RICERCA BIBLIOGRAFICA COVID 19

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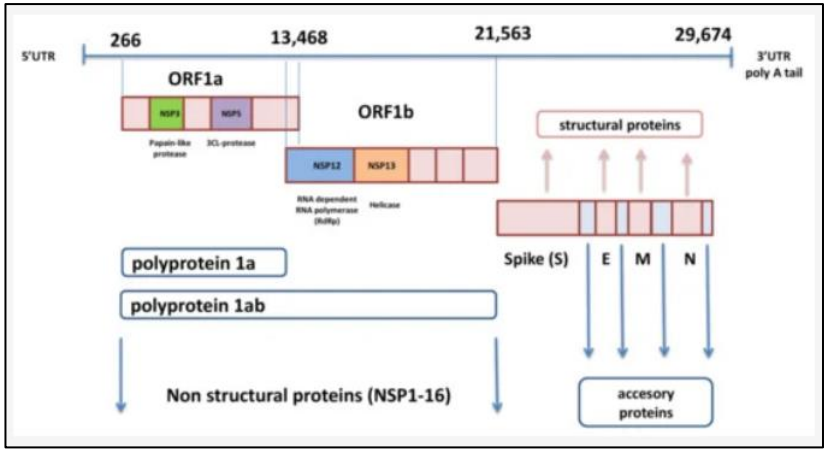
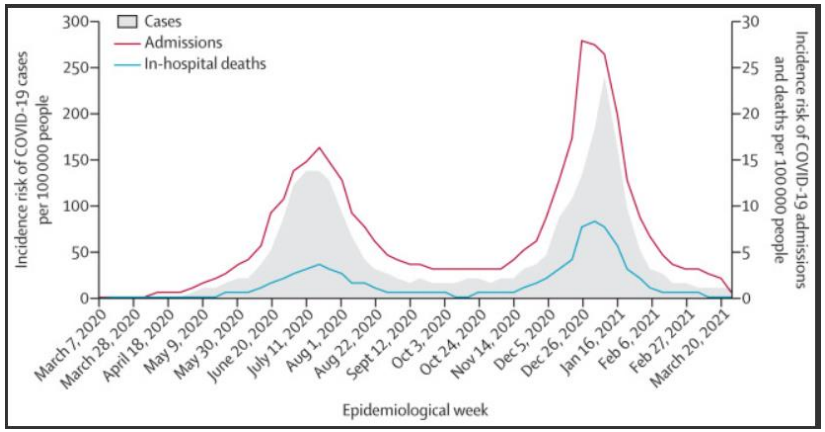
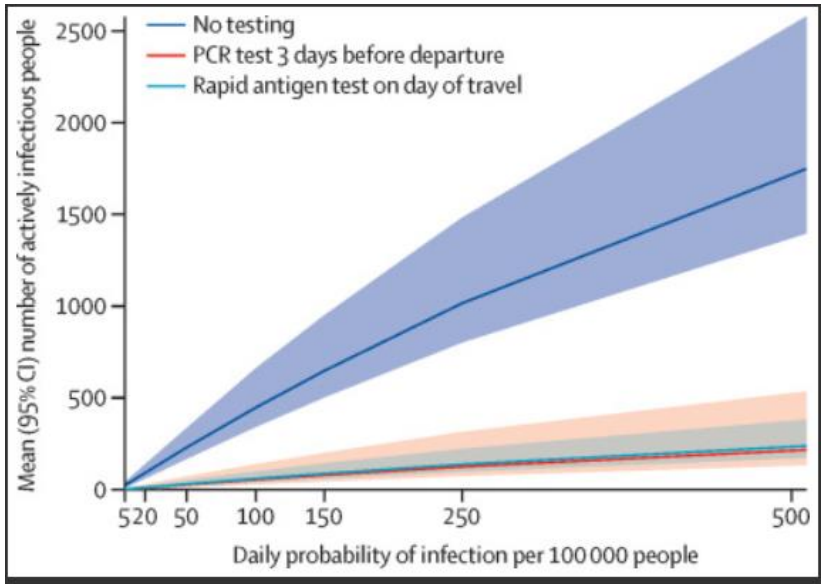
AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
Lazarevic I et al Viruses https://www.mdpi.com/1999-4915/13/7/1192	Immune Evasion of SARS-CoV-2 Emerging Variants: What Have We Learnt So Far?	Una review sulle varianti di SARS-CoV-2.	Despite the slow evolutionary rate of SARS-CoV-2 relative to other RNA viruses, its massive and rapid transmission during the COVID-19 pandemic has enabled it to acquire significant genetic diversity since it first entered the human population. This led to the emergence of numerous variants, some of them recently being labeled “variants of concern” (VOC), due to their potential impact on transmission, morbidity/mortality, and the evasion of neutralization by antibodies elicited by infection, vaccination, or therapeutic application. The potential to evade neutralization is the result of diversity of the target epitopes generated by the accumulation of mutations in the spike protein. While three globally recognized VOCs (Alpha or B.1.1.7, Beta or B.1.351, and Gamma or P.1) remain sensitive to neutralization albeit at reduced levels by the sera of convalescent individuals and recipients of several anti-COVID19 vaccines, the effect of spike variability is much more evident on the neutralization capacity of monoclonal antibodies.

			The newly recognized VOC Delta or lineage B.1.617.2, as well as locally accepted VOCs (Epsilon or B.1.427/29-US and B1.1.7 with the E484K-UK) are indicating the necessity of close monitoring of new variants on a global level. The VOCs characteristics, their mutational patterns, and the role mutations play in immune evasion are summarized in this review. 
Jassat W et al The Lancet https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(21)00289-8/fulltext	Difference in mortality among individuals admitted to hospital with COVID-19 during the first and second waves in South Africa: a cohort study	Aumentata mortalità in una coorte di pazienti ricoverati in Sudafrica per COVID-19 durante la seconda « ondata » rispetto alla prima.	Background The first wave of COVID-19 in South Africa peaked in July, 2020, and a larger second wave peaked in January, 2021, in which the SARS-CoV-2 501Y.V2 (Beta) lineage predominated. We aimed to compare in-hospital mortality and other patient characteristics between the first and second waves. Methods In this prospective cohort study, we analysed data from the DATCOV national active surveillance system for COVID-19 admissions to hospital from March 5, 2020, to March 27, 2021. The system contained data from all hospitals in South Africa that have admitted a patient with COVID-19. We used incidence risk for

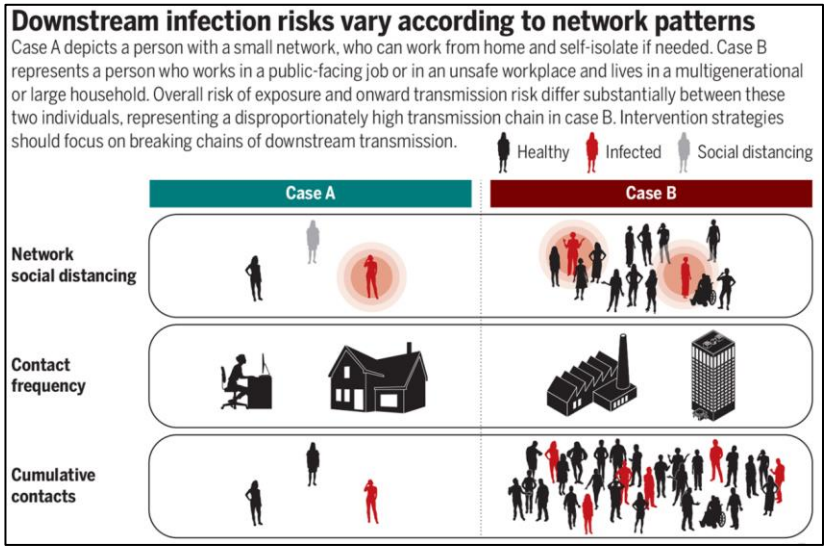
			admission to hospital and determined cutoff dates to define five wave periods: pre-wave 1, wave 1, post-wave 1, wave 2, and post-wave 2. We compared the characteristics of patients with COVID-19 who were admitted to hospital in wave 1 and wave 2, and risk factors for in-hospital mortality accounting for wave period using random-effect multivariable logistic regression. Findings Peak rates of COVID-19 cases, admissions, and in-hospital deaths in the second wave exceeded rates in the first wave: COVID-19 cases, 240·4 cases per 100 000 people vs 136·0 cases per 100 000 people; admissions, 27·9 admissions per 100 000 people vs 16·1 admissions per 100 000 people; deaths, 8·3 deaths per 100 000 people vs 3·6 deaths per 100 000 people. The weekly average growth rate in hospital admissions was 20% in wave 1 and 43% in wave 2 (ratio of growth rate in wave 2 compared with wave 1 was 1·19, 95% CI 1·18–1·20). Compared with the first wave, individuals admitted to hospital in the second wave were more likely to be age 40–64 years (adjusted odds ratio [aOR] 1·22, 95% CI 1·14–1·31), and older than 65 years (aOR 1·38, 1·25–1·52), compared with younger than 40 years; of Mixed race (aOR 1·21, 1·06–1·38) compared with White race; and admitted in the public sector (aOR 1·65, 1·41–1·92); and less likely to be Black (aOR 0·53, 0·47–0·60) and Indian (aOR 0·77, 0·66–0·91), compared with White; and have a comorbid condition (aOR 0·60, 0·55–0·67). For multivariable analysis, after adjusting for weekly COVID-19 hospital admissions, there was a 31% increased risk of in-hospital mortality in the second wave (aOR 1·31, 95% CI 1·28–1·35). In-hospital case-fatality risk increased from 17·7% in weeks of low admission (<3500 admissions) to 26·9% in weeks of very high admission (>8000 admissions; aOR 1·24, 1·17–1·32). Interpretation

			In South Africa, the second wave was associated with higher incidence of COVID-19, more rapid increase in admissions to hospital, and increased in-hospital mortality. Although some of the increased mortality can be explained by admissions in the second wave being more likely in older individuals, in the public sector, and by the increased health system pressure, a residual increase in mortality of patients admitted to hospital could be related to the new Beta lineage. 
Kiang MV et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00134-1/fulltext	Routine asymptomatic testing strategies for airline travel during the COVID-19 pandemic: a simulation study	Strategie per favorire gli spostamenti in aereo contrastando la diffusione di SARS-CoV-2.	Background Routine viral testing strategies for SARS-CoV-2 infection might facilitate safe airline travel during the COVID-19 pandemic and mitigate global spread of the virus. However, the effectiveness of these test-and-travel strategies to reduce passenger risk of SARS-CoV-2 infection and population-level transmission remains unknown. Methods In this simulation study, we developed a microsimulation of SARS-CoV-2 transmission in a cohort of 100 000 US domestic airline travellers using publicly available data on COVID-19 clinical cases and published natural history parameters to assign individuals one

			of five health states of susceptible to infection, latent period, early infection, late infection, or recovered. We estimated a per-day risk of infection with SARS-CoV-2 corresponding to a daily incidence of 150 infections per 100 000 people. We assessed five testing strategies: (1) anterior nasal PCR test within 3 days of departure, (2) PCR within 3 days of departure and 5 days after arrival, (3) rapid antigen test on the day of travel (assuming 90% of the sensitivity of PCR during active infection), (4) rapid antigen test on the day of travel and PCR test 5 days after arrival, and (5) PCR test 5 days after arrival. Strategies 2 and 4 included a 5-day quarantine after arrival. The travel period was defined as 3 days before travel to 2 weeks after travel. Under each scenario, individuals who tested positive before travel were not permitted to travel. The primary study outcome was cumulative number of infectious days in the cohort over the travel period without isolation or quarantine (population-level transmission risk), and the key secondary outcome was the number of infectious people detected on the day of travel (passenger risk of infection). Findings We estimated that in a cohort of 100 000 airline travellers, in a scenario with no testing or screening, there would be 8357 (95% uncertainty interval 6144–12831) infectious days with 649 (505–950) actively infectious passengers on the day of travel. The pre-travel PCR test reduced the number of infectious days from 8357 to 5401 (3917–8677), a reduction of 36% (29–41) compared with the base case, and identified 569 (88% [76–92]) of 649 actively infectious travellers on the day of flight; the addition of post-travel quarantine and PCR reduced the number of infectious days to 2520 days (1849–4158), a reduction of 70% (64–75) compared with the base case. The rapid antigen test on the day of travel reduced the

