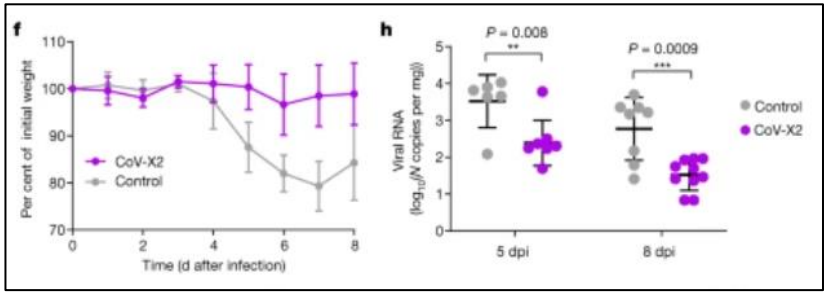
RICERCA BIBLIOGRAFICA COVID 19

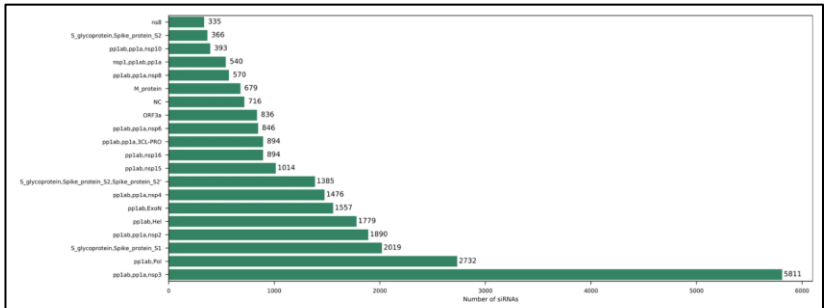
SETTIMANA 26.04 – 02.05.2021

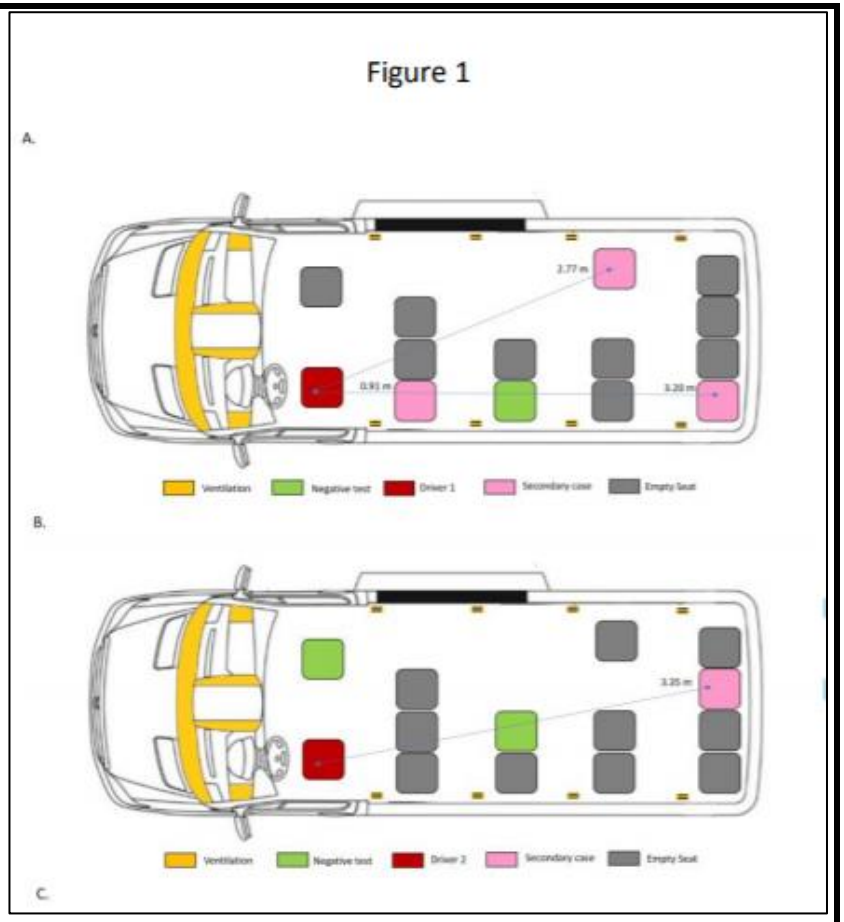
FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE

DOTT.SSA ELEONORA TADDEI

AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
De Gasparo R et al Nature https://www.nature.com/articles/s41586-021-03461-y	Bispecific IgG neutralizes SARS-CoV-2 variants and prevents escape in mice	Anticorpi tipo IgG con doppia specificità per regioni diverse del dominio legante il recettore della proteina Spike di SARS-CoV-2 sono in grado di impedire il legame con ACE2 anche delle varianti del virus e, somministrati al topo di laboratorio, risultano protettivi rispetto agli effetti della malattia.	Neutralizing antibodies that target the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein are among the most promising approaches against COVID-191,2. A bispecific IgG1-like molecule (CoV-X2) has been developed on the basis of C121 and C135, two antibodies derived from donors who had recovered from COVID-193. Here we show that CoV-X2 simultaneously binds two independent sites on the RBD and, unlike its parental antibodies, prevents detectable spike binding to the cellular receptor of the virus, angiotensin-converting enzyme 2 (ACE2). Furthermore, CoV-X2 neutralizes wild-type SARS-CoV-2 and its variants of concern, as well as escape mutants generated by the parental monoclonal antibodies. We also found that in a mouse model of SARS-CoV-2 infection with lung inflammation, CoV-X2 protects mice from disease and suppresses viral escape. Thus, the simultaneous targeting of non-overlapping RBD epitopes by IgG-like bispecific

			antibodies is feasible and effective, and combines the advantages of antibody cocktails with those of single-molecule approaches. 
Medeiros IG et al Scientific Reports https://doi.org/10.1038/s41598-021-88310-8	A small interfering RNA (siRNA) database for SARS-CoV-2.	La cosiddetta RNA interference regola l'espressione genica mediante piccoli RNA a doppio filamento (siRNA) che interagiscono con il DNA. In questo lavoro viene presentata una libreria di possibili bersagli di siRNA da impiegare nella terapia contro SARS-CoV-2.	Coronavirus disease 2019 (COVID-19) rapidly transformed into a global pandemic, for which a demand for developing antivirals capable of targeting the SARS-CoV-2 RNA genome and blocking the activity of its genes has emerged. In this work, we presented a database of SARS-CoV-2 targets for small interference RNA (siRNA) based approaches, aiming to speed the design process by providing a broad set of possible targets and siRNA sequences. The siRNAs sequences are characterized and evaluated by more than 170 features, including thermodynamic information, base context, target genes and alignment information of sequences against the human genome, and diverse SARS-CoV-2 strains, to assess possible bindings to off-target sequences. This dataset is available as a set of four tables, available in a spreadsheet and CSV (Comma-Separated Values) formats, each one corresponding to sequences of 18, 19, 20, and 21 nucleotides length, aiming to meet the diversity of technology and expertise among laboratories around the world. A metadata table (Supplementary Table S1), which describes each feature, is also provided in the aforementioned formats. We hope that this database helps to speed up the development of new target

			antivirals for SARS-CoV-2, contributing to a possible strategy for a faster and effective response to the COVID-19 pandemic.  Distribution of 21nt siRNAs across the twenty more 21nt-siRNA-abundant genes from SARS-CoV-2. Number of siRNA targets per gene, displayed in horizontal bars. Overlapping genes are displayed at the same line, separated by comma.
Jones L et al Clinical Infectious Diseases https://doi.org/10.1093/cid/ciab347	Transmission of SARS-CoV-2 on a Patient Transport Van.	Due casi di potenziale trasmissione di SARS-CoV-2 durante viaggi di due ore all'interno di un pullmino con il conducente positivo, nonostante la presenza di mascherine chirurgiche.	We report 2 episodes of potential SARS-CoV-2 transmission from infected van drivers to passengers despite masking and physical distancing. Whole genome sequencing confirmed relatedness of driver and passenger SARS-CoV-2. With the heater operating, fluorescent microspheres were transported by airflow >3 meters from the front to the back of the van.

			
Gautam N et al Clinical Infectious Diseases https://doi.org/10.1093/cid/ciab341	Medium-term outcome of severe to critically ill patients with SARS-CoV-2 infection.	Studio retrospettivo su 200 pazienti ospedalizzati per COVID-19 grave/critica (40% sottoposti a ventilazione meccanica) nel Regno Unito : a 4-7 mesi dalla diagnosi, più della metà ha ancora sintomi e le persone con dispnea residua hanno	BACKGROUND: The medium and long-term effects of severe SARS-CoV-2 infection on survivors are unknown. Here we studied the medium term effects of COVID-19 on survivors of severe disease. METHODS: This is a retrospective, case series of 200 patients hospitalised across three large Birmingham hospitals with severe-to-critical COVID-19 infection 4-7 months from disease-onset. Patients underwent comprehensive clinical, laboratory, imaging, lung function test, quality of life and cognitive assessments.

		maggiore tendenza ad avere alterazioni radiologiche polmonari e spirometriche.	RESULTS: At 4-7 months from disease-onset, 63.2% of patients experienced persistent breathlessness, 53.5% complained of significant fatigue, 37.5% reduced mobility and 36.8% pain. Serum markers of inflammation and organ injuries that persisted at hospital discharge had normalised on follow-up indicating no sustained immune response causing chronic maladaptive inflammation. Chest radiographs showed a complete resolution in 82.8%; and significantly improved or no change in 17.2%. Lung function test (LFT) revealed gas transfer abnormalities in 80.0% and spirometry in 37.6% patients. Patients with breathlessness had significantly high incidence of comorbidities, abnormal residual chest X-ray and LFT ($p<0.01$ to all). In all parameters assessed and persisting symptoms there was no statically significant difference between patients managed on hospital wards and on ITU groups. All patients reported a significantly reduced quality of life in all domains of the EQ-5D-5L quality of life measures. CONCLUSIONS AND RELEVANCE: A significant proportion of COVID-19 with severe illness experience ongoing symptoms of breathlessness, fatigue, pain, reduced mobility, depression and reduced quality of life at 4-7 months from disease-onset. Symptomatic patients tend to have more residual CXR and LFT abnormalities.

			Table 3: Comparison of clinical characteristics and LFT and radiological report assessed in patients with and without shortness of breath at follow up. **Diagnosis** / **No SOB (n=53) No. (%)** / **SOB (n=91) No. (%)** / **p-value** Obesity: 24 (45.3) / 46 (50.5) / <0.01 Hypertension: 21 (39.6) / 49 (53.8) / <0.01 Diabetes Mellitus: 20 (37.7) / 37 (40.7) / <0.01 Asthma: 9 (16.9) / 22 (24.2) / <0.01 Coronary Heart Diseases: 2 (3.8) / 9 (9.9) / <0.01 Other cardiac Disorder: 1 (1.9) / 7 (7.7) / <0.01 COPD: 0 (0) / 8 (8.8) / <0.01 Interstitial Lung Disease: 0 (0) / 2 (2.2) / <0.01 **Follow-up Chest X-Ray** Complete resolution: 48 (90.6) / 72 (79.1) / <0.01 Partial resolution: 5 (9.4) / 19 (20.9) **Follow- up Lung Function Test** Normal spirometry: 51 (96.2) / 46 (50.5) / <0.01 Abnormal spirometry: 2 3 (8) / 45 (49.5)
Llaydon DJ et al BMJ Open https://bmjopen.bmj.com/content/11/4/e050346	Modelling the impact of the tier system on SARS-CoV-2 transmission in the UK between the first and second national lockdowns.	Secondo il modello riportato in questo studio e relativo alla diffusione di SARS-CoV-2 nel Regno Unito nel periodo fra i due « lockdown » imposti nel paese, mezze misure restrittive non riducono significativamente il contagio se non accompagnate da una ampia vaccinazione.	Objective To measure the effects of the tier system on the COVID-19 pandemic in the UK between the first and second national lockdowns, before the emergence of the B.1.1.7 variant of concern. Design This is a modelling study combining estimates of real-time reproduction number Rt (derived from UK case, death and serological survey data) with publicly available data on regional non-pharmaceutical interventions. We fit a Bayesian hierarchical model with latent factors using these quantities to account for broader national trends in addition to subnational effects from tiers. Setting The UK at lower tier local authority (LTLA) level. 310 LTLAs were included in the analysis. Primary and secondary outcome measures Reduction in real-time reproduction number Rt. Results Nationally, transmission increased between July and late September, regional differences notwithstanding. Immediately prior to the introduction of the tier system, Rt averaged 1.3 (0.9–1.6)

<table>
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<td></td>
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<td>across LTLAs, but declined to an average of 1.1 (0.86–1.42) 2 weeks later. Decline in transmission was not solely attributable to tiers. Tier 1 had negligible effects. Tiers 2 and 3, respectively, reduced transmission by 6% (5%–7%) and 23% (21%–25%). 288 LTLAs (93%) would have begun to suppress their epidemics if every LTLA had gone into tier 3 by the second national lockdown, whereas only 90 (29%) did so in reality.
Conclusions The relatively small effect sizes found in this analysis demonstrate that interventions at least as stringent as tier 3 are required to suppress transmission, especially considering more transmissible variants, at least until effective vaccination is widespread or much greater population immunity has amassed.

