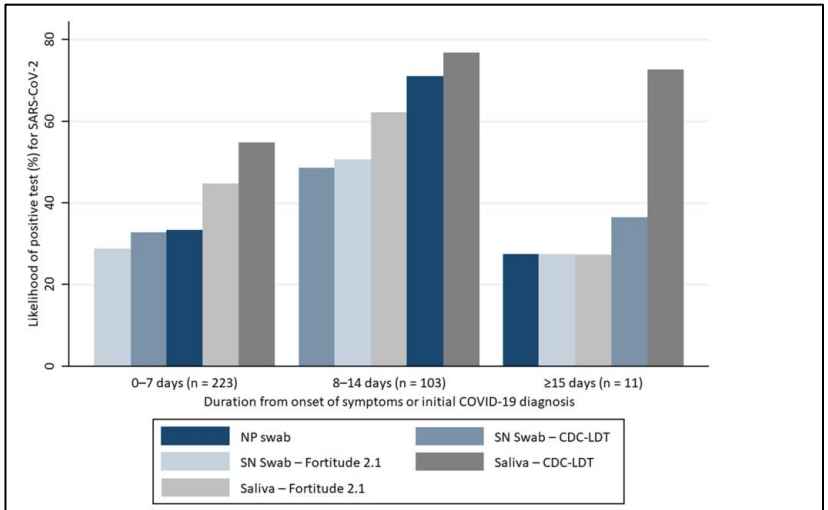
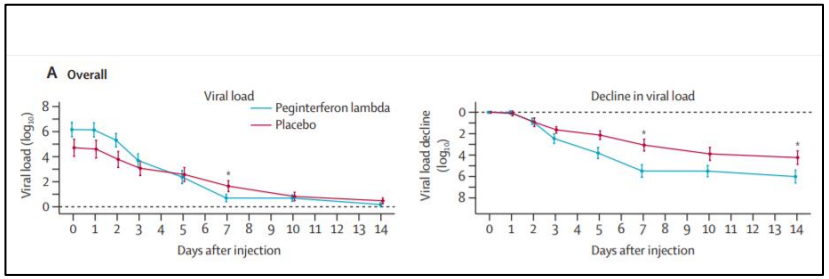
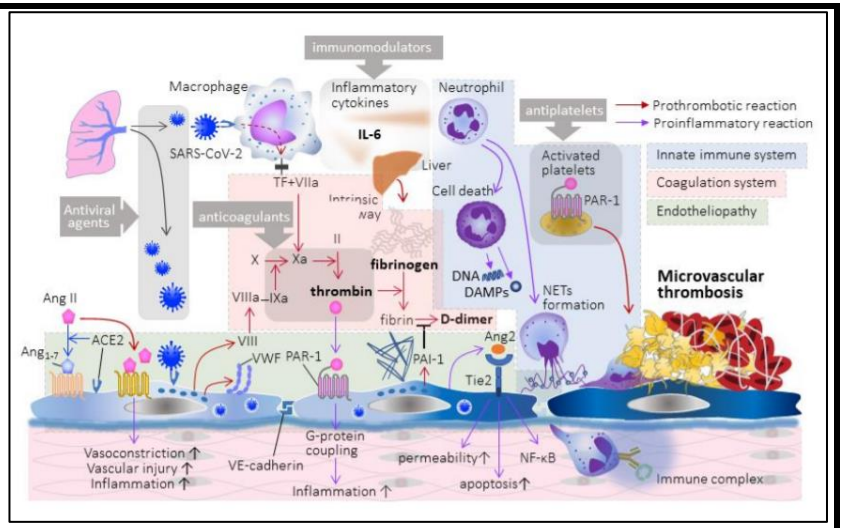
RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 8.02 – 14.02.2021 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Teo AKJ et al Scientific Reports https://www.nature.com/articles/s41598-021-82787-z	Saliva is more sensitive than nasopharyngeal or nasal swabs for diagnosis of asymptomatic and mild COVID-19 infection	Su una coorte di 200 persone fra sintomatici e asintomatici per infezione da SARS-CoV-2, la PCR su saliva è più spesso positiva rispetto al tampone nasofaringeo e al tampone nasale auto-praticato.	We aimed to test the sensitivity of naso-oropharyngeal saliva and self-administered nasal (SN) swab compared to nasopharyngeal (NP) swab for COVID-19 testing in a large cohort of migrant workers in Singapore. We also tested the utility of next-generation sequencing (NGS) for diagnosis of COVID-19. Saliva, NP and SN swabs were collected from subjects who presented with acute respiratory infection, their asymptomatic roommates, and prior confirmed cases who were undergoing isolation at a community care facility in June 2020. All samples were tested using RT-PCR. SARS-CoV-2 amplicon-based NGS with phylogenetic analysis was done for 30 samples. We recruited 200 subjects, of which 91 and 46 were tested twice and thrice respectively. In total, 62.0%, 44.5%, and 37.7% of saliva, NP and SN samples were positive. Cycle threshold (Ct) values were lower during the earlier period of infection across all sample types. The percentage of test-positive saliva was higher than NP and SN swabs. We found a strong

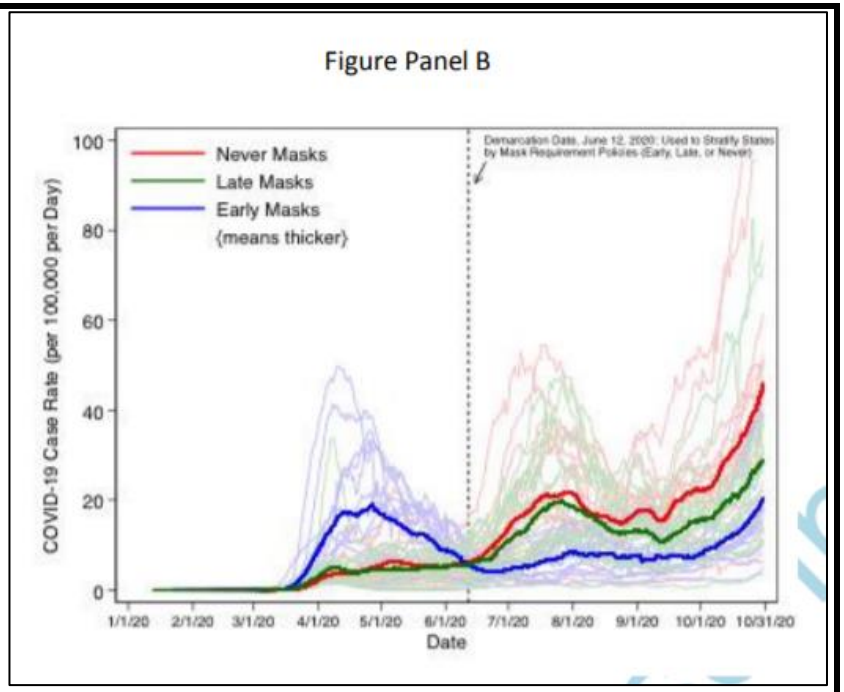
			correlation between viral genome coverage by NGS and Ct values for SARS-CoV-2. Phylogenetic analyses revealed Clade O and lineage B.6 known to be circulating in Singapore. We found saliva to be a sensitive and viable sample for COVID-19 diagnosis.  **Figure 2.** Likelihood of test positivity over time in confirmed COVID-19 subjects. The figure shows the likelihood of positivity for SARS-CoV-2 for nasopharyngeal (NP) swabs, self-administered nasal (SN) swabs, and naso-oropharyngeal saliva samples collected at 0–7 days, 8–14 days, and ≥ 15 days from the onset of symptoms (symptomatic subjects) or initial COVID-19 diagnosis (asymptomatic subjects). NP swabs were tested using via cobas SARS-CoV-2 or Centers for Disease Control and Prevention-Laboratory Developed Test (CDC-LDT).
Feld JJ et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(20)30566-X/fulltext	Peginterferon lambda for the treatment of outpatients with COVID-19: a phase 2, placebo-controlled randomised trial	Studio di fase 2 che valuta sicurezza ed efficacia del PEG-interferone gamma somministrato entro 7 giorni dall'esordio dei sintomi a pazienti con COVID-19 non ospedalizzati, outcome la riduzione della carica virale su tampone nasofaringeo :	Background To date, only monoclonal antibodies have been shown to be effective for outpatients with COVID-19. Interferon lambda-1 is a type III interferon involved in innate antiviral responses with activity against respiratory pathogens. We aimed to investigate the safety and efficacy of peginterferon lambda in the treatment of outpatients with mild-to-moderate COVID-19. Methods

		si ottiene una riduzione significativamente maggiore della carica di SARS-CoV-2 nei 30 trattati rispetto ai 30 randomizzati a placebo.	In this double-blind, placebo-controlled trial, outpatients with laboratory-confirmed COVID-19 were randomly assigned to a single subcutaneous injection of peginterferon lambda 180 µg or placebo within 7 days of symptom onset or first positive swab if asymptomatic. Participants were randomly assigned (1:1) using a computer-generated randomisation list created with a randomisation schedule in blocks of four. At the time of administration, study nurses received a sealed opaque envelope with the treatment allocation number. The primary endpoint was the proportion of patients who were negative for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA on day 7 after the injection, analysed by a $\chi 2$ test following an intention-to-treat principle. Prespecified analysis of the primary endpoint, adjusted for baseline viral load, using bivariate logistic regression was done. The trial is now complete. This trial is registered with ClinicalTrials.gov, NCT04354259. Findings Between May 18, and Sept 4, 2020, we recruited 30 patients per group. The decline in SARS-CoV-2 RNA was greater in those treated with peginterferon lambda than placebo from day 3 onwards, with a difference of 2·42 log copies per mL at day 7 (p=0·0041). By day 7, 24 (80%) participants in the peginterferon lambda group had an undetectable viral load, compared with 19 (63%) in the placebo group (p=0·15). After controlling for baseline viral load, patients in the peginterferon lambda group were more likely to have undetectable virus by day 7 than were those in the placebo group (odds ratio [OR] 4·12 [95% CI 1·15–16·73; p=0·029). Of those with baseline viral load above 106 copies per mL, 15 (79%) of 19 patients in the peginterferon lambda group had undetectable virus on day 7, compared with six (38%) of 16 in the placebo group (OR 6·25 [95%

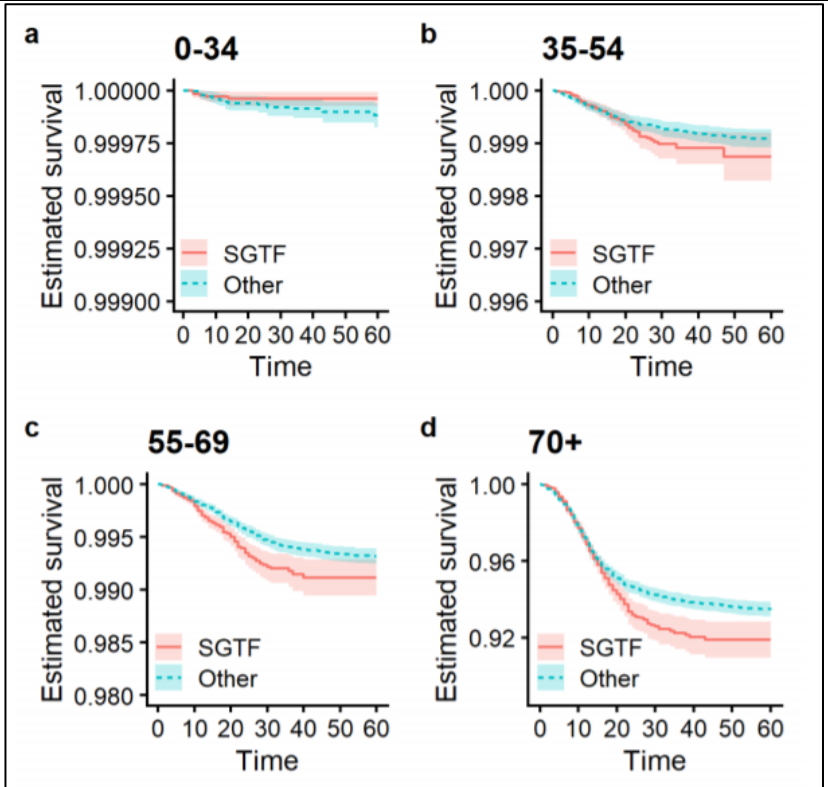
			CI 1·49–31·06]; p=0·012). Peginterferon lambda was well tolerated, and adverse events were similar between groups with mild and transient aminotransferase, concentration increases more frequently observed in the peginterferon lambda group. Two individuals met the threshold of grade 3 increase, one in each group, and no other grade 3 or 4 laboratory adverse events were reported. Interpretation Peginterferon lambda accelerated viral decline in outpatients with COVID-19, increasing the proportion of patients with viral clearance by day 7, particularly in those with high baseline viral load. Peginterferon lambda has potential to prevent clinical deterioration and shorten duration of viral shedding. 
Amit S et al Emerging Infectious Diseases	Post-Vaccination COVID-19 among Healthcare Workers, Israel	Descrizione di 22 casi di operatori sanitari con infezione da SARS-CoV-2 in concomitanza con la vaccinazione : i sintomi di infezione virale andrebbero indagati e non rapidamente attribuiti agli effetti avversi della vaccinazione.	Coronavirus disease (COVID-19) symptoms can be mistaken for vaccine-related side effects during initial days after immunization. Among 4,081 vaccinated healthcare workers in Israel, 22 (0.54%) developed COVID-19 from 1–10 days (median 3.5 days) after immunization. Clinicians should not dismiss postvaccination symptoms as vaccine-related and should promptly test for COVID-19.