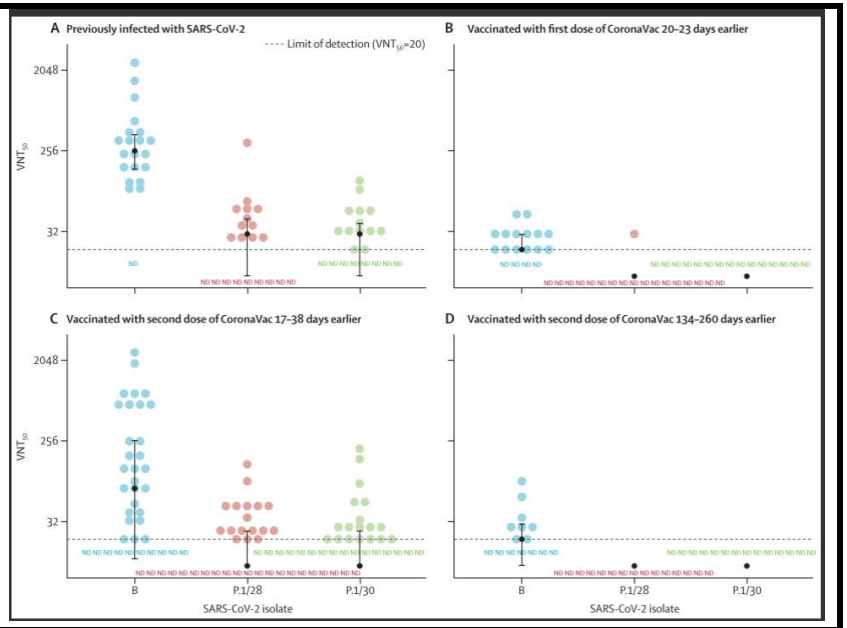
			number of infectious days to 5674 (4126–9081), a reduction of 32% (26–38) compared with the base case, and identified 560 (86% [83–89]) actively infectious travellers; the addition of post-travel quarantine and PCR reduced the number of infectious days to 3124 (2356–495), a reduction of 63% (58–66) compared with the base case. The post-travel PCR alone reduced the number of infectious days to 4851 (3714–7679), a reduction of 42% (35–49) compared with the base case. Interpretation Routine asymptomatic testing for SARS-CoV-2 before travel can be an effective strategy to reduce passenger risk of infection during travel, although abbreviated quarantine with post-travel testing is probably needed to reduce population-level transmission due to importation of infection when travelling from a high to low incidence setting. 

Lavin M et al British Journal of Hematology https://onlinelibrary.wiley.com/doi/10.1111/bjh.17613	Vaccine-induced immune thrombotic thrombocytopenia (VITT) – a novel clinico-pathological entity with heterogeneous clinical presentations	Conoscenze attuali sulla VITT, trombocitopenia trombotica immune indotta da vaccino, a partire da 4 casi clinici.	Vaccine-induced immune thrombotic thrombocytopenia (VITT) is a novel entity that emerged in March 2021 following reports of unusual thrombosis after ChAdOx1 nCoV-19, (AstraZeneca) vaccination. Following the recognition of this syndrome, multiple consensus guidelines have been released to risk stratify patients presenting with possible symptoms after ChAdOx1 nCoV-19 vaccination. All guidelines rapidly identify VITT in patients with the complete triad of thrombocytopenia, thrombosis and elevated D-dimers after ChAdOx1 nCoV-19 vaccination. However, with earlier recognition of the associated symptoms, the clinical manifestations are likely to be more heterogeneous and represent an evolving spectrum of disease. In this setting, current guidelines may lack the sensitivity to detect early cases of VITT and risk missed or delayed diagnoses. The broad clinical phenotype and challenges associated with diagnosis of VITT are highlighted in our present case series of four patients with confirmed VITT. Dependent on the guidance used, each patient could have been classified as a low probability of VITT at presentation. The present study highlights the issues associated with the recognition of VITT, the limitations of current guidance and the need for heightened clinical vigilance as our understanding of the pathophysiology of this novel condition evolves.
Cevik M et al Science https://science.sciencemag.org/content/373/6551/162	Networks of SARS-CoV-2 transmission	Strategie per limitare la diffusione di SARS-CoV-2 e futuri virus pandemici basate sullo studio dei network di trasmissione.	The basic reproduction number, R0 (the number of infections caused by a case in a homogeneously susceptible population), for a particular infection is dependent on the epidemiological triad of the biological characteristics of the pathogen, the environment, and the characteristics of the population (1). Even for diseases with similar transmission characteristics, R0 varies by population owing to differential opportunities for onward transmission according to the contact patterns and the size of the transmission network of an

			infected individual (1). Although transmission can happen in many settings, some factors facilitate a greater risk of infection because of compounded risks often driven by network dynamics (frequent contacts, close proximity, and prolonged contact) and structural-level determinants (such as poverty, occupation, and household size) (2–4). Understanding drivers of transmission risks and heterogeneity could be used to improve modeling and guide population- and setting-specific mitigation strategies. 
Souza WM et al The Lancet https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00129-4/fulltext	Neutralisation of SARS-CoV-2 lineage P.1 by antibodies elicited through natural SARS-CoV-2 infection or vaccination with an inactivated SARS-CoV-2 vaccine: an immunological study	Il plasma di soggetti guariti da SARS-CoV-2 prima della diffusione della variante delta / »brasiliana » neutralizza la variante stessa con titolo quasi 9 volte maggiore (quindi meno efficace).	Background Mutations accrued by SARS-CoV-2 lineage P.1—first detected in Brazil in early January, 2021—include amino acid changes in the receptor-binding domain of the viral spike protein that also are reported in other variants of concern, including B.1.1.7 and B.1.351. We aimed to investigate whether isolates of wild-type P.1 lineage SARS-CoV-2 can escape from neutralising antibodies generated by a polyclonal immune response. Methods

			We did an immunological study to assess the neutralising effects of antibodies on lineage P.1 and lineage B isolates of SARS-CoV-2, using plasma samples from patients previously infected with or vaccinated against SARS-CoV-2. Two specimens (P.1/28 and P.1/30) containing SARS-CoV-2 lineage P.1 (as confirmed by viral genome sequencing) were obtained from nasopharyngeal and bronchoalveolar lavage samples collected from patients in Manaus, Brazil, and compared against an isolate of SARS-CoV-2 lineage B (SARS.CoV2/SP02.2020) recovered from a patient in Brazil in February, 2020. Isolates were incubated with plasma samples from 21 blood donors who had previously had COVID-19 and from a total of 53 recipients of the chemically inactivated SARS-CoV-2 vaccine CoronaVac: 18 individuals after receipt of a single dose and an additional 20 individuals (38 in total) after receipt of two doses (collected 17–38 days after the most recent dose); and 15 individuals who received two doses during the phase 3 trial of the vaccine (collected 134–230 days after the second dose). Antibody neutralisation of P.1/28, P.1/30, and B isolates by plasma samples were compared in terms of median virus neutralisation titre (VNT50, defined as the reciprocal value of the sample dilution that showed 50% protection against cytopathic effects). Findings In terms of VNT50, plasma from individuals previously infected with SARS-CoV-2 had an 8·6 times lower neutralising capacity against the P.1 isolates (median VNT50 30 [IQR <20–45] for P.1/28 and 30 [<20–40] for P.1/30) than against the lineage B isolate (260 [160–400]), with a binominal model showing significant reductions in lineage P.1 isolates compared with the lineage B isolate (p≤0·0001). Efficient neutralisation of P.1 isolates was not seen with plasma samples collected from individuals vaccinated with a first dose of CoronaVac

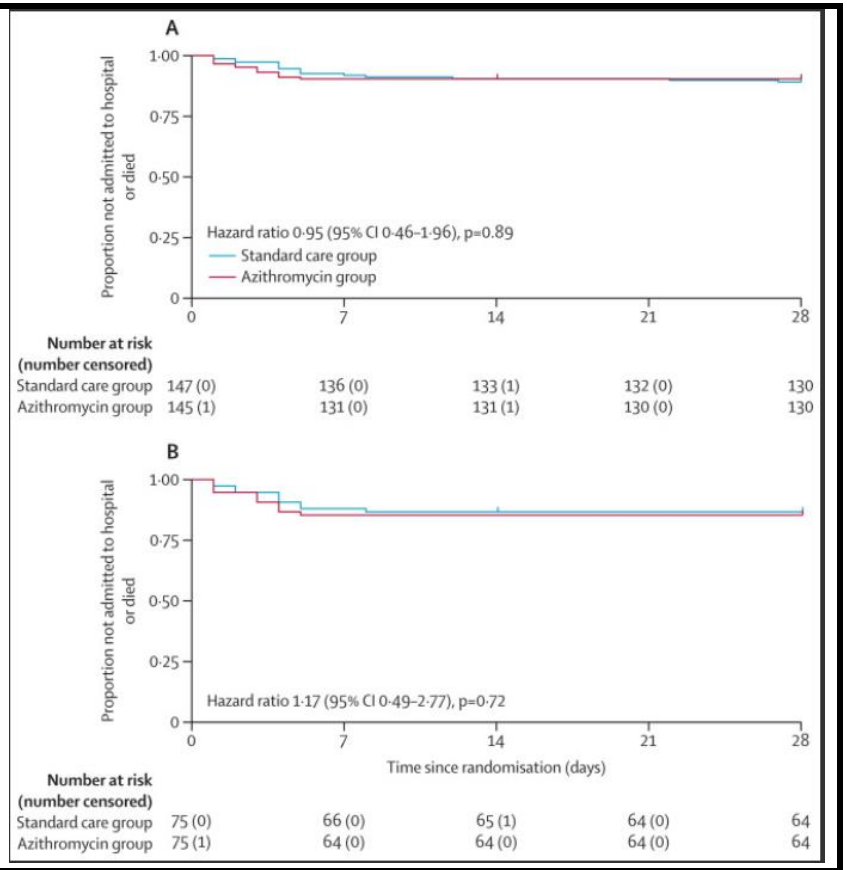
			20–23 days earlier (VNT50s below the limit of detection [<20] for most plasma samples), a second dose 17–38 days earlier (median VNT50 24 [IQR <20–25] for P.1/28 and 28 [<20–25] for P.1/30), or a second dose 134–260 days earlier (all VNT50s below limit of detection). Median VNT50s against the lineage B isolate were 20 (IQR 20–30) after a first dose of CoronaVac 20–23 days earlier, 75 (<20–263) after a second dose 17–38 days earlier, and 20 (<20–30) after a second dose 134–260 days earlier. In plasma collected 17–38 days after a second dose of CoronaVac, neutralising capacity against both P.1 isolates was significantly decreased (p=0·0051 for P.1/28 and p=0·0336 for P.1/30) compared with that against the lineage B isolate. All data were corroborated by results obtained through plaque reduction neutralisation tests. Interpretation SARS-CoV-2 lineage P.1 might escape neutralisation by antibodies generated in response to polyclonal stimulation against previously circulating variants of SARS-CoV-2. Continuous genomic surveillance of SARS-CoV-2 combined with antibody neutralisation assays could help to guide national immunisation programmes. Funding São Paulo Research Foundation, Brazilian Ministry of Science, Technology and Innovation and Funding Authority for Studies, Medical Research Council, National Council for Scientific and Technological Development, National Institutes of Health.

