RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 19.04 – 25.04.2021 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Agenzia Italiana del Farmaco Ufficio Gestione dei Segnali Ufficio di Farmacovigilanza Area Vigilanza Post Marketing https://www.aifa.gov.it/documents/20142/1315190/Rapporto_sorveglianza_vaccini_COVID-19_3.pdf	Rapporto sulla Sorveglianza dei vaccini COVID-19	Terzo rapporto AIFA sugli effetti avversi riportati a seguito della somministrazione dei 3 vaccini contro SARS-CoV-2 autorizzati e utilizzati in Italia (periodo 27/12/2020 – 26/03/2021)	Al 26 marzo 2021 sono state inserite 510 segnalazioni ogni 100.000 dosi somministrate, indipendentemente dal vaccino e dalla dose somministrata Le segnalazioni riguardano soprattutto il vaccino Pfizer BioNTech Comirnaty (81%), che è stato il più utilizzato (77% delle dosi somministrate), e solo in minor misura il vaccino Vaxzevria (ex-COVID-19 Vaccine AstraZeneca; 17%) e il vaccino Moderna (2%).

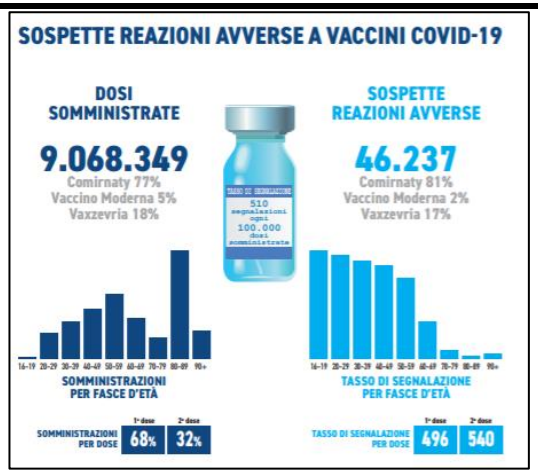
			
Rosenke K et al Nature https://www.nature.com/articles/s41467-021-22580-8	Orally delivered MK-4482 inhibits SARS-CoV-2 replication in the Syrian hamster model	L'analogo nucleosidico molnupiravir (MK-4482) inibisce la replicazione di SARS-CoV-2 dopo somministrazione orale nel criceto, ma in una fascia temporale molto ristretta di 12 ore pre/post acquisizione dell'infezione.	The COVID-19 pandemic progresses unabated in many regions of the world. An effective antiviral against SARS-CoV-2 that could be administered orally for use following high-risk exposure would be of substantial benefit in controlling the COVID-19 pandemic. Herein, we show that MK-4482, an orally administered nucleoside analog, inhibits SARS-CoV-2 replication in the Syrian hamster model. The inhibitory effect of MK-4482 on SARS-CoV-2 replication is observed in animals when the drug is administered either beginning 12 h before or 12 h following infection in a high-risk exposure model. These data support the potential utility of MK-4482 to control SARS-CoV-2 infection in humans following high-risk exposure as well as for treatment of COVID-19 patients.

