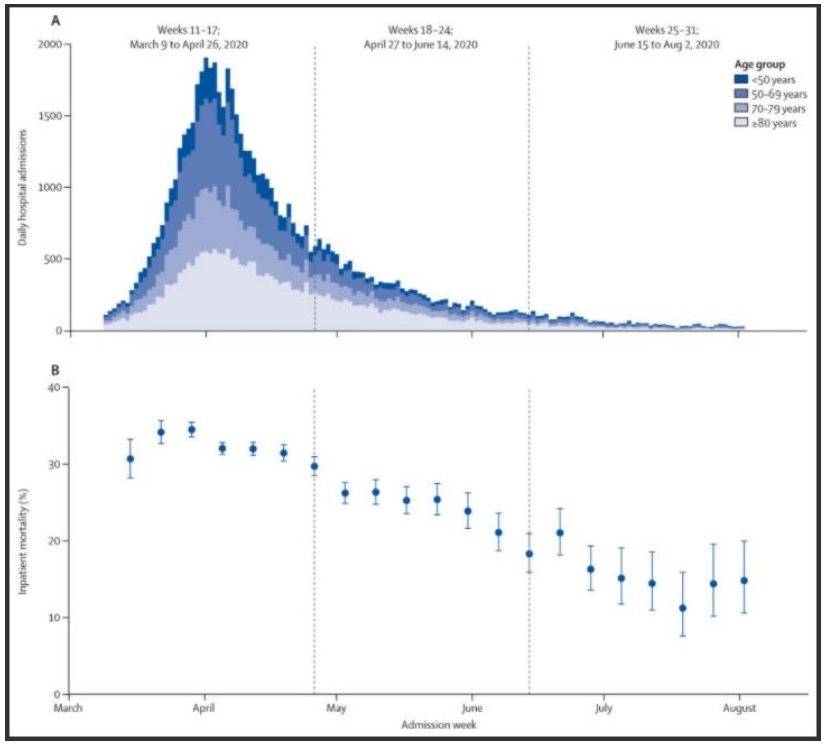
RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 17.05 – 23.05.2021 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Docherty AB et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00175-2/fulltext	Changes in in-hospital mortality in the first wave of COVID-19: a multicentre prospective observational cohort study using the WHO Clinical Characterisation Protocol UK	I pazienti ricoverati durante i primi mesi della prima « ondata » di COVID-19 nel Regno Unito erano più gravi all'ingresso in ospedale rispetto a quelli ricoverati a giugno-luglio 2020. La mortalità si è ridotta progressivamente nel corso del tempo, e si stima che un 22% di questo effetto sia dovuto all'introduzione degli steroidi e al maggior utilizzo della ventilazione non invasiva.	Background : Mortality rates in hospitalised patients with COVID-19 in the UK appeared to decline during the first wave of the pandemic. We aimed to quantify potential drivers of this change and identify groups of patients who remain at high risk of dying in hospital. Methods : In this multicentre prospective observational cohort study, the International Severe Acute Respiratory and Emerging Infections Consortium WHO Clinical Characterisation Protocol UK recruited a prospective cohort of patients with COVID-19 admitted to 247 acute hospitals in England, Scotland, and Wales during the first wave of the pandemic (between March 9 and Aug 2, 2020). We included all patients aged 18 years and older with clinical signs and symptoms of COVID-19 or confirmed COVID-19 (by RT-PCR test) from assumed community-acquired infection. We did a three-way decomposition mediation analysis using natural effects models to explore associations between week of admission and in-hospital

			mortality, adjusting for confounders (demographics, comorbidities, and severity of illness) and quantifying potential mediators (level of respiratory support and steroid treatment). The primary outcome was weekly in-hospital mortality at 28 days, defined as the proportion of patients who had died within 28 days of admission of all patients admitted in the observed week, and it was assessed in all patients with an outcome. This study is registered with the ISRCTN Registry, ISRCTN66726260. Findings : Between March 9, and Aug 2, 2020, we recruited 80 713 patients, of whom 63 972 were eligible and included in the study. Unadjusted weekly in-hospital mortality declined from 32·3% (95% CI 31·8–32·7) in March 9 to April 26, 2020, to 16·4% (15·0–17·8) in June 15 to Aug 2, 2020. Reductions in mortality were observed in all age groups, in all ethnic groups, for both sexes, and in patients with and without comorbidities. After adjustment, there was a 32% reduction in the risk of mortality per 7-week period (odds ratio [OR] 0·68 [95% CI 0·65–0·71]). The higher proportions of patients with severe disease and comorbidities earlier in the first wave (March and April) than in June and July accounted for 10·2% of this reduction. The use of respiratory support changed during the first wave, with gradually increased use of non-invasive ventilation over the first wave. Changes in respiratory support and use of steroids accounted for 22·2%, OR 0·95 (0·94–0·95) of the reduction in in-hospital mortality. Interpretation : The reduction in in-hospital mortality in patients with COVID-19 during the first wave in the UK was partly accounted for by changes in the case-mix and illness severity. A significant reduction in in-hospital mortality was associated with differences in respiratory support and critical care use, which could partly reflect accrual of clinical knowledge. The remaining improvement in in-

			hospital mortality is not explained by these factors, and could be associated with changes in community behaviour, inoculum dose, and hospital capacity strain. 
Wallace M et al MMWR https://www.cdc.gov/mmwr/volumes/70/wr/mm7020e1.htm?s_cid=mm7020e1_w#suggestedcitation	The Advisory Committee on Immunization Practices' Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine in Adolescents Aged 12–15 Years — United States, May 2021	L'FDA ha esteso l'autorizzazione all'uso del vaccino Pfizer contro SARS-CoV-2 alla fascia d'età 12-15 anni.	What is already known about this topic? On May 10, 2021, the Food and Drug Administration expanded Emergency Use Authorization for the Pfizer-BioNTech COVID-19 vaccine to include adolescents aged 12–15 years. What is added by this report? On May 12, 2021, after a systematic review of all available data, the Advisory Committee on Immunization Practices made an interim recommendation for use of the Pfizer-BioNTech COVID-19 vaccine in adolescents aged 12–15 years for the prevention of COVID-19.

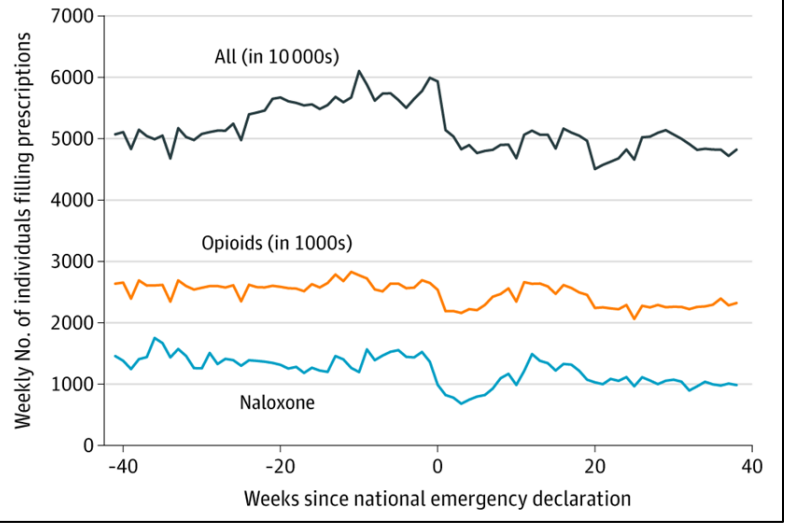
			What are the implications for public health practice? The Pfizer-BioNTech COVID-19 vaccine is the first COVID-19 vaccine approved for use in adolescents and has high efficacy against symptomatic COVID-19. Vaccination will be important to protect adolescents against symptomatic COVID-19 disease and to reduce community transmission of SARS-CoV-2.
Sherry HYC et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779759	Global Incidence of Neurological Manifestations Among Patients Hospitalized With COVID-19—A Report for the GCS-NeuroCOVID Consortium and the ENERGY Consortium	In una coorte di oltre 3700 pazienti ospedalizzati con COVID-19, l'80% ha sintomi neurologici in senso lato, fra cui in particolare cefalea, anosmia e ageusia. Le manifestazioni neurologiche sono associate a maggiore mortalità intraospedaliera. Sarebbe interessante il confronto con un gruppo di pari età di ospedalizzati per infezione acuta.	Importance The COVID-19 pandemic continues to affect millions of people globally, with increasing reports of neurological manifestations but limited data on their incidence and associations with outcome. Objective To determine the neurological phenotypes, incidence, and outcomes among adults hospitalized with COVID-19. Design, Setting, and Participants This cohort study included patients with clinically diagnosed or laboratory-confirmed COVID-19 at 28 centers, representing 13 countries and 4 continents. The study was performed by the Global Consortium Study of Neurologic Dysfunction in COVID-19 (GCS-NeuroCOVID) from March 1 to September 30, 2020, and the European Academy of Neurology (EAN) Neuro-COVID Registry (ENERGY) from March to October 2020. Three cohorts were included: (1) the GCS-NeuroCOVID all COVID-19 cohort (n = 3055), which included consecutive hospitalized patients with COVID-19 with and without neurological manifestations; (2) the GCS-NeuroCOVID COVID-19 neurological cohort (n = 475), which comprised consecutive patients hospitalized with COVID-19 who had confirmed neurological manifestations; and (3) the ENERGY cohort (n = 214), which included patients with COVID-19 who received formal neurological consultation. Exposures Clinically diagnosed or laboratory-confirmed COVID-19. Main Outcomes and Measures Neurological phenotypes were classified as self-reported symptoms or neurological signs and/or

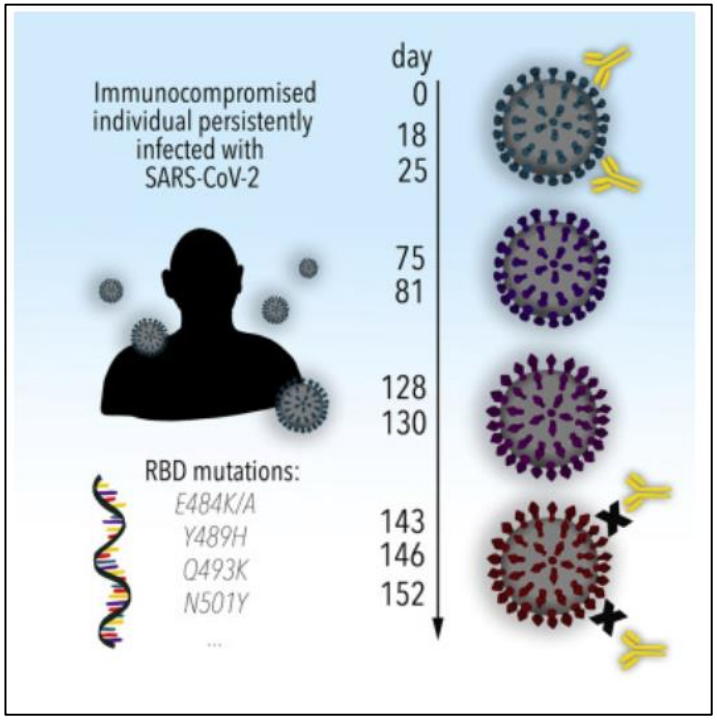
			syndromes assessed by clinical evaluation. Composite incidence was reported for groups with at least 1 neurological manifestation. The main outcome measure was in-hospital mortality. Results Of the 3055 patients in the all COVID-19 cohort, 1742 (57%) were men, and the mean age was 59.9 years (95% CI, 59.3-60.6 years). Of the 475 patients in the COVID-19 neurological cohort, 262 (55%) were men, and the mean age was 62.6 years (95% CI, 61.1-64.1 years). Of the 214 patients in the ENERGY cohort, 133 (62%) were men, and the mean age was 67 years (95% CI, 52-78 years). A total of 3083 of 3743 patients (82%) across cohorts had any neurological manifestation (self-reported neurological symptoms and/or clinically captured neurological sign and/or syndrome). The most common self-reported symptoms included headache (1385 of 3732 patients [37%]) and anosmia or ageusia (977 of 3700 patients [26%]). The most prevalent neurological signs and/or syndromes were acute encephalopathy (1845 of 3740 patients [49%]), coma (649 of 3737 patients [17%]), and stroke (222 of 3737 patients [6%]), while meningitis and/or encephalitis were rare (19 of 3741 patients [0.5%]). Presence of clinically captured neurologic signs and/or syndromes was associated with increased risk of in-hospital death (adjusted odds ratio [aOR], 5.99; 95% CI, 4.33-8.28) after adjusting for study site, age, sex, race, and ethnicity. Presence of preexisting neurological disorders (aOR, 2.23; 95% CI, 1.80-2.75) was associated with increased risk of developing neurological signs and/or syndromes with COVID-19. Conclusions and Relevance In this multicohort study, neurological manifestations were prevalent among patients hospitalized with COVID-19 and were associated with higher in-hospital mortality. Preexisting neurological disorders were associated with increased risk of developing neurological signs and/or syndromes in COVID-19.