Table 1 Coefficient reductions from a given tier

<table>
<tr><th>Variable</th><th>Mean</th><th>2.5% Credible Interval</th><th>97.5% Credible Interval</th></tr>
<tr><td>Tier 1</td><td>1</td><td>1</td><td>1</td></tr>
<tr><td>Tier 2</td><td>0.94</td><td>0.93</td><td>0.95</td></tr>
<tr><td>Tier 3</td><td>0.77</td><td>0.75</td><td>0.79</td></tr>
</table>
Note these have been exponentiated and can be interpreted by directly multiplying them with a given R_t.
R_t, real-time reproduction number.</td>
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<td>Mason M et al

JAMA

https://jamanetwork.com/journals/jama/fullarticle/2779399</td>
<td>The Pandemic Stay-at-Home Order and Opioid-Involved Overdose Fatalities</td>
<td>Associazione tra inizio del « lockdown » nello stato dell’Illinois e il numero di decessi per overdose da diverse sostanze, con aumento delle morti per utilizzo di fentanyl e</td>
<td>In response to the COVID-19 pandemic, Illinois enacted a stay-at-home order on March 21, 2020; the order was lifted on May 30, 2020. This report describes trends in opioid-involved overdose deaths over a 3-year period and highlights the number of deaths during the 11-week Illinois stay-at-home order. Trends in substance involvement are also examined.</td>
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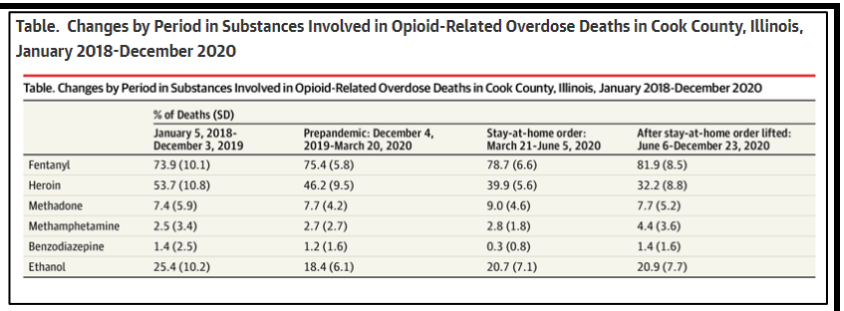
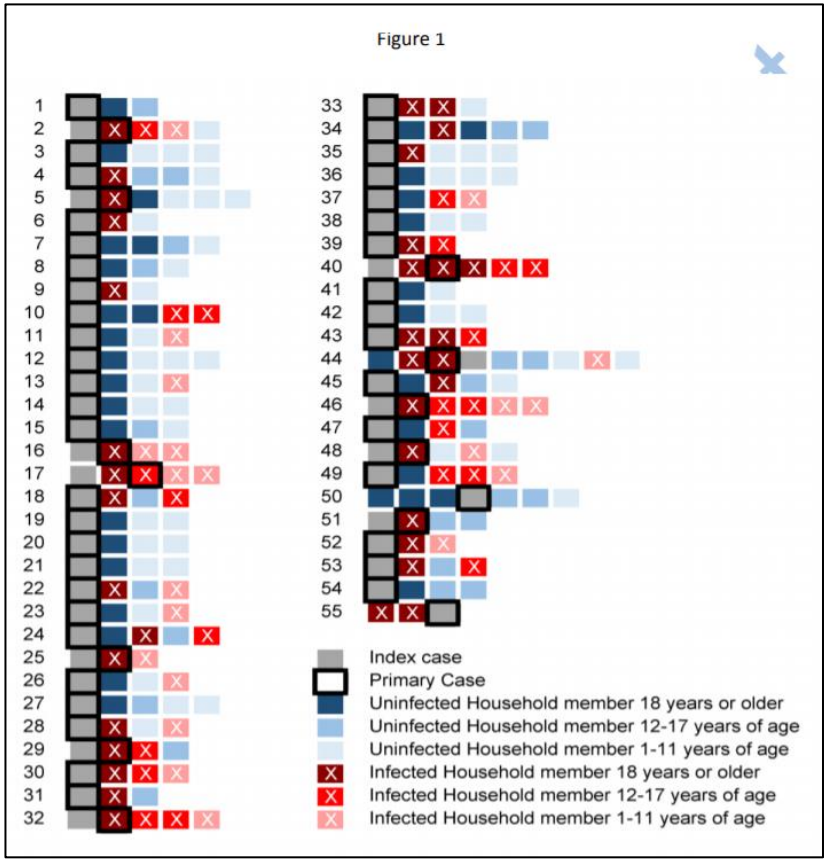
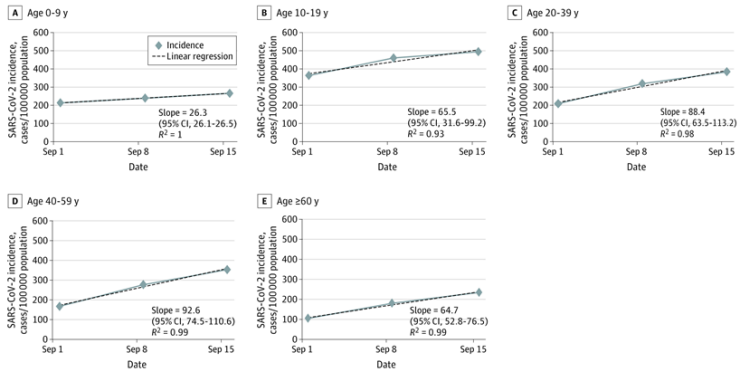
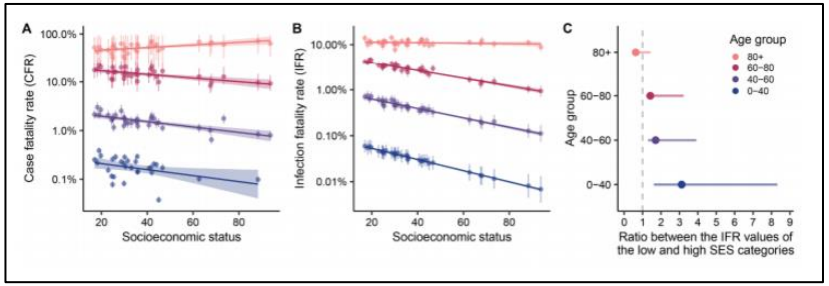
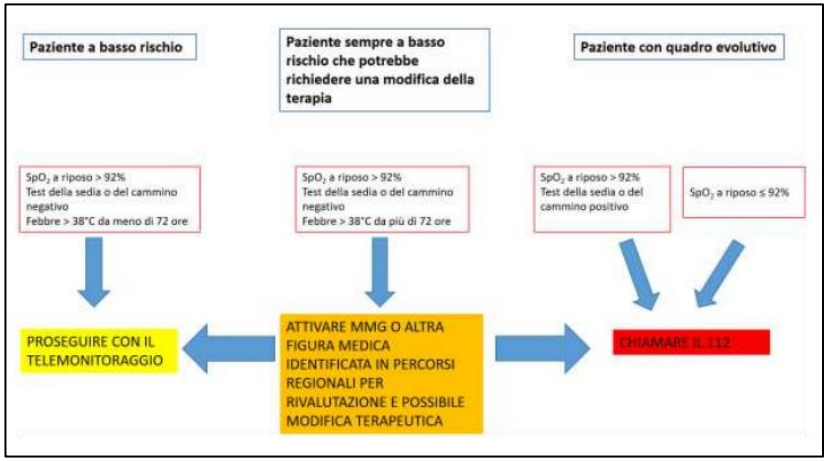
		riduzione di quelle per eroina.	Table. Changes by Period in Substances Involved in Opioid-Related Overdose Deaths in Cook County, Illinois, January 2018-December 2020  Table. Changes by Period in Substances Involved in Opioid-Related Overdose Deaths in Cook County, Illinois, January 2018-December 2020 % of Deaths (SD) January 5, 2018-December 3, 2019 / Prepandemic: December 4, 2019-March 20, 2020 / Stay-at-home order: March 21-June 5, 2020 / After stay-at-home order lifted: June 6-December 23, 2020 Fentanyl 73.9 (10.1) 75.4 (5.8) 78.7 (6.6) 81.9 (8.5) Heroin 53.7 (10.8) 46.2 (9.5) 39.9 (5.6) 32.2 (8.8) Methadone 7.4 (5.9) 7.7 (4.2) 9.0 (4.6) 7.7 (5.2) Methamphetamine 2.5 (3.4) 2.7 (2.7) 2.8 (1.8) 4.4 (3.6) Benzodiazepine 1.4 (2.5) 1.2 (1.6) 0.3 (0.8) 1.4 (1.6) Ethanol 25.4 (10.2) 18.4 (6.1) 20.7 (7.1) 20.9 (7.7)
Reukers DFM et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab237/6209401	High infection secondary attack rates of SARS-CoV-2 in Dutch households revealed by dense sampling	La presenza di casi secondari rispetto a un caso indice di infezione da SARS-CoV-2 nelle abitazioni è più elevato in questo studio condotto nei Paesi Bassi rispetto ad altri studi precedenti (51% negli adulti e 35% nei bambini), probabilmente per via di un campionamento serrato.	Background : Indoor environments are considered one of the main settings for transmission of SARS-CoV-2. Households in particular represent a close-contact environment with high probability of transmission between persons of different ages and with different roles in society. Methods : Complete households with a laboratory-confirmed SARS-CoV-2 positive case in the Netherlands (March-May 2020) were included. At least three home visits were performed during 4-6 week of follow-up, collecting naso- and oropharyngeal swabs, oral fluid, feces and blood samples for molecular and serological analyses of all household members. Symptoms were recorded from two weeks before the first visit through to the final visit. Infection secondary attack rates (SAR) were estimated with logistic regression. A transmission model was used to assess transmission routes in the household. Results : A total of 55 households with 187 household contacts were included. In 17 households no transmission took place, and in 11 households all persons were infected. Estimated infection SARs were high, ranging from 35% (95%CI: 24%-46%) in children to 51% (95%CI: 39%-63%) in adults. Estimated transmission rates in the household were high, with reduced susceptibility of children compared to adolescents and adults (0.67; 95%CI: 0.40-1.1).

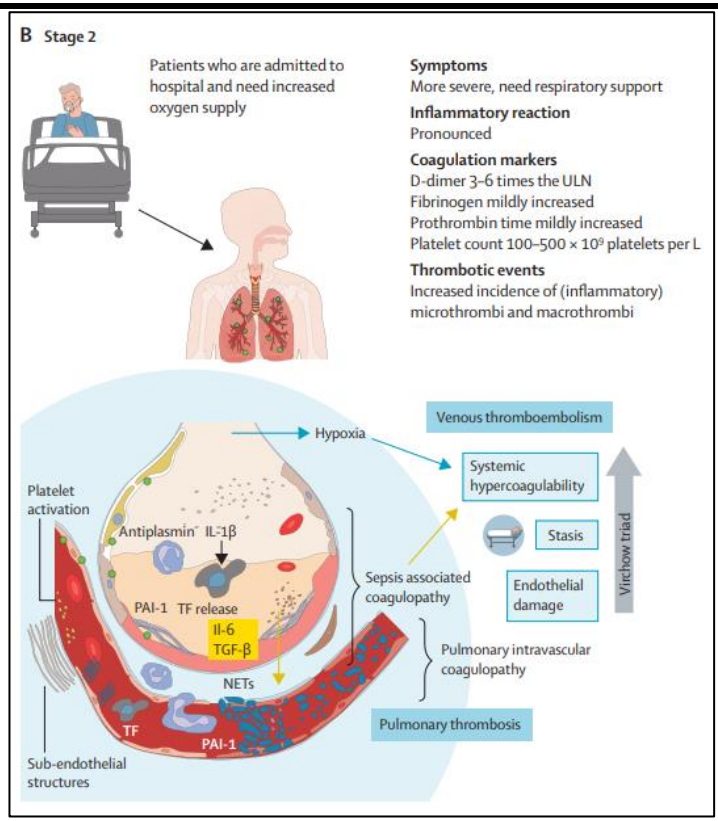
			Conclusion : Estimated infection SARs were higher than reported in earlier household studies, presumably owing to our dense sampling protocol. Children were shown to be less susceptible than adults, but the estimated infection SAR in children was still high. Our results reinforce the role of households as one of the main multipliers of SARS-CoV-2 infection in the population. 