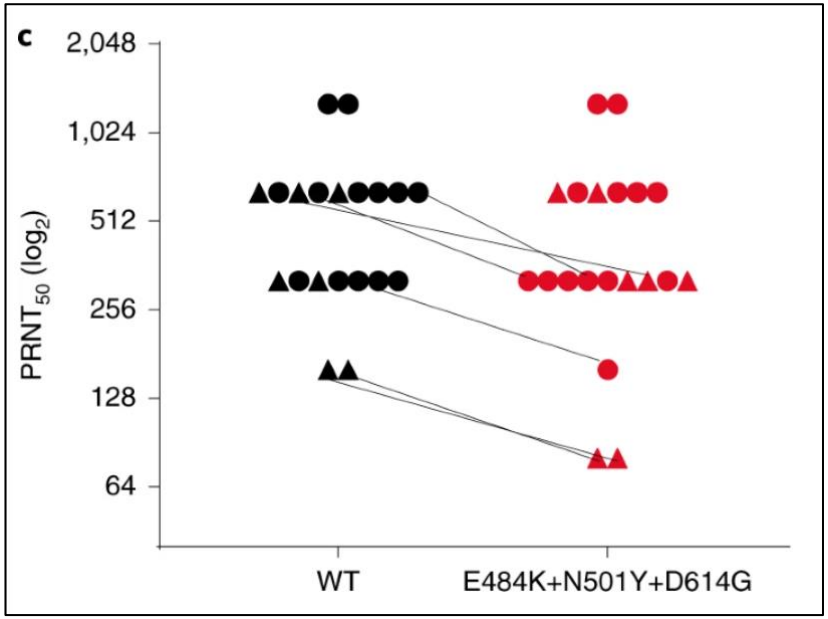
https://wwwnc.cdc.gov/eid/article/27/4/21-0016_article			
Connors JM et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab096/6128795?searchresult=1	Thrombosis and COVID-19: Controversies and (Tentative) Conclusions	Revisione della questio delle complicanze trombotiche in COVID-19 e prospettive di indagine futura.	Infection with SARS-CoV-2, initially isolated to one location in early 2020, rapidly spread to become a global pandemic. In early reports, patients with COVID-19 were noted to have multiple coagulation test abnormalities, including elevated D-dimer levels, and increased thrombotic events (1, 2). These complications have been attributed to “thromboinflammation”, a process in which innate immune responses and inflammation trigger coagulation, and endotheilialitis (3), a result of infection of endothelial cells with SARS-CoV-2. Severity of inflammation has been associated with extent of coagulation test abnormalities: for example, higher IL-6 levels are correlated with increasing fibrinogen levels (4). Autopsy studies, first from China and then from Europe, found microvascular thrombosis in patients with COVID-19; these clots were initially thought to be confined to the lungs but were subsequently found in other organs including the heart and kidneys (1, 5). Microvascular thrombosis may, in turn, lead to hypoxemia, organ failure, and death. The thromboinflammatory response to SARS-COV-2 infection and endothelialitis have been proposed to be driving arterial and venous large vessel thrombosis as well as microvascular thrombosis in people with COVID-19.

			
Rebeiro PF et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab101/6129930?searchresult=1	The Impact of State Mask-Wearing Requirements on the Growth of COVID-19 Cases in the United States	Stima dell'impatto dell'obbligo di indossare una mascherina sui nuovi casi di infezione da SARS-CoV-2 nei diversi stati degli USA che hanno adottato in tempi diversi questa pratica : si conferma l'utilità nel ridurre l'incidenza.	In our ecologic analysis of US states, piecewise multivariable models showed lower post- vs. pre-mask case-rate slopes, with -1.08% per 100,000 per day (95% CI: -1.48%, -0.67%) among early- and -0.37% per 100,000 per day (95% CI: -0.86%, 0.10%) among late- versus never-adopter states. Our findings support statewide mask requirements to mitigate COVID-19 transmission.

			
Davies NG et al medRXiv – not peer reviewed https://www.medrxiv.org/content/10.1101/2021.02.01.21250959v1	Increased hazard of death in community-tested cases of SARS-CoV-2 Variant of Concern 202012/01	Sulla base dei dati di un ampio database di pazienti in Inghilterra, la mortalità delle infezioni da variante « inglese » di SARS-CoV-2 (identificate perchè in quei casi il gene S non viene amplificato dalla PCR diagnostica = S gene target failure, SGTF) sarebbe del 30-35% superiore rispetto ai casi da wildtype.	VOC 202012/01, a SARS-CoV-2 variant first detected in the United Kingdom in September 2020, has spread to multiple countries worldwide. Several studies have established that this novel variant is more transmissible than preexisting variants of SARS-CoV-2, but have not identified whether the new variant leads to any change in disease severity. We analyse a large database of SARS-CoV-2 community test results and COVID-19 deaths for England, representing approximately 47% of all SARS-CoV-2 community tests and 7% of COVID-19 deaths in England from 1 September 2020 to 22 January 2021. Fortuitously, these SARS-CoV-2 tests can identify VOC 202012/01 because mutations in this lineage prevent PCR amplification of the spike gene target (S gene target failure, SGTF). We estimate that the hazard of death among SGTF cases is 30%

			(95% CI 9–56%) higher than among non-SGTF cases after adjustment for age, sex, ethnicity, deprivation level, care home residence, local authority of residence and date of test. In absolute terms, this increased hazard of death corresponds to the risk of death for a male aged 55–69 increasing from 0.56% to 0.73% (95% CI 0.60–0.86%) over the 28 days following a positive SARS-CoV-2 test in the community. Correcting for misclassification of SGTF, we estimate a 35% (12–64%) higher hazard of death associated with VOC 202012/01. Our analysis suggests that VOC 202012/01 is not only more transmissible than preexisting SARS-CoV-2 variants but may also cause more severe illness.

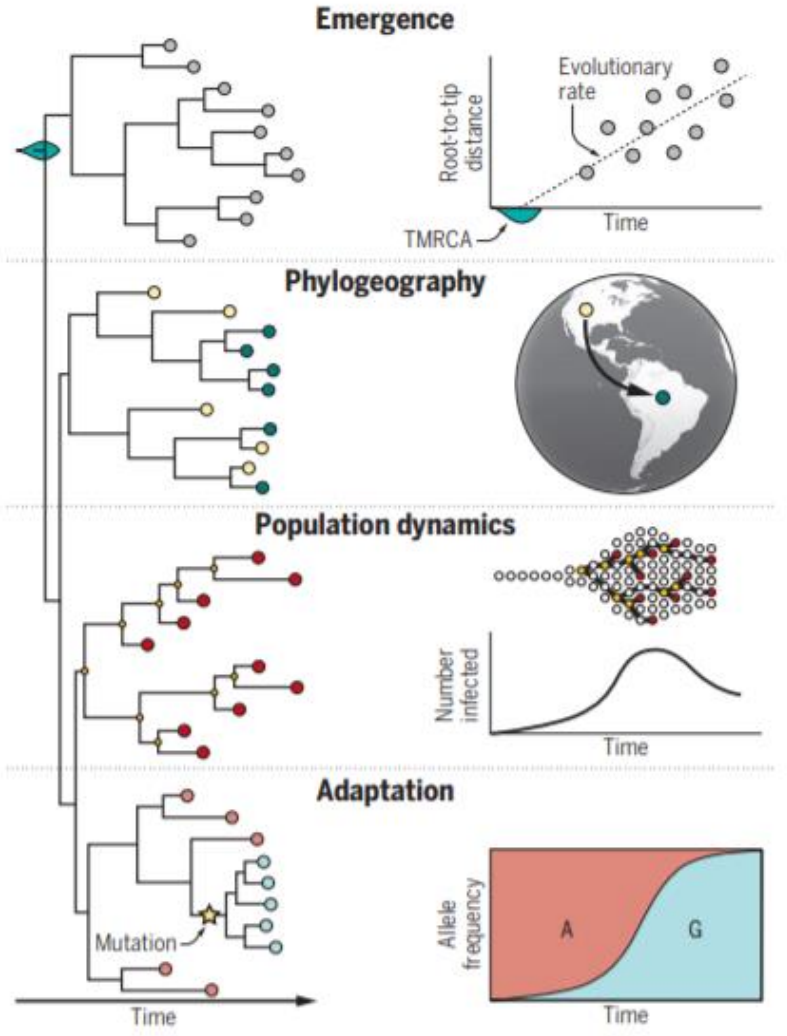
			 **Fig. S2. Kaplan Meier plots of survival within 60 days of positive test for SGTF versus all other positive SARS-CoV-2 tests by age group.** Note that the Y axis differs for each panel.
Mallapaty S et al Nature	What's the risk of dying from a fast-spreading COVID-19 variant?	Commento sull'interpretazione dell'apparente maggiore mortalità dell'infezione da SARS-CoV-2 variante « inglese » riportata nello studio precedente.	The news is sobering, but complicated. Scientists have released the data behind a British government warning last week that the fast-spreading SARS-CoV-2 variant B.1.1.7 increases the risk of dying from COVID-19 compared with previous variants. But some scientists caution that the latest study — like the government warning — is preliminary and still does not indicate whether the

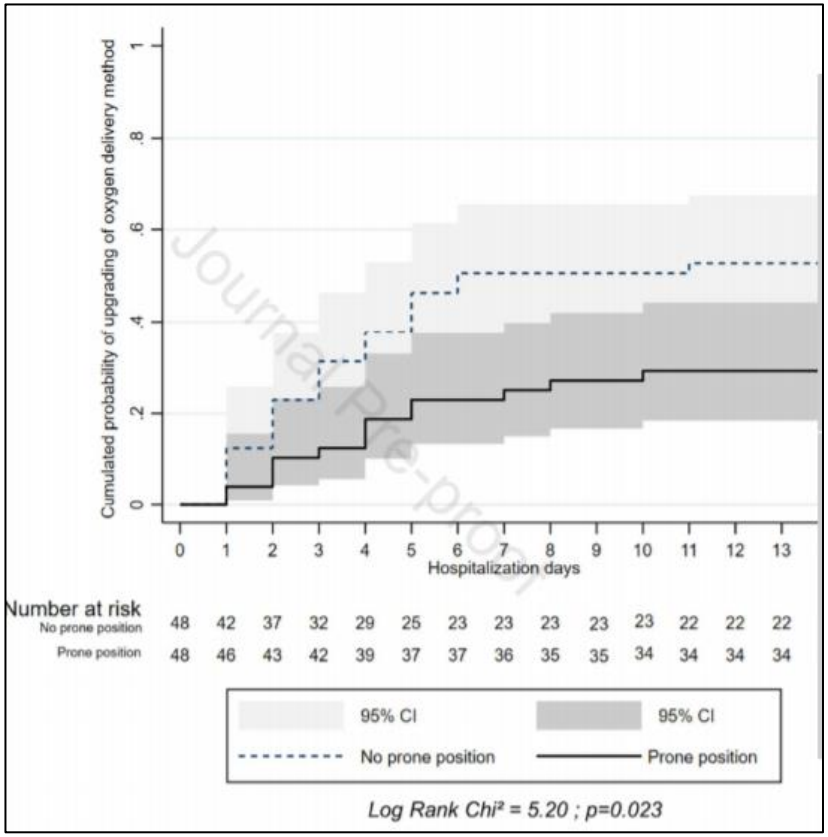
https://www.nature.com/articles/d41586-021-00299-2			variant is more deadly or is just spreading faster and so reaching greater numbers of vulnerable people.
Xie X et al Nature https://www.nature.com/articles/s41591-021-01270-4	Neutralization of SARS-CoV-2 spike 69/70 deletion, E484K and N501Y variants by BNT162b2 vaccine-elicited sera	Il siero di 20 pazienti partecipanti al trial del vaccino Pfizer neutralizza tre tipi di SARS-CoV-2 ingegnerizzato con mutazioni a carico della proteina S ; solo nel caso della combinazione E484K + N501Y + D614G (che mette insieme tre sostituzioni chiave – ma non esaustive - della variante sudafricana) si osserva una lieve riduzione del titolo neutralizzante. Non appare un effetto significativo sull'attività anticorpale, tuttavia gli studi in vitro non rendono conto completamente di quanto avviene nell'organismo umano.	We engineered three severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viruses containing key spike mutations from the newly emerged United Kingdom (UK) and South African (SA) variants: N501Y from UK and SA; 69/70-deletion + N501Y + D614G from UK; and E484K + N501Y + D614G from SA. Neutralization geometric mean titers (GMTs) of 20 BTN162b2 vaccine-elicited human sera against the three mutant viruses were 0.81- to 1.46-fold of the GMTs against parental virus, indicating small effects of these mutations on neutralization by sera elicited by two BNT162b2 doses. 