			Table 2. Neurologic Manifestations in Study Population, Stratified by Cohort[a] Table 2. Neurologic Manifestations in Study Population, Stratified by Cohort[a] Patients, No./total No. (%) GCS-NeuroCOVID Cohort Manifestation / EAN ENERGY Registry (n = 214) / COVID-19 neurological (n = 475) / All COVID-19 (n = 3055) Neurological manifestations Any neurological manifestation[b] 169/214 (79) 475/475 (100) 2439/3054 (80) Clinically captured signs or syndromes[c] 151/169 (89) 385/475 (81) 1628/3055 (53) Self-reported neurological symptoms Headache 56/204 (27) 164/475 (35) 1165/3053 (38) Anosmia or ageusia 46/199 (23) 91/449 (20) 840/3052 (28) Syncope 4/212 (2) 58/475 (12) 152/3054 (5) Clinically verified neurological signs or syndromes Acute encephalopathy 50/212 (24) 254/475 (53) 1541/3053 (50) Stroke, all types 40/208 (19) 88/475 (19) 94/3054 (3) Coma 22/214 (10) 118/475 (25) 509/3048 (17) Seizure and/or status epilepticus 17/213 (8) 46/475 (10) 33/3053 (1) Dysautonomia 16/197 (8) 20/475 (4) 37/3053 (1) Meningitis and/or encephalitis 5/213 (2) 10/475 (2) 4/3053 (<1) Myelopathy 6/213 (3) 13/474 (3) 6/3049 (<2) Plegia and/or paralysis[d] 2/45 (4) 48/411 (12) 25/819 (3) Aphasia[d] 0 47/411 (11) 15/308 (5) New movement abnormalities[d] NA 19/411 (5) 24/814 (3) Abnormal tone[d] 2/45 (4) 51/411 (12) 14/304 (4) Abnormal brainstem reflexes[d] 1/44 (2) 21/352 (6) 23/282 (8) Sensory abnormalities[c] 1/45 (2) 51/411 (12) 15/812 (2)
Colson P et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00226-3/fulltext	Spreading of a new SARS-CoV-2 N501Y spike variant in a new lineage	Ddescrizione di una nuova variante di SARS-CoV-2, con 8 nuove sostituzioni nella sequenza amminoacidica della proteina spike, da parte del gruppo di Didier Raoult.	Objectives : Our surveillance of the SARS-CoV-2 genomic epidemiology led us to detect several variants since summer 2020. We report the recent spread of a new SARS-CoV-2 spike 501Y variant. Methods : SARS-CoV-2 sequences obtained from human nasopharyngeal samples by Illumina next-generation sequencing were analyzed using Nextclade and an in-house Python script and compared using BLASTn to the GISAID database. Phylogeny was performed using the IQ-TREE software. Results : We identified that SARS-CoV-2 genomes from four patients diagnosed in our institute harbored a new set of amino acid

			substitutions including L18F;L452R;N501Y;A653V;H655Y;D796Y;G1219V±Q677H. These spike N501Y genomes are the first of Nextstrain clade 19B. We obtained partial spike gene sequences of this genotype for an additional 43 patients. All patients infected with this genotype were diagnosed since mid-January 2021. We detected 42 other genomes of this genotype in GISAID, which were obtained from samples collected in December 2020 in four cases and in 2021 in 38 cases. The 89 sequences obtained in our institute or other laboratories originated from the Comoros archipelago, Western European countries (mostly metropolitan France), Turkey and Nigeria. Conclusion : These findings warrant further studies to investigate the spread, epidemiological and clinical features, and sensitivity to immune responses of this variant.
Wymant C et al Nature https://www.nature.com/articles/s41586-021-03606-z	The epidemiological impact of the NHS COVID-19 App	Efficacia dell'app per la notifica dei casi e dei contatti, diffusa dal servizio sanitario del Regno Unito, nel prevenire le infezioni da SARS-CoV-2. Si stima che per ogni persona positiva che abbia acconsentito alla notifica ai contatti, si sia evitata una nuova infezione.	The COVID-19 pandemic has seen digital contact tracing emerge around the world to help prevent spread of the disease. A mobile phone app records proximity events between app users, and when a user tests positive for COVID-19, their recent contacts can be notified instantly. Theoretical evidence has supported this new public health intervention1–6, but its epidemiological impact has remained uncertain7. Here we investigated the impact of the NHS COVID-19 app for England and Wales, from its launch on 24 September 2020 through to the end of December 2020. It was used regularly by approximately 16.5 million users (28% of the total population), and sent approximately 1.7 million exposure notifications: 4.4 per index case consenting to contact tracing. We estimated that the fraction of app-notified individuals subsequently showing symptoms and testing positive (the secondary attack rate, SAR) was 6.0%, comparable to the SAR for manually traced close contacts. We estimated the number of cases averted by the app

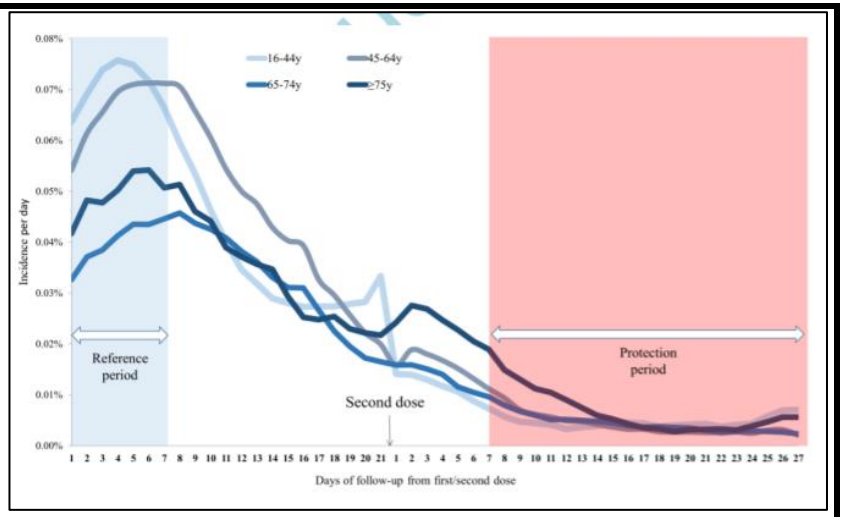
			using two complementary approaches. Modelling based on the notifications and SAR gave 284,000 (108,000-450,000), and statistical comparison of matched neighbouring local authorities gave 594,000 (317,000-914,000). Roughly one case was averted for each case consenting to notification of their contacts. We estimated that for every percentage point increase in app users, the number of cases can be reduced by 0.8% (modelling) or 2.3% (statistical analysis). These findings provide evidence for continued development and deployment of such apps in populations that are awaiting full protection from vaccines.
O'Donoghue AL et al JAMA https://jamanetwork.com/journals/jama-health-forum/fullarticle/2779948	Trends in Filled Naloxone Prescriptions Before and During the COVID-19 Pandemic in the United States	Riduzione delle prescrizioni di naloxone, a fronte di un numero invariato di prescrizioni di oppioidi, durante la pandemia di COVID-19 negli USA. Un altro effetto del minore accesso alle cure.	Substance use, including opioid use, increased during the COVID-19 pandemic. While overall emergency department visits decreased during the pandemic, nonfatal opioid overdose visits more than doubled, but few patients who overdosed on opioids received naloxone prescriptions on discharge. Studies show that increased access to naloxone can reduce fatal overdoses. In this study, we analyze the trends in filled naloxone prescriptions during the COVID-19 pandemic in the United States and compare these with trends in opioid prescriptions and overall prescriptions.

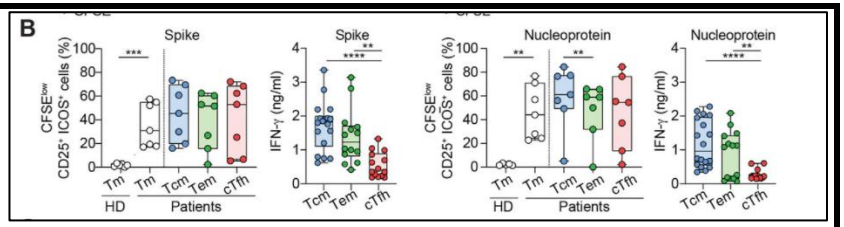
			Figure. Trends in the Weekly Number of Individuals Filling Naloxone Prescriptions, Opioid Prescriptions, and All Prescriptions 
Clark SA et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00355-X	SARS-CoV-2 evolution in an immunocompromised host reveals shared neutralization escape mechanisms	Mutazione della porzione legante il recettore (RBD) della proteina spike di SARS-CoV-2 in un paziente immunocompromesso con infezione persistente.	Many individuals mount nearly identical antibody responses to SARS-CoV-2. To gain insight into how the viral spike (S) protein receptor-binding domain (RBD) might evolve in response to common antibody responses, we studied mutations occurring during virus evolution in a persistently infected immunocompromised individual. We use antibody Fab/RBD structures to predict, and pseudotypes to confirm, that mutations found in late-stage evolved S variants confer resistance to a common class of SARS-CoV-2 neutralizing antibodies we isolated from a healthy COVID-19 convalescent donor. Resistance extends to the polyclonal serum immunoglobulins of four out of four healthy convalescent donors we tested and to monoclonal antibodies in clinical use. We further show that affinity maturation is unimportant for wild-type virus neutralization but is critical to neutralization breadth. Because the mutations we studied foreshadowed emerging variants that are now circulating across the

			globe, our results have implications to the long-term efficacy of S-directed countermeasures. 
Gao X et al Nature https://www.nature.com/articles/s41467-021-23118-8	Crystal structure of SARS-CoV-2 Orf9b in complex with human TOM70 suggests unusual virus-host interactions.	Struttura della proteina Orf9b di SARS-CoV-2 che interagisce con TOM70 dei mitocondri delle cellule bersaglio.	Although the accessory proteins are considered non-essential for coronavirus replication, accumulating evidences demonstrate they are critical to virus-host interaction and pathogenesis. Orf9b is a unique accessory protein of SARS-CoV-2 and SARS-CoV. It is implicated in immune evasion by targeting mitochondria, where it associates with the versatile adapter TOM70. Here, we determined the crystal structure of SARS-CoV-2 orf9b in complex with the cytosolic segment of human TOM70 to 2.2 Å. A central portion of orf9b occupies the deep pocket in the TOM70 C-terminal domain (CTD) and adopts a helical conformation strikingly different from the β-sheet-rich structure of the orf9b homodimer. Interactions