Somekh I et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2778940?resultClick=1	Comparison of COVID-19 Incidence Rates Before and After School Reopening in Israel	Studio osservazionale condotto in Israele in cui si confrontano i nuovi casi di infezione da SARS-CoV-2 dopo la riapertura delle scuole in Novembre 2020, confrontando diverse fasce d'età con particolare attenzione a quella dei bambini di 0-9 anni : questi ultimi non hanno risentito di un significativo aumento di incidenza dopo il rientro a scuola.	Schools reopened in Israel on September 1, 2020, following summer vacation during active SARS-CoV-2 spread when the incidence of new cases of COVID-19 in Israel was one of the highest in the world. During September 2020, COVID-19 cases further surged in Israel, resulting in school closure (September 14), and a countrywide lockdown. Schools were reopened on November 1. We examined the dynamics in infection rates in children and youths aged 0 to 19 years compared with other age groups, with the goal of understanding whether school reopening was associated with SARS-CoV-2 infection in those aged 0 to 9 years. **Figure 2. Weekly Adjusted Incidence Curves in Studied Age Groups**  Weekly adjusted incidence (new SARS-CoV-2 cases per 100 000 population of the specific age group) during September 1 to September 21, 2020. Dates outlined represent day 1 of the studied week. R^2 denotes the R^2 value of the regression line. The slope (with 95% CIs) is for the linear regression line.
Mena GE et al Science https://science.sciencemag.org/content/early/2021/04/26/science.abg5298	Socioeconomic status determines COVID-19 incidence and related mortality in Santiago, Chile	In questo studio condotto a Santiago del Cile si osserva come le persone povere, non potendo smettere di lavorare e ridurre i propri spostamenti e vivendo in quartieri con meno servizi, risentano di una maggiore mortalità per SARS-CoV-2 a	The current COVID-19 pandemic has impacted cities particularly hard. Here, we provide an in-depth characterization of disease incidence and mortality, and their dependence on demographic and socioeconomic strata in Santiago, a highly segregated city and the capital of Chile. Our analyses show a strong association between socioeconomic status and both COVID-19 outcomes and public health capacity. People living in municipalities with low socioeconomic status did not reduce their mobility during

		parità di età anagrafica rispetto ai più ricchi.	lockdowns as much as those in more affluent municipalities. Testing volumes may have been insufficient early in the pandemic in those places, and both test positivity rates and testing delays were much higher. We find a strong association between socioeconomic status and mortality, measured either by COVID-19 attributed deaths or excess deaths. Finally, we show that infection fatality rates in young people are higher in low-income municipalities. Together, these results highlight the critical consequences of socioeconomic inequalities on health outcomes. 
Paules CI et al Med https://www.cell.com/med/fulltext/S2666-6340(21)00164-1?utm_medium=homepage	COVID-19: The therapeutic landscape	Rassegna della « storia » – un solo anno ! - della terapia contro SARS-CoV-2, con il grande capitolo ancora da scrivere sui pazienti non ricoverati.	Therapeutics for hospitalized COVID-19 patients were identified through a robust research response with several lessons learned: clinical trial data should guide therapeutic use, results should not be extrapolated between disease stages, and robust studies should be designed to give clinically relevant data. These lessons should be applied to the outpatient research response.
Ministero della Salute https://www.trovanorme.salute.gov.it/norme/rendererNormsanPdf?anno=202	GESTIONE DOMICILIARE DEI PAZIENTI CON INFEZIONE DA SARS-CoV-2	Linee guida del Ministero della Salute italiano sulla gestione a domicilio dell'infezione da SARS-CoV-2 : controindicati gli steroidi	[…] non utilizzare routinariamente corticosteroidi. L'uso dei corticosteroidi è raccomandato esclusivamente nei soggetti con malattia COVID-19 grave che necessitano di supplementazione di ossigeno. L'impiego di tali farmaci a domicilio può essere considerato solo in pazienti con fattori di rischio di progressione di

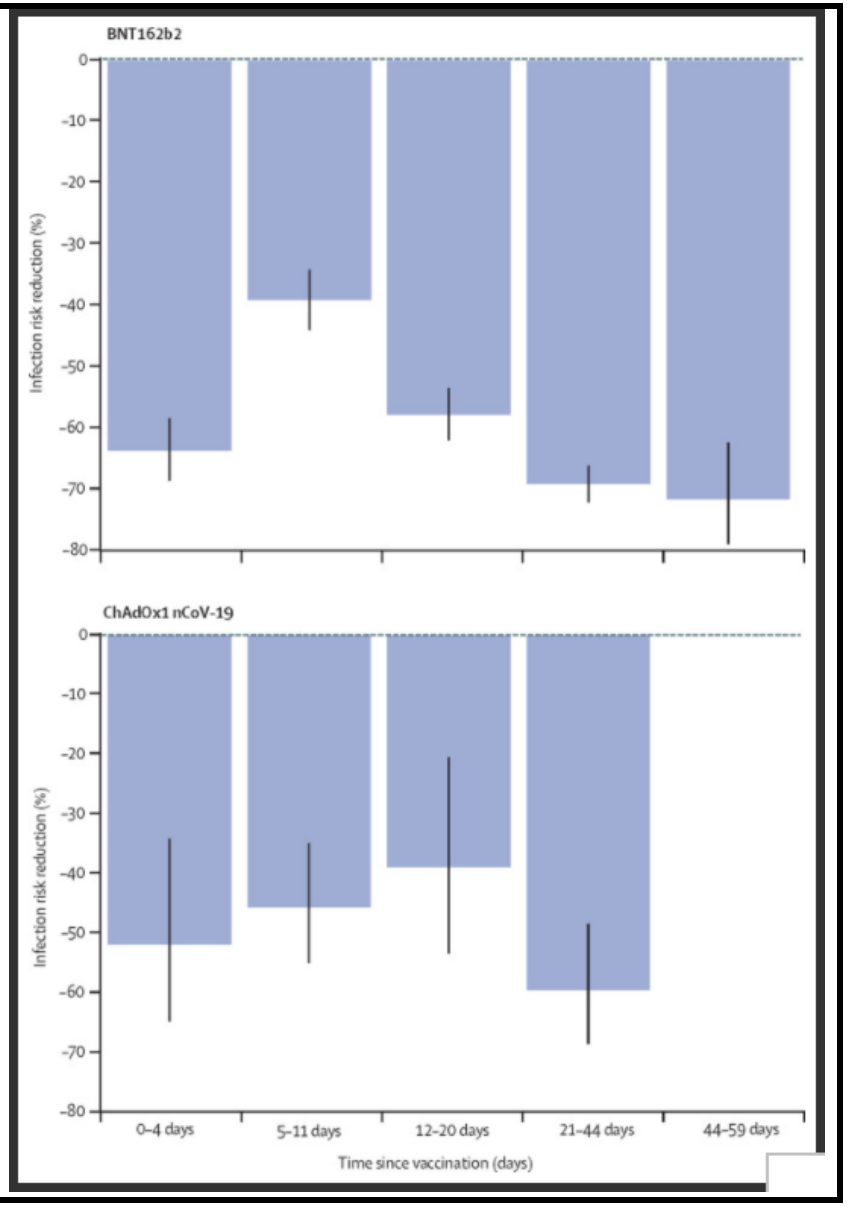
1&codLeg=80056&parte=1%20&serie=null		in assenza di insufficienza respiratoria, l'eparina in assenza di immobilizzazione e gli antibiotici in assenza di un fondato sospetto di infezione batterica. Considerare gli anticorpi monoclonali se il paziente rientra nei criteri per cui sono stati approvati in emergenza da AIFA.	malattiaverso forme severe, in presenza di un peggioramento dei parametri pulsossimetrici che richieda l'ossigenoterapia ove non sia possibile nell'immediato il ricovero per sovraccarico delle strutture ospedaliere. L'utilizzo della terapia precoce con steroidi si è rivelata inutile se non dannosa in quanto in grado di inficiare lo sviluppo di un'adeguata risposta immunitaria […]. 
Taylor L Nature https://www.nature.com/articles/d41586-021-01031-w	'We are being ignored': Brazil's researchers blame anti-science government for devastating COVID surge	La situazione brasiliana e le accuse al Presidente Bolsonaro in merito alla gestione della pandemia di COVID-19 ; la rivista riporta il rifiuto del Presidente a una richiesta di commento a questo articolo.	More than a year after Brazil detected its first case of COVID-19, the country is facing its darkest phase of the pandemic yet. Researchers are devastated by the recent surge in cases and say that the government's failure to follow science-based guidance in responding to the pandemic has made the crisis much worse. They add that President Jair Bolsonaro's administration has publicly undermined science while refusing to implement protective national lockdowns and spreading misinformation.
Leentjens J et al The Lancet	COVID-19-associated coagulopathy and antithrombotic agents—lessons after 1 year	Revisione sui meccanismi e le fasi della coagulopatia associata a COVID-19, con disamina della letteratura a disposizione sulle diverse	COVID-19 is associated with a high incidence of thrombotic complications, which can be explained by the complex and unique interplay between coronaviruses and endothelial cells, the local and systemic inflammatory response, and the coagulation system. Empirically, an intensified dose of thrombosis prophylaxis is being

https://www.thelancet.com/journals/lanhae/article/PIIS2352-3026(21)00105-8/fulltext		popolazioni di pazienti (non ospedalizzati, ospedalizzati con malattia moderato-grave e critici, dimessi dall'ospedale) e delle linee guida pubblicate : la terapia con eparine è raccomandata universalmente per i pazienti ospedalizzati, ma il dosaggio ottimale dovrà essere indicato dai numerosi trial ancora in corso. Il beneficio maggiore di un dosaggio anticoagulante pieno appare al momento nei pazienti ospedalizzati non critici.	used in patients admitted to hospital with COVID-19 and several guidelines on this topic have been published, although the insufficiency of high quality and direct evidence has led to weak recommendations. In this Viewpoint we summarise the pathophysiology of COVID-19 coagulopathy in the context of patients who are ambulant, admitted to hospital, and critically ill or non-critically ill, and those post-discharge from hospital. We also review data from randomised controlled trials in the past year of antithrombotic therapy in patients who are critically ill. These data provide the first high-quality evidence on optimal use of antithrombotic therapy in patients with COVID-19. Pharmacological thromboprophylaxis is not routinely recommended for patients who are ambulant and post-discharge. A first ever trial in non-critically ill patients who were admitted to hospital has shown that a therapeutic dose of low-molecular-weight heparin might improve clinical outcomes in this population. In critically ill patients, this same treatment does not improve outcomes and prophylactic dose anticoagulant thromboprophylaxis is recommended. In the upcoming months we expect numerous data from the ongoing antithrombotic COVID-19 studies to guide clinicians at different stages of the disease.