Martin MA et al Science https://science.sciencemag.org/content/371/6528/466	Insights from SARS-CoV-2 sequences	Perché è importante il sequenziamento virale, con riferimento all'attuale pandemia di COVID-19.	As severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread across the globe, so have efforts to sequence its RNA genome. More than 260,000 sequences are now available in public databases, about a year after the viral genome was first sequenced (1). These sequences and their associated metadata have allowed researchers to estimate the timing of SARS-CoV-2 spillover into humans, characterize the spread of the virus, and gauge virus adaptation to its new host. Such analyses rely on interpreting patterns of nucleotide changes that have occurred in the virus population over time and are brought into focus through the reconstruction of genealogical relationships between sampled viruses that are depicted in phylogenetic trees.

Uses for viral sequence data

Viral phylogenies, rooted at the most recent common ancestor (TMRCA), are inferred on the basis of genetic differences. These phylogenies can be used to estimate viral emergence, characterize the geographic spread of the virus, reconstruct epidemiological dynamics of viral spread within a region, and identify instances of adaptation.



Prud'homme E et al Chest https://journal.chestnet.org/action/showPdf?pii=S0012-3692%2821%2900125-2	Effect of Prone Positioning on the respiratory support of non-intubated patients withCOVID-19 and acute hypoxemic respiratory failure: A retrospective matching cohort study	Studio di coorte retrospettivo su 96 pazienti ricoverati per COVID-19 in Francia, in respiro spontaneo e vigili. Di questi, 48 venivano invitati a rimanere in posizione prona per almeno 3 ore al giorno per 3 giorni, mentre gli altri non ricevevano indicazioni sulla posizione da tenere. A 14 giorni, i pronati avevano un minor rischio di necessitare di aumento dell'intensità dell'assistenza respiratoria.	Coronavirus disease 2019 (COVID-19) associated respiratory illness may lead to acute respiratory distress syndrome (ARDS). In intubated patients with severe ARDS, early, prolonged and repeated sessions of prone positioning (PP) decrease mortality. Awake PP is feasible, improves oxygenation in some patients and may prevent respiratory worsening. The main objective of the present study was to evaluate the effect of PP on the outcome of spontaneously breathing COVID-19 patients with acute respiratory failure. 

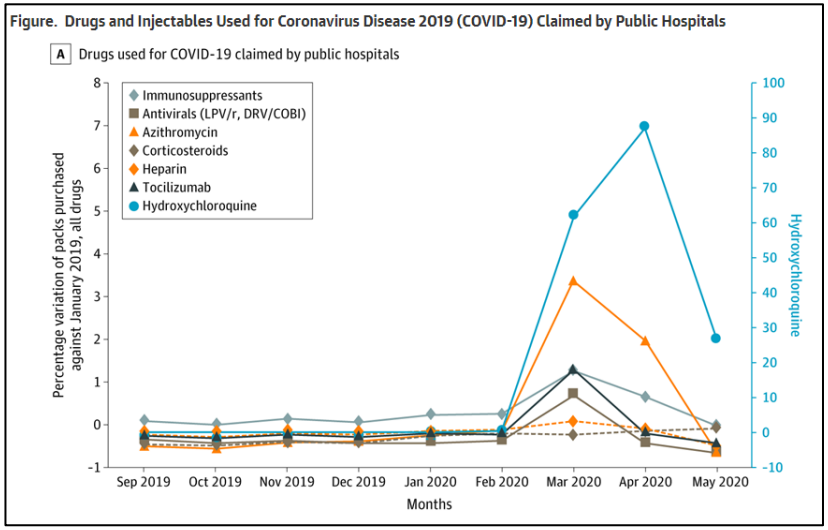
Chapman J et al Critical Care Medicine https://journals.lww.com/ccmjournal/Abstract/2021/02000/CNS_Complications_in_Adult_Patients_Treated_With.12.aspx	CNS Complications in Adult Patients Treated With Extracorporeal Membrane Oxygenation	Il peso delle cure intensive : descrizione delle complicanze a carico del sistema nervoso centrale in una coorte di 412 pazienti sottoposti a ECMO (extracorporeal membrane oxygenation) nel periodo 2009-2017, prima dell'epidemia di COVID-19.	Objectives: To describe the incidence and outcomes of radiologically confirmed acute CNS complications in extracorporeal membrane oxygenation patients at an Australian extracorporeal membrane oxygenation referral center and identify associated patient characteristics. Design: Retrospective cohort study. Setting: Single-center tertiary institution. Patients: Four-hundred twelve consecutive adult patients supported with extracorporeal membrane oxygenation from 2009 to 2017. Results: Fifty-five patients (13.3%) had a CNS complication confirmed by CT or MRI, including ischemic stroke (7.0%), intracerebral hemorrhage (3.4%), hypoxic ischemic encephalopathy (3.6%), and spinal cord injury (1.2%). CNS complication rates in the venoarterial, venovenous, and veno-pulmonary artery extracorporeal membrane oxygenation subgroups were 18.0%, 4.6%, and 13.6%, respectively. Neurologic complications were independently associated with the use of venoarterial extracorporeal membrane oxygenation ($p = 0.002$) and renal replacement therapy ($p = 0.04$). Sixty-five percent of patients with a neurologic complication died during their hospital admission compared with 32% of patients without this complication ($p < 0.001$). Venoarterial extracorporeal membrane oxygenation, renal replacement therapy, and days of extracorporeal membrane oxygenation support were also associated with hospital mortality and remained so after adjustment in a multivariable regression model ($p = 0.01$, $p < 0.001$, and $p = 0.003$, respectively). Conclusions: CNS complications appear to occur more frequently in patients requiring circulatory as opposed to respiratory support on extracorporeal membrane oxygenation and are independently associated with mortality. It remains unclear if these complications

			are causative of a poor outcome or a marker of severity of the underlying condition. Further research is required to better elucidate modifiable or preventable aspects through better patient selection and change in ongoing care.
Tan BI et al JAMA https://jamanetwork.com/journals/jama/article-abstract/2776190	Prevalence and Outcomes of SARS-CoV-2 Infection Among Migrant Workers in Singapore	Gestione e caratteristiche di un cluster di infezioni da SARS-CoV-2 nella comunità dei lavoratori migranti a Singapore.	High-density communal residences are at elevated risk of large outbreaks of respiratory disease. After an initial nationwide outbreak of 231 cases of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Singapore, which was contained as of March 24, 2020, a surge of 244 cases among migrant workers residing in dormitories, largely from Bangladesh and India, occurred from March 25 to April 7. A national task force was formed to coordinate Singapore's outbreak response. A national lockdown from April 7 to June 1 enforced movement restriction and confined workers to their dormitories. Medical posts were deployed on-site in all dormitories, and testing capacity for testing and screening residents increased. All workers with a positive polymerase chain reaction (PCR) test result were admitted to health care facilities for isolation and treatment. We examined the prevalence and outcomes of SARS-CoV-2 infection among migrant workers in Singapore.
University of Oxford https://www.ox.ac.uk/news/2021-02-07-chadox1-ncov-19-provides-minimal-protection-against-mild-moderate-covid-19-infection	ChAdOx1 nCov-19 provides minimal protection against mild-moderate COVID-19 infection from B.1.351 coronavirus variant in young South African adults	Comunicato stampa dell'Università di Oxford in merito a dati preliminari che indicano una scarsa attività protettiva del vaccino ChAdOx1 nCoV-19 (AstraZeneca) nei confronti dell'infezione da SARS-CoV-2 variante « sudafricana ».	In an analysis, submitted as a pre-print prior to peer-review publication, a two-dose regimen of the ChAdOx1 nCoV-19 vaccine provides minimal protection against mild-moderate COVID-19 infection from the B.1.351 coronavirus variant first identified in South Africa.

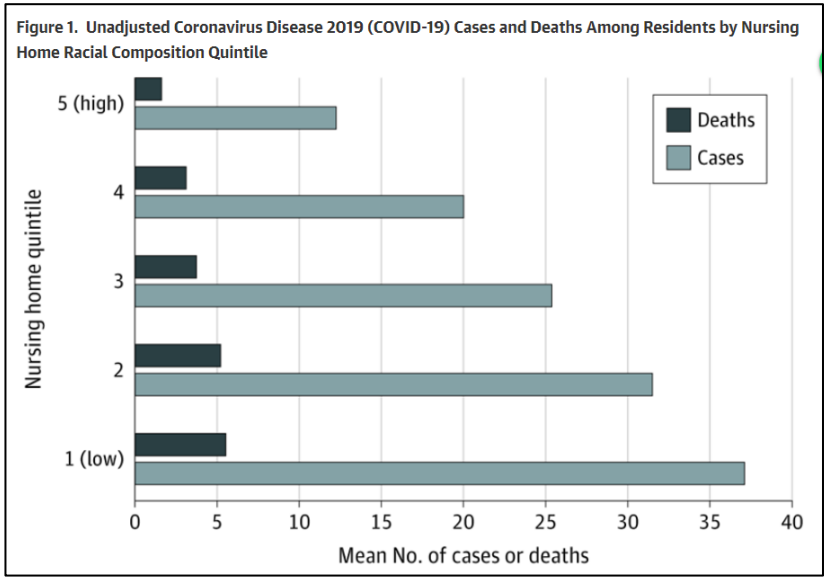
Sepulcri C et al medRXiv https://www.medrxiv.org/content/10.1101/2021.01.23.21249554v1	The longest persistence of viable SARS-CoV-2 with recurrence of viremia and relapsing symptomatic COVID-19 in an immunocompromised patient – a case study	Tampone nasofaringeo per SARS-CoV-2 persistentemente positivo per 8 mesi con virus che cresce in coltura cellulare in un paziente affetto da linfoma. Si dimostra inoltre viremia responsiva al trattamento con remdesivir.	Background Immunocompromised patients show prolonged shedding of SARS-CoV-2 in nasopharyngeal swabs. We report a case of a prolonged persistence of viable SARS-CoV-2 associated with clinical relapses of COVID-19 in a lymphoma patient. Methods Nasopharyngeal swabs and blood samples were tested for SARS-CoV-2 by Real time-PCR (RT-PCR). On five positive nasopharyngeal swabs, we performed viral culture and next generation sequencing. We analysed the patients' adaptive and innate immunity to characterize T and NK cell subsets. Findings SARS-CoV-2 RT-PCR on nasopharyngeal swabs samples remained positive with cycle threshold mean values of 22 ± 1·3 for over 8 months. All five performed viral cultures were positive and genomic analysis confirmed a persistent infection with the same strain. Viremia resulted positive in three out of four COVID-19 clinical relapses and cleared each time after remdesivir treatment. T and NK cells dynamic was different in aviremic and viremic samples and no SARS-CoV-2 specific antibodies were detected throughout the disease course. Interpretation In our patient, SARS-CoV-2 persisted with proven infectivity for over eight months. Viremia was associated with COVID-19 relapses and remdesivir treatment was effective in viremia clearance and symptoms remission, although it was unable to clear the virus from the upper respiratory airways. During the viremic phase, we observed a low frequency of terminal effector CD8+ T lymphocytes in peripheral blood that are probably recruited in inflammatory tissue for viral eradication. In addition we found a high level of NK cells repertoire perturbation with a relevant involvement during SARS-CoV-2 viremia.