			
Mahil SK et al The Lancet https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00212-5/fulltext	The effect of methotrexate and targeted immunosuppression on humoral and cellular immune responses to the COVID-19 vaccine BNT162b2: a cohort study	Risposta cellulo-mediata conservata in pazienti trattati con immunosoppressori per la psoriasi, indipendentemente dal fatto che si osservi una risposta umorale dopo il vaccino.	Background Patients on therapeutic immunosuppressants for immune-mediated inflammatory diseases were excluded from COVID-19 vaccine trials. We therefore aimed to evaluate humoral and cellular immune responses to COVID-19 vaccine BNT162b2 (Pfizer-BioNTech) in patients taking methotrexate and commonly used targeted biological therapies, compared with healthy controls. Given the roll-out of extended interval vaccination programmes to maximise population coverage, we present findings after the first dose. Methods In this cohort study, we recruited consecutive patients with a dermatologist-confirmed diagnosis of psoriasis who were receiving methotrexate or targeted biological monotherapy (tumour necrosis factor [TNF] inhibitors, interleukin [IL]-17 inhibitors, or IL-23 inhibitors) from a specialist psoriasis centre serving London and

			South East England. Consecutive volunteers without psoriasis and not receiving systemic immunosuppression who presented for vaccination at Guy's and St Thomas' NHS Foundation Trust (London, UK) were included as the healthy control cohort. All participants had to be eligible to receive the BNT162b2 vaccine. Immunogenicity was evaluated immediately before and on day 28 (±2 days) after vaccination. The primary outcomes were humoral immunity to the SARS-CoV-2 spike glycoprotein, defined as neutralising antibody responses to wild-type SARS-CoV-2, and spike-specific T-cell responses (including interferon-γ, IL-2, and IL-21) 28 days after vaccination. Findings Between Jan 14 and April 4, 2021, 84 patients with psoriasis (17 on methotrexate, 27 on TNF inhibitors, 15 on IL-17 inhibitors, and 25 on IL-23 inhibitors) and 17 healthy controls were included. The study population had a median age of 43 years (IQR 31–52), with 56 (55%) males, 45 (45%) females, and 85 (84%) participants of White ethnicity. Seroconversion rates were lower in patients receiving immunosuppressants (60 [78%; 95% CI 67–87] of 77) than in controls (17 [100%; 80–100] of 17), with the lowest rate in those receiving methotrexate (seven [47%; 21–73] of 15). Neutralising activity against wild-type SARS-CoV-2 was significantly lower in patients receiving methotrexate (median 50% inhibitory dilution 129 [IQR 40–236]) than in controls (317 [213–487], p=0·0032), but was preserved in those receiving targeted biologics (269 [141–418]). Neutralising titres against the B.1.1.7 variant were similarly low in all participants. Cellular immune responses were induced in all groups, and were not attenuated in patients receiving methotrexate or targeted biologics compared with controls. Interpretation

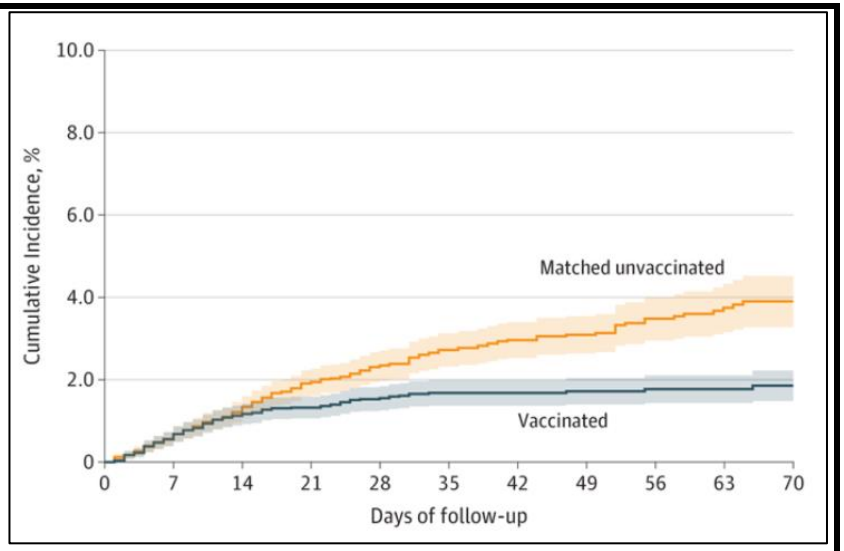
			Functional humoral immunity to a single dose of BNT162b2 is impaired by methotrexate but not by targeted biologics, whereas cellular responses are preserved. Seroconversion alone might not adequately reflect vaccine immunogenicity in individuals with immune-mediated inflammatory diseases receiving therapeutic immunosuppression. Real-world pharmacovigilance studies will determine how these findings reflect clinical effectiveness.
Hinks TSC et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00263-0/fulltext	Azithromycin versus standard care in patients with mild-to-moderate COVID-19 (ATOMIC2): an open-label, randomised trial	L'aggiunta di azitromicina alla terapia standard per COVID-19 moderato-lieve non apporta un beneficio in termini di ospedalizzazione o decesso.	Background The antibacterial, anti-inflammatory, and antiviral properties of azithromycin suggest therapeutic potential against COVID-19. Randomised data in mild-to-moderate disease are not available. We assessed whether azithromycin is effective in reducing hospital admission in patients with mild-to-moderate COVID-19. Methods This prospective, open-label, randomised superiority trial was done at 19 hospitals in the UK. We enrolled adults aged at least 18 years presenting to hospitals with clinically diagnosed, highly probable or confirmed COVID-19 infection, with fewer than 14 days of symptoms, who were considered suitable for initial ambulatory management. Patients were randomly assigned (1:1) to azithromycin (500 mg once daily orally for 14 days) plus standard care or to standard care alone. The primary outcome was death or hospital admission from any cause over the 28 days from randomisation. The primary and safety outcomes were assessed according to the intention-to-treat principle. This trial is registered at ClinicalTrials.gov (NCT04381962) and recruitment is closed. Findings 298 participants were enrolled from June 3, 2020, to Jan 29, 2021. Three participants withdrew consent and requested removal of all data, and three further participants withdrew consent after

			randomisation, thus, the primary outcome was assessed in 292 participants (145 in the azithromycin group and 147 in the standard care group). The mean age of the participants was 45·9 years (SD 14·9). 15 (10%) participants in the azithromycin group and 17 (12%) in the standard care group were admitted to hospital or died during the study (adjusted OR 0·91 [95% CI 0·43–1·92], p=0·80). No serious adverse events were reported. Interpretation In patients with mild-to-moderate COVID-19 managed without hospital admission, adding azithromycin to standard care treatment did not reduce the risk of subsequent hospital admission or death. Our findings do not support the use of azithromycin in patients with mild-to-moderate COVID-19.

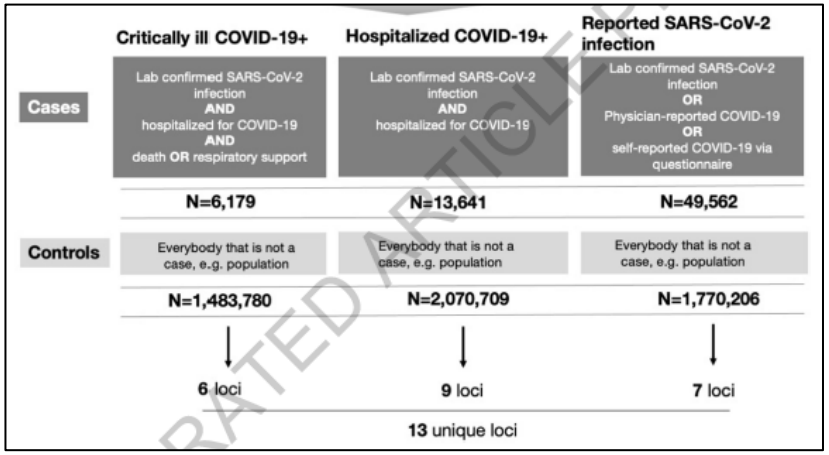
			
Reynolds CJ et al Science https://pubmed.ncbi.nlm.nih.gov/33931567/	Prior SARS-CoV-2 infection rescues B and T cell responses to variants after first vaccine dose	Aumento dell'immunità T e B cellulare, attiva contro le varianti « inglese » e « sudafricana » di SARS-CoV-2, dopo una dose di vaccino Pfizer in persone con storia di COVID-19.	SARS-CoV-2 vaccine rollout has coincided with the spread of variants of concern. We investigated if single dose vaccination, with or without prior infection, confers cross protective immunity to variants. We analyzed T and B cell responses after first dose vaccination with the Pfizer/BioNTech mRNA vaccine BNT162b2 in healthcare workers (HCW) followed longitudinally, with or without prior Wuhan-Hu-1 SARS-CoV-2 infection. After one dose, individuals with prior infection showed enhanced T cell immunity, antibody secreting memory B cell response to spike and neutralizing

			antibodies effective against B.1.1.7 and B.1.351. By comparison, HCW receiving one vaccine dose without prior infection showed reduced immunity against variants. B.1.1.7 and B.1.351 spike mutations resulted in increased, abrogated or unchanged T cell responses depending on human leukocyte antigen (HLA) polymorphisms. Single dose vaccination with BNT162b2 in the context of prior infection with a heterologous variant substantially enhances neutralizing antibody responses against variants.
Goldshtein I et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2782047?guestAccessKey=119e3c9e-dcab-42ff-95ce-e9fb7ff5e1c9&utm_source=silverchair&utm_medium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=071221	Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women	Ridotta incidenza di infezione da SARS-CoV-2 nelle donne in gravidanza vaccinate con vaccino a mRNA secondo questo studio osservazionale.	Importance Data on BNT162b2 messenger RNA (mRNA) vaccine (Pfizer-BioNTech) effectiveness and safety in pregnancy are currently lacking because pregnant women were excluded from the phase 3 trial. Objective To assess the association between receipt of BNT162b2 mRNA vaccine and risk of SARS-CoV-2 infection among pregnant women. Design, Setting, and Participants This was a retrospective cohort study within the pregnancy registry of a large state-mandated health care organization in Israel. Pregnant women vaccinated with a first dose from December 19, 2020, through February 28, 2021, were 1:1 matched to unvaccinated women by age, gestational age, residential area, population subgroup, parity, and influenza immunization status. Follow-up ended on April 11, 2021. Exposures Exposure was defined by receipt of the BNT162b2 mRNA vaccine. To maintain comparability, nonexposed women who were subsequently vaccinated were censored 10 days after their exposure, along with their matched pair. Main Outcomes and Measures The primary outcome was polymerase chain reaction–validated SARS-CoV-2 infection at 28 days or more after the first vaccine dose.