			
Menni C et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00224-3/fulltext	Vaccine side-effects and SARS-CoV-2 infection after vaccination in users of the COVID Symptom Study app in the UK: a prospective observational study	Studio osservazionale prospettico su oltre 600.000 vaccinati nel Regno Unito con almeno una dose di Pfizer/Vaxzevria nel periodo dicembre 2020 – marzo 2021 : si osservano gli effetti avversi riportati in una app e la protezione dall'infezione rispetto ai non vaccinati, presente già dopo 12 giorni	Background : The Pfizer-BioNTech (BNT162b2) and the Oxford-AstraZeneca (ChAdOx1 nCoV-19) COVID-19 vaccines have shown excellent safety and efficacy in phase 3 trials. We aimed to investigate the safety and effectiveness of these vaccines in a UK community setting. Methods : In this prospective observational study, we examined the proportion and probability of self-reported systemic and local side-effects within 8 days of vaccination in individuals using the COVID Symptom Study app who received one or two doses of the BNT162b2 vaccine or one dose of the ChAdOx1 nCoV-19 vaccine.

		da una dose di entrambi i vaccini	We also compared infection rates in a subset of vaccinated individuals subsequently tested for SARS-CoV-2 with PCR or lateral flow tests with infection rates in unvaccinated controls. All analyses were adjusted by age (≤55 years vs >55 years), sex, health-care worker status (binary variable), obesity (BMI <30 kg/m2 vs ≥30 kg/m2), and comorbidities (binary variable, with or without comorbidities). Findings : Between Dec 8, and March 10, 2021, 627 383 individuals reported being vaccinated with 655 590 doses: 282 103 received one dose of BNT162b2, of whom 28 207 received a second dose, and 345 280 received one dose of ChAdOx1 nCoV-19. Systemic side-effects were reported by 13·5% (38 155 of 282 103) of individuals after the first dose of BNT162b2, by 22·0% (6216 of 28 207) after the second dose of BNT162b2, and by 33·7% (116 473 of 345 280) after the first dose of ChAdOx1 nCoV-19. Local side-effects were reported by 71·9% (150 023 of 208 767) of individuals after the first dose of BNT162b2, by 68·5% (9025 of 13 179) after the second dose of BNT162b2, and by 58·7% (104 282 of 177 655) after the first dose of ChAdOx1 nCoV-19. Systemic side-effects were more common (1·6 times after the first dose of ChAdOx1 nCoV-19 and 2·9 times after the first dose of BNT162b2) among individuals with previous SARS-CoV-2 infection than among those without known past infection. Local effects were similarly higher in individuals previously infected than in those without known past infection (1·4 times after the first dose of ChAdOx1 nCoV-19 and 1·2 times after the first dose of BNT162b2). 3106 of 103 622 vaccinated individuals and 50 340 of 464 356 unvaccinated controls tested positive for SARS-CoV-2 infection. Significant reductions in infection risk were seen starting at 12 days after the first dose, reaching 60% (95% CI

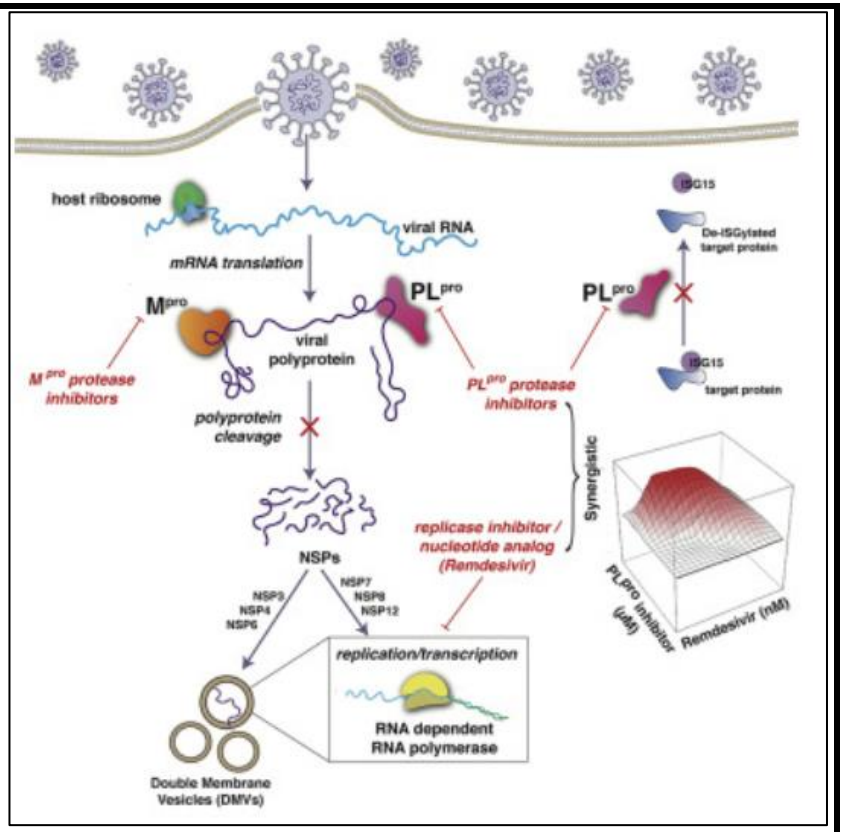
			49–68) for ChAdOx1 nCoV-19 and 69% (66–72) for BNT162b2 at 21–44 days and 72% (63–79) for BNT162b2 after 45–59 days. Interpretation : Systemic and local side-effects after BNT162b2 and ChAdOx1 nCoV-19 vaccination occur at frequencies lower than reported in phase 3 trials. Both vaccines decrease the risk of SARS-CoV-2 infection after 12 days.

			 BNT162b2 0 -10 -20 -30 -40 -50 -60 -70 -80 Infection risk reduction (%) ChAdOx1 nCoV-19 0 -10 -20 -30 -40 -50 -60 -70 -80 Infection risk reduction (%) 0–4 days 5–11 days 12–20 days 21–44 days 44–59 days Time since vaccination (days)

Tleyjeh IM et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00204-4/fulltext	Efficacy and safety of tocilizumab in COVID-19 patients: A living systematic Review and meta-analysis: first update	Revisione sistematica e metanalisi di trial clinici e studi di coorte sulla terapia con tocilizumab (anti IL-6) contro COVID-19 in pazienti ospedalizzati : si osserva una riduzione del rischio di ventilazione meccanica nei trattati.	Background : Cytokine release syndrome with elevated interleukin-6 (IL-6) levels is associated with multiorgan damage and death in severe coronavirus disease 2019 (COVID-19). Objectives : To update data a living systematic review of the literature concerning the efficacy and toxicity of the IL-6 receptor antagonist, tocilizumab, in COVID-19 patients. Data sources : Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Web of Science, Scopus up, preprint servers and Google from October 8, 2020 till February 24, 2021. Study eligibility criteria : Randomized controlled trials (RCTs) and observational studies at low or moderate risk of bias. Participants : Hospitalized COVID-19 patients. Interventions : Tocilizumab versus placebo or standard of care. Methods : We pooled crude risk ratios (RRs) of RCTs with random effects model and evaluated inconsistency between studies with I2. We assessed the certainty of evidence using the GRADE approach. Results : Of 1600 citations, 8 RCTs and 28 cohorts were eligible. The 8 RCTs, at low risk of bias, with 6311 patients examined the effect of tocilizumab on short-term mortality; pooled RR was 0.91 (95%CI 0.78, 1.07, I2 = 25%). Only the REMAP-CAP and RECOVERY trials with the majority of their patients on concomitant corticosteroids, showed lower 30-day mortality with tocilizumab use, RR 0.74 (95%CI 0.59, 0.93) and 0.89 (95%CI 0.81, 0.97), respectively. Seven RCTs, with 5391 patients examined the effect of tocilizumab on risk of mechanical ventilation; pooled RR was 0.84 (95% CI 0.76, 0.93), I2 = 0%, with a corresponding number needed to treat of 20 (95%CI 14.3–33.3). Eight RCTs, with 5,340 patients, examined the effect of

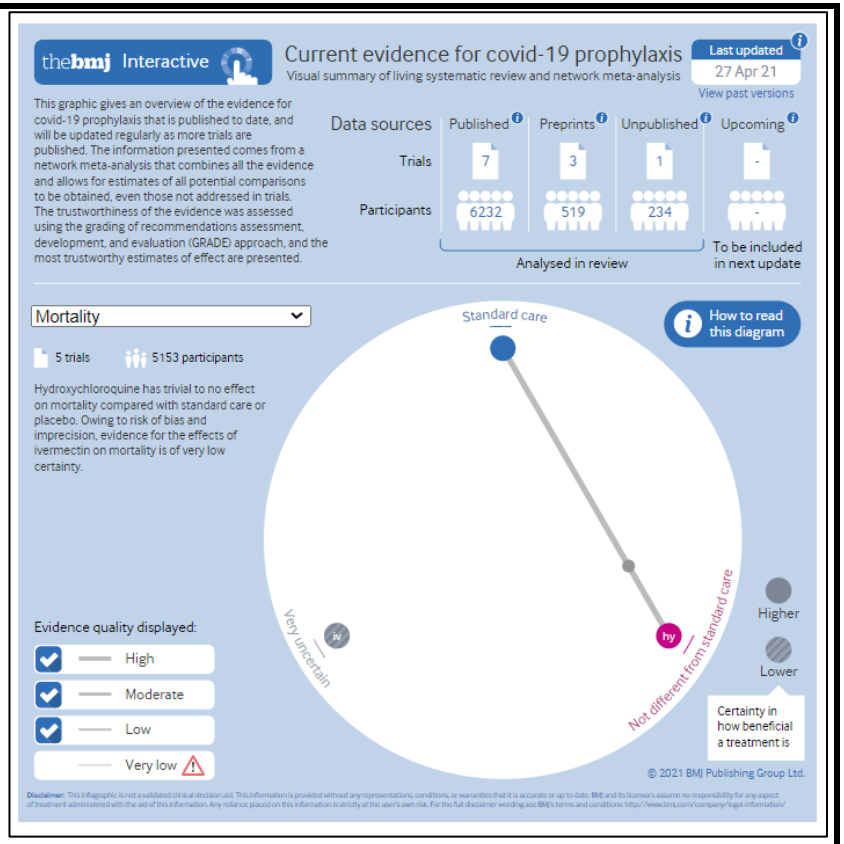
			tocilizumab on a composite of poor outcome; pooled RR was 0.82 (95% CI 0.76, 0.90, I2 = 3%). Data from the RCTs showed a lower risk of infections and no higher risk of serious adverse events with tocilizumab; pooled RR 0.67 (95%CI 0.45, 0.99, eight RCTs) and 0.85 (95%CI 0.63, 1.16, seven RCTs), respectively. Among 28 cohorts with 15484 patients, the pooled adjusted RR for mortality was 0.53 (95%CI 0.43, 0.67, I2 = 76%). Conclusions : Cumulative high certainty evidence shows that tocilizumab reduces the risk of mechanical ventilation in hospitalized patients with severe COVID-19. Moderate certainty evidence shows that tocilizumab reduces the risk of poor outcome and the risk of secondary infections in hospitalized COVID-19 patients. This review will continuously evaluate the role of tocilizumab in COVID-19 treatment.
Maidstone R et al Thorax – BMJ https://thorax.bmj.com/content/early/2021/03/30/thoraxjnl-2020-216651	Shift work is associated with positive COVID-19 status in hospitalised patients	Chi fa turni di notte per lavoro ha un fattore di rischio indipendente per infezione da SARS-CoV-2 secondo questo studio condotto nel Regno Unito.	Introduction Shift work is associated with lung disease and infections. We therefore investigated the impact of shift work on significant COVID-19 illness. Methods 501 000 UK Biobank participants were linked to secondary care SARS-CoV-2 PCR results from Public Health England. Healthcare worker occupational testing and those without an occupational history were excluded from analysis. Results Multivariate logistic regression (age, sex, ethnicity and deprivation index) revealed that irregular shift work (OR 2.42, 95% CI 1.92 to 3.05), permanent shift work (OR 2.5, 95% CI 1.95 to 3.19), day shift work (OR 2.01, 95% CI 1.55 to 2.6), irregular night shift work (OR 3.04, 95% CI 2.37 to 3.9) and permanent night shift work (OR 2.49, 95% CI 1.67 to 3.7) were all associated with positive COVID-19 tests compared with participants that did not perform shift work. This relationship persisted after adding sleep duration, chronotype, premorbid disease, body mass index, alcohol and

			smoking to the model. The effects of workplace were controlled for in three ways: (1) by adding in work factors (proximity to a colleague combined with estimated disease exposure) to the multivariate model or (2) comparing participants within each job sector (non-essential, essential and healthcare) and (3) comparing shift work and non-shift working colleagues. In all cases, shift work was significantly associated with COVID-19. In 2017, 120 307 UK Biobank participants had their occupational history reprofiled. Using this updated occupational data shift work remained associated with COVID-19 (OR 4.48 (95% CI 1.8 to 11.18). Conclusions Shift work is associated with a higher likelihood of in-hospital COVID-19 positivity. This risk could potentially be mitigated via additional workplace precautions or vaccination.
Bafna K et al Cell Reports https://www.cell.com/cell-reports/fulltext/S2211-1247(21)00472-1	Hepatitis C Virus Drugs That Inhibit the SARS-CoV-2 Papain-Like Protease Synergize with Remdesivir to Suppress Viral Replication in Cell Culture	Gli inibitori della proteasi NS3/4A di HCV sono attivi contro le proteasi di SARS-CoV-2 in vitro e alcuni di essi mostrano sinergismo con remdesivir.	Effective control of COVID-19 requires antivirals directed against SARS-CoV-2. We assessed ten hepatitis C virus (HCV) protease-inhibitor drugs as potential SARS-CoV-2 antivirals. There is a striking structural similarity of the substrate binding clefts of SARS-CoV-2 main protease (Mpro) and HCV NS3/4A protease. Virtual docking experiments show that these HCV drugs can potentially bind into the Mpro binding cleft. We show that seven HCV drugs inhibit both SARS-CoV-2 Mpro protease activity and SARS-CoV-2 virus replication in Vero and/or human cells. However, their Mpro inhibiting activities did not correlate with their antiviral activities. This conundrum was resolved by demonstrating that four HCV protease inhibitor drugs, simeprevir, vaniprevir, paritaprevir, and grazoprevir inhibit the SARS CoV-2 papain-like protease (PLpro). HCV drugs that inhibit PLpro synergize with the viral polymerase inhibitor remdesivir to inhibit virus replication, increasing remdesivir's antiviral activity as much as 10-fold, while those that only inhibit Mpro do not synergize with remdesivir.