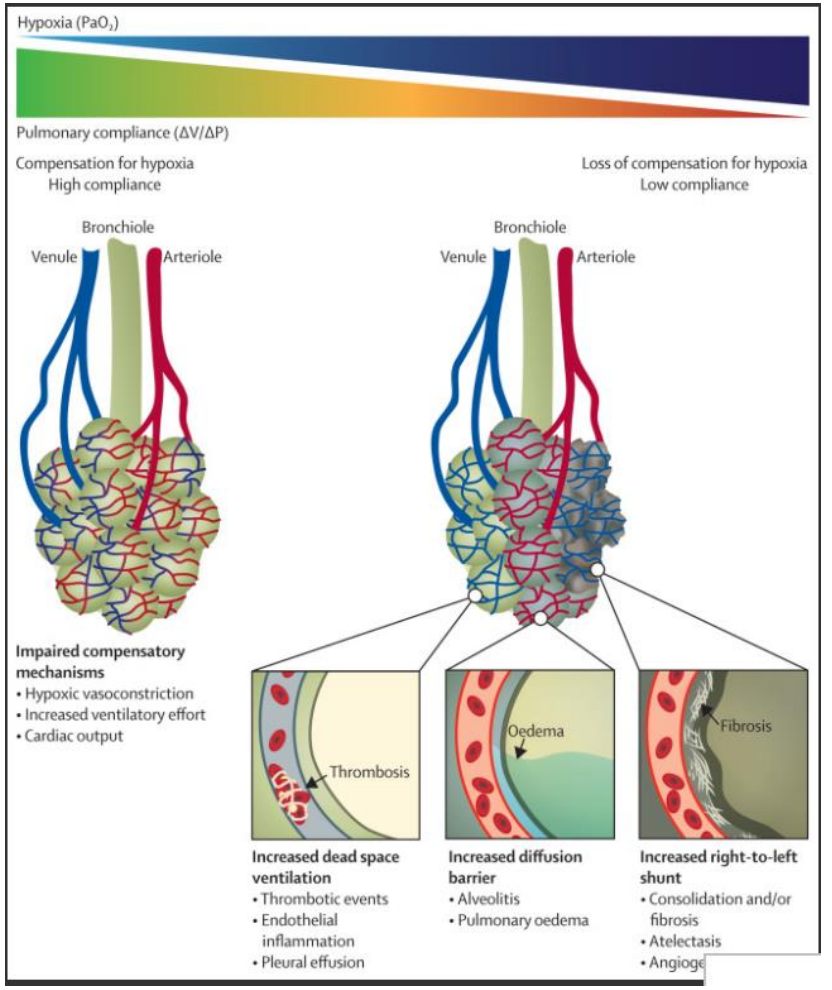
			between orf9b and TOM70 CTD are primarily hydrophobic and distinct from the electrostatic interaction between the heat shock protein 90 (Hsp90) EEVD motif and the TOM70 N-terminal domain (NTD). Using isothermal titration calorimetry (ITC), we demonstrated that the orf9b dimer does not bind TOM70, but a synthetic peptide harboring a segment of orf9b (denoted C-peptide) binds TOM70 with nanomolar KD. While the interaction between C-peptide and TOM70 CTD is an endothermic process, the interaction between Hsp90 EEVD and TOM70 NTD is exothermic, which underscores the distinct binding mechanisms at NTD and CTD pockets. Strikingly, the binding affinity of Hsp90 EEVD motif to TOM70 NTD is reduced by ~29-fold when orf9b occupies the pocket of TOM70 CTD, supporting the hypothesis that orf9b allosterically inhibits the Hsp90/TOM70 interaction. Our findings shed light on the mechanism underlying SARS-CoV-2 orf9b mediated suppression of interferon responses.
Roeker LE et al Leukemia https://www.nature.com/articles/s41375-021-01270-w	COVID-19 vaccine efficacy in patients with chronic lymphocytic leukemia	Efficacia della vaccinazione con vaccini a mRNA contro SARS-CoV-2 in 44 pazienti con leucemia linfatica cronica : maggiore nei soggetti mai sottoposti a terapia e più giovani di 70 anni	While randomized controlled trials demonstrated 94–95% efficacy of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike messenger RNA (mRNA) vaccines, efficacy in immunocompromised patients has not been established. We aimed to understand serologic response to mRNA vaccination in patients with chronic lymphocytic leukemia (CLL), a population of interest given the immunocompromised state associated with this malignancy and disease-directed therapies, as well as incomplete immune responses following other vaccinations
Chodick G et al CID	The effectiveness of the TWO-DOSE BNT162b2 vaccine: analysis of real-world data	Dati sull'efficacia nella vita reale del vaccino Pfizer contro SARS-CoV-2 in Istraele (oltre 1 milione di vaccinati) : 90% nella	Background : COVID-19 mRNA vaccines were shown to be highly efficacious in preventing the disease in randomized controlled trials; nonetheless, evidence on the real-world effectiveness of this vaccine is limited. Study objective was to evaluate the effectiveness

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab438/6276888		popolazione generale, 71% fra gli immunocompromessi nel prevenire l'infezione.	of BNT162b2 vaccine in preventing SARS-CoV-2 infection and COVID-19-related hospitalization and mortality. Methods : This historical cohort study included members of a large health provider in Israel that were vaccinated with at least one dose of BNT162b2. The primary outcome was incidence rate of a SARS-CoV-2 infection confirmed with rt-PCR, between 7 to 27 days after second dose (protection-period), as compared to days 1 to 7 after the first dose, where no protection by the vaccine is assumed (reference-period). Results : Data of 1,178,597 individuals vaccinated with BNT162b2 were analyzed (mean age 47.7 years [SD=18.1], 48.4% males) of whom 872,454 (74.0%) reached the protection period. Overall, 4514 infections occurred during the reference period compared to 728 during the protection period, yielding a weighted mean daily incidence of 54.8 per 100,000 (95%CI: 26.1-115.0 per 100,000) and 5.4 per 100,000 (95%CI: 3.5-8.4 per 100,000), respectively. The vaccine effectiveness in preventing infection was 90% (95%CI:79%-95%) and 94% (95%CI:88%-97%) against COVID-19. Among immunosuppressed patients, vaccine effectiveness against infection was 71% (95%CI:37%-87%). The adjusted hazard ratios for hospitalization in those infected were 0.82 (95%CI:0.36-1.88), 0.45 (95%CI:0.23-0.90), and 0.56 (95%CI:0.36-0.89) in the age groups 16-44, 45-64 and 75 and above, respectively. Conclusions : The effectiveness of the BNT162b2 vaccine is comparable to the one reported in the phase III clinical trial.

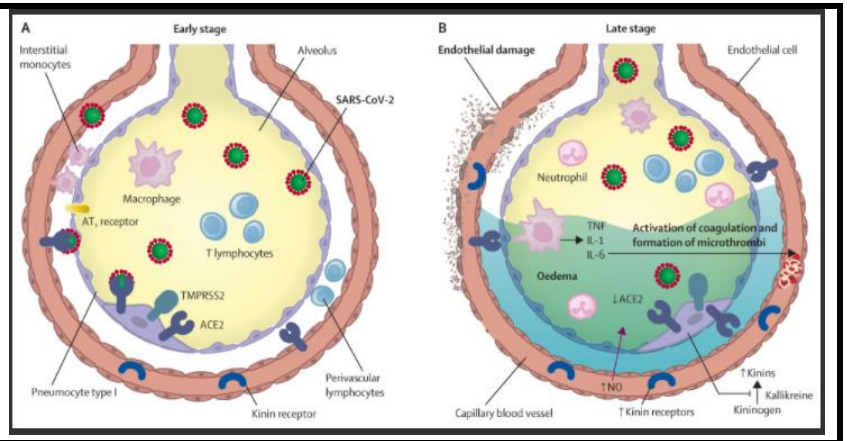
			
Low JS et al Science https://science.sciencemag.org/content/early/2021/05/17/science.abg8985	Clonal analysis of immunodominance and cross-reactivity of the CD4 T cell response to SARS-CoV-2	In 34 individui guariti da COVID-19, la gran parte (93%) ha linfociti T diretti contro una regione conservata della proteina S, che potrebbe essere modello di ulteriori vaccini.	The identification of CD4+ T cell epitopes is instrumental for the design of subunit vaccines for broad protection against coronaviruses. Here we demonstrate in COVID-19-recovered individuals a robust CD4+ T cell response to naturally processed SARS-CoV-2 spike (S) and nucleoprotein (N), including effector, helper, and memory T cells. By characterizing 2943 S-reactive T cell clones from 34 individuals, we found that 34% of clones and 93% of individuals recognized a conserved immunodominant S346-365 region within the RBD comprising nested HLA-DR- and HLA-DP-restricted epitopes. Using pre- and post-COVID-19 samples and S proteins from endemic coronaviruses, we identify cross-reactive T cells targeting multiple S protein sites. The immunodominant and cross-reactive epitopes identified can inform vaccination strategies to counteract emerging SARS-CoV-2 variants.

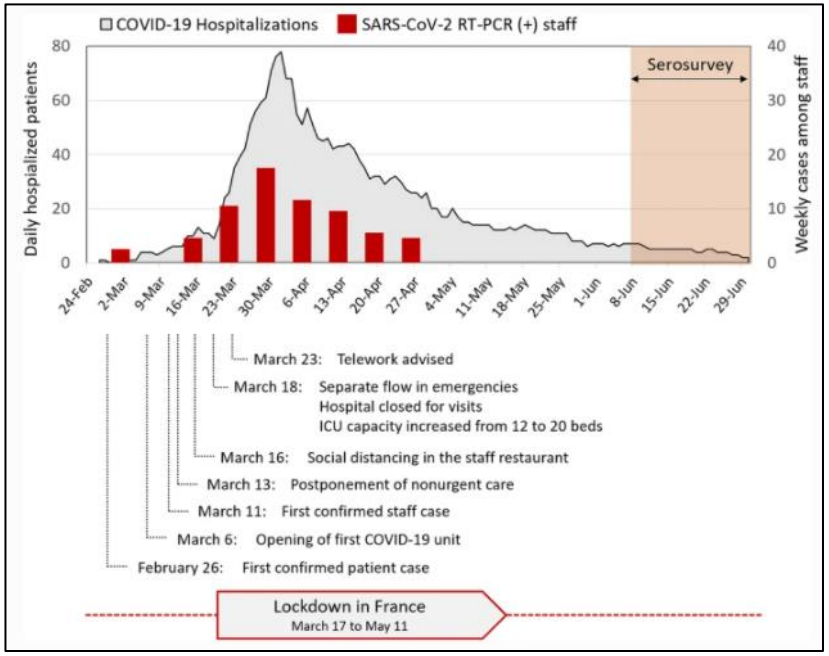
			
Bartolini B medRXiv - preprint https://www.medrxiv.org/content/10.1101/2020.11.28.20237016v1	The newly introduced SARS-CoV-2 variant A222V is rapidly spreading in Lazio region, Italy	Rapida introduzione di un clade di SARS-CoV-2 portatore della sostituzione A222V nella sequenza della proteina S; tale mutazione è presente nell'11.2% delle sequenze disponibili per il Lazio nel periodo giugno-ottobre 2020 e pur non riguardando la regione legante il recettore (RBD) sembra conferire un vantaggio nella diffusione del virus.	A new SARS-CoV-2 clade (GV) characterized by S substitution A222V, first reported from Spain in March, is rapidly spreading across Europe. To establish the A222V variant involvement in the infection rise in Italy, all GISAID sequences from Italy and those from our Laboratory (Lazio) in the period June-October were analysed. A222V, first recognized in August, represents 11.2% of sequences in this period, reaching 100% of autochthonous sequences in October, supporting increased GV circulation in Italy.
Lanini S et al medRXiv - preprint https://www.medrxiv.org/content/10.1101/2021.04.10.21255202v1	GRAd-COV2, a gorilla adenovirus based candidate vaccine against COVID-19, is safe and immunogenic in young and older adults	Sicurezza e immunogenicità di un candidato vaccino contro SARS-CoV-2 basato su vettore adenovirale di gorilla.	Safe and effective vaccines against coronavirus disease 2019 (COVID-19) are urgently needed to control the ongoing pandemic. Although impressive progress has been made with several COVID-19 vaccines already approved, it is clear that those developed so far cannot meet the global vaccine demand. We have developed a COVID-19 vaccine based on a replication-defective gorilla adenovirus expressing the stabilized pre-fusion SARS-CoV-2 Spike protein, named GRAd-COV2. We aimed to assess the safety and immunogenicity of a single-dose regimen of this vaccine in healthy younger and older adults to select the appropriate dose for each age group. To this purpose, a phase 1, dose-escalation, open-label