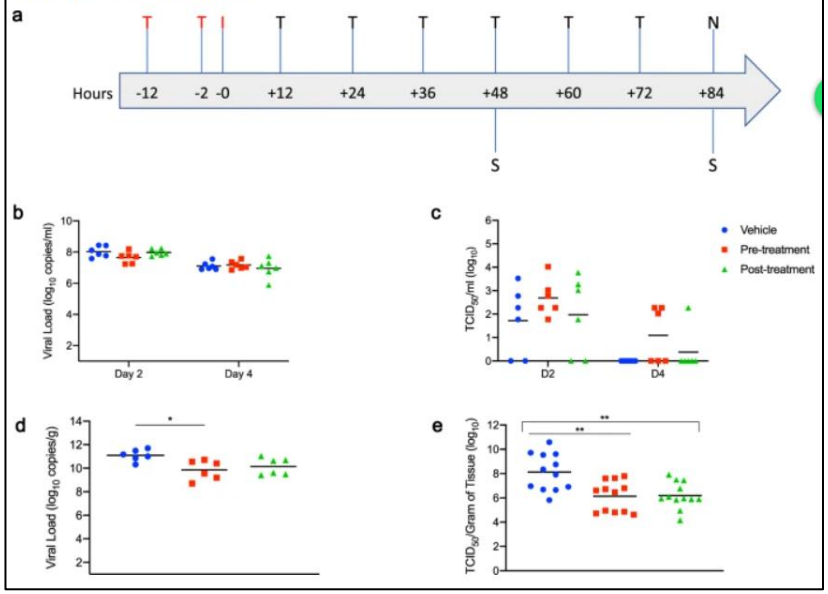
			Fig. 2: Syrian hamster model—study design, viral shedding, viral load, infectious titers, and viral antigen. 
Sickbert-Bennett EE et al JAMA https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2778913	Fitted Filtration Efficiency of Double Masking During the COVID-19 Pandemic	Usare una doppia mascherina (chirurgica + filtrante) migliora l'efficienza di filtro, non perché si aggiunga uno strato ma perché migliora l'aderenza dei bordi della mascherina al viso. Infatti la chirurgica andrebbe sotto.	Although global vaccination efforts against SARS-CoV-2 are underway, the public is urged to continue using face masks as a primary intervention to control transmission. Recently, US public health officials have also encouraged doubling masks as a strategy to counter elevated transmission associated with infectious SARS-CoV-2 variants. US Centers for Disease Control and Prevention investigators reported that doubling masks increased effectiveness, but their assessment was limited in type and combinations of masks tested, as well as by the use of head forms rather than humans. To address these limitations, this study compared the fitted filtration efficiency (FFE) of commonly available masks worn singly, doubled, or in combinations.

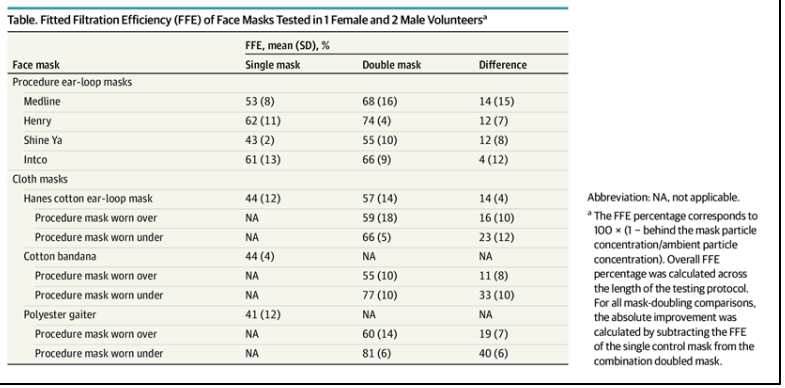
			Table. Fitted Filtration Efficiency (FFE) of Face Masks Tested in 1 Female and 2 Male Volunteers[a] 
Ghai RR et al Emerging Infectious Diseases https://wwwnc.cdc.gov/eid/article/27/4/20-3945_article	Animal Reservoirs and Hosts for Emerging Alphacoronaviruses and Betacoronaviruses	Revisione delle caratteristiche, le origini e i reservoir dei Coronavirus conosciuti prima di SARS-CoV-2.	The ongoing global pandemic caused by coronavirus disease has once again demonstrated the role of the family Coronaviridae in causing human disease outbreaks. Because severe acute respiratory syndrome coronavirus 2 was first detected in December 2019, information on its tropism, host range, and clinical manifestations in animals is limited. Given the limited information, data from other coronaviruses might be useful for informing scientific inquiry, risk assessment, and decision-making. We reviewed endemic and emerging infections of alphacoronaviruses and betacoronaviruses in wildlife, livestock, and companion animals and provide information on the receptor use, known hosts, and clinical signs associated with each host for 15 coronaviruses detected in humans and animals. This information can be used to guide implementation of a One Health approach that involves human health, animal health, environmental, and other relevant partners in developing strategies for preparedness, response, and control to current and future coronavirus disease threats.