			
Bartoszko JJ et al BMJ https://pubmed.ncbi.nlm.nih.gov/33903131/	Prophylaxis against COVID-19: living systematic review and meta-analysis	Revisione sistematica e metanalisi di trial clinici su farmaci utilizzati come profilassi dell'infezione da SARS-CoV-2 : i due farmaci considerati, idrossiclorochina e ivermectina, non mostrano beneficio.	Objective To determine and compare the effects of drug prophylaxis on SARS-CoV-2 infection and covid-19. Design Living systematic review and network meta-analysis. Data sources World Health Organization covid-19 database, a comprehensive multilingual source of global covid-19 literature to 25 March 2021, and six additional Chinese databases to 20 February 2021. Study selection Randomised trials of people at risk of covid-19 who were assigned to receive prophylaxis or no prophylaxis (standard

			care or placebo). Pairs of reviewers independently screened potentially eligible articles. Methods Random effects bayesian network meta-analysis was performed after duplicate data abstraction. Included studies were assessed for risk of bias using a modification of the Cochrane risk of bias 2.0 tool, and certainty of evidence was assessed using the grading of recommendations assessment, development, and evaluation (GRADE) approach. Results The first iteration of this living network meta-analysis includes nine randomised trials—six of hydroxychloroquine (n=6059 participants), one of ivermectin combined with iota-carrageenan (n=234), and two of ivermectin alone (n=540), all compared with standard care or placebo. Two trials (one of ramipril and one of bromhexine hydrochloride) did not meet the sample size requirements for network meta-analysis. Hydroxychloroquine has trivial to no effect on admission to hospital (risk difference 1 fewer per 1000 participants, 95% credible interval 3 fewer to 4 more; high certainty evidence) or mortality (1 fewer per 1000, 2 fewer to 3 more; high certainty). Hydroxychloroquine probably does not reduce the risk of laboratory confirmed SARS-CoV-2 infection (2 more per 1000, 18 fewer to 28 more; moderate certainty), probably increases adverse effects leading to drug discontinuation (19 more per 1000, 1 fewer to 70 more; moderate certainty), and may have trivial to no effect on suspected, probable, or laboratory confirmed SARS-CoV-2 infection (15 fewer per 1000, 64 fewer to 41 more; low certainty). Owing to serious risk of bias and very serious imprecision, and thus very low certainty of evidence, the effects of ivermectin combined with iota-carrageenan on laboratory confirmed covid-19 (52 fewer per 1000, 58 fewer to 37 fewer), ivermectin alone on laboratory confirmed infection (50 fewer per

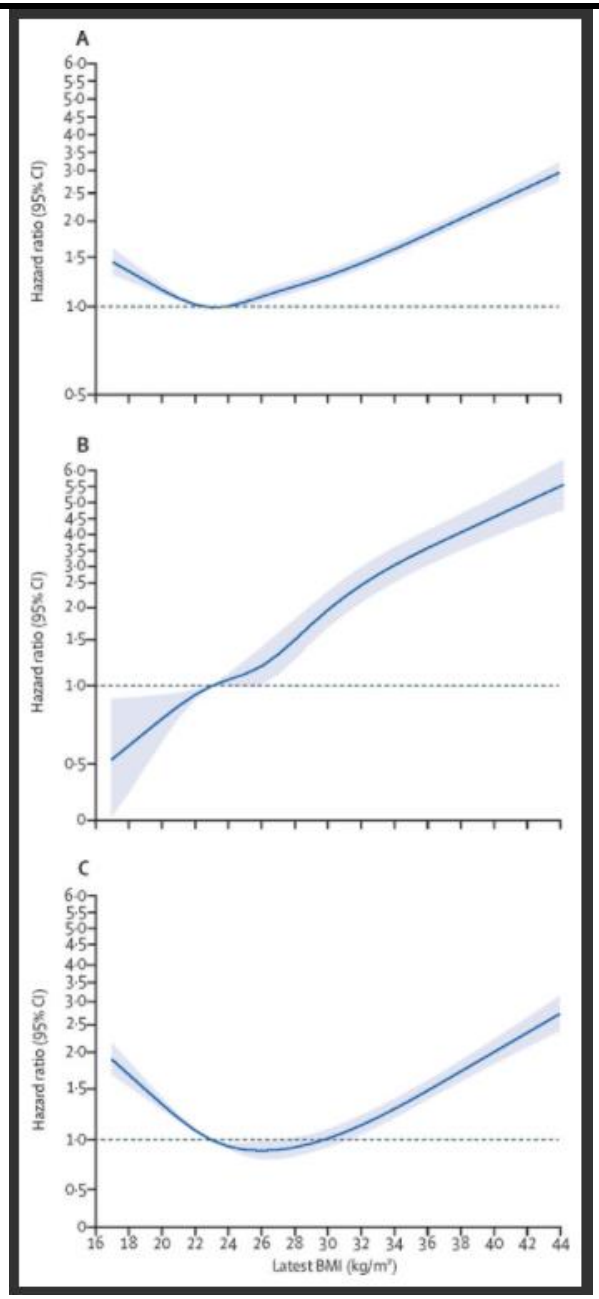
			1000, 59 fewer to 16 fewer) and suspected, probable, or laboratory confirmed infection (159 fewer per 1000, 165 fewer to 144 fewer) remain very uncertain. Conclusions Hydroxychloroquine prophylaxis has trivial to no effect on hospital admission and mortality, probably increases adverse effects, and probably does not reduce the risk of SARS-CoV-2 infection. Because of serious risk of bias and very serious imprecision, it is highly uncertain whether ivermectin combined with iota-carrageenan and ivermectin alone reduce the risk of SARS-CoV-2 infection. Systematic review registration This review was not registered. The protocol established a priori is included as a supplement. Readers' note This article is a living systematic review that will be updated to reflect emerging evidence. Updates may occur for up to two years from the date of original publication.

			
Gao M et al The Lancet https://www.thelancet.com/journals/landia/article/PIIS2213-8587(21)00089-9/fulltext	Associations between BMI and COVID-19 severity in 6.9 million people in England: a prospective, community-based, cohort study	Studio di coorte prospettico condotto in Inghilterra su adulti di età superiore a 20 anni, in cui si osserva un aumento del rischio di malattia grave da SARS-CoV-2 e di morte per COVID-19 all'aumentare del BMI, in particolare nei giovani di età inferiore a 40 anni.	Background Obesity is a major risk factor for adverse outcomes after infection with SARS-CoV-2. We aimed to examine this association, including interactions with demographic and behavioural characteristics, type 2 diabetes, and other health conditions. Methods In this prospective, community-based, cohort study, we used de-identified patient-level data from the QResearch database of general practices in England, UK. We extracted data for patients aged 20 years and older who were registered at a practice eligible

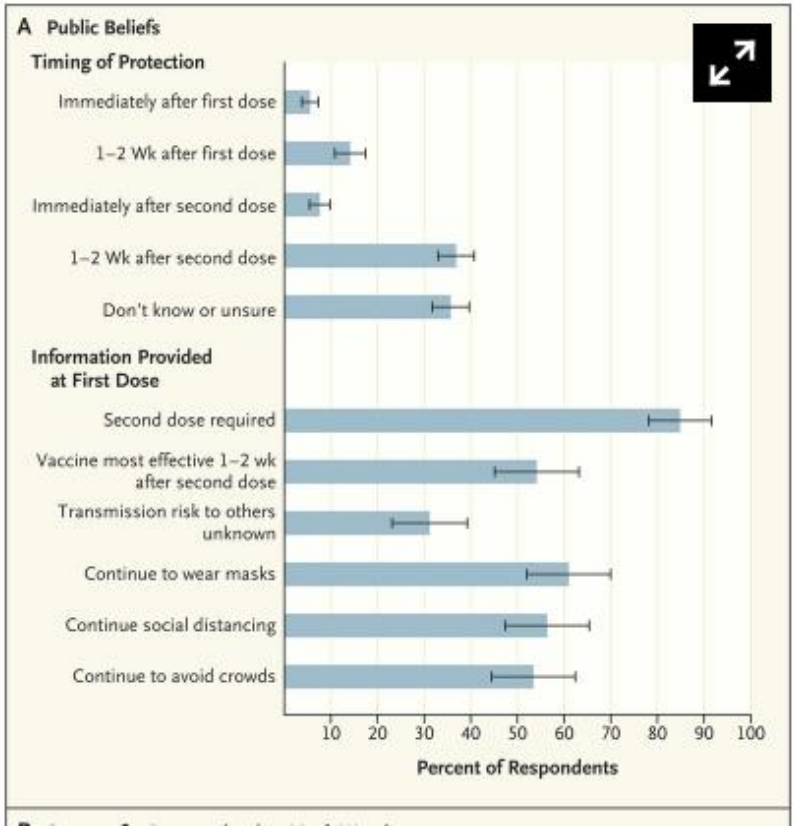
			for inclusion in the QResearch database between Jan 24, 2020 (date of the first recorded infection in the UK) and April 30, 2020, and with available data on BMI. Data extracted included demographic, clinical, clinical values linked with Public Health England's database of positive SARS-CoV-2 test results, and death certificates from the Office of National Statistics. Outcomes, as a proxy measure of severe COVID-19, were admission to hospital, admission to an intensive care unit (ICU), and death due to COVID-19. We used Cox proportional hazard models to estimate the risk of severe COVID-19, sequentially adjusting for demographic characteristics, behavioural factors, and comorbidities. Findings Among 6 910 695 eligible individuals (mean BMI 26·78 kg/m2 [SD 5·59]), 13 503 (0·20%) were admitted to hospital, 1601 (0·02%) to an ICU, and 5479 (0·08%) died after a positive test for SARS-CoV-2. We found J-shaped associations between BMI and admission to hospital due to COVID-19 (adjusted hazard ratio [HR] per kg/m2 from the nadir at BMI of 23 kg/m2 of 1·05 [95% CI 1·05–1·05]) and death (1·04 [1·04–1·05]), and a linear association across the whole BMI range with ICU admission (1·10 [1·09–1·10]). We found a significant interaction between BMI and age and ethnicity, with higher HR per kg/m2 above BMI 23 kg/m2 for younger people (adjusted HR per kg/m2 above BMI 23 kg/m2 for hospital admission 1·09 [95% CI 1·08–1·10] in 20–39 years age group vs 80–100 years group 1·01 [1·00–1·02]) and Black people than White people (1·07 [1·06–1·08] vs 1·04 [1·04–1·05]). The risk of admission to hospital and ICU due to COVID-19 associated with unit increase in BMI was slightly lower in people with type 2 diabetes, hypertension, and cardiovascular disease than in those without these morbidities. Interpretation

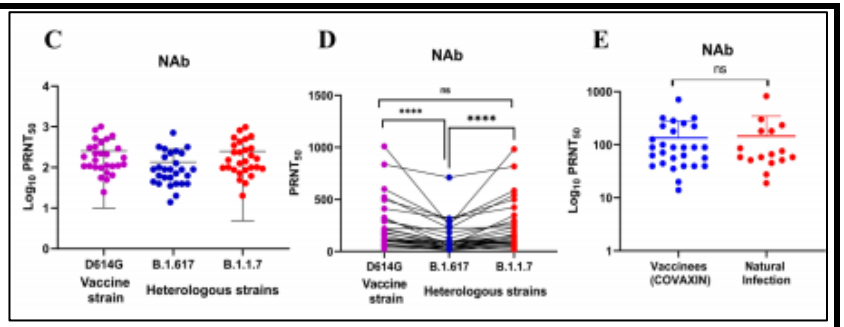
			At a BMI of more than 23 kg/m2, we found a linear increase in risk of severe COVID-19 leading to admission to hospital and death, and a linear increase in admission to an ICU across the whole BMI range, which is not attributable to excess risks of related diseases. The relative risk due to increasing BMI is particularly notable people younger than 40 years and of Black ethnicity. Funding NIHR Oxford Biomedical Research Centre. • View related content for this article Introduction Early in the COVID-19 pandemic, obesity was implicated as a clinically significant risk factor for severe disease.1, 2 Multiple studies have supported this theory, and several systematic reviews and meta-analyses on this subject have been published to date.3, 4, 5 However, this association might occur due to a special form of collider bias, termed index event bias.6 Almost all studies of this potential association to date have examined outcomes of patients admitted to hospital and compared progression to intensive care unit (ICU) or death between those with and without obesity. Because either obesity itself or the severity of COVID-19 disease could prompt admission to hospital, the association between these factors might be spurious. A large population-based study, which avoided the risk of collider bias, found that having a body-mass index (BMI) of 30 kg/m2 or higher was associated with a slightly greater risk of death from COVID-19 than a BMI of less than 30 kg/m2.7 However, this study did not examine the risk of unit increases in BMI across the population, of which a large proportion have a BMI lower than 30 kg/m2.