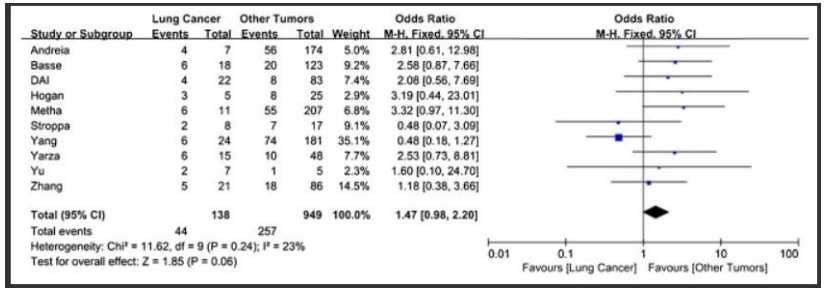
			trial was conducted including 90 healthy subjects, (45 aged 18-55 years and 45 aged 65-85 years), who received a single intramuscular administration of GRAd-CoV2 at three escalating doses. Local and systemic adverse reactions were mostly mild or moderate and of short duration, and no serious AE was reported. Four weeks after vaccination, seroconversion to Spike/RBD was achieved in 43/44 young volunteers and in 45/45 older subjects. Consistently, neutralizing antibodies were detected in 42/44 younger age and 45/45 older age volunteers. In addition, GRAd-COV2 induced a robust and Th1-skewed T cell response against the S antigen in 89/90 subjects from both age groups. Overall, the safety and immunogenicity data from the phase 1 trial support further development of this vaccine.
Series from The Lancet journals https://www.thelancet.com/series/COVID-19-pathophysiology	COVID-19: Pathophysiology of Acute Disease	Serie della rivista Lancet sulla fisiopatologia, i fenotipi clinici e le possibilità terapeutiche di COVID-19.	Acute respiratory manifestations are the most common feature of severe COVID-19, but extrapulmonary features of acute disease have also been reported. Emerging evidence indicates that COVID-19 has distinctive pathophysiological features that set the disease apart from respiratory failure of other origins. In the first of a Series of four papers, Ignacio Rubio and colleagues provide a comprehensive review of the pathophysiology and phenotypes of COVID-19. The challenges and promise of therapeutically targeting the pleiotropic cytokine interleukin-6 are considered in the second and third papers in the Series. Finally, a fourth paper considers the contributions of viral infection of the alveolar compartment and immunothrombosis of the juxtaposed pulmonary vascular compartment in severe COVID-19. Important questions remain about the clinical complexities and underlying mechanisms of COVID-19. Directions for future research are proposed with the aim of gaining a fuller understanding of the pathophysiology of COVID-

			19 and subsequently improving management and outcomes for patients. 

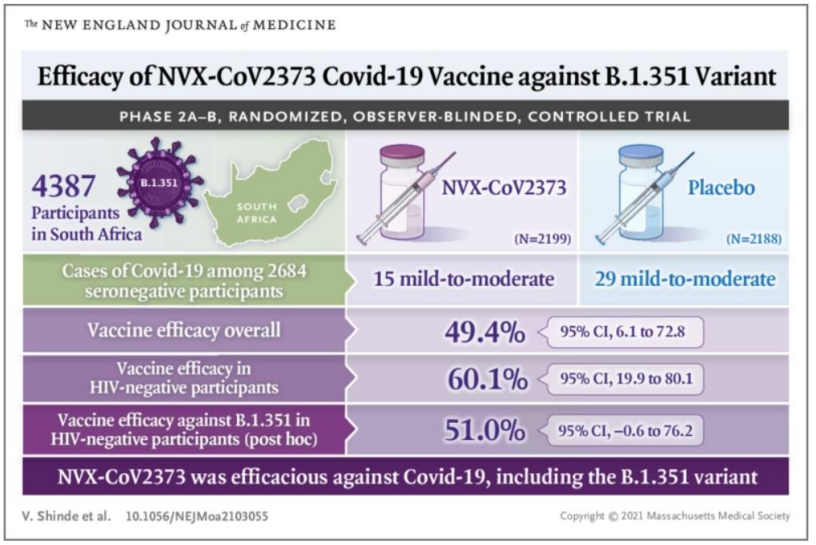
Osuchowski MF et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00218-6/fulltext	The COVID-19 puzzle: deciphering pathophysiology and phenotypes of a new disease entity	Articolo della serie sopra citata che tratta della fisiopatologia, in particolare a livello polmonare, dell'infezione da SARS-CoV-2.	The zoonotic SARS-CoV-2 virus that causes COVID-19 continues to spread worldwide, with devastating consequences. While the medical community has gained insight into the epidemiology of COVID-19, important questions remain about the clinical complexities and underlying mechanisms of disease phenotypes. Severe COVID-19 most commonly involves respiratory manifestations, although other systems are also affected, and acute disease is often followed by protracted complications. Such complex manifestations suggest that SARS-CoV-2 dysregulates the host response, triggering wide-ranging immuno-inflammatory, thrombotic, and parenchymal derangements. We review the intricacies of COVID-19 pathophysiology, its various phenotypes, and the anti-SARS-CoV-2 host response at the humoral and cellular levels. Some similarities exist between COVID-19 and respiratory failure of other origins, but evidence for many distinctive mechanistic features indicates that COVID-19 constitutes a new disease entity, with emerging data suggesting involvement of an endotheliopathy-centred pathophysiology. Further research, combining basic and clinical studies, is needed to advance understanding of pathophysiological mechanisms and to characterise immuno-inflammatory derangements across the range of phenotypes to enable optimum care for patients with COVID-19.

			
Vivier E et al Annals of Intensive Care https://doi.org/10.1186/s13613-021-00868-8	Specific exposure of ICU staff to SARS-CoV-2 seropositivity: a wide seroprevalence study in a French city-center hospital.	Sieroprevalenza dell'infezione da SARS-CoV-2 nel personale di terapia intensiva e rianimazione di un ospedale francese, alla ricerca di fattori di rischio di sierologia positiva : lavorare nella Rianimazione COVID, rispetto ad esempio agli ambienti del pronto soccorso, è un fattore protettivo.	BACKGROUND: Most hospital organizations have had to face the burden of managing the ongoing COVID-19 outbreak. One of the challenges in overcoming the influx of COVID-19 patients is controlling patient-to-staff transmission. Measuring the specific extent of ICU caregiver exposure to the virus and identifying the associated risk factors are, therefore, critical issues. We prospectively studied SARS-CoV-2 seroprevalence in the staff of a hospital in Lyon, France, several weeks after a first epidemic wave. Risk factors for the presence of SARS-CoV-2 antibodies were identified using a questionnaire survey. RESULTS: The overall seroprevalence was 9% (87/971 subjects). Greater exposure was associated with higher seroprevalence, with a rate of 3.2% [95% CI 1.1-5.2%] among non-healthcare staff, 11.3% [8.9-13.7%] among all healthcare staff, and 16.3% [12.3-20.2%] among healthcare staff in COVID-19 units. The seroprevalence was dramatically lower (3.7% [1.0-6.7%]) in the COVID-19 ICU. Risk factors for seropositivity were contact with a COVID-19-confirmed household (odds ratio (OR), 3.7 [1.8-7.4]), working in a COVID-19 unit (OR, 3.5 [2.2-5.7], and contact with a confirmed COVID-19 coworker (OR, 1.9 [1.2-3.1]). Conversely, working in the COVID-19-ICU was negatively associated

			with seropositivity (OR, 0.33 [0.15-0.73]). CONCLUSIONS: In this hospital, SARS-CoV-2 seroprevalence was higher among staff than in the general population. Seropositivity rates were particularly high for staff in contact with COVID-19 patients, especially those in the emergency department and in the COVID-19 unit, but were much lower in ICU staff. 
Lei H et al Lung Cancer https://doi.org/10.1016/j.lungcan.2021.05.002	Higher mortality in lung cancer patients with COVID-19? A systematic review and meta-analysis.	Metanalisi di 13 studi sulla mortalità nei pazienti con neoplasie polmonari rispetto alle altre neoplasie affetti da COVID-19: in Cina non si osserva una differenza fra i due gruppi, che emerge invece in altri Paesi come USA o	OBJECTIVE: Given that the coronavirus disease 2019 (COVID-19) mainly spreads through the respiratory system and is associated with severe pulmonary complications, lung cancer patients may have worse outcomes than those with other tumors. There is no confirmed evidence about the mortality comparison between COVID-19 patients with lung cancer and other tumors. We performed a systematic review and pooled analysis to provide precise estimates of the mortality rate of COVID-19 patients with

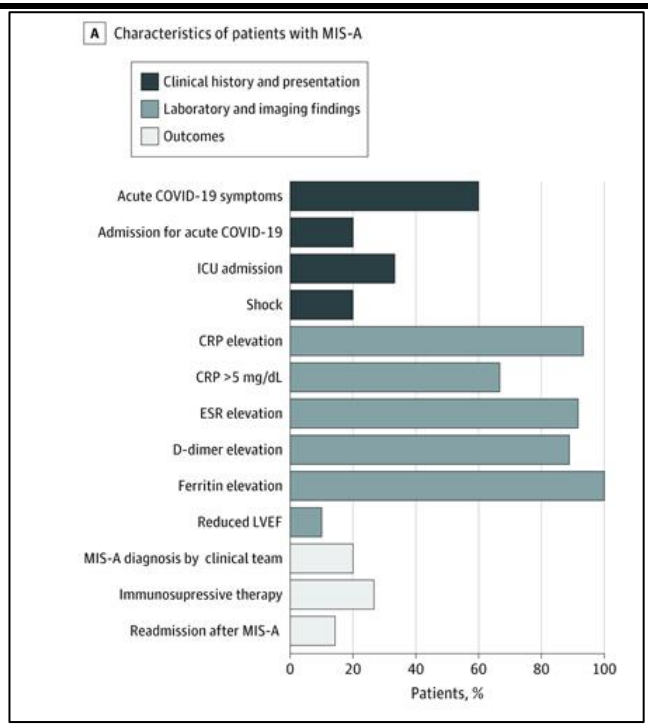
		Italia. Gli autori interpretano il risultato considerando che nei Paesi in via di sviluppo si abbia minore accesso ai trattamenti antineoplastici, per cui in particolare i pazienti con tumore del polmone non avrebbero le caratteristiche che si osservano nei Paesi più sviluppati e che li espongono a maggiore mortalità per infezioni respiratorie.	lung cancer and other tumors. MATERIALS AND METHODS: Our study systemically included and reviewed 13 studies on the characteristics of COVID-19 patients with lung cancer published up to November 1, 2020. The primary endpoint was all-cause mortality. We also compared the all-cause mortality rates in China and other regions as a secondary endpoint. The mortality rate was assessed with a fixed-effects model, which was used to derive the pooled mortality and 95 % con fi dence interval (CI). RESULTS: Thirteen studies from different countries, involving 1,229 patients with both COVID-19 and cancer, were selected for the pooled analysis. A total of 343 deaths were recorded in this population: 86 for lung cancers and 257 for other tumors. The mortality rate varies from 18 % to 60 % for patients with lung cancer and COVID-19 and 10%-41% for other tumor patients with COVID-19. The overall meta-analysis did not show a significant mortality difference for the lung cancer and other tumor subgroups (OR = 1.47, 95 %CI = 0.98-2.20, p = 0.06, I(2) = 23 %). Nevertheless, in regions other than China, the pooled mortality of lung cancer patients with COVID-19 was 42 %, which was significantly higher than that of other tumors (24 %) (OR = 2.73, 95 % CI = 1.54-4.86, p = 0.0006, I(2) = 16 %). CONCLUSION: Appropriate and aggressive preventive measures should be implemented to reduce the risk of COVID-19 in patients with cancer and optimally manage those who contract the infection. 

