationality, presence of

comorbidities and drug interventions (Odds ratio 0.40, 95% confidence intervals 0.142, 1.148). Further investigation that extends to both, hospitalized and non-hospitalized COVID-19 patients, is warranted to study this potential association.

**Reference**

https://www.nature.com/articles/s41598-021-98712-3

**Publication Date: Sep 27, 2021**

## Viral S protein histochemistry reveals few potential SARS-CoV-2 entry sites in human ocular tissues

**Abstract**

Despite the reported low expression of the primary SARS-CoV-2 receptor ACE2 in distinct ocular tissues, some clinical evidence suggests that SARS-CoV-2 can infect the eye. In this study, we explored potential entry sites for SARS-CoV-2 by viral S protein histochemistry on various ocular tissues and compared the staining patterns with RNA and protein expression of TMPRSS2 and ACE2. Potential viral entry sites were investigated by histochemistry using tagged recombinant viral S protein on 52 ocular tissue samples including specimens of the cornea, conjunctiva, lid margin, lacrimal gland tissue, retina, choroid, and RPE. In addition, ACE2 and TMPRSS2 immunohistochemistry were performed on the same ocular tissue, each with distinct antibodies binding to different epitopes. Lung tissue samples were used as positive controls. Finally, bulk RNA sequencing (RNA-Seq) was used to determine the expression of ACE2 and its auxiliary factors in the tissues mentioned above. S protein histochemistry revealed a positive staining in lung tissue but absent staining in the cornea, the conjunctiva, eye lid samples, the lacrimal glands, the retina and the optic nerve which was supported by hardly any immunoreactivity for ACE2 and TMPRSS2 and scarce ACE2 and TMPRSS2 RNA expression. Negligible staining with antibodies targeting ACE2 or TMPRSS2 was seen in the main and accessory lacrimal glands. In contrast, ocular staining (S protein, ACE2, TMPRSS2) was distinctly present in pigmented cells of the RPE and choroid, as well as in the ciliary body and the iris stroma. S protein histochemistry revealed hardly any SARS-CoV-2 entry sites in all ocular tissues examined. Similarly, no significant ACE2 or TMPRSS2 expression was

found in extra- and intraocular tissue. While this study suggest a rather low risk of ocular infection with SARS-CoV-2, it should be noted, that potential viral entry sites may increase in response to inflammation or in certain disease states.

**Reference**

https://www.nature.com/articles/s41598-021-98709-y

## Cross-neutralizing antibodies bind a SARS-CoV-2 cryptic site and resist circulating variants

**Abstract**

The emergence of numerous variants of SARS-CoV-2, the causative agent of COVID-19, has presented new challenges to the global efforts to control the COVID-19 pandemic. Here, we obtain two cross-neutralizing antibodies (7D6 and 6D6) that target Sarbecoviruses' receptor-binding domain (RBD) with sub-picomolar affinities and potently neutralize authentic SARS-CoV-2. Crystal structures show that both antibodies bind a cryptic site different from that recognized by existing antibodies and highly conserved across Sarbecovirus isolates. Binding of these two antibodies to the RBD clashes with the adjacent N-terminal domain and disrupts the viral spike. Both antibodies confer good resistance to mutations in the currently circulating SARS-CoV-2 variants. Thus, our results have direct relevance to public health as options for passive antibody therapeutics and even active prophylactics. They can also inform the design of pan-sarbecovirus vaccines.

**Reference**

https://www.nature.com/articles/s41467-021-25997-3

## Pharmacological inhibition of fatty acid synthesis blocks SARS-CoV-2 replication

**Abstract**

Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 is a virus-induced inflammatory disease of the airways and lungs that leads to severe multi-organ damage and death. Here we show that cellular lipid synthesis is required for SARS-CoV-2 replication and offers an opportunity for pharmacological intervention. Screening a short-hairpin RNA sublibrary that targets metabolic genes, we identified

genes that either inhibit or promote SARS-CoV-2 viral infection, including two key candidate genes, ACACA and FASN, which operate in the same lipid synthesis pathway. We further screened and identified several potent inhibitors of fatty acid synthase (encoded by FASN), including the US Food and Drug Administration-approved anti-obesity drug orlistat, and found that it inhibits in vitro replication of SARS-CoV-2 variants, including more contagious new variants, such as Delta. In a mouse model of SARS-CoV-2 infection (K18-hACE2 transgenic mice), injections of orlistat resulted in lower SARS-CoV-2 viral levels in the lung, reduced lung pathology and increased mouse survival. Our findings identify fatty acid synthase inhibitors as drug candidates for the prevention and treatment of COVID-19 by inhibiting SARS-CoV-2 replication. Clinical trials are needed to evaluate the efficacy of repurposing fatty acid synthase inhibitors for severe COVID-19 in humans.