Table. Fitted Filtration Efficiency (FFE) of Face Masks Tested in 1 Female and 2 Male Volunteers[a]

Face mask	FFE, mean (SD), %		
	Single mask	Double mask	Difference
Procedure ear-loop masks			
Medline	53 (8)	68 (16)	14 (15)
Henry	62 (11)	74 (4)	12 (7)
Shine Ya	43 (2)	55 (10)	12 (8)
Intco	61 (13)	66 (9)	4 (12)
Cloth masks			
Hanes cotton ear-loop mask	44 (12)	57 (14)	14 (4)
Procedure mask worn over	NA	59 (18)	16 (10)
Procedure mask worn under	NA	66 (5)	23 (12)
Cotton bandana	44 (4)	NA	NA
Procedure mask worn over	NA	55 (10)	11 (8)
Procedure mask worn under	NA	77 (10)	33 (10)
Polyester gaiter	41 (12)	NA	NA
Procedure mask worn over	NA	60 (14)	19 (7)
Procedure mask worn under	NA	81 (6)	40 (6)

Abbreviation: NA, not applicable.

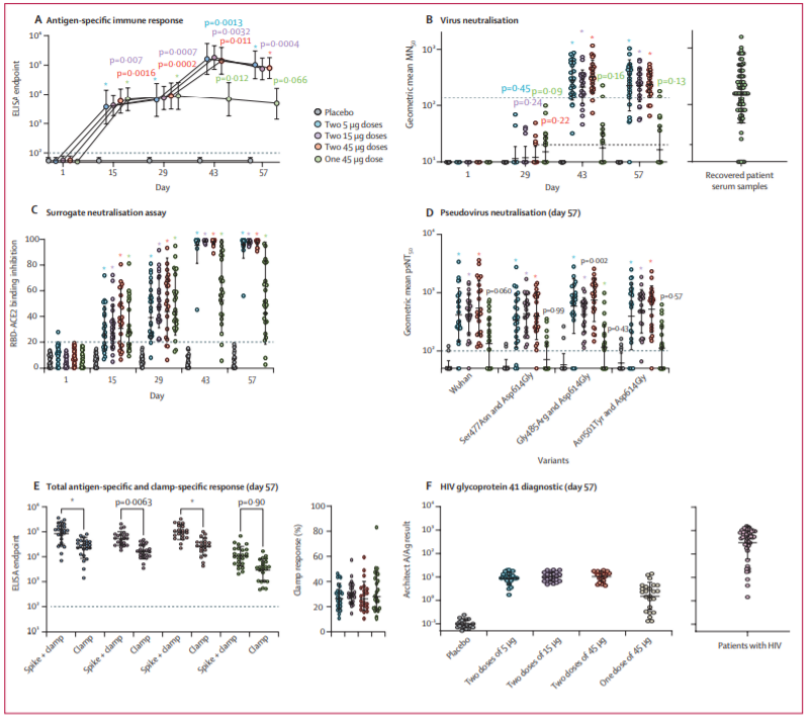
[a] The FFE percentage corresponds to 100 × (1 − behind the mask particle concentration/ambient particle concentration). Overall FFE percentage was calculated across the length of the testing protocol. For all mask-doubling comparisons, the absolute improvement was calculated by subtracting the FFE of the single control mask from the combination doubled mask.

Moulson N et al Circulation https://www.ahajournals.org/doi/pdf/10.1161/CIRCULATIONAHA.121.054824	SARS-CoV-2 Cardiac Involvement in Young Competitive Athletes	Studio osservazionale su una coorte di 3018 giovani atleti con storia di COVID-19 seguiti per valutare la prevalenza di sequele cardiache : bassa (anomalie ECG 0.7%, elevazione delle troponine 0.9%, alterazioni ecocardiografiche 0.9%) e nessun evento avverso cardiaco registrato, perlomeno a breve termine. Un follow-up cardiologico approfondito negli asintomatici senza fattori di rischio non appare indicato.	Background: Cardiac involvement among hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is common and associated with adverse outcomes. The objective of this study was to determine the prevalence and clinical implications of SARS-CoV-2 cardiac involvement in young competitive athletes. Methods: In this prospective multicenter observational cohort study with data from 42 colleges/universities, we assessed the revalence, clinical characteristics, and outcomes of SARS-CoV-2 cardiac involvement among collegiate athletes in the United States. Data were collected from September 1, 2020 to December 31, 2020. The primary outcome was the prevalence of definite, probable, or possible SARS-CoV-2 cardiac involvement based on imaging definitions adapted from the Updated Lake Louise Criteria. Secondary outcomes included the diagnostic yield of cardiac testing, predictors for cardiac involvement, and adverse cardiovascular events or hospitalizations. Results: Among 19,378 athletes tested for SARS-CoV-2 infection, 3018 (mean age 20 years [SD,1 year]; 32% female) tested positive and underwent cardiac evaluation. A total of 2820 athletes underwent at least one element of cardiac 'triad' testing [12-lead electrocardiography (ECG), troponin, and/or transthoracic echocardiography(TTE)] followed by cardiac magnetic resonance (CMR) if clinically indicated. In contrast, primary screening CMR was performed in 198 athletes. Abnormal findings suggestive of SARS-CoV-2 cardiac involvement were detected by ECG (21/2999,0.7%), cardiac troponin (24/2719,0.9%), and TTE (24/2556,0.9%). Definite, probable, or possible SARS-COV-2 cardiac involvement was identified in 21/3018 (0.7%) athletes, including 15/2820 (0.5%) who underwent clinically indicated CMR (n=119) and 6/198 (3.0%) who underwent primary screening CMR. Accordingly, the diagnostic yield