Shinde V et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2103055?query=featured_home	Efficacy of NVX-CoV2373 Covid-19 Vaccine against the B.1.351 Variant	Studio di fase II su efficacia e sicurezza di un vaccino contro SARS-CoV-2 basato su proteina S ricombinante in soggetti adulti non affetti da HIV in Sudafrica.	BACKGROUND : The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants threatens progress toward control of the coronavirus disease 2019 (Covid-19) pandemic. In a phase 1–2 trial involving healthy adults, the NVX-CoV2373 nanoparticle vaccine had an acceptable safety profile and was associated with strong neutralizing-antibody and antigen-specific polyfunctional CD4+ T-cell responses. Evaluation of vaccine efficacy was needed in a setting of ongoing SARS-CoV-2 transmission. METHODS : In this phase 2a–b trial in South Africa, we randomly assigned human immunodeficiency virus (HIV)–negative adults between the ages of 18 and 84 years or medically stable HIV-positive participants between the ages of 18 and 64 years in a 1:1 ratio to receive two doses of either the NVX-CoV2373 vaccine (5 µg of recombinant spike protein with 50 µg of Matrix-M1 adjuvant) or placebo. The primary end points were safety and vaccine efficacy against laboratory-confirmed symptomatic Covid-19 at 7 days or more after the second dose among participants without previous SARS-CoV-2 infection. RESULTS : Of 6324 participants who underwent screening, 4387 received at least one injection of vaccine or placebo. Approximately 30% of the participants were seropositive for SARS-CoV-2 at baseline. Among 2684 baseline seronegative participants (94% HIV-negative and 6% HIV-positive), predominantly mild-to-moderate Covid-19 developed in 15 participants in the vaccine group and in 29 in the placebo group (vaccine efficacy, 49.4%; 95% confidence interval [CI], 6.1 to 72.8). Vaccine efficacy among HIV-negative participants was 60.1% (95% CI, 19.9 to 80.1). Of 41 sequenced isolates, 38 (92.7%) were the B.1.351 variant. Post hoc vaccine efficacy against B.1.351 was 51.0% (95% CI, −0.6 to 76.2) among the

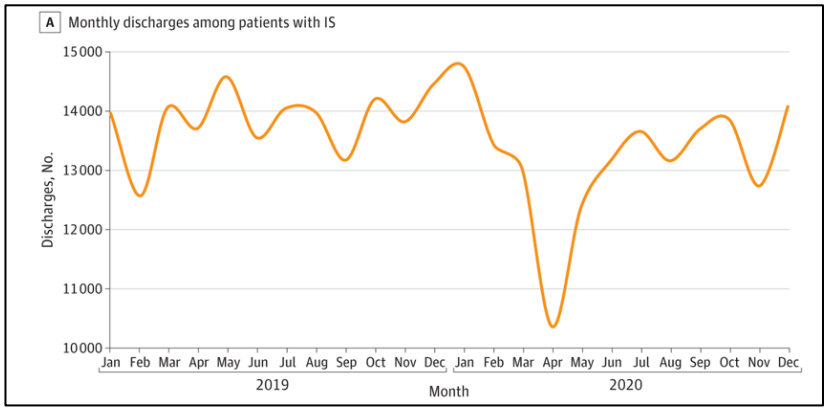
			HIV-negative participants. Preliminary local and systemic reactogenicity events were more common in the vaccine group; serious adverse events were rare in both groups. CONCLUSIONS : The NVX-CoV2373 vaccine was efficacious in preventing Covid-19, with higher vaccine efficacy observed among HIV-negative participants. Most infections were caused by the B.1.351 variant. 
Yokota I et al The Lancet https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00092-6/fulltext	A novel strategy for SARS-CoV-2 mass screening with quantitative antigen testing of saliva: a diagnostic accuracy study	Studio sulla accuratezza diagnostica di un test di chemioluminescenza su saliva per la diagnosi di infezione da SARS-CoV-2 pensato per lo screening di massa.	Background : Quantitative RT-PCR (RT-qPCR) of nasopharyngeal swab (NPS) samples for SARS-CoV-2 detection requires medical personnel and is time consuming, and thus is poorly suited to mass screening. In June, 2020, a chemiluminescent enzyme immunoassay (CLEIA; Lumipulse G SARS-CoV-2 Ag kit, Fujirebio, Tokyo, Japan) was developed that can detect SARS-CoV-2 nucleoproteins in NPS or saliva samples within 35 min. In this study, we assessed the utility of CLEIA in mass SARS-CoV-2 screening. Methods : We did a diagnostic accuracy study to develop a mass-screening strategy for salivary detection of SARS-CoV-2 by CLEIA,

			enrolling hospitalised patients with clinically confirmed COVID-19, close contacts identified at community health centres, and asymptomatic international arrivals at two airports, all based in Japan. All test participants were enrolled consecutively. We assessed the diagnostic accuracy of CLEIA compared with RT-qPCR, estimated according to concordance (Kendall's coefficient of concordance, W), and sensitivity (probability of CLEIA positivity given RT-qPCR positivity) and specificity (probability of CLEIA negativity given RT-qPCR negativity) for different antigen concentration cutoffs (0·19 pg/mL, 0·67 pg/mL, and 4·00 pg/mL; with samples considered positive if the antigen concentration was equal to or more than the cutoff and negative if it was less than the cutoff). We also assessed a two-step testing strategy post hoc with CLEIA as an initial test, using separate antigen cutoff values for test negativity and positivity from the predefined cutoff values. The proportion of intermediate results requiring secondary RT-qPCR was then quantified assuming prevalence values of RT-qPCR positivity in the overall tested population of 10%, 30%, and 50%. Findings : Self-collected saliva was obtained from 2056 participants between June 12 and Aug 6, 2020. Results of CLEIA and RT-qPCR were concordant in 2020 (98·2%) samples (Kendall's W=0·99). Test sensitivity was 85·4% (76 of 89 positive samples; 90% credible interval [CrI] 78·0–90·3) at the cutoff of 0·19 pg/mL; 76·4% (68 of 89; 68·2–82·8) at the cutoff of 0·67 pg/mL; and 52·8% (47 of 89; 44·1–61·3) at the cutoff of 4·0 pg/mL. Test specificity was 91·3% (1796 of 1967 negative samples; 90% CrI 90·2–92·3) at the cutoff of 0·19 pg/mL, 99·2% (1952 of 1967; 98·8–99·5) at the cutoff of 0·67 pg/mL, and 100·0% (1967 of 1967; 99·8–100·0) at the cutoff of 4·00 pg/mL. Using a two-step testing strategy with a CLEIA negativity cutoff of 0·19 pg/mL (to maximise sensitivity) and a CLEIA positivity

			cutoff of 4·00 pg/mL (to maximise specificity), the proportions of indeterminate results (ie, samples requiring secondary RT-qPCR) would be approximately 11% assuming a prevalence of RT-qPCR positivity of 10%, 16% assuming a prevalence of RT-qPCR positivity of 30%, and 21% assuming a prevalence of RT-qPCR positivity of 50%. Interpretation : CLEIA testing of self-collected saliva is simple and provides results quickly, and is thus suitable for mass testing. To improve accuracy, we propose a two-step screening strategy with an initial CLEIA test followed by confirmatory RT-qPCR for intermediate concentrations, varying positive and negative thresholds depending on local prevalence. Implementation of this strategy has expedited sample processing at Japanese airports since July, 2020, and might apply to other large-scale mass screening initiatives.
Davogustto GE et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779957	Characteristics Associated With Multisystem Inflammatory Syndrome Among Adults With SARS-CoV-2 Infection	Studio di coorte sulla sindrome infiammatoria multisistemica nell'adulto con infezione da SARS-CoV-2.	A postacute COVID-19 multisystem inflammatory syndrome (MIS) has been recognized as a rare, yet severe, complication of SARS-CoV-2 infection. First characterized in children, MIS in adults (MIS-A) has now been reported, leading to the publication of a working case definition by the Centers for Disease Control and Prevention. The goal of this cohort study was to describe the spectrum of MIS-A presentation after SARS-CoV-2 infection. We identified cases of MIS-A among all adults with laboratory-proven subacute or convalescent SARS-CoV-2 infection at a single tertiary care medical center and described their clinical characteristics and outcomes.

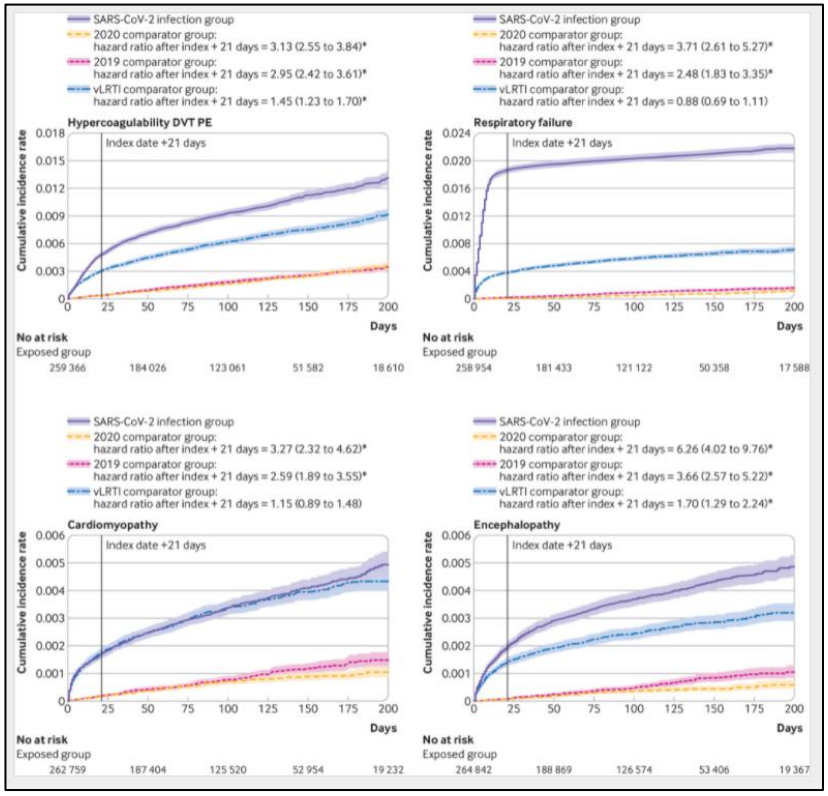
			
de Havenon A et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779926	Characteristics and Outcomes Among US Patients Hospitalized for Ischemic Stroke Before vs During the COVID-19 Pandemic	Ricoveri per ictus ischemico nel corso della pandemia di COVID-19 negli USA.	Importance After the emergence of COVID-19, studies reported a decrease in hospitalizations of patients with ischemic stroke (IS), but there are little to no data regarding hospitalizations for the remainder of 2020, including outcome data from a large cohort of patients with IS and comorbid COVID-19. Objective To assess hospital discharge rates, demographic factors, and outcomes of hospitalization associated with the COVID-19 pandemic among US patients with IS before vs during the COVID-19 pandemic. Design, Setting, and Participants This retrospective cohort study used data from the Vizient Clinical Data Base on 324 013 patients with IS at 478 nonfederal hospitals in 43 US states between January 1, 2019, and December 31, 2020. Patients were eligible if they were