**Reference**

https://www.nature.com/articles/s42255-021-00479-4

## AGO CLIP-based imputation of potent siRNA sequences targeting SARS-CoV-2 with antifibrotic miRNA-like activity

**Abstract**

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is associated with fatal pulmonary fibrosis. Small interfering RNAs (siRNAs) can be developed to induce RNA interference against SARS-CoV-2, and their susceptible target sites can be inferred by Argonaute crosslinking immunoprecipitation sequencing (AGO CLIP). Here, by reanalysing AGO CLIP data in RNA viruses, we delineated putative AGO binding in the conserved non-structural protein 12 (nsp12) region encoding RNA-dependent RNA polymerase (RdRP) in SARS-CoV-2. We utilised the inferred AGO binding to optimise the local RNA folding parameter to calculate target accessibility and predict all potent siRNA target sites in the SARS-CoV-2 genome, avoiding sequence variants. siRNAs loaded onto AGO also repressed seed (positions 2–8)-matched transcripts by acting as microRNAs (miRNAs). To utilise this, we further screened 13 potential siRNAs whose seed sequences were matched to known antifibrotic miRNAs and confirmed their miRNA-like activity. A miR-27-mimicking siRNA designed to target the nsp12 region (27/RdRP) was validated to

silence a synthesised nsp12 RNA mimic in lung cell lines and function as an antifibrotic miR-27 in regulating target transcriptomes related to TGF-β signalling. siRNA sequences with an antifibrotic miRNA-like activity that could synergistically treat COVID-19 are available online (http://clip.korea.ac.kr/covid19).

**Reference**

https://www.nature.com/articles/s41598-021-98708-z

**Publication Date: Sep 25, 2021**

## CD147 antibody specifically and effectively inhibits infection and cytokine storm of SARS-CoV-2 and its variants delta, alpha, beta, and gamma

**Abstract**

SARS-CoV-2 mutations contribute to increased viral transmissibility and immune escape, compromising the effectiveness of existing vaccines and neutralizing antibodies. An in-depth investigation on COVID-19 pathogenesis is urgently needed to develop a strategy against SARS-CoV-2 variants. Here, we identified CD147 as a universal receptor for SARS-CoV-2 and its variants. Meanwhile, Meplazeumab, a humanized anti-CD147 antibody, could block cellular entry of SARS-CoV-2 and its variants—alpha, beta, gamma, and delta, with inhibition rates of 68.7, 75.7, 52.1, 52.1, and 62.3% at 60 μg/ml, respectively. Furthermore, humanized CD147 transgenic mice were susceptible to SARS-CoV-2 and its two variants, alpha and beta. When infected, these mice developed exudative alveolar pneumonia, featured by immune responses involving alveoli-infiltrated macrophages, neutrophils, and lymphocytes and activation of IL-17 signaling pathway. Mechanistically, we proposed that severe COVID-19-related cytokine storm is induced by a “spike protein-CD147-CyPA signaling axis”: Infection of SARS-CoV-2 through CD147 initiated the JAK-STAT pathway, which further induced expression of cyclophilin A (CyPA); CyPA reciprocally bound to CD147 and triggered MAPK pathway. Consequently, the MAPK pathway regulated the expression of cytokines and chemokines, which promoted the development of cytokine storm. Importantly, Meplazumab could effectively inhibit viral entry and inflammation caused by SARS-CoV-2 and its variants. Therefore, our findings provided a new perspective for

severe COVID-19-related pathogenesis. Furthermore, the validated universal receptor for SARS-CoV-2 and its variants can be targeted for COVID-19 treatment.

**Reference**

https://www.nature.com/articles/s41392-021-00760-8

**Titers of SARS CoV-2 antibodies in cord blood of neonates whose mothers contracted SARS CoV-2 (COVID-19) during pregnancy and in those whose mothers were vaccinated with mRNA to SARS CoV-2 during pregnancy**

**Abstract**

*Objective*: We compared neonatal immunity after vaccination against SARS-CoV-2 during pregnancy to that achieved after maternal infection.

*Study design*: We tested cord blood from women infected with SARS-CoV-2 during pregnancy (group 1, n = 29), women who were vaccinated during pregnancy (group 2, n = 29) and from women not infected and not vaccinated (Group 3, n = 21) for titers of antibodies to both SARS-CoV-2 spike and 'N' proteins.

*Results*: Seventy-nine women were included: Antibodies against SARS-CoV-2 spike protein were detected in all samples from Group 1 and 2. Antibodies to the 'N' protein were detected in 25/29 samples in Group 1. None of the samples from Group 3 had antibodies to either protein. Mean titers of SARS-CoV-2 antibodies were significantly higher in Group 2 than in Group 1 ($p < 0.05$).

*Conclusions*: Neonates born to mothers vaccinated during pregnancy have higher antibody titers and may therefore have more prolonged protection than those born to women infected during pregnancy.