			Results The cohort included 7530 vaccinated and 7530 matched unvaccinated women, 46% and 33% in the second and third trimester, respectively, with a mean age of 31.1 years (SD, 4.9 years). The median follow-up for the primary outcome was 37 days (interquartile range, 21-54 days; range, 0-70). There were 118 SARS-CoV-2 infections in the vaccinated group and 202 in the unvaccinated group. Among infected women, 88 of 105 (83.8%) were symptomatic in the vaccinated group vs 149 of 179 (83.2%) in the unvaccinated group (P ≥ .99). During 28 to 70 days of follow-up, there were 10 infections in the vaccinated group and 46 in the unvaccinated group. The hazards of infection were 0.33% vs 1.64% in the vaccinated and unvaccinated groups, respectively, representing an absolute difference of 1.31% (95% CI, 0.89%-1.74%), with an adjusted hazard ratio of 0.22 (95% CI, 0.11-0.43). Vaccine-related adverse events were reported by 68 patients; none was severe. The most commonly reported symptoms were headache (n = 10, 0.1%), general weakness (n = 8, 0.1%), nonspecified pain (n = 6, <0.1%), and stomachache (n = 5, <0.1%). Conclusions and Relevance In this retrospective cohort study of pregnant women, BNT162b2 mRNA vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection. Interpretation of study findings is limited by the observational design.

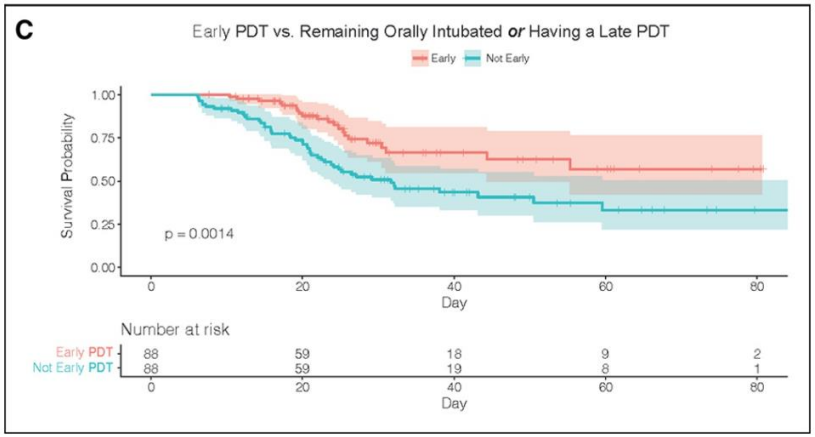
			
Gan HH et al JMB https://doi.org/10.1016/j.jmb.2021.167051	Structural Modeling of the SARS-CoV-2 Spike/Human ACE2 Complex Interface can Identify High-Affinity Variants Associated with Increased Transmissibility	Modello dell'interazione fra ACE2 e RBD della proteina spike di SARS-CoV-2 alla ricerca delle mutazioni associate a maggiore affinità-	The COVID-19 pandemic has triggered concerns about the emergence of more infectious and pathogenic viral strains. As a public health measure, efficient screening methods are needed to determine the func- tional effects of new sequence variants. Here we show that structural modeling of SARS-CoV-2 Spike protein binding to the human ACE2 receptor, the first step in host-cell entry, predicts many novel variant combinations with enhanced binding affinities. By focusing on natural variants at the Spike-hACE2 inter- face and assessing over 700 mutant complexes, our analysis reveals that high-affinity Spike mutations (including N440K, S443A, G476S, E484R, G502P) tend to cluster near known human ACE2 recognition sites (K31 and K353). These Spike regions are tructurally flexible, allowing certain mutations to optimize interface interaction energies. Although most human ACE2 variants tend to weaken binding affinity, they can interact with Spike mutations to generate high-affinity double mutant complexes, suggesting variation

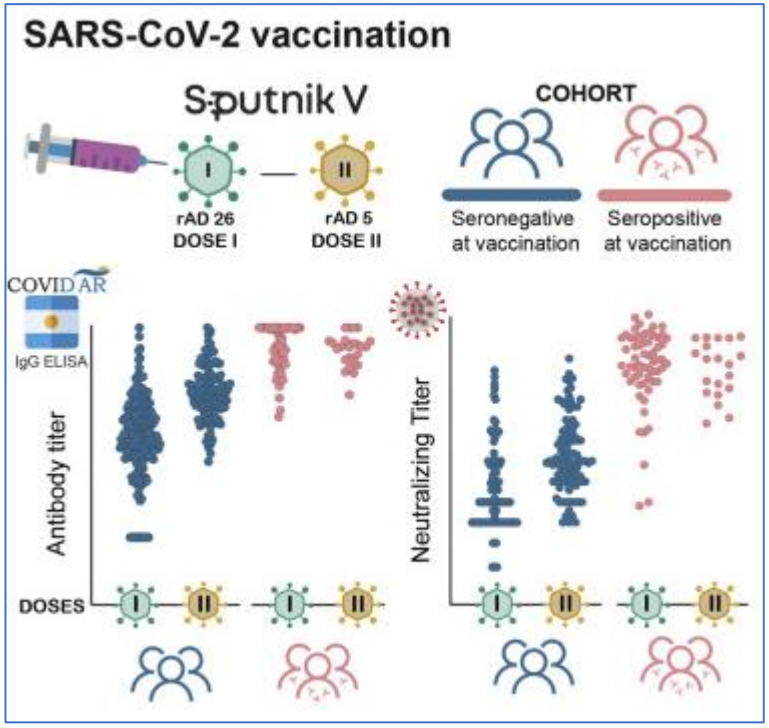
			in individual susceptibility to infection. Applying structural analysis to highly transmissible variants, we find that circulating point mutations S477N, E484K and N501Y form high-affinity complexes (~40% more than wild-type). By combining predicted affinities and available antibody escape data, we show that fast-spreading viral variants exploit combinatorial mutations possessing both enhanced affinity and antibody resistance, including S477N/E484K, E484K/N501Y and K417T/E484K/N501Y. Thus, three-dimensional modeling of the Spike/hACE2 complex predicts changes in structure and binding affinity that correlate with transmissibility and therefore can help inform future intervention strategies.
COVID-19 Host genetic initiative Nature https://www.nature.com/articles/s41586-021-03767-x	Mapping the human genetic architecture of COVID-19	Porzioni del genoma umano associate al rischio di COVID-19 grave. Non sorprende che alcune siano già note per associazione con patologie infiammatorie polmonari e autoimmunità.	The genetic makeup of an individual contributes to susceptibility and response to viral infection. While environmental, clinical and social factors play a role in exposure to SARS-CoV-2 and COVID-19 disease severity1,2, host genetics may also be important. Identifying host-specific genetic factors may reveal biological mechanisms of therapeutic relevance and clarify causal relationships of modifiable environmental risk factors for SARS-CoV-2 infection and outcomes. We formed a global network of researchers to investigate the role of human genetics in SARS-CoV-2 infection and COVID-19 severity. We describe the results of three genome-wide association meta-analyses comprised of up to 49,562 COVID-19 patients from 46 studies across 19 countries. We reported 13 genome-wide significant loci that are associated with SARS-CoV-2 infection or severe manifestations of COVID-19. Several of these loci correspond to previously documented associations to lung or autoimmune and inflammatory diseases3–7. They also represent potentially actionable mechanisms in response to infection. Mendelian Randomization analyses support a causal role for smoking and body mass index for severe COVID-19 although not for type II diabetes.

			The identification of novel host genetic factors associated with COVID-19, with unprecedented speed, was made possible by the community of human genetic researchers coming together to prioritize sharing of data, results, resources and analytical frameworks. This working model of international collaboration underscores what is possible for future genetic discoveries in emerging pandemics, or indeed for any complex human disease. 
Barizien N et al Scientific Reports https://www.nature.com/articles/s41598-021-93546-5	Clinical characterization of dysautonomia in long COVID-19 patients	Disautonomie nei pazienti con « long » COVID-19.	Increasing numbers of COVID-19 patients, continue to experience symptoms months after recovering from mild cases of COVID-19. Amongst these symptoms, several are related to neurological manifestations, including fatigue, anosmia, hypogeusia, headaches and hypoxia. However, the involvement of the autonomic nervous system, expressed by a dysautonomia, which can aggregate all these neurological symptoms has not been prominently reported. Here, we hypothesize that dysautonomia, could occur in secondary COVID-19 infection, also referred to as “long COVID” infection. 39 participants were included from December 2020 to January 2021 for assessment by the Department of physical medicine to enhance their physical capabilities: 12 participants with COVID-19 diagnosis

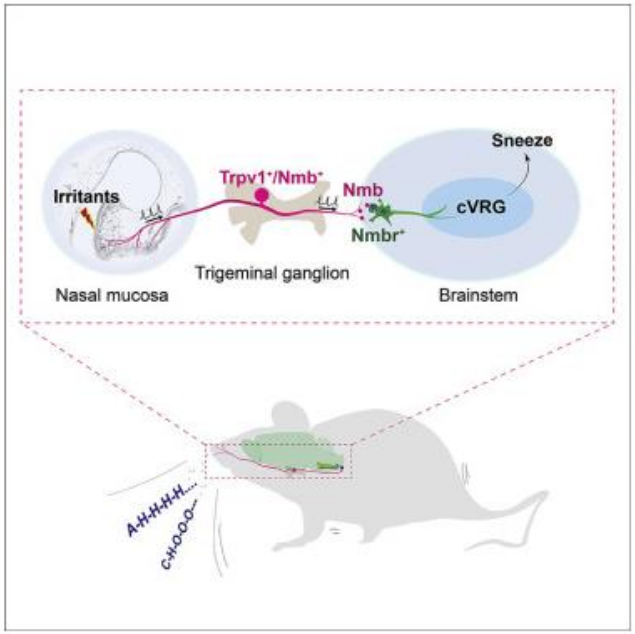
			and fatigue, 15 participants with COVID-19 diagnosis without fatigue and 12 control participants without COVID-19 diagnosis and without fatigue. Heart rate variability (HRV) during a change in position is commonly measured to diagnose autonomic dysregulation. In this cohort, to reflect HRV, parasympathetic/sympathetic balance was estimated using the NOL index, a multiparameter artificial intelligence-driven index calculated from extracted physiological signals by the PMD-200 pain monitoring system. Repeated-measures mixed-models testing group effect were performed to analyze NOL index changes over time between groups. A significant NOL index dissociation over time between long COVID-19 participants with fatigue and control participants was observed (p = 0.046). A trend towards significant NOL index dissociation over time was observed between long COVID-19 participants without fatigue and control participants (p = 0.109). No difference over time was observed between the two groups of long COVID-19 participants (p = 0.904). Long COVID-19 participants with fatigue may exhibit a dysautonomia characterized by dysregulation of the HRV, that is reflected by the NOL index measurements, compared to control participants. Dysautonomia may explain the persistent symptoms observed in long COVID-19 patients, such as fatigue and hypoxia.
Angel LF et al Critical Care Medicine https://journals.lww.com/ccmjournal/Fulltext/2021/07000/Percutaneous_Dil	Percutaneous Dilational Tracheostomy for Coronavirus Disease 2019 Patients Requiring Mechanical Ventilation	Il confezionamento precoce di tracheostomia percutanea in pazienti sottoposti a ventilazione meccanica per COVID-19 è associato a migliori outcome clinici ed è sicuro per il personale.	OBJECTIVES: To assess the impact of percutaneous dilational tracheostomy in coronavirus disease 2019 patients requiring mechanical ventilation and the risk for healthcare providers. DESIGN: Prospective cohort study; patients were enrolled between March 11, and April 29, 2020. The date of final follow-up was July 30, 2020. We used a propensity score matching approach to compare