			admitted to the hospital on a nonelective basis and were not receiving hospice care at the time of admission. A total of 41 166 discharged between January and March 2020 were excluded from the analysis because they had unreliable data on COVID-19 status, leaving 282 847 patients for the study. Exposure Ischemic stroke and laboratory-confirmed COVID-19. Main Outcomes and Measures Monthly counts of discharges among patients with IS in 2020. Demographic characteristics and outcomes, including in-hospital death, among patients with IS who were discharged in 2019 (control group) were compared with those of patients with IS with or without comorbid COVID-19 (COVID-19 and non–COVID-19 groups, respectively) who were discharged between April and December 2020. Results Of the 282 847 patients included in the study, 165 912 (50.7% male; 63.4% White; 26.3% aged ≥80 years) were allocated to the control group; 111 418 of 116 935 patients (95.3%; 51.9% male; 62.8% White; 24.6% aged ≥80 years) were allocated to the non–COVID-19 group and 5517 of 116 935 patients (4.7%; 58.0% male; 42.5% White; 21.3% aged ≥80 years) to the COVID-19 group. A mean (SD) of 13 846 (553) discharges per month among patients with IS was reported in 2019. Discharges began decreasing in February 2020, reaching a low of 10 846 patients in April 2020 before returning to a prepandemic level of 13 639 patients by July 2020. A mean (SD) of 13 492 (554) discharges per month was recorded for the remainder of 2020. Black and Hispanic patients accounted for 21.4% and 7.0% of IS discharges in 2019, respectively, but accounted for 27.5% and 16.0% of those discharged with IS and comorbid COVID-19 in 2020. Compared with patients in the control and non–COVID-19 groups, those in the COVID-19 group were less likely to smoke (16.0% vs 17.2% vs 6.4%, respectively) and to have

			hypertension (73.0% vs 73.1% vs 68.2%) or dyslipidemia (61.2% vs 63.2% vs 56.6%) but were more likely to have diabetes (39.8% vs 40.5% vs 53.0%), obesity (16.2% vs 18.4% vs 24.5%), acute coronary syndrome (8.0% vs 9.2% vs 15.8%), or pulmonary embolus (1.9% vs 2.4% vs 6.8%) and to require intubation (11.3% vs 12.3% vs 37.6%). After adjusting for baseline factors, patients with IS and COVID-19 were more likely to die in the hospital than were patients with IS in 2019 (adjusted odds ratio, 5.17; 95% CI, 4.83-5.53; National Institutes of Health Stroke Scale adjusted odds ratio, 3.57; 95% CI, 3.15-4.05). Conclusions and Relevance In this cohort study, after the emergence of COVID-19, hospital discharges of patients with IS decreased in the US but returned to prepandemic levels by July 2020. Among patients with IS between April and December 2020, comorbid COVID-19 was relatively common, particularly among Black and Hispanic populations, and morbidity was high. 
Wang EY et al Nature	Diverse Functional Autoantibodies in Patients with COVID-19	Alterazione del sistema immunitario nei pazienti con COVID-19, in cui si osserva una incrementata	COVID-19 manifests with a wide spectrum of clinical phenotypes that are characterized by exaggerated and misdirected host immune responses. While pathological innate immune activation is well documented in severe disease, the impact of autoantibodies on

https://www.nature.com/articles/s41586-021-03631-y		produzione di autoanticorpi rispeto ai soggetti non infetti, in particolare diretti contro proteine immunomodulatorie.	disease progression is less defined. Here, we used a high-throughput autoantibody (AAb) discovery technique called Rapid Extracellular Antigen Profiling (REAP)7 to screen a cohort of 194 SARS-CoV-2 infected COVID-19 patients and healthcare workers for autoantibodies against 2,770 extracellular and secreted proteins (the “exoproteome”). We found that COVID-19 patients exhibit dramatic increases in autoantibody reactivities compared to uninfected controls, with a high prevalence of autoantibodies against immunomodulatory proteins including cytokines, chemokines, complement components, and cell surface proteins. We established that these autoantibodies perturb immune function and impair virological control by inhibiting immunoreceptor signaling and by altering peripheral immune cell composition, and found that murine surrogates of these autoantibodies exacerbate disease severity in a mouse model of SARS-CoV-2 infection. Analysis of autoantibodies against tissue-associated antigens revealed associations with specific clinical characteristics and disease severity. In summary, these findings implicate a pathological role for exoproteome-directed autoantibodies in COVID-19 with diverse impacts on immune functionality and associations with clinical outcomes.
Daugherty SE et al BMJ https://www.bmj.com/content/373/bmj.n1098	Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study	Aumentato rischio di complicanze a lungo termine dopo infezione da SARS-CoV-2 rispetto a persone non infette o affette da altre infezioni respiratorie.	Objective To evaluate the excess risk and relative hazards for developing incident clinical sequelae after the acute phase of SARS-CoV-2 infection in adults aged 18-65. Design Retrospective cohort study. Setting Three merged data sources from a large United States health plan: a large national administrative claims database, an outpatient laboratory testing database, and an inpatient hospital admissions database.

			Participants Individuals aged 18-65 with continuous enrollment in the health plan from January 2019 to the date of a diagnosis of SARS-CoV-2 infection. Three comparator groups, matched by propensity score, to individuals infected with SARS-CoV-2: a 2020 comparator group, an historical 2019 comparator group, and an historical comparator group with viral lower respiratory tract illness. Main outcome measures More than 50 clinical sequelae after the acute phase of SARS-CoV-2 infection (defined as the date of first SARS-CoV-2 diagnosis (index date) plus 21 days) were identified using ICD-10 (international classification of diseases, 10th revision) codes. Excess risk in the four months after acute infection and hazard ratios with Bonferroni corrected 95% confidence intervals were calculated. Results 14% of adults aged ≤65 who were infected with SARS-CoV-2 (27 074 of 193 113) had at least one new type of clinical sequelae that required medical care after the acute phase of the illness, which was 4.95% higher than in the 2020 comparator group. The risk for specific new sequelae attributable to SARS-Cov-2 infection after the acute phase, including chronic respiratory failure, cardiac arrythmia, hypercoagulability, encephalopathy, peripheral neuropathy, amnesia (memory difficulty), diabetes, liver test abnormalities, myocarditis, anxiety, and fatigue, was significantly greater than in the three comparator groups (2020, 2019, and viral lower respiratory tract illness groups) (all $P<0.001$). Significant risk differences because of SARS-CoV-2 infection ranged from 0.02 to 2.26 per 100 people (all $P<0.001$), and hazard ratios ranged from 1.24 to 25.65 compared with the 2020 comparator group. Conclusions The results indicate the excess risk of developing new clinical sequelae after the acute phase of SARS-CoV-2 infection, including specific types of sequelae less commonly seen in other

			viral illnesses. Although individuals who were older, had pre-existing conditions, and were admitted to hospital because of covid-19 were at greatest excess risk, younger adults (aged ≤50), those with no pre-existing conditions, or those not admitted to hospital for covid-19 also had an increased risk of developing new clinical sequelae. The greater risk for incident sequelae after the acute phase of SARS-CoV-2 infection is relevant for healthcare planning. 
Li Y et al JAMA	Assessment of the Association of Vitamin D Level With SARS-CoV-2	Assenza di associazione fra bassi livelli di vitamina D e sieropositività per SARS-	Importance Low vitamin D levels have been reported to be associated with increased risk of SARS-CoV-2 infection. Independent, well-powered studies could further our understanding of this association.

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779952?resultClick=1	Seropositivity Among Working-Age Adults	CoV-2 in un ampio studio di coorte.	Objective To examine whether low levels of vitamin D are associated with SARS-CoV-2 seropositivity, an indicator of previous infection. Design, Setting, and Participants This is a cohort study of employees and spouses who elected to be tested for SARS-CoV-2 IgG as part of an annual employer-sponsored health screening program conducted in August to November 2020. This program includes commonly assessed demographic, biometric, and laboratory variables, including total vitamin D measurement. Baseline (prepandemic) levels of vitamin D and potential confounders were obtained from screening results from the previous year (September 2019 to January 2020). Data analysis was performed from December 2020 to March 2021. Exposures Low total serum 25-hydroxyvitamin D, defined as either less than 20 ng/mL or less than 30 ng/mL. Main Outcomes and Measures The main outcome was SARS-CoV-2 seropositivity, as determined with US Food and Drug Administration emergency use–authorized assays. The association of SARS-CoV-2 seropositivity with vitamin D levels was assessed by multivariable logistic regression analyses and propensity score analyses. Results The 18 148 individuals included in this study had test results for SARS-CoV-2 IgG in 2020 and vitamin D levels from the prepandemic and pandemic periods. Their median (interquartile range) age was 47 (37-56) years, 12 170 (67.1%) were women, 900 (5.0%) were seropositive, 4498 (24.8%) had a vitamin D level less than 20 ng/mL, and 10 876 (59.9%) had a vitamin D level less than 30 ng/mL before the pandemic. In multivariable models adjusting for age, sex, race/ethnicity, education, body mass index, blood pressure, smoking status, and geographical location, SARS-CoV-2 seropositivity was not associated with having a vitamin D level less

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<td>than 20 ng/mL before (odds ratio [OR], 1.04; 95% CI, 0.88-1.22) or during (OR, 0.93; 95% CI, 0.79-1.09) the pandemic; it was also not associated with having a vitamin D level less than 30 ng/mL before (OR, 1.09; 95% CI, 0.93-1.27) or during (OR, 1.05; 95% CI, 0.91-1.23) the pandemic. Similar results were observed in propensity score analyses. SARS-CoV-2 seropositivity was associated with obesity (OR, 1.26; 95% CI, 1.08-1.46), not having a college degree (OR, 1.40; 95% CI, 1.21-1.62), and Asian (OR, 1.46; 95% CI, 1.13-1.87), Black (OR, 2.74; 95% CI, 2.25-3.34), Hispanic (OR, 2.65; 95% CI, 2.15-3.27), American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander (OR, 2.01; OR, 1.54-2.62) race/ethnicity, and was inversely associated with high blood pressure (OR, 0.82; 95% CI, 0.70-0.96), smoking (OR, 0.60; 95% CI, 0.47-0.78), and residing in the US Northeast (OR, 0.75; 95% CI, 0.62-0.92) and West (OR, 0.54; 95% CI, 0.44-0.67).
Conclusions and Relevance In this cohort study, SARS-CoV-2 seropositivity was not associated with low levels of vitamin D independently of other risk factors.
Table 3. Association Between Vitamin D Levels and SARS-CoV-2 Seropositivity
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<table>
<tr><th></th><th colspan="2">Multivariable regression analysis[a]</th><th colspan="2">Propensity score analysis[b]</th></tr>
<tr><th>Vitamin D level comparison and year</th><th>OR (95% CI)</th><th>P value</th><th>OR (95% CI)</th><th>P value</th></tr>
<tr><td><30 vs ≥30 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>2019</td><td>1.09 (0.93-1.27)</td><td>.29</td><td>1.12 (0.91-1.36)</td><td>.28</td></tr>
<tr><td>2020</td><td>1.05 (0.91-1.23)</td><td>.49</td><td>1.07 (0.88-1.29)</td><td>.52</td></tr>
<tr><td><20 vs ≥20 ng/mL</td><td></td><td></td><td></td><td></td></tr>
<tr><td>2019</td><td>1.04 (0.88-1.22)</td><td>.66</td><td>1.04 (0.84-1.27)</td><td>.74</td></tr>
<tr><td>2020</td><td>0.93 (0.79-1.09)</td><td>.36</td><td>0.99 (0.81-1.21)</td><td>.93</td></tr>
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<td>White EM et al