Delbue S et al Emerging Microbes & Infections https://www.tandfonline.com/doi/full/10.1080/22221751.2021.1884003	Isolation of SARS-CoV-2 strains carrying a nucleotide mutation, leading to a stop codon in the ORF 6 protein	Descrizione di una variante « milanese » di SARS-COV-2 portatrice di una mutazione a carico di ORF6, proteina virale che antagonizza l'interferone I, senza effetti sull'affinità con gli anticorpi anti-SARS-CoV-2.	We report the complete sequence of SARS-CoV-2 strains originally isolated from nasopharyngeal swabs from two Italian physicians, affected with COVID-19, and working in a COVID-19 division of a general hospital of Milano, Italy. Among the SARS-CoV-2 accessory proteins, ORF6, a small peptide of 61 aa, has been previously identified as possible type I interferon (IFN) antagonist based also upon its similarity to the p6 encoded by SARS-CoV, which is able to prevent the host antiviral response, binding directly to the NPIPB3 protein, and preventing the activation of the STAT-1 pathway. This is the first report of a SARS-CoV-2 sequence carrying a nucleotide mutation leading to a stop codon in the ORF6 coding region.
Kaka AS et al Annals of Internal Medicine https://www.acpjournals.org/doi/10.7326/M20-8148	Major Update: Remdesivir for Adults With COVID-19: A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points	Revisione sistematica e metanalisi sulla terapia con remdesivir per COVID-19 : in definitiva, il farmaco utilizzato negli ospedalizzati potrebbe aumentare il numero di guariti, ridurre il tempo di guarigione e gli eventi avversi gravi dell'infezione.	Background: Remdesivir is being studied and used for treatment of coronavirus disease 2019 (COVID-19). Purpose: To update a previous review of remdesivir for adults with COVID-19, including new meta-analyses of patients with COVID-19 of any severity compared with control. Data Sources: Several sources from 1 January 2020 through 7 December 2020. Study Selection: English-language, randomized controlled trials (RCTs) of remdesivir for COVID-19. New evidence is incorporated by using living review methods. Data Extraction: 1 reviewer abstracted data; a second reviewer verified the data. The Cochrane Risk of Bias Tool and GRADE (Grading of Recommendations Assessment, Development and Evaluation) method were used. Data Synthesis: The update includes 5 RCTs, incorporating data from a new large RCT and the final results of a previous RCT. Compared with control, a 10-day course of remdesivir probably results in little to no reduction in mortality (risk ratio [RR], 0.93 [95% CI, 0.82 to

			1.06]; 4 RCTs) but may result in a small reduction in the proportion of patients receiving mechanical ventilation (RR, 0.71 [CI, 0.56 to 0.90]; 3 RCTs). Remdesivir probably results in a moderate increase in the percentage of patients who recovered and a moderate decrease in serious adverse events and may result in a large reduction in time to recovery. Effect on hospital length of stay or percentage remaining hospitalized is mixed. Compared with a 10-day course for those not requiring ventilation at baseline, a 5-day course may reduce mortality, the need for ventilation, and serious adverse events while increasing the percentage of patients who recovered or clinically improved. Limitation: Summarizing findings was challenging because of varying disease severity definitions and outcomes. Conclusion: In hospitalized adults with COVID-19, remdesivir probably results in little to no mortality difference but probably improves the percentage recovered and reduces serious harms and may result in a small reduction in the proportion receiving ventilation. For patients not receiving ventilation, a 5-day course may provide greater benefits and fewer harms with lower drug costs than a 10-day course.
Ammassari A et al JAMA Open Comparison of Demand for Drugs Used for COVID-19 Treatment and Other Drugs During the	Comparison of Demand for Drugs Used for COVID-19 Treatment and Other Drugs During the Early Phase of the COVID-19 Pandemic in Italy	Andamento dell'approvvigionamento di farmaci (e dunque indirettamente delle prescrizioni)	In February 2020, Italy was the first European country to detect coronavirus disease 2019 (COVID-19) in individuals and rapidly turned into one of the most-affected regions of the world. The National Health Service (NHS), which provides universal coverage to citizens, was challenged as never before in the history of the institution. Because no approved drug was available, patients received potentially effective drugs, participated in clinical trials, accessed compassionate drug use programs, or self-medicated. The aim of this study was to evaluate changes in drug demand during

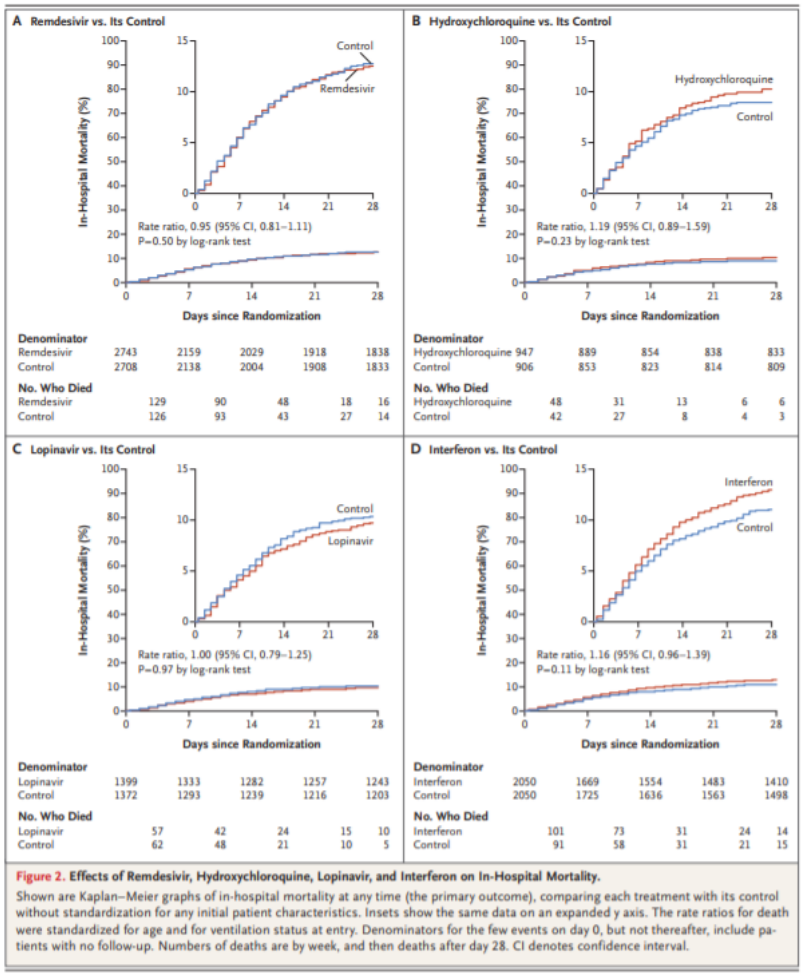
Early Phase of the COVID-19 Pandemic in Italy | Critical Care Medicine | JAMA Network Open | JAMA Network			the early phase of the COVID-19 outbreak in Italy compared with the period before the outbreak. 
Gorges RJ et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776102	Factors Associated With Racial Differences in Deaths Among Nursing Home Residents With COVID-19 Infection in the US	La mortalità per COVID-19 nelle strutture di lungodegenza negli USA abitate in prevalenza da bianchi è inferiore a quella delle altre in base a questo studio cross-sectional che ha coivolto oltre 13.000 strutture.	Importance It is important to understand differences in coronavirus disease 2019 (COVID-19) deaths by nursing home racial composition and the potential reasons for these differences so that limited resources can be distributed equitably. Objective To describe differences in the number of COVID-19 deaths by nursing home racial composition and examine the factors associated with these differences. Design, Setting, and Participants This cross-sectional study of 13 312 nursing homes in the US used the Nursing Home COVID-19 Public File from the Centers for Medicare and Medicaid Services, which contains COVID-19 cases and deaths among nursing home residents as self-reported by nursing homes beginning between January 1, 2020, and May 24, 2020, and ending on September 13, 2020. Data were analyzed from July 28 to December 18, 2020.

			Exposures Confirmed or suspected COVID-19 infection. Confirmed cases were defined as COVID-19 infection confirmed by a diagnostic laboratory test. Suspected cases were defined as signs and/or symptoms of COVID-19 infection or patient-specific transmission-based precautions for COVID-19 infection. Main Outcomes and Measures Deaths associated with COVID-19 among nursing home residents. Death counts were compared by nursing home racial composition, which was measured as the proportion of White residents. Results Among 13 312 nursing homes included in the study, the overall mean (SD) age of residents was 79.5 (6.7) years. A total of 51 606 COVID-19–associated deaths among residents were reported, with a mean (SD) of 3.9 (8.0) deaths per facility. The mean (SD) number of deaths in nursing homes with the lowest proportion of White residents (quintile 1) vs nursing homes with the highest proportions of White residents (quintile 5) were 5.6 (9.2) and 1.7 (4.8), respectively. Facilities in quintile 1 experienced a mean (SE) of 3.9 (0.2) more deaths than those in quintile 5, representing a 3.3-fold higher number of deaths in quintile 1 compared with quintile 5. Adjustment for the number of certified beds reduced the mean (SE) difference between these 2 nursing home groups to 2.2 (0.2) deaths. Controlling for case mix measures and other nursing home characteristics did not modify this association. Adjustment for county-level COVID-19 prevalence further reduced the mean (SE) difference to 1.0 (0.2) death. Conclusions and Relevance In this study, nursing homes with the highest proportions of non-White residents experienced COVID-19 death counts that were 3.3-fold higher than those of facilities with the highest proportions of White residents. These differences were associated with factors such as larger nursing home size and higher

			infection burden in counties in which nursing homes with high proportions of non-White residents were located. Focusing limited available resources on facilities with high proportions of non-White residents is needed to support nursing homes during potential future outbreaks.  Figure 1. Unadjusted Coronavirus Disease 2019 (COVID-19) Cases and Deaths Among Residents by Nursing Home Racial Composition Quintile
Zhang W et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2776543	Emergence of a Novel SARS-CoV-2 Variant in Southern California	Identificazione della variante CAL.20C di SARS-CoV-2 in California, caratterizzata da tre mutazioni nella proteina S, di cui una (L452R) in una regione implicata nella affinità con alcuni anticorpi monoclonali. Gli effetti sulla infettività e sugli outcome clinici rimangono da stabilire.	A spike in coronavirus disease 2019 (COVID-19) has occurred in Southern California since October 2020. Analysis of the severe acute respiratory syndrome coronavirus (SARS-CoV-2) in Southern California prior to October indicated most isolates originated from clade 20C that likely emerged from New York via Europe early in the pandemic. Since then, novel variants of SARS-CoV-2 including those seen in the UK (20I/501Y.V1/B.1.1.7), South Africa (20H/501Y.V2/B.1.351), and Brazil (P.1/20J/501Y.V3/B.1.1.248) have emerged with the concern of increased infectivity and virulence. Thus, we analyzed variants of SARS-CoV-2 in Southern

			California to establish whether one of these known strains or a novel variant had emerged.
Brookman S et al The Lancet https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(21)00030-4/fulltext	Effect of the new SARS-CoV-2 variant B.1.1.7 on children and young people.	Revisione e confronto delle caratteristiche dei bambini ricoverati al King's College Hospital durante la prima e la seconda « ondata » di COVID-19 nel Regno Unito. Non emergono differenze significative fra i due gruppi, a suggerire che la variante B.1.1.7, circolante durante la seconda ondata, non influenzi il decorso della malattia nei bambini.	The clinical impact of the new SARS-CoV-2 lineage B.1·1.7 on children and young people (aged 18 years or younger) regarding acute respiratory COVID-19 is yet to be fully defined. Media reports of increases in admissions to hospital and more serious illness in children and young people have resulted in public confusion and implicated the B.1.1.7 variant as a more pathogenic infection within this group. This uncertainty has necessitated a public statement from the Royal College of Paediatrics and Child Health.
WHO Solidarity Trial Consortium NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2023184?query=featured_home	Repurposed Antiviral Drugs for Covid-19 — Interim WHO Solidarity Trial Results	Risultati ad interim del trial Solidarity su 11330 adulti ospedalizzati con COVID-19 : nessuno fra lopinavir/r, idrossiclorochina, interferone e remdesivir modifica la mortalità, la necessità di ventilazione meccanica o la durata della degenza.	BACKGROUND : World Health Organization expert groups recommended mortality trials of four repurposed antiviral drugs — remdesivir, hydroxychloroquine, lopinavir, and interferon beta-1a — in patients hospitalized with coronavirus disease 2019 (Covid-19). METHODS : We randomly assigned inpatients with Covid-19 equally between one of the trial drug regimens that was locally available and open control (up to five options, four active and the local standard of care). The intention-to-treat primary analyses examined in-hospital mortality in the four pairwise comparisons of each trial drug and its control (drug available but patient assigned to the same care without that drug). Rate ratios for death were calculated with stratification according to age and status regarding mechanical ventilation at trial entry.

			RESULTS : At 405 hospitals in 30 countries, 11,330 adults underwent randomization; 2750 were assigned to receive remdesivir, 954 to hydroxychloroquine, 1411 to lopinavir (without interferon), 2063 to interferon (including 651 to interferon plus lopinavir), and 4088 to no trial drug. Adherence was 94 to 96% midway through treatment, with 2 to 6% crossover. In total, 1253 deaths were reported (median day of death, day 8; interquartile range, 4 to 14). The Kaplan–Meier 28-day mortality was 11.8% (39.0% if the patient was already receiving ventilation at randomization and 9.5% otherwise). Death occurred in 301 of 2743 patients receiving remdesivir and in 303 of 2708 receiving its control (rate ratio, 0.95; 95% confidence interval [CI], 0.81 to 1.11; P=0.50), in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P=0.23), in 148 of 1399 patients receiving lopinavir and in 146 of 1372 receiving its control (rate ratio, 1.00; 95% CI, 0.79 to 1.25; P=0.97), and in 243 of 2050 patients receiving interferon and in 216 of 2050 receiving its control (rate ratio, 1.16; 95% CI, 0.96 to 1.39; P=0.11). No drug definitely reduced mortality, overall or in any subgroup, or reduced initiation of ventilation or hospitalization duration. CONCLUSIONS : These remdesivir, hydroxychloroquine, lopinavir, and interferon regimens had little or no effect on hospitalized patients with Covid-19, as indicated by overall mortality, initiation of ventilation, and duration of hospital stay.