ational_Tracheostomy_for.6.aspx			outcomes. Study outcomes were formulated before data collection and analysis. SETTING: Critical care units at two large metropolitan hospitals in New York City. PATIENTS: Five-hundred forty-one patients with confirmed severe coronavirus disease 2019 respiratory failure requiring mechanical ventilation. INTERVENTIONS: Bedside percutaneous dilational tracheostomy with modified visualization and ventilation. MEASUREMENTS AND MAIN RESULTS: Required time for discontinuation off mechanical ventilation, total length of hospitalization, and overall patient survival. Of the 541 patients, 394 patients were eligible for a tracheostomy. One-hundred sixteen were early percutaneous dilational tracheostomies with median time of 9 days after initiation of mechanical ventilation (interquartile range, 7–12 d), whereas 89 were late percutaneous dilational tracheostomies with a median time of 19 days after initiation of mechanical ventilation (interquartile range, 16–24 d). Compared with patients with no tracheostomy, patients with an early percutaneous dilational tracheostomy had a higher probability of discontinuation from mechanical ventilation (absolute difference, 30%; $p < 0.001$; hazard ratio for successful discontinuation, 2.8; 95% CI, 1.34–5.84; $p = 0.006$) and a lower mortality (absolute difference, 34%, $p < 0.001$; hazard ratio for death, 0.11; 95% CI, 0.06–0.22; $p < 0.001$). Compared with patients with late percutaneous dilational tracheostomy, patients with early percutaneous dilational tracheostomy had higher discontinuation rates from mechanical ventilation (absolute difference 7%; $p < 0.35$; hazard ratio for

			successful discontinuation, 1.53; 95% CI, 1.01–2.3; p = 0.04) and had a shorter median duration of mechanical ventilation in survivors (absolute difference, –15 d; p < 0.001). None of the healthcare providers who performed all the percutaneous dilational tracheostomies procedures had clinical symptoms or any positive laboratory test for severe acute respiratory syndrome coronavirus 2 infection. CONCLUSIONS: In coronavirus disease 2019 patients on mechanical ventilation, an early modified percutaneous dilational tracheostomy was safe for patients and healthcare providers and associated with improved clinical outcomes. 
Rossi AH et al Cell https://www.cell.com/cell-reports-	Sputnik V Vaccine Elicits Seroconversion and Neutralizing Capacity to SARS CoV-2 after a Single Dose	Effetto di una singola dose di vaccino Sputnik V in soggetti con e senza storia di COVID-19.	Massive vaccination offers great promise for halting the global COVID-19 pandemic. However, limited supply and uneven vaccine distribution create an urgent need to optimize vaccination strategies. We evaluate SARS-CoV-2-specific antibody responses after Sputnik V vaccination of healthcare workers in Argentina, measuring IgG anti-spike titers and neutralizing capacity after one and two doses in a cohort of naïve or previously infected

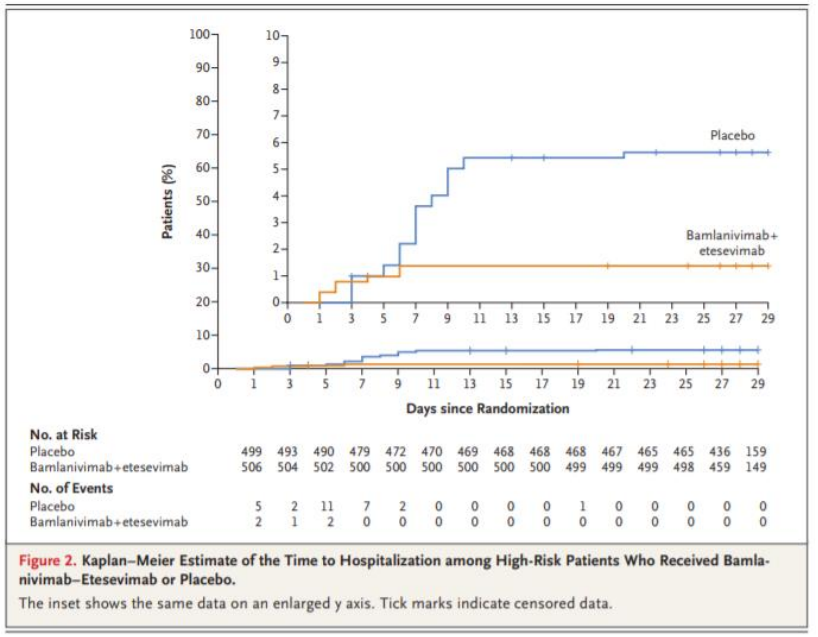
medicine/fulltext/S2666-3791(21)00208-1			volunteers. By 21 days after receiving the first dose of vaccine, 94% of naïve participants develop spike-specific IgG antibodies. A single Sputnik V dose elicits higher antibody levels and virus neutralizing capacity in previously infected individuals than in naïve ones receiving the full two-dose schedule. The high seroconversion rate after a single dose in naïve participants suggests a benefit of delaying second dose administration to increase the number of people vaccinated. The data presented provide information for guiding public health decisions in light of the current global health emergency. 

Li F et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00634-6	Sneezing reflex is mediated by a peptidergic pathway from nose to brainstem	Arco riflesso dello starnuto, un sintomo che pur non essendo molto associato a COVID-19 genera notoriamente imbarazzo e riprovazione collettiva in questi ultimi tempi.	Sneezing is a vital respiratory reflex frequently associated with allergic rhinitis and viral respiratory infections. However, its neural circuit remains largely unknown. A sneeze-evoking region was discovered in both cat and human brainstems, corresponding anatomically to the central recipient zone of nasal sensory neurons. Therefore, we hypothesized that a neuronal population postsynaptic to nasal sensory neurons mediates sneezing in this region. By screening major presynaptic neurotransmitters/neuropeptides released by nasal sensory neurons, we found that neuromedin B (NMB) peptide is essential for signaling sneezing. Ablation of NMB-sensitive postsynaptic neurons in the sneeze-evoking region or deficiency in NMB receptor abolished the sneezing reflex. Remarkably, NMB-sensitive neurons further project to the caudal ventral respiratory group (cVRG). Chemical activation of NMB-sensitive neurons elicits action potentials in cVRG neurons and leads to sneezing behavior. Our study delineates a peptidergic pathway mediating sneezing, providing molecular insights into the sneezing reflex arc.

			
Gupta T et al Rev Med Virol https://doi.org/10.1002/rmv.2276	Hydroxychloroquine in the treatment of coronavirus disease 2019: Rapid updated systematic review and meta-analysis	Revisione sistematica e metanalisi sul ruolo di idrossiclorochina nella terapia di COVID-19, a più di un anno dallo studio ritirato da Lancet.	Coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 continues to grow and spread throughout the world since being declared a pandemic. Despite extensive scientific research globally including repurposing of several existing drugs, there is no effective or proven therapy for this enigmatic disease which is still largely managed empirically This systematic review evaluated the role of hydroxychloroquine (HCQ) in the treatment of COVID-19 infection and was conducted using Cochrane methodology for systematic reviews of interventional studies including risk of bias assessment and grading of the quality of evidence. Only prospective clinical trials randomly assigning COVID-19 patients to HCQ plus standard of care therapy (test arm) versus placebo/standard of care (control arm) were included. Data were pooled using the random-effects model and expressed as risk

			ratio (RR) with 95% confidence interval (CI). A total of 10,492 patients from 19 randomised controlled trials were included. The use of HCQ was not associated with higher rates of clinical improvement (RR = 1.00, 95% CI: 0.96-1.03, p = 0.79) or reduction in all-cause mortality by Day14 (RR = 1.07, 95% CI: 0.97-1.19, p = 0.19) or Day28 (RR = 1.08, 95% CI: 0.99-1.19, p = 0.09) compared to placebo/standard of care. There was no significant difference in serious adverse events between the two arms (RR = 1.01, 95% CI: 0.85-1.19, p = 0.95). There is low-to-moderate certainty evidence that HCQ therapy is generally safe but does not reduce mortality or enhance recovery in patients with COVID-19 infection.
Dougan M et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2102685?query=featured_home	Bamlanivimab plus Etesevimab in Mild or Moderate Covid-19	Trial clinico di fase 3 in cui si osserva come il trattamento con bamlamivimab + etesevimab in pazienti non ospedalizzati con COVID-19, trattati entro 3 giorni dall'esordio e a rischio di progressione, riduce le ospedalizzazioni.	BACKGROUND Patients with underlying medical conditions are at increased risk for severe coronavirus disease 2019 (Covid-19). Whereas vaccine-derived immunity develops over time, neutralizing monoclonal-antibody treatment provides immediate, passive immunity and may limit disease progression and complications. METHODS In this phase 3 trial, we randomly assigned, in a 1:1 ratio, a cohort of ambulatory patients with mild or moderate Covid-19 who were at high risk for progression to severe disease to receive a single intravenous infusion of either a neutralizing monoclonal-antibody combination agent (2800 mg of bamlanivimab and 2800 mg of etesevimab, administered together) or placebo within 3 days after a laboratory diagnosis of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The primary outcome was the overall clinical status of the patients, defined as Covid-19–related hospitalization or death from any cause by day 29. RESULTS

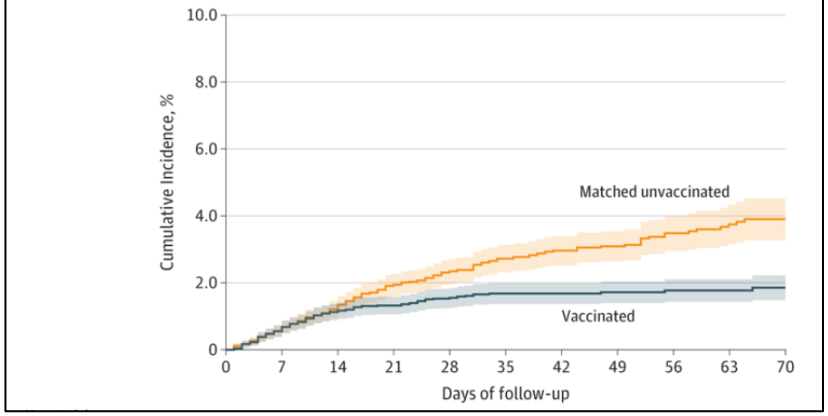
			A total of 1035 patients underwent randomization and received an infusion of bamlanivimab–etesevimab or placebo. The mean (±SD) age of the patients was 53.8±16.8 years, and 52.0% were adolescent girls or women. By day 29, a total of 11 of 518 patients (2.1%) in the bamlanivimab–etesevimab group had a Covid-19–related hospitalization or death from any cause, as compared with 36 of 517 patients (7.0%) in the placebo group (absolute risk difference, −4.8 percentage points; 95% confidence interval [CI], −7.4 to −2.3; relative risk difference, 70%; P<0.001). No deaths occurred in the bamlanivimab–etesevimab group; in the placebo group, 10 deaths occurred, 9 of which were designated by the trial investigators as Covid-19–related. At day 7, a greater reduction from baseline in the log viral load was observed among patients who received bamlanivimab plus etesevimab than among those who received placebo (difference from placebo in the change from baseline, −1.20; 95% CI, −1.46 to −0.94; P<0.001). CONCLUSIONS Among high-risk ambulatory patients, bamlanivimab plus etesevimab led to a lower incidence of Covid-19–related hospitalization and death than did placebo and accelerated the decline in the SARS-CoV-2 viral load.