NEJM</td>
<td>Incident SARS-CoV-2 Infection among mRNA-Vaccinated and</td>
<td>Efficacia della vaccinazione contro SARS-CoV-2 in una ampia coorte di persone residenti in strutture per</td>
<td>The sample included 18,242 residents who received at least one dose of mRNA vaccine; 14,669 residents (80.4%) received the Pfizer–BioNTech vaccine, and 3573 (19.6%) received the Moderna vaccine. Of these 18,242 residents, 13,048 also received the second</td>
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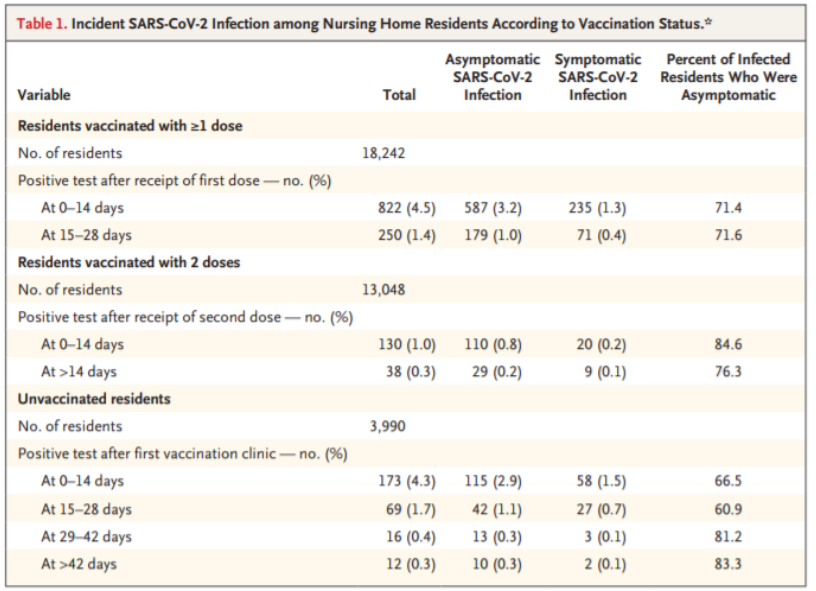
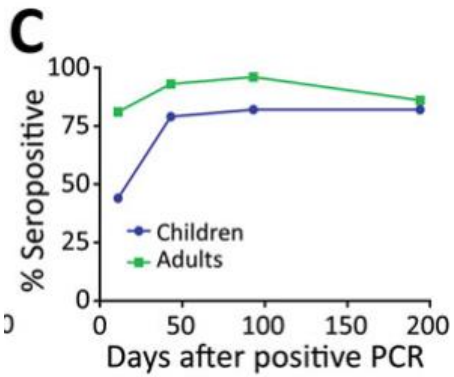
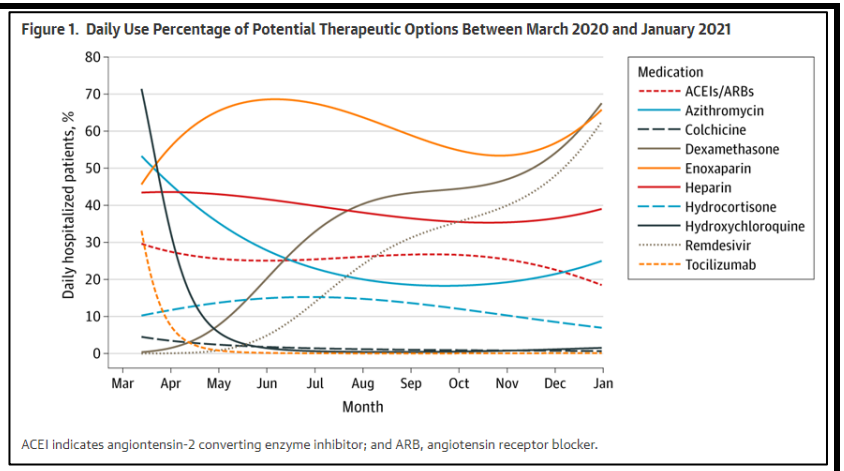
<td>https://www.nejm.org/doi/full/10.1056/NEJMc2104849?query=featured_coronavirus</td>
<td>Unvaccinated Nursing Home Residents</td>
<td>lungodegenza, anche all’interno della popolazione non vaccinata.</td>
<td>dose of vaccine. A total of 3990 residents were unvaccinated. Table S1 in the Supplementary Appendix summarizes the characteristics of the residents.
The incidence of infection decreased over time among both vaccinated residents and unvaccinated residents.
 
<table>
<tr><th colspan="5">Table 1. Incident SARS-CoV-2 Infection among Nursing Home Residents According to Vaccination Status.*</th></tr>
<tr><th>Variable</th><th>Total</th><th>Asymptomatic SARS-CoV-2 Infection</th><th>Symptomatic SARS-CoV-2 Infection</th><th>Percent of Infected Residents Who Were Asymptomatic</th></tr>
<tr><td>Residents vaccinated with ≥1 dose</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No. of residents</td><td>18,242</td><td></td><td></td><td></td></tr>
<tr><td>Positive test after receipt of first dose — no. (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>At 0–14 days</td><td>822 (4.5)</td><td>587 (3.2)</td><td>235 (1.3)</td><td>71.4</td></tr>
<tr><td>At 15–28 days</td><td>250 (1.4)</td><td>179 (1.0)</td><td>71 (0.4)</td><td>71.6</td></tr>
<tr><td>Residents vaccinated with 2 doses</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No. of residents</td><td>13,048</td><td></td><td></td><td></td></tr>
<tr><td>Positive test after receipt of second dose — no. (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>At 0–14 days</td><td>130 (1.0)</td><td>110 (0.8)</td><td>20 (0.2)</td><td>84.6</td></tr>
<tr><td>At >14 days</td><td>38 (0.3)</td><td>29 (0.2)</td><td>9 (0.1)</td><td>76.3</td></tr>
<tr><td>Unvaccinated residents</td><td></td><td></td><td></td><td></td></tr>
<tr><td>No. of residents</td><td>3,990</td><td></td><td></td><td></td></tr>
<tr><td>Positive test after first vaccination clinic — no. (%)</td><td></td><td></td><td></td><td></td></tr>
<tr><td>At 0–14 days</td><td>173 (4.3)</td><td>115 (2.9)</td><td>58 (1.5)</td><td>66.5</td></tr>
<tr><td>At 15–28 days</td><td>69 (1.7)</td><td>42 (1.1)</td><td>27 (0.7)</td><td>60.9</td></tr>
<tr><td>At 29–42 days</td><td>16 (0.4)</td><td>13 (0.3)</td><td>3 (0.1)</td><td>81.2</td></tr>
<tr><td>At >42 days</td><td>12 (0.3)</td><td>10 (0.3)</td><td>2 (0.1)</td><td>83.3</td></tr>
</table></td>
</tr>
<tr>
<td>Renner K et al

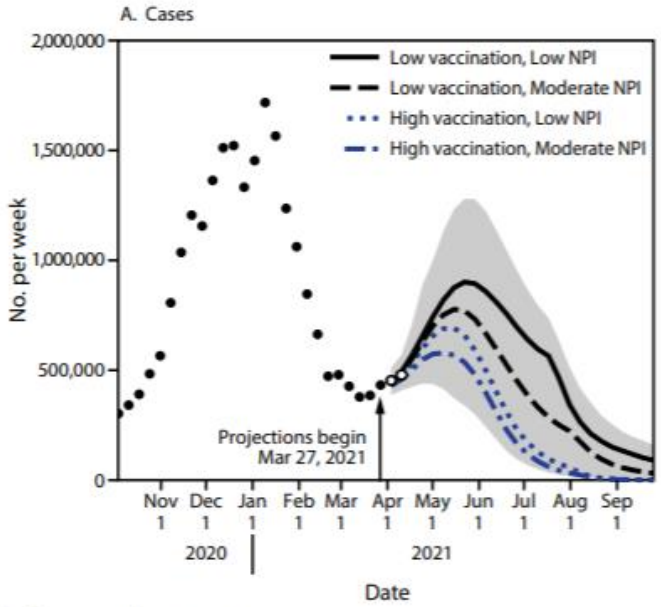
Nature

https://www.nature.com/articles/s41467-021-23334-2</td>
<td>Severe T cell hyporeactivity in ventilated COVID-19 patients correlates with prolonged virus persistence and poor outcomes</td>
<td>Una minore reattività dei linfociti T (misurata in base agli effetti a monte, come l’attivazione dei monociti) caratterizza i pazienti con maggiore gravità dell’infezione da SARS-CoV-2 ; l’effetto sarebbe da attribuire a fattori inibitori circolanti la cui produzione è stimolata dallo stesso virus.</td>
<td>Coronavirus disease 2019 (COVID-19) can lead to pneumonia and hyperinflammation. Here we show a sensitive method to measure polyclonal T cell activation by downstream effects on responder cells like basophils, plasmacytoid dendritic cells, monocytes and neutrophils in whole blood. We report a clear T cell hyporeactivity in hospitalized COVID-19 patients that is pronounced in ventilated patients, associated with prolonged virus persistence and reversible with clinical recovery. COVID-19-induced T cell hyporeactivity is T cell extrinsic and caused by plasma components, independent of occasional immunosuppressive medication of the patients.</td>
</tr>
</table>

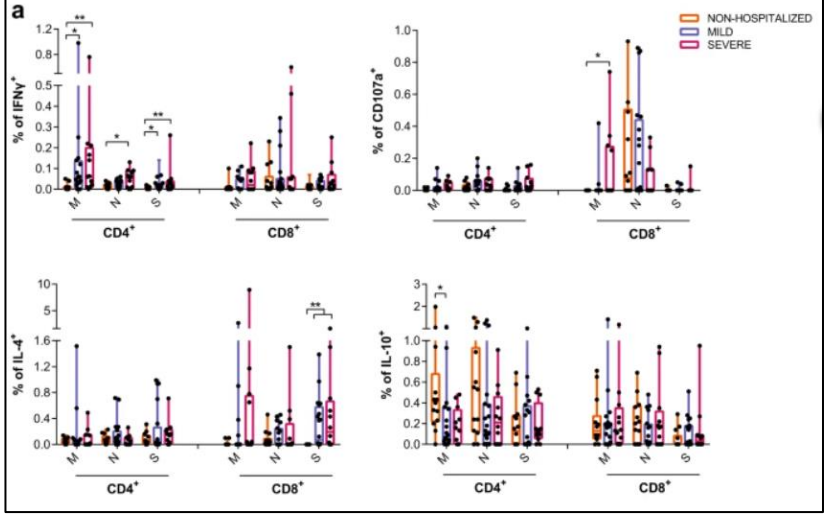
			Monocytes respond stronger in males than females and IL-2 partially restores T cell activation. Downstream markers of T cell hyporeactivity are also visible in fresh blood samples of ventilated patients. Based on our data we developed a score to predict fatal outcomes and identify patients that may benefit from strategies to overcome T cell hyporeactivity.
Oogata AF et al CID https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab465/6279075	Circulating SARS-CoV-2 Vaccine Antigen Detected in the Plasma of mRNA-1273 Vaccine Recipients	Presenza dell'antigene S1 nel plasma di 11/13 soggetti vaccinati con vaccino a mRNA contro SARS-CoV-2, un giorno dopo laprima dose ; la spiegazione è la possibilità di clivaggio, da parte di alcune proteasi umane, dell'antigene S sintetizzato a partire dall'mRNA del vaccino.	SARS-CoV-2 proteins were measured in longitudinal plasma samples collected from 13 participants who received two doses of mRNA-1273 vaccine. 11 of 13 participants showed detectable levels of SARS-CoV-2 protein as early as day one after first vaccine injection. Clearance of detectable SARS-CoV-2 protein correlated with production of IgG and IgA.
Toh ZQ et al Emerging Infectious Diseases https://wwwnc.cdc.gov/eid/article/27/8/21-0965_article	Persistence of SARS-CoV-2–Specific IgG in Children 6 Months After Infection, Australia	Persistenza di IgG anti-SARS-CoV-2 in 15 bambini con infezione lieve o asintomatica, a 6 mesi dall'esordio.	The duration of the humoral immune response in children infected with severe acute respiratory syndrome coronavirus 2 is unknown. We detected specific IgG 6 months after infection in children who were asymptomatic or had mild symptoms of coronavirus disease. These findings will inform vaccination strategies and other prevention measures.