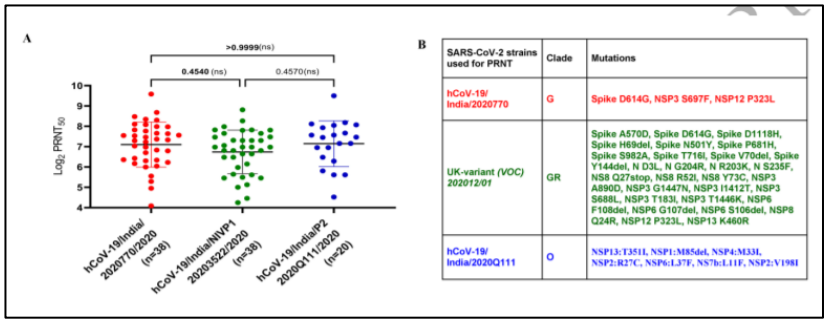
			Some studies have found that male gender, some ethnic groups, and people with type 2 diabetes and other chronic conditions might be at higher risk of adverse outcomes from severe SARS-CoV-2 infection.7, 8, 9, 10, 11 Whether these characteristics interact with the effect of excess weight is unclear. Here we report results of a large, representative community-based cohort study of 6·9 million people in England, UK, to thoroughly characterise the association between BMI and severe COVID-19 outcomes and to explore interactions with demographic characteristics and other known risk factors.


A
B
C
Hazard ratio (95% CI)
6·0
5·5
5·0
4·5
4·0
3·5
3·0
2·5
2·0
1·5
1·0
0·5
0
16 18 20 22 24 26 28 30 32 34 36 38 40 42 44
Latest BMI (kg/m²)

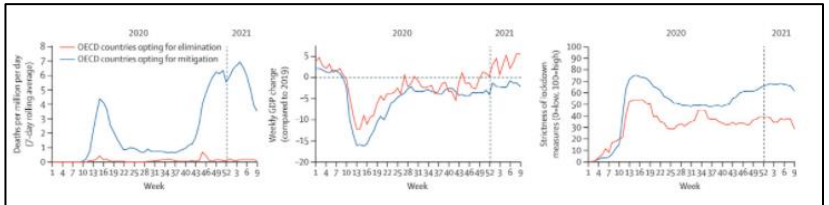
Paul Sax HIV and ID Observations – NEJM	The decision on the Johnson and Johnson COVID-19 vaccine surprised me, here's why	L'infettivologo Paul Sax discute la decisione di riprendere la vaccinazione con Janssen contro SARS-CoV-2 negli USA senza porre controindicazioni ad alcuna fascia di età : considerando i seppur rarissimi casi di trombosi grave e meccanismo verosimilmente analogo alla HIT che sono stati associati al vaccino, sarebbe stato ragionevole secondo lui controindicare il vaccino nelle donne di età inferiore a 50 anni.	The "pause" on the one-shot Johnson & Johnson (J&J) COVID-19 vaccine is over. Based on a further review of safety data that occurred on April 23, both the CDC and the FDA said the vaccine may resume here in the U.S., provided the label includes a warning about a serious, but rare, side effect — thrombosis with thrombocytopenia syndrome (TTS). I confess this decision surprised me. My hunch was that they would advise limiting the vaccine in the U.S. to women older than 50, with no age criterion for men. Instead, it's now available for all. This was no doubt a tricky decision, one reflected in the 10-4 vote of the Advisory Committee on Immunization Practices (ACIP).
Goldfarb JL et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMp2104527	Beyond the first dose – COVID19 vaccine follow-through and continued protective measures	In base ai risultati di questo sondaggio condotto negli USA, l'informazione in merito alla protezione conferita dai vaccini contro SARS-CoV-2 nella popolazione è frammentaria.	Perhaps the greatest barrier to the campaign's success is public hesitancy to be vaccinated, which is the focus of extensive research.1 Additional hurdles exist, however, including follow-through with a multidose vaccination regimen2 and adherence to public health guidance about continuing appropriate prophylactic measures. With these challenges in mind, we designed a national survey examining people's understandings about the timing of vaccine protection, willingness to continue to wear masks after being vaccinated, and the extent to which vaccinees are informed of Centers for Disease Control and Prevention (CDC) recommendations on postvaccination behaviors. Uncovering the public's beliefs about vaccination and postvaccination behaviors is crucial for informing

			effective education efforts. Our survey was administered to 1027 U.S. adults between February 11 and 15, 2021, using the National Opinion Research Center's nationally representative, probability-based AmeriSpeak panel. 
Yadav PD et al bioRXiv	Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees	Il siero di 28 individui vaccinati con il vaccino indiano Covaxin (BBV152 a virus inattivato, attualmente approvato in India e Messico) neutralizza la	The drastic rise in the number of cases in Maharashtra, India has created a matter of concern for public health experts. Twelve isolates of VUI lineage B.1.617 were propagated in VeroCCL81 cells and characterized. Convalescent sera of the COVID-19 cases and recipients of BBV152 (Covaxin) were able to neutralize VUI B.1.617.

https://www.biorxiv.org/content/10.1101/2021.04.23.441101v1		variante « indiana » di SARS-CoV-2(VUI B.1.617) anche se in modo meno efficace rispetto a quella più « antica » con mutazione D614G (su cui il vaccino è basato) e alla variante « inglese » B.1.1.7. Il siero di pazienti guariti – non è chiarito il momento dell'infezione - ha una attività comparabile al siero dei vaccinati sulla variante « indiana ».	
Sapkal GN et al Journal of Travel Medicine https://academic.oup.com/jtm/advance-article/doi/10.1093/jtm/taab051/6193609	Inactivated COVID-19 vaccine BBV152/COVAXIN effectively neutralizes recently emerged B 1.1.7 variant of SARS-CoV-2	Il siero di 38 pazienti vaccinati con il vaccino indiano Covaxin mostra attività comparabile contro ceppi più antichi di SARS-CoV-2 e contro due varianti contenenti la mutazione N501Y, tipica della variante « inglese » del virus.	All sera had equivalent NAb titers to hCoV-19/India/2020770 homologous strain and two heterologous strains including the characteristic N501Y substitution of the UK-variant; hCoV19/India/20203522 (UK strain) as well as hCoV-19/India/2020Q111 (Figure 1 A and B). The median ratio of 50% neutralisation of sera was 0.8 compared with hCoV-19/India/2020770 against mutant hCoV-19/India/20203522 (UK-variant), and 0.9 while compared with hCoV19/India/2020Q111. Non-parametric Kruskal-Wallis test for the comparison of the PRNT50 values from different groups revealed non-significant

			difference (p >0.05) 
See I et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2779731	US Case Reports of Cerebral Venous Sinus Thrombosis With Thrombocytopenia After Ad26.COV2.S Vaccination, March 2 to April 21, 2021	Descrizione di 12 casi di grave trombosi venosa cerebrale (su circa 7 milioni di dosi somministrate) a seguito di vaccinazione con Janssen contro SARS-CoV-2 negli USA: si tratta di donne caucasiche di età inferiore a 60 anni, nessuna delle quali esposta precedentemente a eparina, in parte con fattori di rischio protrombotici.	Importance Cerebral venous sinus thrombosis (CVST) with thrombocytopenia, a rare and serious condition, has been described in Europe following receipt of the ChAdOx1 nCoV-19 vaccine (Oxford/AstraZeneca), which uses a chimpanzee adenoviral vector. A mechanism similar to autoimmune heparin-induced thrombocytopenia (HIT) has been proposed. In the US, the Ad26.COV2.S COVID-19 vaccine (Janssen/Johnson & Johnson), which uses a human adenoviral vector, received Emergency Use Authorization (EUA) on February 27, 2021. By April 12, 2021, approximately 7 million Ad26.COV2.S vaccine doses had been given in the US, and 6 cases of CVST with thrombocytopenia had been identified among the recipients, resulting in a temporary national pause in vaccination with this product on April 13, 2021. Objective To describe reports of CVST with thrombocytopenia following Ad26.COV2.S vaccine receipt. Design, Setting, and Participants Case series of 12 US patients with CVST and thrombocytopenia following use of Ad26.COV2.S vaccine under EUA reported to the Vaccine Adverse Event Reporting System (VAERS) from March 2 to April 21, 2021 (with follow-up reported through April 21, 2021). Exposures Receipt of Ad26.COV2.S vaccine.

			Main Outcomes and Measures Clinical course, imaging, laboratory tests, and outcomes after CVST diagnosis obtained from VAERS reports, medical record review, and discussion with clinicians. Results Patients' ages ranged from 18 to younger than 60 years; all were White women, reported from 11 states. Seven patients had at least 1 CVST risk factor, including obesity (n = 6), hypothyroidism (n = 1), and oral contraceptive use (n = 1); none had documented prior heparin exposure. Time from Ad26.COV2.S vaccination to symptom onset ranged from 6 to 15 days. Eleven patients initially presented with headache; 1 patient initially presented with back pain and later developed headache. Of the 12 patients with CVST, 7 also had intracerebral hemorrhage; 8 had non-CVST thromboses. After diagnosis of CVST, 6 patients initially received heparin treatment. Platelet nadir ranged from 9 ×103/μL to 127 ×103/μL. All 11 patients tested for the heparin-platelet factor 4 HIT antibody by enzyme-linked immunosorbent assay (ELISA) screening had positive results. All patients were hospitalized (10 in an intensive care unit [ICU]). As of April 21, 2021, outcomes were death (n = 3), continued ICU care (n = 3), continued non-ICU hospitalization (n = 2), and discharged home (n = 4). Conclusions and Relevance The initial 12 US cases of CVST with thrombocytopenia after Ad26.COV2.S vaccination represent serious events. This case series may inform clinical guidance as Ad26.COV2.S vaccination resumes in the US as well as investigations into the potential relationship between Ad26.COV2.S vaccine and CVST with thrombocytopenia.
Oliu-Barton M et al The Lancet	SARS-CoV-2 elimination, not mitigation, creates best outcomes for health, the economy, and civil liberties	Le mezze misure, ovvero la « mitigazione » della pandemia da SARS-CoV-2, non sarebbero vantaggiose nemmeno in termini	We compared COVID-19 deaths, gross domestic product (GDP) growth, and strictness of lockdown measures during the first 12 months of the pandemic for Organisation for Economic Co-operation and Development (OECD) countries that aim for

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00978-8/fulltext		economici rispetto a misure più radicali volte a eliminare la circolazione del virus da un Paese secondo questa analisi che confronta l'esito dell'applicazione dei due modelli in diverse nazioni del mondo.	elimination or mitigation (figure).2, 3, 4 Although all indicators favour elimination, our analysis does not prove a causal connection between varying pandemic response strategies and the different outcome measures. COVID-19 deaths per 1 million population in OECD countries that opted for elimination (Australia, Iceland, Japan, New Zealand, and South Korea) have been about 25 times lower than in other OECD countries that favoured mitigation (figure). Mortality is a proxy for a country's broader disease burden. For example, decision makers should also consider the increasing evidence of long-term morbidities after SARS-CoV-2 infection.  Figure COVID-19 deaths, GDP growth, and strictness of lockdown measures for OECD countries choosing SARS-CoV-2 elimination versus mitigation
Stoeklé H et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00795-9/fulltext?dgcid=raven_jbs_etoc_email	The COVID-19 pandemic: a time for ethical reflection?	L'emergenza è un momento che si presta a prevaricazione dei diritti e privazione della libertà nel nome di un interesse collettivo superiore : questa breve riflessione si concentra sulla necessità di tenere in considerazione le minoranze, con particolare riferimento alla imposizione di quarantena in assenza di condizioni sanitarie	It is important to remember that ethics are not morals and do not apply standards or values; ethics address questions about the feasibility and desirability of actions to benefit society.3 Seemingly in Germany, and probably also in other countries, the interests of migrants were not sufficiently considered during the development of these guidelines. Moving forward, governments and administrative agencies need to think about what will happen after the COVID-19 pandemic, which is far from over, to prepare for any possible pandemics in the future.