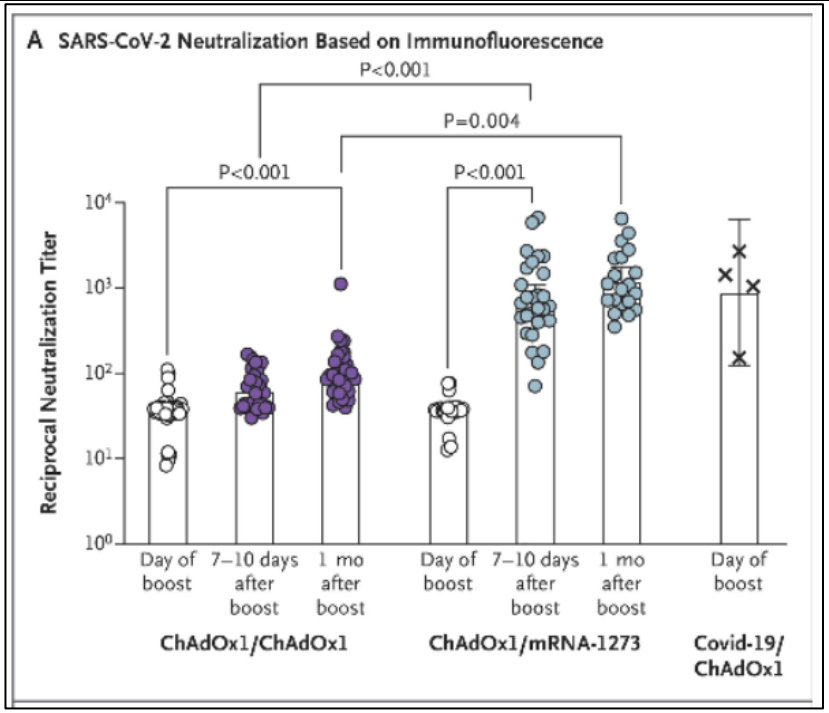
			 **Figure 2. Kaplan–Meier Estimate of the Time to Hospitalization among High-Risk Patients Who Received Bamlanivimab–Etesevimab or Placebo.** The inset shows the same data on an enlarged y axis. Tick marks indicate censored data.
Rubin EJ et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMe2111903?query=featured_home	Monoclonal Antibodies and Vaccine Boosts	Discussione sullo studio precedente da parte degli editori del NEJM.	What physicians need to know about transmission, diagnosis, and treatment of Covid-19 is the subject of ongoing updates from infectious disease experts at the Journal. In this audio interview conducted on July 13, 2021, the editors discuss new studies of combination monoclonal therapy against Covid-19, as well as new evidence on vaccine boosts.
Binu VJ et al JAMA https://jamanetwork.com/journals/jamainternalme	Association of BNT162b2 mRNA and mRNA-1273 Vaccines With COVID-19 Infection and Hospitalization Among Patients With Cirrhosis	Studio di coorte in cui si osserva la riduzione delle ospedalizzazioni per COVID-19 dopo vaccinazione con vaccino a mRNA nel cirrotico.	Importance Two mRNA-based vaccines against coronavirus disease 2019 (COVID-19) were found to be highly efficacious in phase 3 clinical trials in the US. However, patients with chronic illnesses, including cirrhosis, were excluded from clinical trials. Patients with cirrhosis have immune dysregulation that is associated with vaccine hyporesponsiveness.

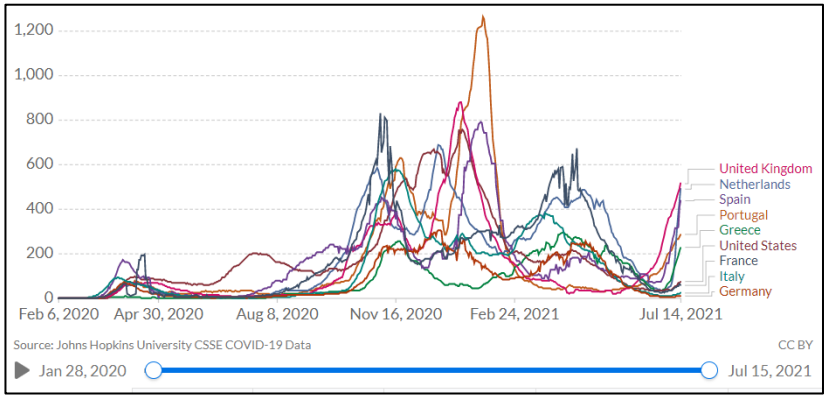
dicine/fullarticle/2782121?resultClick=1			Objective To study the association of receipt of the Pfizer BNT162b2 mRNA or the Moderna mRNA-1273 vaccines in patients with cirrhosis compared with a propensity-matched control group of patients at similar risk of infection and severe disease from COVID-19. Design, Setting, and Participants We performed a retrospective cohort study of patients with cirrhosis who received at least 1 dose of a COVID-19 mRNA vaccine at the Veterans Health Administration. Patients who received at least 1 dose of the vaccine (n = 20 037) were propensity matched with 20 037 controls to assess the associations of vaccination with new COVID-19 infection and COVID-19 hospitalization and death. Exposures Receipt of at least 1 dose of the BNT162b2 mRNA or the mRNA-1273 vaccines between December 18, 2020, and March 17, 2021. Main Outcomes and Measures COVID-19 infection as documented by a positive result for COVID-19 by polymerase chain reaction, hospitalization, and death due to COVID-19 infection. Results The median (interquartile range) age of the vaccinated individuals in the study cohort was 69.1 (8.4) years and 19 465 (97.2%) of the participants in each of the vaccinated and unvaccinated groups were male, consistent with a US veteran population. The mRNA-1273 vaccine was administered in 10 236 (51%) and the BNT162b2 mRNA in 9801 (49%) patients. Approximately 99.7% of patients who received the first dose of either vaccine with a follow-up of 42 days or more received a second dose. The number of COVID-19 infections in the vaccine recipients was similar to the control group in days 0 to 7, 7 to 14, 14 to 21, and 21 to 28 after the first dose. After 28 days, receipt of 1 dose of an mRNA vaccine was associated with a 64.8% reduction in

			COVID-19 infections and 100% protection against hospitalization or death due to COVID-19 infection. The association of reduced COVID-19 infections after the first dose was lower among patients with decompensated (50.3%) compared with compensated cirrhosis (66.8%).Receipt of a second dose was associated with a 78.6% reduction in COVID-19 infections and 100% reduction in COVID-19–related hospitalization or death after 7 days. Conclusions and Relevance This cohort study of US veterans found that mRNA vaccine administration was associated with a delayed but modest reduction in COVID-19 infection but an excellent reduction in COVID-19–related hospitalization or death in patients with cirrhosis.
Goldshtein I et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2782047?resultClick=1	Association Between BNT162b2 Vaccination and Incidence of SARS-CoV-2 Infection in Pregnant Women	Riduzione del numero di infezioni da SARS-CoV-2, diagnosticate con PCR, in una coorte di donne in gravidanza vaccinate con Pfizer rispetto alle non vaccinate.	Importance Data on BNT162b2 messenger RNA (mRNA) vaccine (Pfizer-BioNTech) effectiveness and safety in pregnancy are currently lacking because pregnant women were excluded from the phase 3 trial. Objective To assess the association between receipt of BNT162b2 mRNA vaccine and risk of SARS-CoV-2 infection among pregnant women. Design, Setting, and Participants This was a retrospective cohort study within the pregnancy registry of a large state-mandated health care organization in Israel. Pregnant women vaccinated with a first dose from December 19, 2020, through February 28, 2021, were 1:1 matched to unvaccinated women by age, gestational age, residential area, population subgroup, parity, and influenza immunization status. Follow-up ended on April 11, 2021. Exposures Exposure was defined by receipt of the BNT162b2 mRNA vaccine. To maintain comparability, nonexposed women who were subsequently vaccinated were censored 10 days after their exposure, along with their matched pair.

			Main Outcomes and Measures The primary outcome was polymerase chain reaction–validated SARS-CoV-2 infection at 28 days or more after the first vaccine dose. Results The cohort included 7530 vaccinated and 7530 matched unvaccinated women, 46% and 33% in the second and third trimester, respectively, with a mean age of 31.1 years (SD, 4.9 years). The median follow-up for the primary outcome was 37 days (interquartile range, 21-54 days; range, 0-70). There were 118 SARS-CoV-2 infections in the vaccinated group and 202 in the unvaccinated group. Among infected women, 88 of 105 (83.8%) were symptomatic in the vaccinated group vs 149 of 179 (83.2%) in the unvaccinated group (P ≥ .99). During 28 to 70 days of follow-up, there were 10 infections in the vaccinated group and 46 in the unvaccinated group. The hazards of infection were 0.33% vs 1.64% in the vaccinated and unvaccinated groups, respectively, representing an absolute difference of 1.31% (95% CI, 0.89%-1.74%), with an adjusted hazard ratio of 0.22 (95% CI, 0.11-0.43). Vaccine-related adverse events were reported by 68 patients; none was severe. The most commonly reported symptoms were headache (n = 10, 0.1%), general weakness (n = 8, 0.1%), nonspecified pain (n = 6, <0.1%), and stomachache (n = 5, <0.1%). Conclusions and Relevance In this retrospective cohort study of pregnant women, BNT162b2 mRNA vaccination compared with no vaccination was associated with a significantly lower risk of SARS-CoV-2 infection. Interpretation of study findings is limited by the observational design.

			Figure 2. Cumulative Incidence of SARS-CoV-2 in Vaccinated vs Matched Unvaccinated Pregnant Women 
AIFA https://www.startmag.it/wp-content/uploads/Rapporto_sorveglianza_vaccini_COVID-19_6.pdf	Rapporto sulla Sorveglianza dei vaccini COVID-19 6	Sesto rapporto di farmacovigilanza AIFA sui vaccini contro SARS-CoV-2.	Questo Rapporto descrive le segnalazioni di reazioni che sono state osservate dopo la somministrazione del vaccino. Ciò non significa che queste reazioni siano state causate dal vaccino. Potrebbero essere un sintomo di un̓altra malattia o potrebbero essere associate a un altro prodotto assunto dalla persona che si è vaccinata. Indagare sul significato e sulle cause di queste reazioni è compito della farmacovigilanza.
Normark J NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2110716?query=featured_home	Heterologous ChAdOx1 nCoV-19 and mRNA-1273 Vaccination.	Il richiamo con vaccino Moderna dopo una dose di Vaxzevria protegge contro la variante « sudafricana » più di due dosi di Vaxzevria. Tuttavia gli effetti avversi sono più intensi.	Because of concerns about thrombotic events after vaccination with ChAdOx1 nCoV-19 (Oxford–AstraZeneca),1 several European countries have recommended heterologous messenger RNA (mRNA) boost strategies for persons younger than 60 or 65 years of age who have received one dose of ChAdOx1 nCoV-19.2 To date, data on the safety and immunogenicity of these regimens are limited.