			
Watanabe JH et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780277	Medication Use Patterns in Hospitalized Patients With COVID-19 in California During the Pandemic	Alba e tramonto dei farmaci «anti» SARS-CoV-2 da marzo 2020 a gennaio 2021 in California.	This cohort study found that, early in the COVID-19 pandemic, antimicrobials azithromycin and hydroxychloroquine were each used in more than 40% of hospitalized patients. By June, use was below 30% and 5%, respectively. Enoxaparin use remained above 50% throughout 2020, perhaps because enoxaparin serves both for thrombosis prophylaxis and thrombophilia treatment triggered by COVID-19.3 Dexamethasone and remdesivir use grew substantially. One possible explanation is that remdesivir use may have corresponded with availability, as early in the pandemic it was predominantly available through trials in the UC system. Hydroxychloroquine use fell from over 40% to below 5% 2 months later. A small study conducted early in the pandemic favored use of hydroxychloroquine, but later, larger controlled studies found no benefit. While demographic characteristics of the study population were consistent with California, our findings are limited by their generalizability to the US. To our knowledge, this study represents the first analysis of medication utilization for hospitalized patients with COVID-19 in a large, diverse, statewide health system.

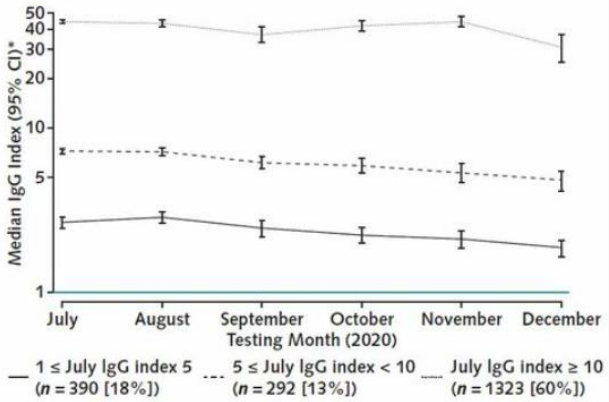
			
Wilensky GR et al JAMA Forum https://jamanetwork.com/journals/jama-health-forum/fullarticle/2780393	It Is Time for Hospitals to Liberalize Their Visitation Policies	L'accesso in ospedale dei visitatori è un tema rilevante dal punto di vista sanitario, che richiede di essere considerato da parte di linee guida ufficiali.	The reopening of hospitals to visitors should remain a decision that individual hospitals are allowed to make, but guidance from the US Centers for Disease Control and Prevention (CDC) would be helpful. Both the public and those who determine visitation policies need to understand the limited risks posed by fully immunized individuals, who have had at least 2 weeks since their second dose of the Pfizer or Moderna vaccine or single dose of the Johnson & Johnson vaccine, or who have had a negative COVID-19 test within the past 24 to 48 hours.
Borchering RK et al Morbidity and Mortality Weekly Report https://www.cdc.gov/mmwr/volumes/70/wr/mm7019e3.htm?s_cid=mm7019e3_w	Modeling of Future COVID-19 Cases, Hospitalizations and Deaths by Vaccination Rates and Nonpharmaceutical Intervention Scenarios	Con l'aumento della proporzione di persone vaccinate e l'utilizzo dei DPI e del distanziamento sociale, si prevede una riduzione netta dei casi di infezione da SARS-CoV-2, delle ospedalizzazioni e dei decessi a partire da Luglio 2021 negli USA.	What is already known about this topic? Increases in COVID-19 cases in March and early April occurred despite a large-scale vaccination program. Increases coincided with the spread of SARS-CoV-2 variants and relaxation of nonpharmaceutical interventions (NPIs). What is added by this report? Data from six models indicate that with high vaccination coverage and moderate NPI adherence, hospitalizations and deaths will likely remain low nationally, with a sharp decline in cases projected by July 2021. Lower NPI adherence could lead to substantial increases

			in severe COVID-19 outcomes, even with improved vaccination coverage. What are the implications for public health practice? High vaccination coverage and compliance with NPIs are essential to control COVID-19 and prevent surges in hospitalizations and deaths in the coming months.  See footnotes on the next page.
Advisory Committee on Immunization Practices (ACIP) https://www.cdc.gov/vaccines/acip/work-groups-vast/technical-report-2021-05-17.html	COVID-19 Vaccine Safety Technical (VaST) Work Group Technical Report	Discussione di alcuni casi di miocardite riportati a seguito di vaccinazione contro SARS-CoV-2, prevalentemente in adolescenti. L'incidenza è paragonabile a quella attesa nella popolazione, tuttavia si	The Advisory Committee on Immunization Practices (ACIP) COVID-19 Vaccine Safety Technical (VaST) Work Group has reviewed post-authorization COVID-19 vaccine safety data on a weekly basis since the start of the U.S. vaccination program. Updates of VaST activities and VaST assessments of safety data were presented at ACIP meetings on January 27, March 1, April 14, April 23, and May 12; ACIP meetings are open to the public.

		tratta di eventi meritevoli di monitoraggio.	The VaST session on May 17, 2021, included several presentations on myocarditis following mRNA vaccines, from the Department of Defense (DoD), the Vaccine Adverse Event Reporting System (VAERS), and Vaccine Safety Datalink (VSD). There were also brief updates from the Veteran's Administration (VA) and the Clinical Immunization Safety Assessment (CISA) groups about their plans for future investigation of myocarditis.
Grau-Exposito J et al Nature https://www.nature.com/articles/s41467-021-23333-3	Peripheral and lung resident memory T cell responses against SARS-CoV-2	Caratterizzazione della risposta T cellulare contro SARS-CoV-2 nei pazienti ospedalizzati e non ospedalizzati : nei primi prevale la risposta effettrice basata su IFN-gamma. Inoltre, i linfociti T residenti nei polmoni si ritrovano fino a 10 mesi dall'esordio.	Resident memory T cells (TRM) positioned within the respiratory tract are probably required to limit SARS-CoV-2 spread and COVID-19. Importantly, TRM are mostly non-recirculating, which reduces the window of opportunity to examine these cells in the blood as they move to the lung parenchyma. Here, we identify circulating virus-specific T cell responses during acute infection with functional, migratory and apoptotic patterns modulated by viral proteins and associated with clinical outcome. Disease severity is associated predominantly with IFNγ and IL-4 responses, increased responses against S peptides and apoptosis, whereas non-hospitalized patients have increased IL-12p70 levels, degranulation in response to N peptides and SARS-CoV-2-specific CCR7+ T cells secreting IL-10. In convalescent patients, lung-TRM are frequently detected even 10 months after initial infection, in which contemporaneous blood does not reflect tissue-resident profiles. Our study highlights a balanced anti-inflammatory antiviral response associated with a better outcome and persisting TRM cells as important for future protection against SARS-CoV-2 infection.

			Fig. 1: Functional characteristics of acute SARS-CoV-2-specific T cells. 
Anand S et al Aannals of Internal Medicine https://www.acpjournals.org/doi/10.7326/M21-0256	Serial SARS-CoV-2 Receptor-Binding Domain Antibody Responses in Patients Receiving Dialysis	Risposta anticorpale IgG contro SARS-CoV-2 in un'ampia coorte di oltre 2000 pazienti dializzati : persistenza del titolo oltre 6 mesi dall'esordio.	Background: Assessing the evolution of SARS-CoV-2 immune response among patients receiving dialysis can define its durability in a highly clinically relevant context because patients receiving dialysis share the characteristics of persons most susceptible to SARS-CoV-2 infection. Objective: To evaluate the persistence of SARS-CoV-2 receptor-binding domain (RBD) IgG in seroprevalent patients receiving dialysis. Design: Prospective. Setting: Nationwide sample from dialysis facilities. Patients: 2215 patients receiving dialysis who had evidence of SARS-CoV-2 infection as of July 2020. Measurements: Remainder plasma from routine monthly laboratories was used to measure semiquantitative RBD IgG index value over 6 months.

			Results: A total of 2063 (93%) seroprevalent patients reached an assay detectable response (IgG index value ≥1). Most (n = 1323, 60%) had responses in July with index values classified as high (IgG ≥10); 1003 (76%) remained within this stratum. Adjusted median index values declined slowly but continuously (July vs. December values were 21 vs. 13; P < 0.001). The trajectory of the response did not vary by age group, sex, race/ethnicity, or diabetes status. Patients without an assay detectable response (n = 137) were more likely to be White and in the younger (18 to 44 years) or older (≥80 years) age groups and less likely to have diabetes and hypoalbuminemia. Limitation: Lack of data on symptoms or reverse transcriptase polymerase chain reaction diagnosis, cohort of persons who survived infection, and use of a semiquantitative assay. Conclusion: Despite impaired immunity, most seropositive patients receiving dialysis maintained RBD antibody levels over 6 months. A slow and continual decline in median antibody levels over time was seen, but no indication that subgroups with impaired immunity had a shorter-lived humoral response was found.

			 Figure 1. The RBD IgG response in a seroprevalent cohort of patients receiving dialysis.
Vayne C et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2106383?query=featured_coronavirus	PF4 Immunoassays in Vaccine-Induced Thrombotic Thrombocytopenia	Nel sospetto di trombocitopenia indotta da vaccino, in base a questa casistica la ricerca di anticorpi anti-PF4 andrebbe svolta con test immunomediati, che sono più sensibili e danno risultati quantitativi, e non con test rapidi, che possono dare falsi negativi.	Our results provide further support to show that rapid immunoassays should be avoided in the detection of PF4-specific antibodies in patients with suspected VITT. Therefore, the use of a sensitive, quantitative, immunologic test is strongly recommended, because according to the recently proposed algorithm, nonheparin anticoagulants should be preferred when clinically significant levels of anti-PF4 antibodies are detected.
Jacobson JO JAMA https://jamanetwork.com/journals/jamaoncology/fullarticle/2780053	Accompanying Patients in the Time of COVID-19	La pandemia di COVID-19 ha escluso in parte i familiari dal rapporto medico-paziente : questo potrebbe aver consentito una relazione più franca fra le due parti, che andrà mantenuta in futuro.	The pandemic has created mayhem and disrupted the way that we practice medicine. It has done immeasurable harm. But it has also provided opportunities for self-reflection for those of us ministering to patients. It has reminded me of the need to cultivate full presence, no matter what conditions are present. Francis Peabody, who lived through the influenza pandemic a century ago and who

			battled his own cancer wrote, “One of the essential qualities of the clinician is interest in humanity.”