		adeguate in alcuni centri per migranti in Germania.	
Mathur R et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00634-6/fulltext	Ethnic differences in SARS-CoV-2 infection and COVID-19-related hospitalisation, intensive care unit admission, and death in 17 million adults in England: an observational cohort study using the OpenSAFELY platform	Studio osservazionale condotto nel Regno Unito durante le due « ondate » di infezioni da SARS-CoV-2 in merito a diagnosi, ospedalizzazione e cure intensive in persone di differenti etnie : rispetto ai caucasici, le altre etnie avevano un maggiore rischio di avere un test positivo e di essere ospedalizzate per COVID-19, maggiormente nella prima « ondata » rispetto alla seconda.	Background : COVID-19 has disproportionately affected minority ethnic populations in the UK. Our aim was to quantify ethnic differences in SARS-CoV-2 infection and COVID-19 outcomes during the first and second waves of the COVID-19 pandemic in England. Methods : We conducted an observational cohort study of adults (aged ≥18 years) registered with primary care practices in England for whom electronic health records were available through the OpenSAFELY platform, and who had at least 1 year of continuous registration at the start of each study period (Feb 1 to Aug 3, 2020 [wave 1], and Sept 1 to Dec 31, 2020 [wave 2]). Individual-level primary care data were linked to data from other sources on the outcomes of interest: SARS-CoV-2 testing and positive test results and COVID-19-related hospital admissions, intensive care unit (ICU) admissions, and death. The exposure was self-reported ethnicity as captured on the primary care record, grouped into five high-level census categories (White, South Asian, Black, other, and mixed) and 16 subcategories across these five categories, as well as an unknown ethnicity category. We used multivariable Cox regression to examine ethnic differences in the outcomes of interest. Models were adjusted for age, sex, deprivation, clinical factors and comorbidities, and household size, with stratification by geographical region. Findings : Of 17 288 532 adults included in the study (excluding care home residents), 10 877 978 (62·9%) were White, 1 025 319 (5·9%) were South Asian, 340 912 (2·0%) were Black, 170 484 (1·0%) were of mixed ethnicity, 320 788 (1·9%) were of other ethnicity, and

			4 553 051 (26·3%) were of unknown ethnicity. In wave 1, the likelihood of being tested for SARS-CoV-2 infection was slightly higher in the South Asian group (adjusted hazard ratio 1·08 [95% CI 1·07–1·09]), Black group (1·08 [1·06–1·09]), and mixed ethnicity group (1·04 [1·02–1·05]) and was decreased in the other ethnicity group (0·77 [0·76–0·78]) relative to the White group. The risk of testing positive for SARS-CoV-2 infection was higher in the South Asian group (1·99 [1·94–2·04]), Black group (1·69 [1·62–1·77]), mixed ethnicity group (1·49 [1·39–1·59]), and other ethnicity group (1·20 [1·14–1·28]). Compared with the White group, the four remaining high-level ethnic groups had an increased risk of COVID-19-related hospitalisation (South Asian group 1·48 [1·41–1·55], Black group 1·78 [1·67–1·90], mixed ethnicity group 1·63 [1·45–1·83], other ethnicity group 1·54 [1·41–1·69]), COVID-19-related ICU admission (2·18 [1·92–2·48], 3·12 [2·65–3·67], 2·96 [2·26–3·87], 3·18 [2·58–3·93]), and death (1·26 [1·15–1·37], 1·51 [1·31–1·71], 1·41 [1·11–1·81], 1·22 [1·00–1·48]). In wave 2, the risks of hospitalisation, ICU admission, and death relative to the White group were increased in the South Asian group but attenuated for the Black group compared with these risks in wave 1. Disaggregation into 16 ethnicity groups showed important heterogeneity within the five broader categories. Interpretation : Some minority ethnic populations in England have excess risks of testing positive for SARS-CoV-2 and of adverse COVID-19 outcomes compared with the White population, even after accounting for differences in sociodemographic, clinical, and household characteristics. Causes are likely to be multifactorial, and delineating the exact mechanisms is crucial. Tackling ethnic inequalities will require action across many fronts, including

			reducing structural inequalities, addressing barriers to equitable care, and improving uptake of testing and vaccination.
RECOVERY Collaborative Group The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext	Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial	Trial clinico su oltre 4000 adulti ricoverati per COVID-19 nel Regno Unito, di cui 82% trattati con steroidi, randomizzati fra tocilizumab (da 400 a 900 mg EV una tantum in base al peso, con possibilità di seconda dose a giudizio dei curanti) e standard of care : la terapia con tocilizumab è associata a maggiore probabilità di essere dimessi dall'ospedale a 28 giorni e, nei pazienti non in ventilazione meccanica, a minore probabilità di outcome avverso composito definito come ventilazione meccanica o morte.	Background : In this study, we aimed to evaluate the effects of tocilizumab in adult patients admitted to hospital with COVID-19 with both hypoxia and systemic 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 ≥75 mg/L) were eligible for random assignment in a 1:1 ratio to usual standard of care alone versus usual standard of care plus tocilizumab at a dose of 400 mg–800 mg (depending on weight) given intravenously. A second dose could be given 12–24 h 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 April 23, 2020, and Jan 24, 2021, 4116 adults of 21 550 patients enrolled into the RECOVERY trial were included in the assessment of tocilizumab, including 3385 (82%) patients receiving systemic corticosteroids. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (rate ratio 0·85; 95% CI 0·76–0·94; p=0·0028). Consistent results were seen in all prespecified subgroups of patients, including those receiving systemic corticosteroids. Patients allocated to tocilizumab were more likely to be discharged from hospital within 28 days (57% vs

			50%; rate ratio 1·22; 1·12–1·33; 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 (35% vs 42%; risk ratio 0·84; 95% CI 0·77–0·92; p<0·0001). 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 amount of respiratory support and were additional to the benefits of systemic corticosteroids.
Tenforde MW et al Morbidity and Mortality Weekly Report https://www.cdc.gov/mmwr/volumes/70/wr/mm7018e1.htm?s_cid=mm7018e1_w	Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years — United States, January–March 2021	Effetto di almeno una dose di vaccino a mRNA contro SARS-CoV-2 in termini di ricoveri per COVID-19 nella popolazione USA di età superiore a 65 anni.	What is already known about this topic? Clinical trials suggest high efficacy for COVID-19 vaccines, but evaluation of vaccine effectiveness against severe outcomes in real-world settings and in populations at high risk, including older adults, is needed. What is added by this report? In a multistate network of U.S. hospitals during January–March 2021, receipt of Pfizer-BioNTech or Moderna COVID-19 vaccines was 94% effective against COVID-19 hospitalization among fully vaccinated adults and 64% effective among partially vaccinated adults aged ≥65 years. What are the implications for public health practice? SARS-CoV-2 vaccines significantly reduce the risk for COVID-19–associated hospitalization in older adults and, in turn, might lead to commensurate reductions in post-COVID conditions and deaths.

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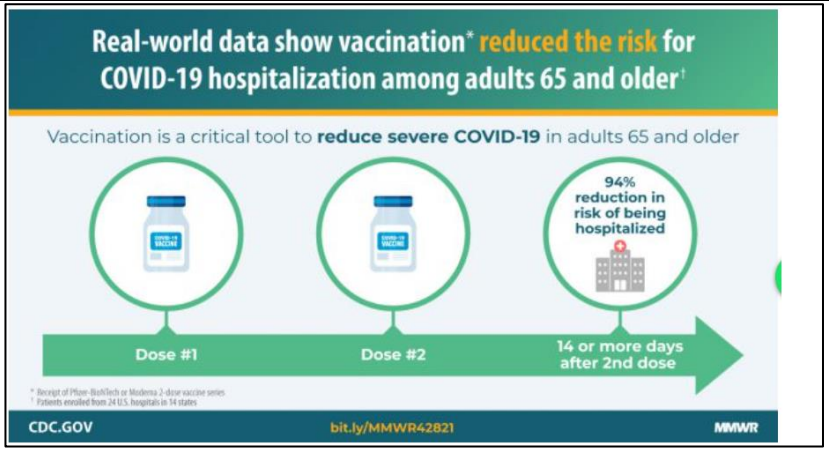
<td> 
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<td>Koskien A et al

JAMA

https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2779393</td>
<td>Complications of COVID-19 Nasopharyngeal Swab Test</td>
<td>Le complicanze dell’esecuzione di un tampone nasofaringeo per la ricerca di SARS-CoV-2 sono rarissime : in questa case series su 7 mesi di osservazione vengono riportati 4 casi di epistassi grave (1 complicato da infezione sistemica da S.aureus) e 4 di rottura del tampone nasale (1 paziente ha ingoiato l’estremità rotta, senza ulteriori conseguenze).</td>
<td>During the COVID-19 pandemic, numerous swab samples have been taken for SARS-CoV-2 reverse transcriptase–polymerase chain reaction (RT-PCR) testing. Nasopharyngeal sampling is considered safe, despite adjacent vital structures (eg, orbit, skull base, rich vasculature). However, single case reports and clinical observations indicate the possibility of severe complications. This case series investigated the frequency and type of SARS-CoV-2 nasopharyngeal test complications.

Table. Treatment and Sequelae of 8 Patients Treated for Complications After SARS-CoV-2 Nasopharyngeal Swab Test