**Reference**

https://www.nature.com/articles/s41372-021-01216-1

## Distinct immune signatures discriminate between asymptomatic and presymptomatic SARS-CoV-2$^{pos}$ subjects


### Abstract

Increasing numbers of SARS-CoV-2-positive (SARS-CoV-2pos) subjects are detected at silent SARS-CoV-2 infection stage (SSIS). Yet, SSIS represents a poorly examined time-window wherein unknown immunity patterns may contribute to the fate determination towards persistently asymptomatic or overt disease. Here, we retrieved blood samples from 19 asymptomatic and 12 presymptomatic SARS-CoV-2pos subjects, 47 age/gender-matched patients with mild or moderate COVID-19 and 27 normal subjects, and interrogated them with combined assays of 44-plex CyTOF, RNA-seq and Olink. Notably, both asymptomatic and presymptomatic subjects exhibited numerous readily detectable immunological alterations, while certain parameters including more severely decreased frequencies of CD107alow classical monocytes, intermediate monocytes, non-classical monocytes and CD62Lhi CD8+ Tnaïve cells, reduced plasma STC1 level but an increased frequency of CD4+ NKT cells combined to distinguish the latter. Intercorrelation analyses revealed a particular presymptomatic immunotype mainly manifesting as monocytic overactivation and differentiation blockage, a likely lymphocyte exhaustion and immunosuppression, yielding mechanistic insights into SSIS fate determination, which could potentially improve SARS-CoV-2 management.


### Reference

https://www.nature.com/articles/s41422-021-00562-1

## The combined treatment of Molnupiravir and Favipiravir results in a potentiation of antiviral efficacy in a SARS-CoV-2 hamster infection model

**Abstract**

*Background*: Favipiravir and Molnupiravir, orally available antivirals, have been reported to exert antiviral activity against SARS-CoV-2. First efficacy data have been recently reported in COVID-19 patients.

*Methods*: We here report on the combined antiviral effect of both drugs in a SARS-CoV-2 Syrian hamster infection model. The infected hamsters were treated twice daily with the vehicle (the control group) or a suboptimal dose of each compound or a combination of both compounds.

*Findings*: When animals were treated with a combination of suboptimal doses of Molnupiravir and Favipiravir at the time of infection, a marked combined potency at endpoint is observed. Infectious virus titers in the lungs of animals treated with the combination are reduced by ~5 log10 and infectious virus are no longer detected in the lungs of >60% of treated animals. When start of treatment was delayed with one day a reduction of titers in the lungs of 2.4 log10 was achieved. Moreover, treatment of infected animals nearly completely prevented transmission to co-housed untreated sentinels. Both drugs result in an increased mutation frequency of the remaining viral RNA recovered from the lungs of treated animals. In the combo-treated hamsters, an increased frequency of C-to-T mutations in the viral RNA is observed as compared to the single treatment groups which may explain the pronounced antiviral potency of the combination.

*Interpretation*: Our findings may lay the basis for the design of clinical studies to test the efficacy of the combination of Molnupiravir/Favipiravir in the treatment of COVID-19.

**Reference**

https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00388-1/fulltext

## Time since SARS-CoV-2 infection and humoral immune response following BNT162b2 mRNA vaccination


### Abstract

*Background*: To optimise the use of available SARS-CoV-2 vaccines, some advocate delaying second vaccination for individuals infected within six months. We studied whether post-vaccination immune response is equally potent in individuals infected over six months prior to vaccination.

*Methods*: We tested serum IgG binding to SARS-CoV-2 spike protein and neutralising capacity in 110 healthcare workers, before and after both BNT162b2 messenger RNA (mRNA) vaccinations. We compared outcomes between participants with more recent infection (n = 18, median two months, IQR 2-3), with infection-vaccination interval over six months (n = 19, median nine months, IQR 9-10), and to those not previously infected (n = 73).

*Findings*: Both recently and earlier infected participants showed comparable humoral immune responses after a single mRNA vaccination, while exceeding those of previously uninfected persons after two vaccinations with 2.5 fold ($p = 0.003$) and 3.4 fold ($p < 0.001$) for binding antibody levels, and 6.4 and 7.2 fold for neutralisation titres, respectively (both $p < 0.001$). The second vaccine dose yielded no further substantial improvement of the humoral response in the previously infected participants (0.97 fold, $p = 0.92$), while it was associated with a 4 fold increase in antibody binding levels and 18 fold increase in neutralisation titres in previously uninfected participants (both $p < 0.001$). Adjustment for potential confounding of sex and age did not affect these findings.

*Interpretation*: Delaying the second vaccination in individuals infected up to ten months prior may constitute a more efficient use of limited vaccine supplies.


### Reference


https://www.thelancet.com/journals/ebiom/article/PIIS2352-3964(21)00382-0/fulltext