			
Powell AA Eurosurveillance https://doi.org/10.2807/1560-7917.ES.2021.26.28.2100634	Real-world data shows increased reactogenicity in adults after heterologous compared to homologous prime-boost COVID-19 vaccination, March–June 2021, England.	La vaccinazione « eterologa » in qualsiasi ordine è più reattogenica della « omologa », anche se con più effetti avversi.	Adults receiving heterologous COVID-19 immunisation with mRNA (Comirnaty) or adenoviral-vector (Vaxzevria) vaccines had higher reactogenicity rates and sought medical attention more often after two doses than homologous schedules. Reactogenicity was higher among ≤ 50 than > 50 year-olds, women and those with prior symptomatic/confirmed COVID-19. Adults receiving heterologous schedules on clinical advice after severe first-dose reactions had lower reactogenicity after dose 2 following Vaxzevria/Comirnaty (93.4%; 95% confidence interval: 90.5–98.1 vs 48% (41.0–57.7) but not Comirnaty/Vaxzevria (91.7%; (77.5–98.2 vs 75.0% (57.8–87.9).

Radtke T et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2782164?resultClick=1	Long-term Symptoms After SARS-CoV-2 Infection in Children and Adolescents.	I bambini soffrono poco di « Long COVID ».	Children can experience SARS-CoV-2 postviral syndromes, but it is unclear to what extent these individuals are affected by long COVID. Evidence is predominantly limited to select populations without control groups,1-4 which does not allow estimating the overall prevalence and burden in a general pediatric population. We compared symptoms compatible with long COVID in children and adolescents (hereafter “children”) reported within 6 months after SARS-CoV-2 serologic testing.
Our World in Data https://ourworldindata.org/explorers/coronavirus-data-explorer?zoomToSelection=true&time=2020-02-06..2021-07-14&pickerSort=asc&pickerMetric=location&Metric=Confirmed+cases&Interval=7-day+rolling+average&Relative+to+Population=true&Align+outbreaks=false&country=DEU~ITA~USA~GRC~GBR~ESP~NLD~PRT~FRA	Daily new confirmed COVID-19 cases per million people	Dove stiamo andando ?	Only if we end the pandemic everywhere can we end the pandemic anywhere. The entire world has the same goal: cases of COVID-19 need to go to zero. The COVID-19 Data Explorer shows which countries are making progress towards this goal and which are not. 
Pascarella S et al Journal of Medical Virology	SARS-CoV-2 B.1.617 Indian variants: are electrostatic potential changes	Mutazioni tipiche della variante delta e kappa di SARS-CoV-2 alla base di una modifica del potenziale	Lineage B.1.617+, also known as G/452R.V3 and now denoted by WHO with the Greek letters δ and κ, is a recently described SARS-CoV-2 variant under investigation (VUI) firstly identified in October 2020 in India. As of May 2021, three sublineages labelled as

	responsible for a higher transmission rate?	elettrostatico della porzione legante il recettore della proteina S, che potrebbe spiegare la maggiore affinità e quindi trasmissione.	B.1.617.1 (κ), B.1.617.2 ((δ) and B.1.617.3 have been already identified, and their potential impact on the current pandemic is being studied. This variant has 13 amino acid changes, three in its spike protein, which are currently of particular concern: E484Q, L452R and P681R. Here we report a major effect of the mutations characterizing this lineage, represented by a marked alteration of the surface electrostatic potential (EP) of the Receptor Binding Domain (RBD) of the spike protein. Enhanced RBD-EP is particularly noticeable in the B.1.617.2 ((δ)) sublineage, which shows multiple replacements of neutral or negatively-charged amino acids with positively-charged amino acids. We here hypothesize that this EP change can favor the interaction between the B.1.617+ RBD and the negatively charged ACE2 thus conferring a potential increase in the virus transmission.
Oldenburg CE et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2782166	Effect of Oral Azithromycin vs Placebo on COVID-19 Symptoms in Outpatients With SARS-CoV-2 Infection A Randomized Clinical Trial	Una dose di azitromicina all'esordio dei sintomi di COVID-19 non riduce la durata dei sintomi stessi in pazienti gestiti a domicilio.	Importance Azithromycin has been hypothesized to have activity against SARS-CoV-2. Objective To determine whether oral azithromycin in outpatients with SARS-CoV-2 infection leads to absence of self-reported COVID-19 symptoms at day 14. Design, Setting, and Participants Randomized clinical trial of azithromycin vs matching placebo conducted from May 2020 through March 2021. Outpatients from the US were enrolled remotely via internet-based surveys and followed up for 21 days. Eligible participants had a positive SARS-CoV-2 diagnostic test result (nucleic acid amplification or antigen) within 7 days prior to enrollment, were aged 18 years or older, and were not hospitalized at the time of enrollment. Among 604 individuals screened, 297 were ineligible, 44 refused participation, and 263 were enrolled. Participants, investigators, and study staff were masked to treatment randomization.

			Interventions Participants were randomized in a 2:1 fashion to a single oral 1.2-g dose of azithromycin (n = 171) or matching placebo (n = 92). Main Outcomes and Measures The primary outcome was absence of self-reported COVID-19 symptoms at day 14. There were 23 secondary clinical end points, including all-cause hospitalization at day 21. Results Among 263 participants who were randomized (median age, 43 years; 174 [66%] women; 57% non-Hispanic White and 29% Latinx/Hispanic), 76% completed the trial. The trial was terminated by the data and safety monitoring committee for futility after the interim analysis. At day 14, there was no significant difference in proportion of participants who were symptom free (azithromycin: 50%; placebo: 50%; prevalence difference, 0%; 95% CI, −14% to 15%; P > .99). Of 23 prespecified secondary clinical end points, 18 showed no significant difference. By day 21, 5 participants in the azithromycin group had been hospitalized compared with 0 in the placebo group (prevalence difference, 4%; 95% CI, −1% to 9%; P = .16). Conclusions and Relevance Among outpatients with SARS-CoV-2 infection, treatment with a single dose of azithromycin compared with placebo did not result in greater likelihood of being symptom free at day 14. These findings do not support the routine use of azithromycin for outpatient SARS-CoV-2 infection.

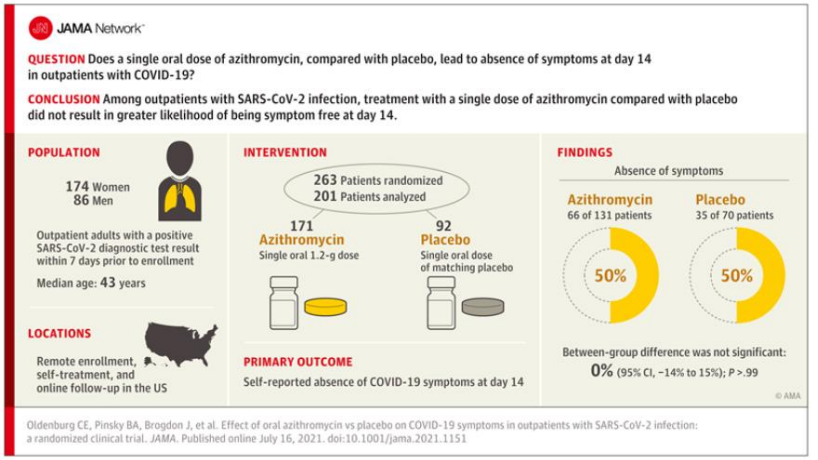
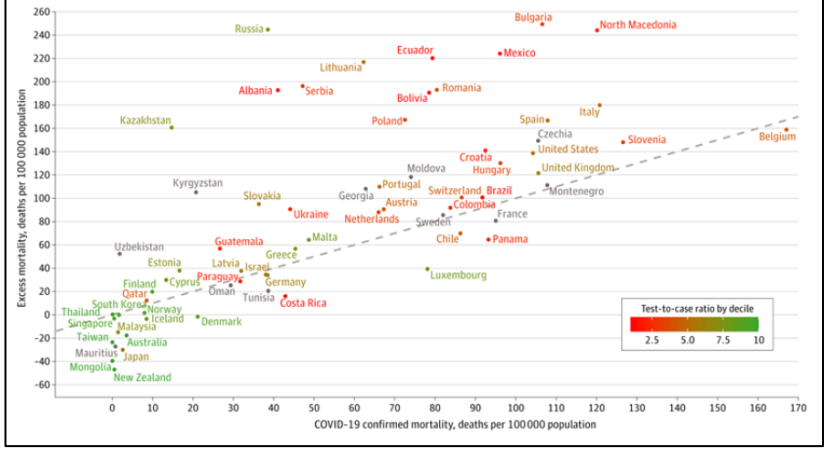
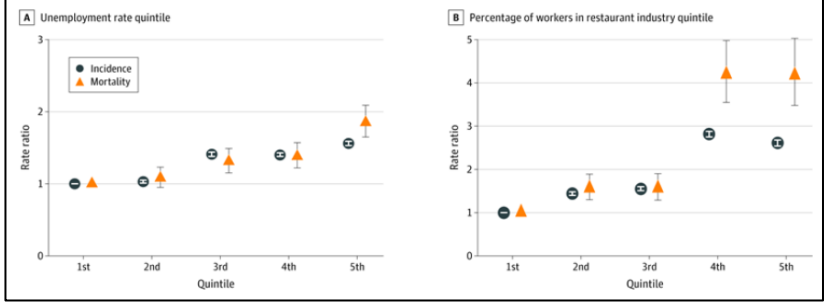
			
Sanmarchi F et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781968	Exploring the Gap Between Excess Mortality and COVID-19 Deaths in 67 Countries	Mortalità per COVID-19 in 67 Paesi del mondo.	In this cross-sectional study, we retrieved aggregated country-level data on population and COVID-19 overall confirmed cases, deaths, and testing as of December 31, 2020, from Our World in Data. Data on countries' overall deaths from 2015 to 2020 were obtained from the World Mortality Data set (eAppendix in the Supplement). This research was based on public use datasets that do not include identifiable personal information and, per the Common Rule, was exempt from Institutional Review Board review and approval. For the same reason, no informed consent was required. This study follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

			Figure. Scatterplot of COVID-19 Confirmed Mortality vs Excess Mortality in 67 Countries, February 26 to December 31, 2020 
Williamson EJ et al BMJ https://www.bmj.com/content/374/bmj.n1592	Risks of covid-19 hospital admission and death for people with learning disability: population based cohort study using the OpenSAFELY platform	Aumentato rischio di ospedalizzazione e morte per COVID-19 nelle persone con disturbi dell'apprendimento.	Objective To assess the association between learning disability and risk of hospital admission and death from covid-19 in England among adults and children. Design Population based cohort study on behalf of NHS England using the OpenSAFELY platform. Setting Patient level data were obtained for more than 17 million people registered with a general practice in England that uses TPP software. Electronic health records were linked with death data from the Office for National Statistics and hospital admission data from NHS Secondary Uses Service. Participants Adults (aged 16-105 years) and children (<16 years) from two cohorts: wave 1 (registered with a TPP practice as of 1 March 2020 and followed until 31 August 2020); and wave 2 (registered 1 September 2020 and followed until 8 February 2021). The main exposure group consisted of people on a general practice learning disability register; a subgroup was defined as those having profound or severe learning disability. People with Down's