<table>
<tr><th>Clinical event</th><th>Specific occurrence</th><th>Measure of occurrence</th><th></th></tr>
<tr><td>Predisposing condition</td><td></td><td>Broken swab (n = 4)</td><td>Epistaxis (n = 4)</td></tr>
<tr><td>Previous rhinosurgery</td><td>Septoplasty</td><td>1</td><td>1</td></tr>
<tr><td>Rhinologic disorder</td><td>Nasal congestion</td><td>1</td><td>1</td></tr>
<tr><td></td><td>Septal deviation</td><td>1</td><td>1</td></tr>
<tr><td>Hematologic disorder</td><td>Idiopathic thrombocytopenic purpura</td><td>0</td><td>1</td></tr>
<tr><td>Cardiovascular disease</td><td>Coronary heart disease</td><td>1</td><td>1</td></tr>
<tr><td>Medication</td><td>Anticoagulant</td><td>1</td><td>1</td></tr>
<tr><td>Other</td><td>Pregnancy</td><td>0</td><td>1</td></tr>
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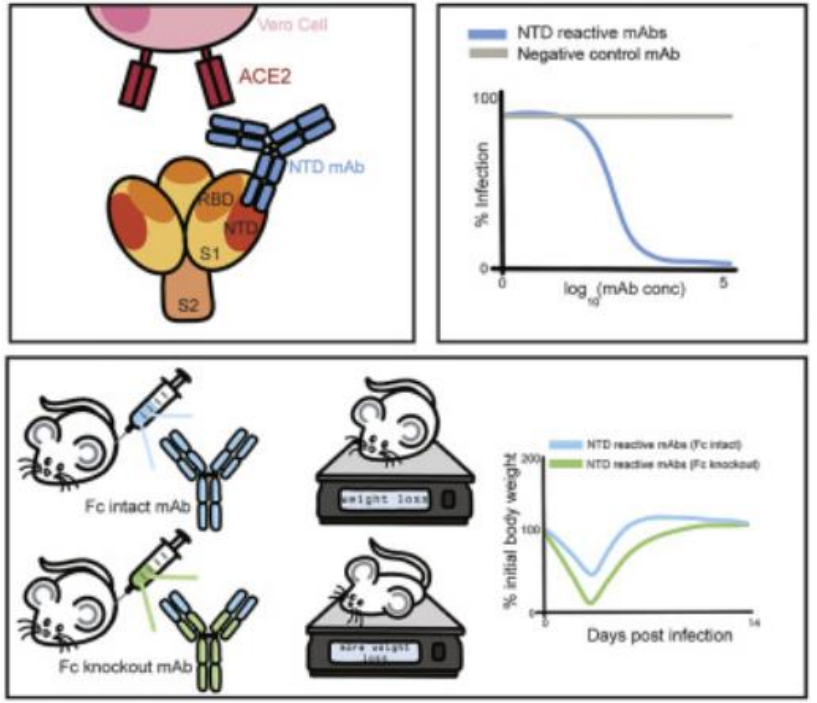
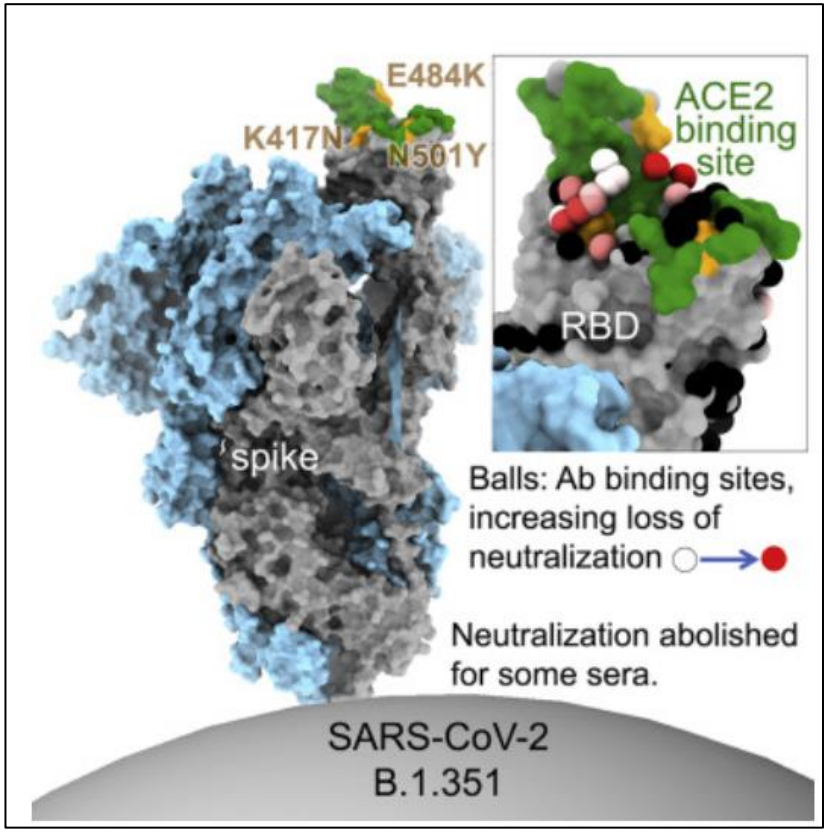
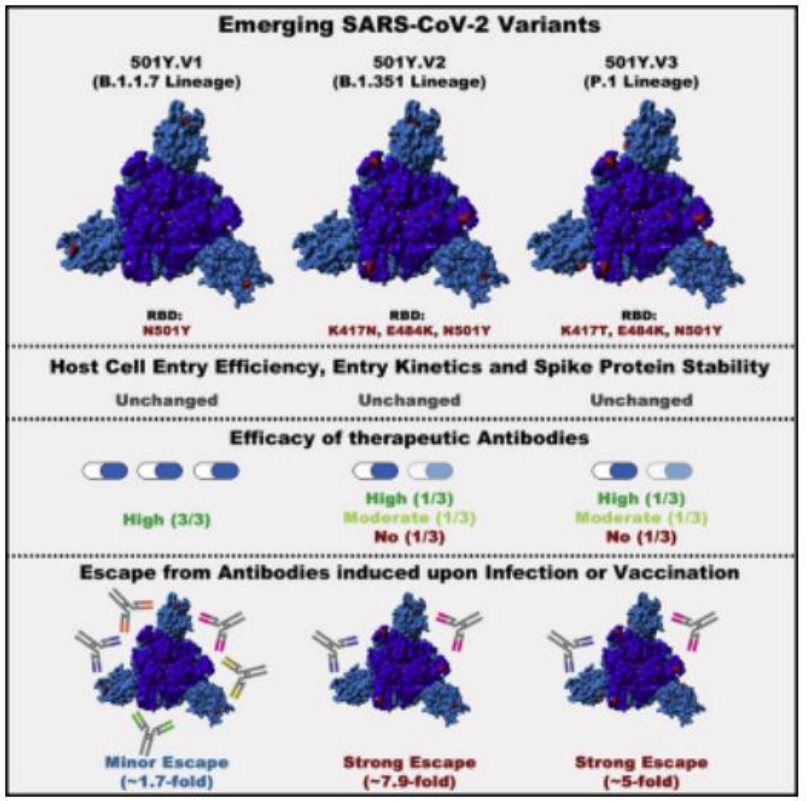
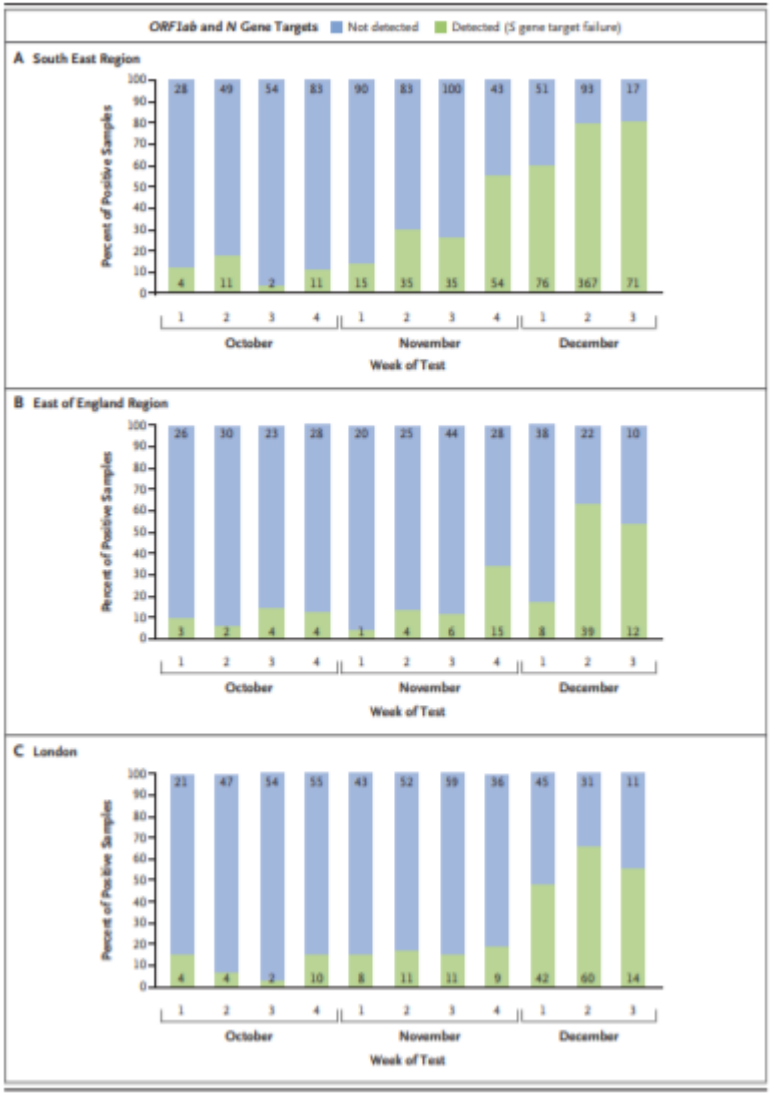
Gill PJ et al JAMA https://jamanetwork.com/journals/jama/article-abstract/2779208	Reasons for Admissions to US Children's Hospitals During the COVID-19 Pandemic	La riduzione dei ricoveri negli ospedali pediatrici osservata nel 2020 ha molte spiegazioni, fra cui la minore circolazione di alcune infezioni a seguito dell'introduzione delle misure di prevenzione della diffusione SARS-CoV-2 ma anche la reticenza della popolazione ad accedere in ospedale durante la pandemia.	Measures to mitigate the COVID-19 pandemic affected children's access to health services and their physical and mental health. Reductions in hospitalizations for children occurred in 2020 compared with prior years.1 Little is known about the reasons for the decline and whether it varied by patient characteristics. Children's hospitals provide inpatient care for the most diverse, high-severity, and complex illnesses2 and are located in large urban areas, which were particularly affected by COVID-19 outbreaks. Centralization of pediatric inpatient care into children's hospitals was urged to free beds in non–children's hospitals for adult COVID-19 patients. We compared hospitalizations in US children's hospitals before and during the pandemic.
Suryadevara N et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00357-3	Neutralizing and protective human monoclonal antibodies recognizing the N-terminal domain of the SARS-CoV-2 spike protein	Sviluppo di due anticorpi monoclonali diretti contro SARS-CoV-2 e in particolare in grado di impedire l'infezione di nuove cellule, candidati a un possibile uso in profilassi.	Most human monoclonal antibodies (mAbs) neutralizing SARS-CoV-2 recognize the spike (S) protein receptor-binding domain and block virus interactions with the cellular receptor angiotensin-converting enzyme. We describe a panel of human mAbs binding to diverse epitopes on the N-terminal domain (NTD) of S protein from SARS-CoV-2 convalescent donors and found a minority of these possessed neutralizing activity. Two mAbs (COV2-2676 and COV2-2489) inhibited infection of authentic SARS-CoV-2 and recombinant VSV/SARS-CoV-2 viruses. We mapped their binding epitopes by alanine-scanning mutagenesis and selection of functional SARS-CoV-2 S neutralization escape variants. Mechanistic studies showed that these antibodies neutralize in part by inhibiting a post-attachment step in the infection cycle. COV2-2676 and COV2-2489 offered protection either as prophylaxis or therapy, and Fc effector functions were required for optimal protection. Thus, natural infection induces a subset of potent NTD-specific mAbs that leverage neutralizing and Fc-mediated activities to protect against SARS-CoV-2 infection using multiple functional attributes.

			
Zhou D et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00226-9	Evidence of escape of SARS-CoV-2 variant B.1.351 from natural and vaccine-induced sera	Le mutazioni tipiche della variante sudafricana di SARS-CoV-2 conferiscono la capacità di escape dall'attività degli anticorpi monoclonali in uso e una ridotta neutralizzazione da parte del siero di soggetti guariti o vaccinati con i vaccini in uso.	The race to produce vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began when the first sequence was published, and this forms the basis for vaccines currently deployed globally. Independent lineages of SARS-CoV-2 have recently been reported: UK, B.1.1.7; South Africa, B.1.351; and Brazil, P.1. These variants have multiple changes in the immunodominant spike protein that facilitates viral cell entry via the angiotensin-converting enzyme-2 (ACE2) receptor. Mutations in the receptor recognition site on the spike are of great concern for their potential for immune escape. Here, we describe a structure-function analysis of B.1.351 using a large cohort of convalescent and vaccinee serum samples. The receptor-binding domain mutations provide tighter ACE2 binding and widespread escape from

			monoclonal antibody neutralization largely driven by E484K, although K417N and N501Y act together against some important antibody classes. In a number of cases, it would appear that convalescent and some vaccine serum offers limited protection against this variant. 
Hoffmann M et al Cell	SARS-CoV-2 variants B.1.351 and P.1 escape from neutralizing antibodies	Le nanoparticelle, promessa della terapia contro SARS-CoV-2, appaiono più efficaci degli anticorpi monoclonali e del siero di soggetti guariti	The global spread of SARS-CoV-2/COVID-19 is devastating health systems and economies worldwide. Recombinant or vaccine-induced neutralizing antibodies are used to combat the COVID-19 pandemic. However, the recently emerged SARS-CoV-2 variants B.1.1.7 (UK), B.1.351 (South Africa), and P.1 (Brazil) harbor

https://www.cell.com/cell/fulltext/S0092-8674(21)00367-6		o vaccinati con vaccino Pfizer nell'impedire in vitro l'ingresso di SARS-COV-2, varianti sudafricana e brasiliana nelle cellule.	mutations in the viral spike (S) protein that may alter virus-host cell interactions and confer resistance to inhibitors and antibodies. Here, using pseudoparticles, we show that entry of all variants into human cells is susceptible to blockade by the entry inhibitors soluble ACE2, Camostat, EK-1, and EK-1-C4. In contrast, entry of the B.1.351 and P.1 variant was partially (Casirivimab) or fully (Bamlanivimab) resistant to antibodies used for COVID-19 treatment. Moreover, entry of these variants was less efficiently inhibited by plasma from convalescent COVID-19 patients and sera from BNT162b2-vaccinated individuals. These results suggest that SARS-CoV-2 may escape neutralizing antibody responses, which has important implications for efforts to contain the pandemic.

			
Krutikov M et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2035906?query=featured_home	Spread of a Variant SARS-CoV-2 in Long-Term Care Facilities in England	Fra ottobre e dicembre 2020, la variante inglese di SARS-CoV-2 è divenuta prevalente rispetto a tutte le altre in tutte le regioni del Regno Unito, come si osserva in questo studio condotto sui residenti in strutture di lungodegenza.	We investigated the proportion of SARS-CoV-2 infections caused by the variant in staff and residents of long-term care facilities in England between October 5 and December 17, 2020. Participants were tested for SARS-CoV-2 by reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay of nasopharyngeal swabs collected weekly from staff or monthly from residents.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Krass P et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779380	US Pediatric Emergency Department Visits for Mental Health Conditions During the COVID-19 Pandemic	Studio sugli accessi in pronto soccorso pediatrico per problemi di salute mentale durante la pandemia di COVID-19 a confronto con il passato : nell'ambito di una riduzione complessiva degli accessi, si osserva un incremento relativo di quelli per problemi di salute mentale.	The mental health (MH) of youth in the United States has been negatively impacted by the COVID-19 global pandemic. Containment measures, including restrictions and school closures, have been associated with the development and exacerbation of pediatric MH disorders. Pediatric emergency departments (EDs) have served an increasing role in assessing and triaging children with MH conditions over the past decade, and the COVID-19 pandemic has changed the system of pediatric MH care delivery. Therefore, we conducted this cross-sectional study to describe the changes in the demographic characteristics and clinical outcomes of pediatric ED visits for MH conditions during the COVID-19 pandemic. **Figure. Monthly Pediatric Emergency Department (ED) Visits and Admissions for Mental Health (MH) Conditions, 2018-2020**