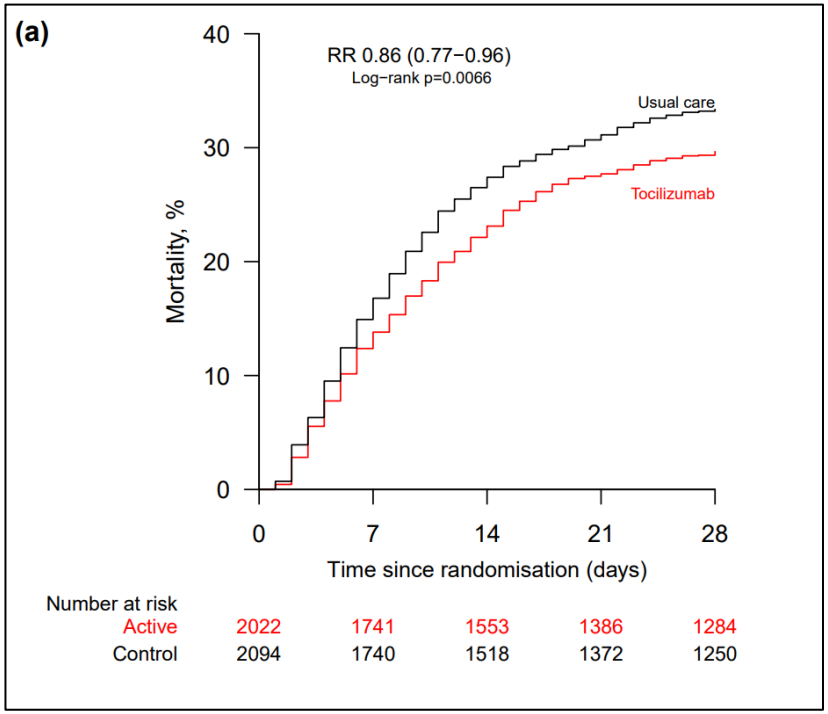
			 **Figure 2. Effects of Remdesivir, Hydroxychloroquine, Lopinavir, and Interferon on In-Hospital Mortality.** Shown are Kaplan–Meier graphs of in-hospital mortality at any time (the primary outcome), comparing each treatment with its control without standardization for any initial patient characteristics. Insets show the same data on an expanded y axis. The rate ratios for death were standardized for age and for ventilation status at entry. Denominators for the few events on day 0, but not thereafter, include patients with no follow-up. Numbers of deaths are by week, and then deaths after day 28. CI denotes confidence interval.
Lacout A et al NEJM	Hydroxychloroquine in Hospitalized Patients with Covid-19	Commento e risposta sui dosaggi di idrossiclorochina utilizzati nel trial RECOVERY, considerati troppo elevati e a rischio di un potenziale effetto anti-interferone,	In vitro studies show that the effect of hydroxychloroquine is mainly mediated by alkalinization of the phagolysosomes, where it can concentrate about 1500 times more than in plasma. This effect can be obtained with low doses of hydroxychloroquine because of its long elimination half-life.

https://www.nejm.org/doi/full/10.1056/NEJMc2035374		dannoso in corso di infezione virale.	
Fiolet T et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30505-X/fulltext	Effect of hydroxychloroquine with or without azithromycin on the mortality of coronavirus disease 2019 (COVID-19) patients: a systematic review and meta-analysis	Revisione sistematica e metanalisi sull'effetto di idrossiclorochina con eventuale aggiunta di azitromicina sulla mortalità da COVID-19 negli adulti : l'idrossiclorochina da sola non riduce la mortalità, se combinata con azitromicina addirittura la aumenta rispetto allo standard of care.	Background : Hydroxychloroquine or chloroquine with or without azithromycin have been widely promoted to treat coronavirus disease 2019 (COVID-19) following early in vitro antiviral effects against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Objective : The aim of this systematic review and meta-analysis was to assess whether chloroquine or hydroxychloroquine with or without azithromycin decreased COVID-19 mortality compared with the standard of care. Data sources : PubMed, Web of Science, Embase Cochrane Library, Google Scholar and MedRxiv were searched up to 25 July 2020. Study eligibility criteria : We included published and unpublished studies comparing the mortality rate between patients treated with chloroquine or hydroxychloroquine with or without azithromycin and patients managed with standard of care. Participants : Patients ≥18 years old with confirmed COVID-19. Interventions : Chloroquine or hydroxychloroquine with or without azithromycin. Methods : Effect sizes were pooled using a random-effects model. Multiple subgroup analyses were conducted to assess drug safety. Results : The initial search yielded 839 articles, of which 29 met our inclusion criteria. All studies except one were conducted on hospitalized patients and evaluated the effects of hydroxychloroquine with or without azithromycin. Among the 29 articles, three were randomized controlled trials, one was a non-randomized trial and 25 were observational studies, including 11

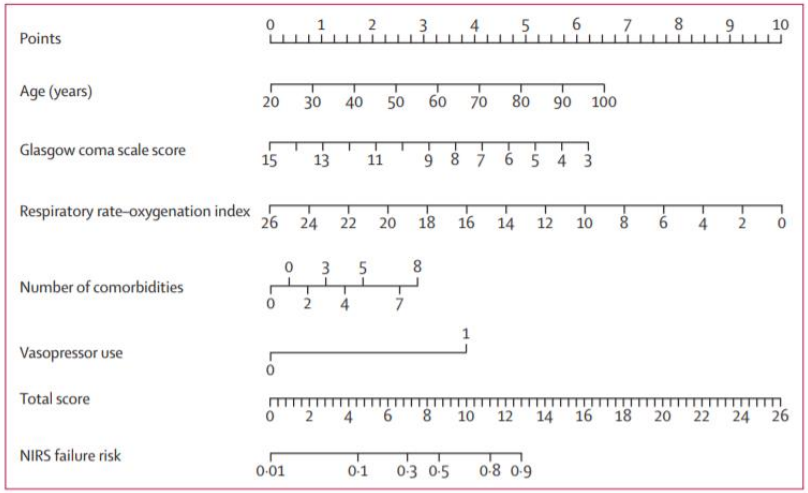
			with a critical risk of bias and 14 with a serious or moderate risk of bias. After excluding studies with critical risk of bias, the meta-analysis included 11 932 participants for the hydroxychloroquine group, 8081 for the hydroxychloroquine with azithromycin group and 12 930 for the control group. Hydroxychloroquine was not significantly associated with mortality: pooled relative risk (RR) 0.83 (95% CI 0.65–1.06, n = 17 studies) for all studies and RR = 1.09 (95% CI 0.97–1.24, n = 3 studies) for randomized controlled trials. Hydroxychloroquine with azithromycin was associated with an increased mortality (RR = 1.27; 95% CI 1.04–1.54, n = 7 studies). We found similar results with a Bayesian meta-analysis. Conclusion : Hydroxychloroquine alone was not associated with reduced mortality in hospitalized COVID-19 patients but the combination of hydroxychloroquine and azithromycin significantly increased mortality.
Paul M et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30642-X/fulltext	Has the door closed on hydroxychloroquine for SARS-COV-2?	Commento di Mical Paul alla metanalisi precedente, che non lascia spazio secondo lei all'utilizzo di idrossiclorochina nel trattamento di COVID-19.	Shortly following the onset of the SARS-COV-2 pandemic, Raoult's group from Marseille published a study describing improved virological cure with hydroxychloroquine (HCQ), especially in combination with azithromycin. Beyond being "non-randomized" this was a small, unadjusted comparison including 36 patients in total, reporting only on virological cure and excluding from the analysis the most severely ill patients. It was probably meant as an alert for a potentially useful treatment and reported as responsible sharing of the local experience given the urgent situation (as the authors noted "we believe that our results should be shared with the scientific community"). Yet this publication launched a heated debate of HCQ believers and non-believers, moving far beyond the realm of science, with politicians expressing views, countries stockpiling the drug and people taking it prophylactically. This also led to a flurry of studies, resulting now in more than 25 systematic

			reviews and/or meta-analyses summarizing specifically the efficacy of HCQ for COVID-19 from these studies on PubMed and 12 unpublished on medRxiv. A systematic review of observational studies and randomized controlled (RCTs) published recently in Clinical Microbiology and Infection concluded no benefit for HCQ and increased mortality with HCQ and azithromycin. Is this the last word on HCQ for corona?
Raoult D et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30643-1/fulltext	Rational for meta-analysis and randomized treatment: the COVID-19 example	Commento di Dider Raoult sulla metanalisi precedente e in generale sul conflitto che egli percepisce fra il mondo clinico e quello dei ricercatori di professione.	All in all, there is no indisputable science of therapeutic trials and their evaluation. It cannot be said that significant progress has been made in the practice of care by randomized trials in infectious diseases. They have generated a new specialty, particularly in the medical world, which is that of methodologists and analysts who, by definition, are convinced that their method is the best. In principle, over the history of hydroxychloroquine, depending on the studies that one decides to exclude, one is likely to retain one hypothesis or another.
Leibovici L Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(20)30644-3/fulltext	Difficult editorial decisions	Le pene editoriali di Leonard Leibovici nel pubblicare i tre contributi precedenti su CMI.	In the present issue of CMI we publish a systematic review and meta-analysis on hydroxychloroquine with and without azithromycin for treating COVID-19; two accompanying commentaries; and letters to the editor addressing the systematic review, including the authors' response. Almost all involved difficult editorial decisions, although of different kinds. This is a partial explanation on how we made these decisions.
RECOVERY Collaborative Group MedRXiv – not peer reviewed	Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): preliminary results of a	Secondo i risultati ad interim del trial RECOVERY, tocilizumab endovena sembra conferire un beneficio contro l'outcome	Background: Tocilizumab is a monoclonal antibody that binds to the receptor for interleukin (IL)-6, reducing inflammation, and is commonly used to treat rheumatoid arthritis. We evaluated the safety and efficacy of tocilizumab in adult patients admitted to hospital with COVID-19 with evidence of both hypoxia and systemic

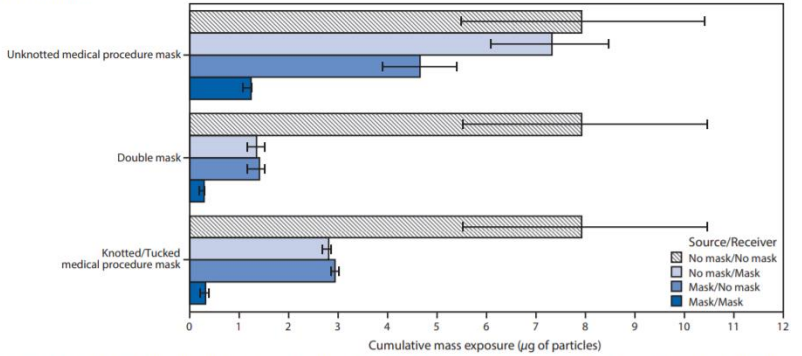
: https://doi.org/10.1101/2021.02.11.21249258	randomised, controlled, open-label, platform trial	avverso di mortalità/necessità di ventilazione invasiva e sul tempo di dimissione nei pazienti con COVID-19, in aggiunta al trattamento con steroidi.	inflammation. Methods: This randomised, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), is assessing several possible treatments in patients hospitalised with COVID-19 in the UK. Those trial participants with hypoxia (oxygen saturation <92% on air or requiring oxygen therapy) and evidence of systemic inflammation (C-reactive protein [CRP] ≥75 mg/L) were eligible for randomisation to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg to 800 mg (depending on weight) given intravenously. A second dose could be given 12 to 24 hours later if the patient's condition had not improved. The primary outcome was 28-day mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN (50189673) and clinicaltrials.gov (NCT04381936). Findings: Between 23 April 2020 and 24 January 2021, 4116 adults were included in the assessment of tocilizumab, including 562 (14%) patients receiving invasive mechanical ventilation, 1686 (41%) receiving non-invasive respiratory support, and 1868 (45%) receiving no respiratory support other than oxygen. Median CRP was 143 [IQR 107-204] mg/L and 3385 (82%) patients were receiving systemic corticosteroids at randomisation. Overall, 596 (29%) of the 2022 patients allocated tocilizumab and 694 (33%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0·86; 95% confidence interval [CI] 0·77-0·96; p=0·007). Consistent results were seen in all pre-specified subgroups of patients. In particular, a clear mortality benefit was seen in those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital alive within 28 days (54% vs. 47%; rate ratio 1·22; 95% CI 1·12- 1·34; p<0·0001). Among those not receiving invasive mechanical ventilation at baseline, patients allocated tocilizumab were less likely to reach the

			composite endpoint of invasive mechanical ventilation or death (33% vs. 38%; risk ratio 0·85; 95% CI 0·78-0·93; p=0·0005). Interpretation: In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the level of respiratory support and were additional to the benefits of systemic corticosteroids. 
Liu L et al The Lancet https://www.thelancet.com/journals/landig/article/	A simple nomogram for predicting failure of non-invasive respiratory strategies in adults with COVID-19: a retrospective multicentre study	Studio retrospettivo osservazionale su 652 pazienti adulti trattati con strategie non invasive di ossigeno-terapia (NIV e cannule nasali ad alto	Background : Non-invasive respiratory strategies (NIRS) including high-flow nasal cannula (HFNC) and non-invasive ventilation (NIV) have become widely used in patients with COVID-19 who develop acute respiratory failure. However, use of these therapies, if ineffective, might delay initiation of invasive mechanical ventilation (IMV) in some patients. We aimed to determine early predictors of