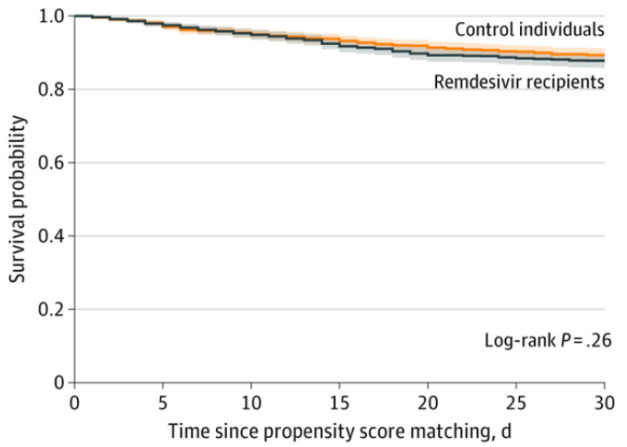
			syndrome and cerebral palsy were identified (whether or not they were on the learning disability register). Main outcome measure Covid-19 related hospital admission and covid-19 related death. Non-covid-19 deaths were also explored. Results For wave 1, 14 312 023 adults aged ≥16 years were included, and 90 307 (0.63%) were on the learning disability register. Among adults on the register, 538 (0.6%) had a covid-19 related hospital admission; there were 222 (0.25%) covid-19 related deaths and 602 (0.7%) non-covid deaths. Among adults not on the register, 29 781 (0.2%) had a covid-19 related hospital admission; there were 13 737 (0.1%) covid-19 related deaths and 69 837 (0.5%) non-covid deaths. Wave 1 hazard ratios for adults on the learning disability register (adjusted for age, sex, ethnicity, and geographical location) were 5.3 (95% confidence interval 4.9 to 5.8) for covid-19 related hospital admission and 8.2 (7.2 to 9.4) for covid-19 related death. Wave 2 produced similar estimates. Associations were stronger among those classified as having severe to profound learning disability, and among those in residential care. For both waves, Down's syndrome and cerebral palsy were associated with increased hazards for both events; Down's syndrome to a greater extent. Hazard ratios for non-covid deaths followed similar patterns with weaker associations. Similar patterns of increased relative risk were seen for children, but covid-19 related deaths and hospital admissions were rare, reflecting low event rates among children. Conclusions People with learning disability have markedly increased risks of hospital admission and death from covid-19, over and above the risks observed for non-covid causes of death. Prompt access to covid-19 testing and healthcare is warranted for this vulnerable group, and prioritisation for covid-19 vaccination and other targeted preventive measures should be considered.

Said M et al JAMA https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2782044?resultClick=1	A Rapid Olfactory Test as a Potential Screening Tool for COVID-19	Sensibilità e specificità di un test olfattivo per la diagnosi di infezione da SARS-CoV-2, utilizzando la PCR come gold standard.	Olfactory dysfunction (OD) is one of the earliest and strongest predictors of COVID-19 infection, and thus is promising as a disease screening tool. Compared with objective testing, subjective olfactory assessments significantly underreport OD. Thus, an inexpensive, quick, and sensitive method of assessing olfaction may be beneficial for the early diagnosis and spread prevention of COVID-19. In this study, we evaluate the feasibility of a novel, objective olfactory test as part of an initial screening for COVID-19 in adults with unknown disease status.
Yoshikawa Y et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781935?resultClick=1	Association of Socioeconomic Characteristics With Disparities in COVID-19 Outcomes in Japan	Importanza dei determinanti socioeconomici nell'outcome di COVID-19 in Giappone.	Importance Socioeconomic factors in the disparities in COVID-19 outcomes have been reported in studies from the US and other Western countries. However, no studies have documented national- or subnational-level outcome disparities in Asian countries. Objective To assess the association between regional COVID-19 outcome disparities and socioeconomic characteristics in Japan. Design, Setting, and Participants This cross-sectional study collected and analyzed confirmed COVID-19 cases and deaths (through February 13, 2021) as well as population and socioeconomic data in all 47 prefectures in Japan. The data sources were government surveys for which prefecture-level data were available. Exposures Prefectural socioeconomic characteristics included mean annual household income, Gini coefficient, proportion of the population receiving public assistance, educational attainment, unemployment rate, employment in industries with frequent close contacts with the public, household crowding, smoking rate, and obesity rate. Main Outcomes and Measures Rate ratios (RRs) of COVID-19 incidence and mortality by prefecture-level socioeconomic characteristics.

			Results All 47 prefectures in Japan (with a total population of 126.2 million) were included in this analysis. A total of 412 126 confirmed COVID-19 cases (326.7 per 100 000 people) and 6910 deaths (5.5 per 100 000 people) were reported as of February 13, 2021. Elevated adjusted incidence and mortality RRs of COVID-19 were observed in prefectures with the lowest household income (incidence RR: 1.45 [95% CI, 1.43-1.48] and mortality RR: 1.81 [95% CI, 1.59-2.07]); highest proportion of the population receiving public assistance (1.55 [95% CI, 1.52-1.58] and 1.51 [95% CI, 1.35-1.69]); highest unemployment rate (1.56 [95% CI, 1.53-1.59] and 1.85 [95% CI, 1.65-2.09]); highest percentage of workers in retail industry (1.36 [95% CI, 1.34-1.38] and 1.45 [95% CI, 1.31-1.61]), transportation and postal industries (1.61 [95% CI, 1.57-1.64] and 2.55 [95% CI, 2.21-2.94]), and restaurant industry (2.61 [95% CI, 2.54-2.68] and 4.17 [95% CI, 3.48-5.03]); most household crowding (1.35 [95% CI, 1.31-1.38] and 1.04 [95% CI, 0.87-1.24]); highest smoking rate (1.63 [95% CI, 1.60-1.66] and 1.54 [95% CI, 1.33-1.78]); and highest obesity rate (0.93 [95% CI, 0.91-0.95] and 1.17 [95% CI, 1.01-1.34]) compared with prefectures with the most social advantages. Among potential mediating variables, higher smoking rate (RR, 1.54; 95% CI, 1.33-1.78) and obesity rate (RR, 1.17; 95% CI, 1.01-1.34) were associated with higher mortality RRs, even after adjusting for prefecture-level covariates and other socioeconomic variables. Conclusions and Relevance This cross-sectional study found a pattern of socioeconomic disparities in COVID-19 outcomes in Japan that was similar to that observed in the US and Europe. National policy in Japan could consider prioritizing populations in socially disadvantaged regions in the COVID-19 response, such as vaccination planning, to address this pattern.

			Figure 1. Japanese COVID-19 Incidence Rate Ratio and Mortality Rate Ratio by Prefectural Unemployment Rate Quintile and Percentage of Workers in Restaurant Industry Quintile as of February 13, 2021 
Ohl ME et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2781959?resultClick=1	Association of Remdesivir Treatment With Survival and Length of Hospital Stay Among US Veterans Hospitalized With COVID-19	Studio di coorte sull'utilizzo della terapia con remdesivir in COVID-19 : non dimostrato un beneficio in sopravvivenza in questa coorte.	Importance Randomized clinical trials have yielded conflicting results about the effects of remdesivir therapy on survival and length of hospital stay among people with COVID-19. Objective To examine associations between remdesivir treatment and survival and length of hospital stay among people hospitalized with COVID-19 in routine care settings. Design, Setting, and Participants This retrospective cohort study used data from the Veterans Health Administration (VHA) to identify adult patients in 123 VHA hospitals who had a first hospitalization with laboratory-confirmed COVID-19 from May 1 to October 8, 2020. Propensity score matching of patients initiating remdesivir treatment to control patients who had not initiated remdesivir treatment by the same hospital day was used to create the analytic cohort. Exposures Remdesivir treatment. Main Outcomes and Measures Time to death within 30 days of remdesivir treatment initiation (or corresponding hospital day for matched control individuals) and time to hospital discharge with time to death as a competing event. Associations between

			remdesivir treatment and these outcomes were assessed using Cox proportional hazards regression in the matched cohort. Results The initial cohort included 5898 patients admitted to 123 hospitals, 2374 (40.3%) of whom received remdesivir treatment (2238 men [94.3%]; mean [SD] age, 67.8 [12.8] years) and 3524 (59.7%) of whom never received remdesivir treatment (3302 men [93.7%]; mean [SD] age, 67.0 [14.4] years). After propensity score matching, the analysis included 1172 remdesivir recipients and 1172 controls, for a final matched cohort of 2344 individuals. Remdesivir recipients and matched controls were similar with regard to age (mean [SD], 66.6 [14.2] years vs 67.5 [14.1] years), sex (1101 men [93.9%] vs 1101 men [93.9%]), dexamethasone use (559 [47.7%] vs 559 [47.7%]), admission to the intensive care unit (242 [20.7%] vs 234 [19.1%]), and mechanical ventilation use (69 [5.9%] vs 45 [3.8%]). Standardized differences were less than 10% for all measures. Remdesivir treatment was not associated with 30-day mortality (143 remdesivir recipients [12.2%] vs 124 controls [10.6%]; log rank P = .26; adjusted hazard ratio [HR], 1.06; 95% CI, 0.83-1.36). Results were similar for people receiving vs not receiving dexamethasone at remdesivir initiation (dexamethasone recipients: adjusted HR, 0.93; 95% CI, 0.64-1.35; nonrecipients: adjusted HR, 1.19; 95% CI, 0.84-1.69). Remdesivir recipients had a longer median time to hospital discharge compared with matched controls (6 days [interquartile range, 4-12 days] vs 3 days [interquartile range, 1-7 days]; P < .001). Conclusions and Relevance In this cohort study of US veterans hospitalized with COVID-19, remdesivir treatment was not associated with improved survival but was associated with longer hospital stays. Routine use of remdesivir may be associated with

			increased use of hospital beds while not being associated with improvements in survival. **Figure 2. Kaplan-Meier Survival Curves for Remdesivir Recipients and Control Individuals in the Propensity Score–Matched Cohort**  No. at risk Control individuals 1172 1129 1098 1075 1054 1041 1030 Remdesivir recipients 1172 1142 1112 1075 1047 1034 1034
Barros AJ et al Critical Care Medicine https://journals.lww.com/ccmjournal/Fulltext/2021/08000/Cardiopulmonary_Resuscitation_in_Coronavirus.24.aspx	Cardiopulmonary Resuscitation in Coronavirus Disease 2019 Patients Experiencing In-Hospital Cardiac Arrest: More Data Are Needed	Commento relativo all'opportunità di tentare la rianimazione cardiopolmonare nei pazienti con COVID-19, data la scarsa riuscita nelle casistiche pubblicate.	In carefully selected patients hospitalized with COVID-19 who experience cardiac arrest, attempts at resuscitation is appropriate medically and potentially efficacious; furthermore, with adequate provider education and appropriate personal protective equipment for the healthcare team, resuscitation is a safe procedure. We agree with the authors that pooled outcomes data from multiple institutions are needed to address the utility of attempting cardiac arrest resuscitation in patients with COVID-19. Although the authors make no statement about the utility of cardiac arrest resuscitation attempts in IHCA from COVID-19, we are concerned that readers may withhold cardiopulmonary resuscitation and other resuscitative interventions given these reported less-than-optimal outcomes, and we caution labeling a practice as futile without more robust data.