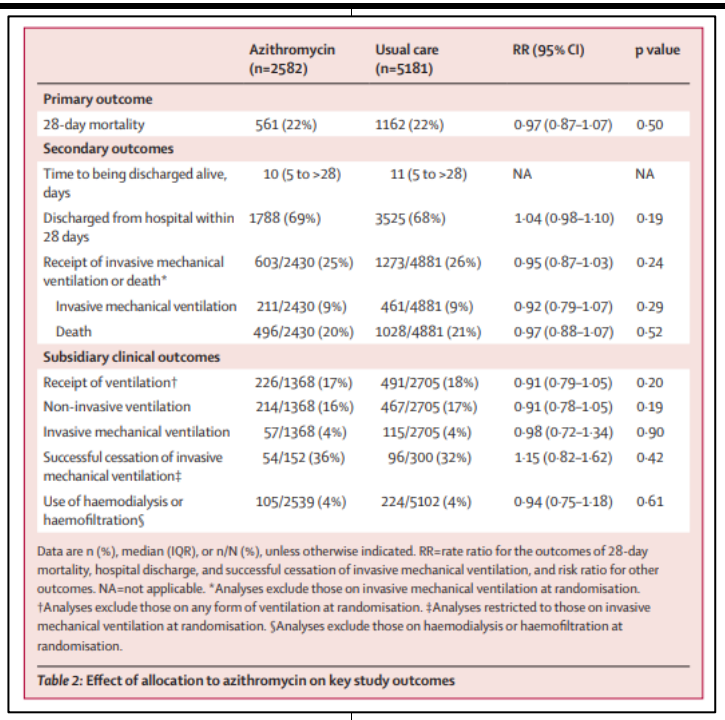
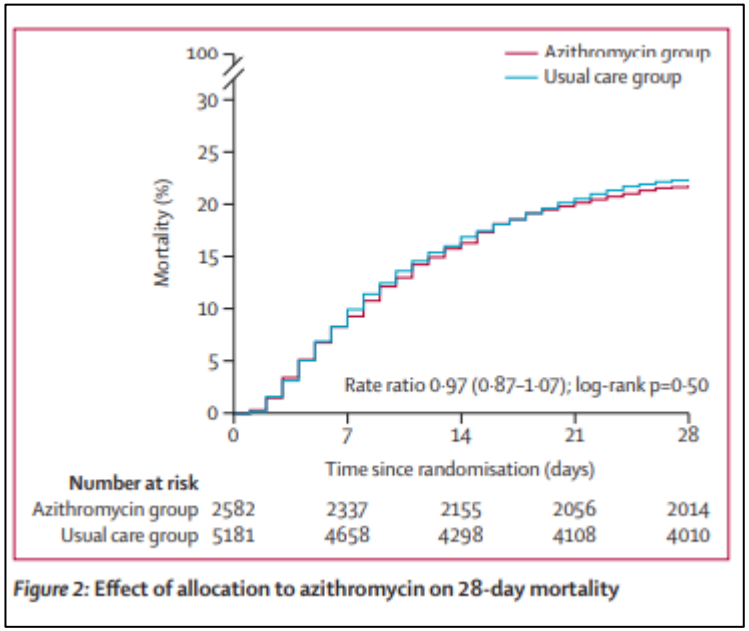
PIIS2589-7500(20)30316-2/fulltext		flusso) per insufficienza respiratoria COVID-19 relata: sono predittori di fallimento e necessità di ventilazione meccanica l'età, il numero di comorbidità, il ROX index (rapporto spO2/FiO2*frequenza respiratoria), il punteggio nella scala di Glasgow e l'utilizzo di vasopressori durante il primo giorno di ossigenoterapia.	NIRS failure and develop a simple nomogram and online calculator that can identify patients at risk of NIRS failure. Methods : We did a retrospective, multicentre observational study in 23 hospitals designated for patients with COVID-19 in China. Adult patients (≥18 years) with severe acute respiratory syndrome coronavirus 2 infection and acute respiratory failure receiving NIRS were enrolled. A training cohort of 652 patients (21 hospitals) was used to identify early predictors of NIRS failure, defined as subsequent need for IMV or death within 28 days after intensive care unit admission. A nomogram was developed by multivariable logistic regression and concordance statistics (C-statistics) computed. C-statistics were validated internally by cross-validation in the training cohort, and externally in a validation cohort of 107 patients (two hospitals). Findings : Patients were enrolled between Jan 1 and Feb 29, 2020. NIV failed in 211 (74%) of 286 patients and HFNC in 204 (56%) of 366 patients in the training cohort. NIV failed in 48 (81%) of 59 patients and HFNC in 26 (54%) of 48 patients in the external validation cohort. Age, number of comorbidities, respiratory rate–oxygenation index (ratio of pulse oximetry oxygen saturation/fraction of inspired oxygen to respiratory rate), Glasgow coma scale score, and use of vasopressors on the first day of NIRS in the training cohort were independent risk factors for NIRS failure. Based on the training dataset, the nomogram had a C-statistic of 0·80 (95% CI 0·74–0·85) for predicting NIV failure, and a C-statistic of 0·85 (0·82–0·89) for predicting HFNC failure. C-statistic values were stable in both internal validation (NIV group mean 0·79 [SD 0·10], HFNC group mean 0·85 [0·07]) and external validation (NIV group value 0·88 [95% CI 0·72–0·96], HFNC group value 0·86 [0·72–0·93]).

			Interpretation : We have developed a nomogram and online calculator that can be used to identify patients with COVID-19 who are at risk of NIRS failure. These patients might benefit from early triage and more intensive monitoring.  ***Figure 1:*** **Characteristics in the nomogram to predict probability of NIRS failure in patients with severe acute respiratory syndrome coronavirus 2 pneumonia** Patient prognostic values are located on the axis of each variable; a line is then drawn upwards at a 90° angle to determine the number of points for that particular variable. The sum of these numbers is located on the total score axis, and a line is drawn at a 90° angle downward to the NIRS failure risk axis to determine the likelihood of failure of non-invasive respiratory therapies. Alternatively, failure risk can be ascertained from the online calculator. Vasopressor use was represented on the axis at an arbitrary value of 1 (no use=0). NIRS=non-invasive respiratory support.
Gao C et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00055-0/fulltext	Prevalence and impact factors of recurrent positive SARS-CoV-2 detection in 599 hospitalized COVID-19 patients	Caratteristiche di 65 persone con tampone nasofaringeo nuovamente positivo dopo due negativi per SARS-CoV-2 e fattori di rischio legati alla ri-positivizzazione.	Objectives : Re-positive tests for SARS-CoV-2 in Coronavirus Disease 2019 (COVID-19) patients were common. We aimed to investigate the rate and risk factors of recurrent positive detection of SARS-CoV-2 in hospitalized COVID-19 patients. Methods : Oropharyngeal and nasopharyngeal swabs (n=3513) were collected to detect SARS-CoV-2 during the hospitalization. We analyzed the recurrent positive rate after consecutive negative results and its relationship to demographic characteristics.

			Results : Among 599 enrolled COVID-19 patients, the median time for viral RNA shedding was 24 days (IQR, 19-33 days). The positive rate of RT-PCR was 35.9% (215/599), 17.0% (65/383) and 12.4% (23/185) after one, two and three consecutive negative RT-PCR test results respectively. Medians of CT-values of initial positive test, rebound positive after two consecutive negative results, and rebound positive after three consecutive negative results were 28.8, 32.8 and 36.1 respectively. Compare with male patients, females had a significant higher rate of recurrent positive RT-PCR after three consecutive negative results (18.2%, 18/99 vs. 5.8%, 5/86, p=0.013). Older age (≥55 yrs) had a significant higher rate of recurrent positive RT-PCR after one negative result (42.3%, 165/390, vs. 23.9%, 50/209, p<0.001). Nasopharyngeal swab tests produced a higher positive rate than oropharyngeal swab tests (37.3%, 152/408 vs. 35.8%, 1111/3105). Conclusions : Our study revealed the prevalence and dynamic characteristics of recurrent positive RT-PCR to SARS-CoV-2. We showed that around 17.0% (65/383) patients were tested positive for SARS-CoV-2 after two consecutive negative results. Patients with rebound positive RT-PCR test had a low viral load. Older age and female were risk factors for recurrent positive results.
Brooks JT et al Advanced Search Morbidity and Mortality Weekly Report (MMWR) https://www.cdc.gov/mmwr/volumes/70/wr/mm7	Maximizing Fit for Cloth and Medical Procedure Masks to Improve Performance and Reduce SARS-CoV-2 Transmission and Exposure, 2021	Indicazioni dei CDC per ottimizzare la protezione da SARS-CoV-2 con le mascherine : fondamentale, come è intuitivo, una buona aderenza al viso.	What is already known about this topic? Universal masking is recommended to slow the spread of COVID-19. Cloth masks and medical procedure masks substantially reduce exposure from infected wearers (source control) and reduce exposure of uninfected wearers (wearer exposure). What is added by this report? CDC conducted experiments to assess two ways of improving the fit of medical procedure masks: fitting a cloth mask over a medical procedure mask, and knotting the ear loops of a medical procedure mask and then tucking in and flattening

007e1.htm?s_cid=mm7007e1_w			the extra material close to the face. Each modification substantially improved source control and reduced wearer exposure. What are the implications for public health? These experiments highlight the importance of good fit to maximize mask performance. There are multiple simple ways to achieve better fit of masks to more effectively slow the spread of COVID-19. **FIGURE 2. Mean cumulative exposure* for various combinations of no mask, double masks, and unknotted and knotted/tucked medical procedure masks†**  * To an aerosol of 0.1–7 μm potassium chloride particles (with 95% confidence intervals indicated by error bars) measured at mouthpiece of receiver headform configured face to face 6 ft from a source headform, with no ventilation and replicated 3 times. Mean improvements in cumulative exposures compared with no mask/no mask (i.e., no mask wearing, or 100% exposure) were as follows: *unknotted medical procedure mask*: no mask/mask = 7.5%, mask/no mask = 41.3%, mask/mask = 84.3%; *double mask*: no mask/mask = 83.0%, mask/no mask = 82.2%, mask/mask = 96.4%; *knotted/tucked medical procedure mask*: no mask/mask = 64.5%, mask/no mask = 62.9%, mask/mask = 95.9%. † Double mask refers to a three-ply medical procedure mask covered by a three-ply cloth cotton mask. A knotted and tucked medical procedure mask is created by bringing together the corners and ear loops on each side, knotting the ears loops together where they attach to the mask, and then tucking in and flattening the resulting extra mask material to minimize the side gaps.
RECOVERY Collaborative Group The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00149-5/fulltext	Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	Esito dell'analisi ad interim del RECOVERY trial sui pazienti ospedalizzati per COVID-19 e randomizzati ad azitromicina contro standard of care : nessun beneficio sulla mortalità a 28 giorni né su alcun outcome secondario, per cui il farmaco è indicato solo come antibiotico, in caso di	Background : Azithromycin has been proposed as a treatment for COVID-19 on the basis of its immunomodulatory actions. We aimed to evaluate the safety and efficacy of azithromycin in patients admitted to hospital with COVID-19. Methods : In this randomised, controlled, open-label, adaptive platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), several possible treatments were compared with usual care in patients admitted to hospital with COVID-19 in the UK. The trial is underway at 176 hospitals in the UK. Eligible and consenting patients were randomly allocated to either usual standard of care alone or usual standard of care plus azithromycin 500 mg once per day by mouth or intravenously for 10 days or until discharge (or

		sospetta sovrainfezione batterica.	allocation to one of the other RECOVERY treatment groups). Patients were assigned via web-based simple (unstratified) randomisation with allocation concealment and were twice as likely to be randomly assigned to usual care than to any of the active treatment groups. Participants and local study staff were not masked to the allocated treatment, but all others involved in the trial were masked to the outcome data during the trial. The primary outcome was 28-day all-cause mortality, assessed in the intention-to-treat population. The trial is registered with ISRCTN, 50189673, and ClinicalTrials.gov, NCT04381936. Findings : Between April 7 and Nov 27, 2020, of 16 442 patients enrolled in the RECOVERY trial, 9433 (57%) were eligible and 7763 were included in the assessment of azithromycin. The mean age of these study participants was 65·3 years (SD 15·7) and approximately a third were women (2944 [38%] of 7763). 2582 patients were randomly allocated to receive azithromycin and 5181 patients were randomly allocated to usual care alone. Overall, 561 (22%) patients allocated to azithromycin and 1162 (22%) patients allocated to usual care died within 28 days (rate ratio 0·97, 95% CI 0·87–1·07; p=0·50). No significant difference was seen in duration of hospital stay (median 10 days [IQR 5 to >28] vs 11 days [5 to >28]) or the proportion of patients discharged from hospital alive within 28 days (rate ratio 1·04, 95% CI 0·98–1·10; p=0·19). Among those not on invasive mechanical ventilation at baseline, no significant difference was seen in the proportion meeting the composite endpoint of invasive mechanical ventilation or death (risk ratio 0·95, 95% CI 0·87–1·03; p=0·24). Interpretation : In patients admitted to hospital with COVID-19, azithromycin did not improve survival or other prespecified clinical outcomes. Azithromycin use in patients admitted to hospital with

			COVID-19 should be restricted to patients in whom there is a clear antimicrobial indication. 
Mahdi SA et al MedRXiv – not peer reviewed https://www.medrxiv.org/content/10.1101/2021.02.10.21251247v1	Safety and efficacy of the ChAdOx1 nCoV-19 (AZD1222) Covid-19 vaccine against the B.1.351 variant in South Africa	Un ciclo con due dosi del vaccino adenovirale anti SARS-CoV-2 ChAdOx1-nCoV19 (AstraZeneca) non protegge dalls malattia lieve-moderata dovuta alla variante « sudafricana » del virus B.1.351, che è prevalente in Sudafrica (39/42 infezioni rilevate sono dovute a B.1.351).	Background Assessing safety and efficacy of Covid-19 vaccines in different populations is essential, as is investigation of efficacy against emerging SARS-CoV-2 variants of concern including the B.1.351 (501Y.V2) variant first identified in South Africa. Methods We conducted a randomized multicentre, double blinded controlled trial on safety and efficacy of ChAdOx1-nCoV19 in HIV-uninfected people in South Africa. Participants age 18 to <65 years randomized (1:1) to two doses of vaccine containing 5x1010 viral particles or placebo (0.9%NaCl) 21-35 days apart. Post 2nd-dose serum samples (n=25) were tested by pseudotyped (PSVNA) and live virus (LVNA) neutralization assays against the D614G and B.1.351 variants. Primary endpoints were safety and vaccine efficacy (VE) >14 days following second dose against laboratory confirmed symptomatic

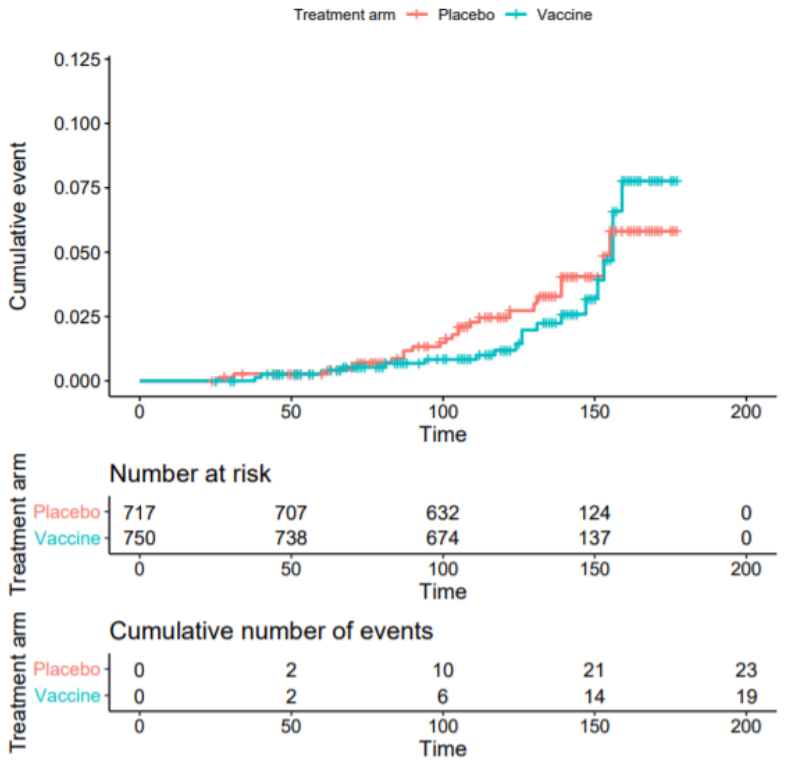
	Azithromycin (n=2582)	Usual care (n=5181)	RR (95% CI)	p value
Primary outcome				
28-day mortality	561 (22%)	1162 (22%)	0·97 (0·87–1·07)	0·50
Secondary outcomes				
Time to being discharged alive, days	10 (5 to >28)	11 (5 to >28)	NA	NA
Discharged from hospital within 28 days	1788 (69%)	3525 (68%)	1·04 (0·98–1·10)	0·19
Receipt of invasive mechanical ventilation or death*	603/2430 (25%)	1273/4881 (26%)	0·95 (0·87–1·03)	0·24
Invasive mechanical ventilation	211/2430 (9%)	461/4881 (9%)	0·92 (0·79–1·07)	0·29
Death	496/2430 (20%)	1028/4881 (21%)	0·97 (0·88–1·07)	0·52
Subsidiary clinical outcomes				
Receipt of ventilation†	226/1368 (17%)	491/2705 (18%)	0·91 (0·79–1·05)	0·20
Non-invasive ventilation	214/1368 (16%)	467/2705 (17%)	0·91 (0·78–1·05)	0·19
Invasive mechanical ventilation	57/1368 (4%)	115/2705 (4%)	0·98 (0·72–1·34)	0·90
Successful cessation of invasive mechanical ventilation‡	54/152 (36%)	96/300 (32%)	1·15 (0·82–1·62)	0·42
Use of haemodialysis or haemofiltration§	105/2539 (4%)	224/5102 (4%)	0·94 (0·75–1·18)	0·61

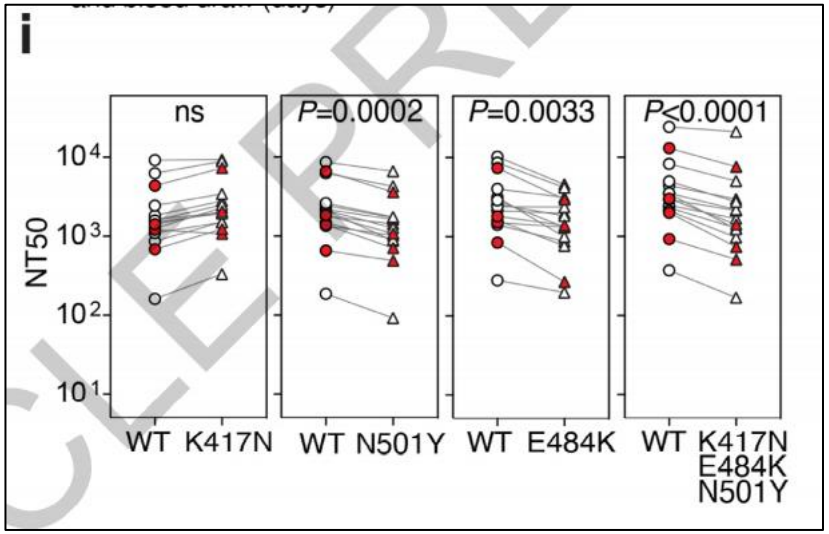
Data are n (%), median (IQR), or n/N (%), unless otherwise indicated. RR=rate ratio for the outcomes of 28-day mortality, hospital discharge, and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. NA=not applicable. *Analyses exclude those on invasive mechanical ventilation at randomisation. †Analyses exclude those on any form of ventilation at randomisation. ‡Analyses restricted to those on invasive mechanical ventilation at randomisation. §Analyses exclude those on haemodialysis or haemofiltration at randomisation.

Table 2: **Effect of allocation to azithromycin on key study outcomes**

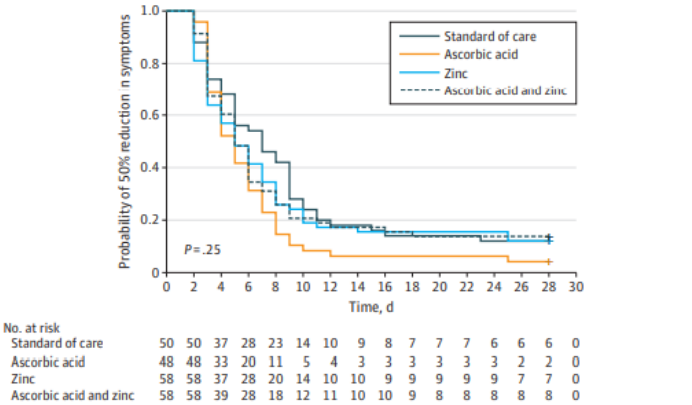
Figure 2: **Effect of allocation to azithromycin on 28-day mortality**

			Covid-19. Results 2026 HIV-uninfected adults were enrolled between June 24th and Nov 9th, 2020; 1010 and 1011 received at least one dose of placebo or vaccine, respectively. Median age was 31 years. The B.1.351 variant showed increased resistance to vaccinee sera using the PSVNA and LVNA. In the primary endpoint analysis, 23/717 (3.2%) placebo and 19/750 (2.5%) vaccine recipients developed mild-moderate Covid-19; VE 21.9% (95%Confidence Interval: -49.9; 59.8). Of the primary endpoint cases, 39/42 (92.9%) were the B.1.351 variant; against which VE was 10.4% (95%CI: -76.8; 54.8) analyzed as a secondary objective. The incidence of serious adverse events was balanced between the vaccine and placebo groups. Conclusions A two-dose regimen of ChAdOx1-nCoV19 did not show protection against mild-moderate Covid-19 due to B.1.351 variant, however, VE against severe Covid-19 is undetermined.

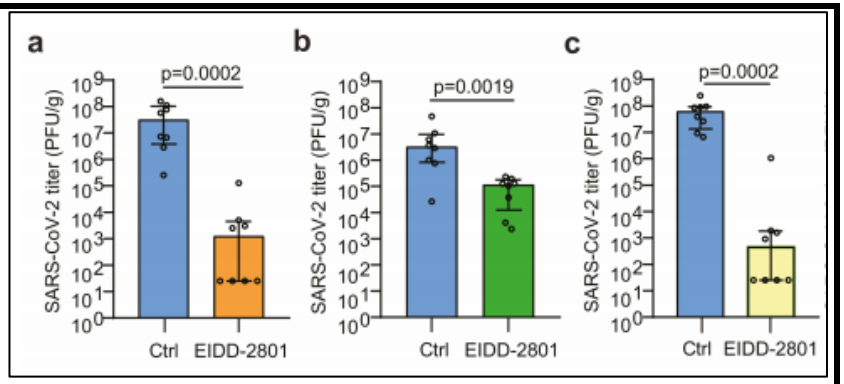
			Figure 3: Kaplan-Meyer plot of ChAdOx-1 nCoV19 against all-severity symptomatic Covid-19 illness following two doses versus placebo. 
Wang Z et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2776557	mRNA vaccine-elicited antibodies to SARS-CoV-2 and circulating variants	Il siero di 20 vaccinati (in rosso nella figura) a 8 settimane dal vaccino a mRNA Moderna o Pfizer contro SARS-CoV-2 contiene un elevato livello di IgM e IgG contro la proteina spike, simili tra loro e simili a quelle degli individui con	Here we report on the antibody and memory B cell responses in a cohort of 20 volunteers who received either the Moderna (mRNA-1273) or Pfizer-BioNTech (BNT162b2) vaccines. Eight weeks after the second vaccine injection volunteers showed high levels of IgM, and IgG anti-SARS-CoV-2 spike protein (S) and receptor binding domain (RBD) binding titers. Moreover, the plasma neutralizing activity, and the relative numbers of RBD-specific memory B cells were equivalent to individuals who recovered from natural infection. However, activity against SARS-CoV-2 variants encoding E484K or N501Y or the

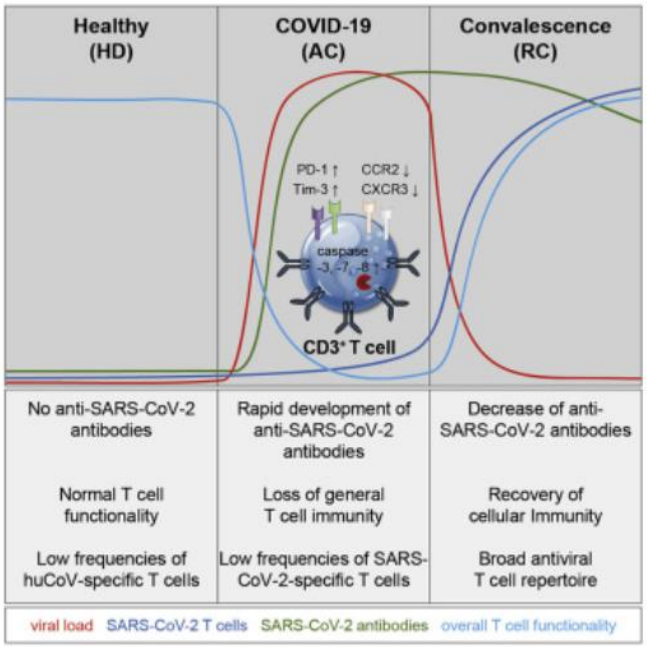
		storia di malattia naturale (bianco). Le sostituzioni K417N, E484K ed N501Y, tipiche delle varianti attualmente in circolazione di SARS-CoV-2, riducono il potere neutralizzante degli anticorpi monoclonali maggiormente rappresentati nei sieri, anche se il significato in vivo di questa riduzione del titolo neutralizzante non è chiaro.	K417N:E484K:N501Y combination was reduced by a small but significant margin. Vaccine-elicited monoclonal antibodies (mAbs) potently neutralize SARS-CoV-2, targeting a number of different RBD epitopes in common with mAbs isolated from infected donors. However, neutralization by 14 of the 17 most potent mAbs tested was reduced or abolished by either K417N, or E484K, or N501Y mutations. Notably, the same mutations were selected when recombinant vesicular stomatitis virus (rVSV)/SARS-CoV-2 S was cultured in the presence of the vaccine elicited mAbs. Taken together the results suggest that the monoclonal antibodies in clinical use should be tested against newly arising variants, and that mRNA vaccines may need to be updated periodically to avoid potential loss of clinical efficacy. 
Zucman N et al Clinical Infectious Diseases	Severe reinfection with South African SARS-CoV-2 variant 501Y.V2: A case report	Prima infezione da SARS-COV-2 in settembre 2020 e reinfezione grave – con necessità di ventilazione	We here report a case of severe SARS-CoV-2 reinfection with South African variant 501Y.V2, four months after recovering from a first episode of COVID-19.

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab129/6132402		meccanica - da variante « sudafricana » B1.351 in gennaio 2021 in un uomo non immunocompromesso di 58 anni.	
Suma T et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776305	Effect of High-Dose Zinc and Ascorbic Acid Supplementation vs Usual Care on Symptom Length and Reduction Among Ambulatory Patients With SARS-CoV-2 Infection	Il trattamento con zinco, vitamina C o entrambi non ridce la durata dei sintomi da COVID-19 lieve in questo trial su 214 pazienti trattati in regime ambulatoriale.	Importance : There is limited evidence regarding early treatment of novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection to mitigate symptom progression. Objective : To examine whether high-dose zinc and/or high-dose ascorbic acid reduce the severity or duration of symptoms compared with usual care among ambulatory patients with SARS-CoV-2 infection. Design, Setting, and Participants : This multicenter, single health system randomized clinical factorial open-label trial enrolled 214 adult patients with a diagnosis of SARS-CoV-2 infection confirmed with a polymerase chain reaction assay who received outpatient care in sites in Ohio and Florida. The trial was conducted from April 27, 2020, to October 14, 2020. Intervention Patients were randomized in a 1:1:1:1 allocation ratio to receive either 10 days of zinc gluconate (50 mg), ascorbic acid (8000 mg), both agents, or standard of care. Outcomes The primary end point was the number of days required to reach a 50% reduction in symptoms, including severity of fever, cough, shortness of breath, and fatigue (rated on a 4-point scale for each symptom). Secondary end points included days required to reach a total symptom severity score of 0, cumulative severity score at day 5, hospitalizations, deaths, adjunctive prescribed medications, and adverse effects of the study supplements. Results : A total of 214 patients were randomized, with a mean (SD) age of 45.2 (14.6) years and 132 (61.7%) women. The study was

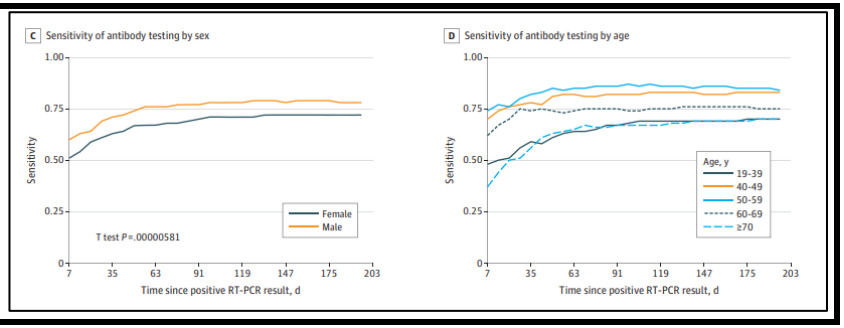
			stopped for a low conditional power for benefit with no significant difference among the 4 groups for the primary end point. Patients who received usual care without supplementation achieved a 50% reduction in symptoms at a mean (SD) of 6.7 (4.4) days compared with 5.5 (3.7) days for the ascorbic acid group, 5.9 (4.9) days for the zinc gluconate group, and 5.5 (3.4) days for the group receiving both (overall P = .45). There was no significant difference in secondary outcomes among the treatment groups. Conclusions and Relevance In this randomized clinical trial of ambulatory patients diagnosed with SARS-CoV-2 infection, treatment with high-dose zinc gluconate, ascorbic acid, or a combination of the 2 supplements did not significantly decrease the duration of symptoms compared with standard of care. **Figure 3. Kaplan-Meier Curves for the Primary End Point by Treatment Group** 
Shimabukuro TT et al JAMA	Reports of Anaphylaxis After Receipt of mRNA COVID-19 Vaccines in the US—December 14, 2020-January 18, 2021	Descrizione dei casi di anafilassi dopo somministrazione di vaccini a mRNA contro SARS-CoV-2 negli USA : 47 da vaccino	In December 2020, the US Food and Drug Administration (FDA) issued Emergency Use Authorizations for 2 mRNA-based vaccines for prevention of coronavirus disease 2019 (COVID-19): Pfizer-BioNTech COVID-19 vaccine (EUA issued December 11; 2 doses, 3 weeks apart) and Moderna COVID-19 vaccine (EUA issued December 18; 2 doses,

https://jamanetwork.com/journals/jama/fullarticle/2776557		Pfizer-BioNTec, ovvero 4.7/milione, e 19 da vaccino Moderna ovvero 2.5 casi/milione.	1 month apart). Shortly after each authorization, the Advisory Committee on Immunization Practices issued interim recommendations for use.
Wahl A et al Nature https://www.nature.com/articles/s41586-021-03312-w	SARS-CoV-2 infection is effectively treated and prevented by EIDD-2801	Dimostrazione dell'effetto citopatico di SARS-CoV-2 e di altri Coronavirus del pipistrello su un modello murino di polmone umano. Inoltre, riduzione della carica virale in vivo dopo somministrazione dell'antivirale EIDD-2801, un analogo nucleosidico formulato per assunzione orale e attualmente in corso di sperimentazione di fase II-III nell'infezione da SARS-CoV-2 [nella figura è mostrata la riduzione della carica virale a 24h, 48h e 2 giorni dalla terapia].	All known recently emerged human coronaviruses probably originated in bats. Here we used a single experimental platform based on human lung-only mice (LoM) to demonstrate efficient in vivo replication of all recently emerged human coronaviruses (SARS-CoV, MERS-CoV and SARS-CoV-2) and two highly relevant endogenous pre-pandemic SARS-like bat coronaviruses. Virus replication in this model occurs in bona fide human lung tissue and does not require any type of adaptation of the virus or the host. Our results indicate that bats harbour endogenous coronaviruses capable of direct transmission into humans. Further detailed analysis of pandemic SARS-CoV-2 in vivo infection of LoM human lung tissue showed predominant infection of human lung epithelial cells, including type II pneumocytes present in alveoli and ciliated airway cells. Acute SARS-CoV-2 infection was highly cytopathic and induced a robust and sustained type I interferon and inflammatory cytokine/chemokine response. Finally, we evaluated a therapeutic and pre-exposure prophylaxis strategy for coronavirus infection. Our results show that therapeutic and prophylactic administration of EIDD-2801, an oral broad spectrum antiviral currently in phase II–III clinical trials, dramatically inhibited SARS-CoV-2 replication in vivo and thus has significant potential for the prevention and treatment of COVID-19.

			
Bonifacius A et al Immunity https://www.cell.com/immunity/fulltext/S1074-7613(21)00031-5	COVID-19 immune signatures reveal stable antiviral T cell function despite declining humoral responses	I linfociti T CD4+ produttori di interferone-gamma sono poco numerosi in fase acuta, ma più duraturi della risposta anticorpale in soggetti con storia di infezione da SARS-CoV-2.	Cellular and humoral immunity to SARS-CoV-2 is critical to control primary infection and correlates with severity of disease. The role of SARS-CoV-2-specific T cell immunity, its relationship to antibodies, and pre-existing immunity against endemic coronaviruses (huCoV), which has been hypothesized to be protective, were investigated in 82 healthy donors (HDs), 204 recovered (RCs), and 92 active COVID-19 patients (ACs). ACs had high amounts of anti-SARS-CoV-2 nucleocapsid and spike IgG but lymphopenia and overall reduced antiviral T cell responses due to the inflammatory milieu, expression of inhibitory molecules (PD-1, Tim-3) as well as effector caspase-3, -7, and -8 activity in T cells. SARS-CoV-2-specific T cell immunity conferred by polyfunctional, mainly interferon-γ-secreting CD4+ T cells remained stable throughout convalescence, whereas humoral responses declined. Immune responses toward huCoV in RCs with mild disease and strong cellular SARS-CoV-2 T cell reactivity imply a protective role of pre-existing immunity against huCoV.

			
Wong CKH et al EClinicalMedicine – The Lancet https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00023-7/fulltext	Clinical outcomes of different therapeutic options for COVID-19 in two Chinese case cohorts: A propensity-score analysis	Analisi degli outcome di 4771 pazienti con infezione sintomatica da SARS-CoV-2 lieve-moderata: si osserva un vantaggio contro l'outcome decesso/ventilazione meccanica/trasferimento in terapia intensiva e sulla durata del ricovero con la somministrazione di interferone beta indipendentemente dall'esordio di malattia, e un vantaggio contro lo stesso	Background : The timing of administration of agents and use of combination treatments in COVID-19 remain unclear. We assessed the effectiveness of therapeutics in cohorts in Hong Kong SAR and Anhui, China. Methods : We conducted propensity-score analysis of 4771 symptomatic patients from Hong Kong between 21st January and 6th December 2020, and 648 symptomatic patients from Anhui between 1st January and 27th February 2020. We censored all observations as at 13st December 2020. Time from hospital admission to discharge, and composite outcome of death, invasive mechanical ventilation or intensive care unit admission across 1) all therapeutic options including lopinavir-ritonavir, ribavirin, umifenovir, interferon-alpha-2b, interferon-beta-1b, corticosteroids, antibiotics, and Chinese

		outcome avverso con la somministrazione di ribavirina entro 7 giorni dall'esordio.	medicines, and 2) four interferon-beta-1b combination treatment groups were investigated. Findings : Interferon-beta-1b was associated with an improved composite outcome (OR=0.55, 95%CI 0.38, 0.80) and earlier discharge (−8.8 days, 95%CI −9.7, −7.9) compared to those not administered interferon-beta-1b. Oral ribavirin initiated within 7 days from onset was associated with lower risk of the composite outcome in Hong Kong (OR=0.51, 95%CI 0.29, 0.90). Lopinavir-ritonavir, intravenous ribavirin, umifenovir, corticosteroids, interferon-alpha-2b, antibiotics or Chinese medicines failed to show consistent clinical benefit. Interferon-beta-1b co-administered with ribavirin was associated with improved composite outcome (OR=0.50, 95%CI 0.32, 0.78) and earlier discharge (−2.35 days, 95%CI −3.65, −1.06) compared to interferon-beta-1b monotherapy. Interpretation : Our findings support the early administration of interferon-beta-1b alone or in combination with oral ribavirin for COVID-19 patients.
Vashisht R et al JAMA Open https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2776300	Age- and Sex-Associated Variations in the Sensitivity of Serological Tests Among Individuals Infected With SARS-CoV-2	Il maggiore intervallo dalla diagnosi di infezione, il sesso maschile e la fascia d'età 50-59 anni sono associati a maggiore sensibilità dei test sierologici per SARS-CoV-2.	Antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are known to appear 2 to 3 weeks after infection,1-3 but patient characteristics and measurement timing could influence this immune response. This cohort study investigated the sensitivity of antibody tests to detect previous SARS-CoV-2 infection using existing clinical data across the University of California Health (UC Health) system.

			 C Sensitivity of antibody testing by sex 1.00 0.75 0.50 0.25 0 Sensitivity T test P=.00000581 Female Male 7 35 63 91 119 147 175 203 Time since positive RT-PCR result, d D Sensitivity of antibody testing by age 1.00 0.75 0.50 0.25 0 Sensitivity Age, y 19-39 40-49 50-59 60-69 ≥70 7 35 63 91 119 147 175 203 Time since positive RT-PCR result, d