			of CMR for SARS-COV-2 cardiac involvement was 4.2 times higher for a clinically indicated CMR (15/119,12.6%) versus a primary screening CMR (6/198,3.0%). After adjustment for race and sex, predictors of SARS-CoV-2 cardiac involvement included cardiopulmonary symptoms (OR:3.1,95% CI:1.2,7.7) or at least one abnormal triad test (OR:37.4,95% CI:13.3,105.3). Five (0.2%) athletes required hospitalization for non-cardiac complications of SARS-CoV-2. During clinical surveillance (median follow-up 113 days [IQR=90,146]), there was one (0.03%) adverse cardiac event likely unrelated to SARS-CoV-2 infection. Conclusions: SARS-CoV-2 infection among young competitive athletes is associated with a low prevalence of cardiac involvement and a low risk of clinical events in short term follow-up.
Chappell KJ et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00200-0/fulltext?dgcid=hubspot_email_newsletter_lancetcovid21&utm_campaign=lancetcovid21&utm_medium=email&_hsmi=122384162&_hsenc=p2ANqtz--YMFvj4FssEMg8u8shKMrd_sjyroY3YZEaJen8FalKIcdP2SOw1KGfzHX2Sny8kAg9qiox5P4yGaJpRsJPRdfBF	Safety and immunogenicity of an MF59-adjuvanted spike glycoprotein-clamp vaccine for SARS-CoV-2: a randomised, double-blind, placebo-controlled, phase 1 trial	Trial di fase I su un vaccino a subunità contro SARS-CoV-2, che stimola una risposta anticorpale adeguata dopo tutti gli schemi di dosaggio utilizzati. Si osserva tuttavia una interferenza con alcuni test antigenici per HIV a causa della presenza della sequenza di gp41 nel vaccino.	Background Given the scale of the ongoing COVID-19 pandemic, the development of vaccines based on different platforms is essential, particularly in light of emerging viral variants, the absence of information on vaccine-induced immune durability, and potential paediatric use. We aimed to assess the safety and immunogenicity of an MF59-adjuvanted subunit vaccine for COVID-19 based on recombinant SARS-CoV-2 spike glycoprotein stabilised in a pre-fusion conformation by a novel molecular clamp (spike glycoprotein-clamp [sclamp]). Methods We did a phase 1, double-blind, placebo-controlled, block-randomised trial of the sclamp subunit vaccine in a single clinical trial site in Brisbane, QLD, Australia. Healthy adults (aged ≥18 to ≤55 years) who had tested negative for SARS-CoV-2, reported no close contact with anyone with active or previous SARS-CoV-2 infection, and tested negative for pre-existing SARS-CoV-2 immunity were

TQ39ZkfORjyVwyF8r64sJyB2I0&utm_content=122384162&utm_source=hs_email			included. Participants were randomly assigned to one of five treatment groups and received two doses via intramuscular injection 28 days apart of either placebo, sclamp vaccine at 5 µg, 15 µg, or 45 µg, or one dose of sclamp vaccine at 45 µg followed by placebo. Participants and study personnel, except the dose administration personnel, were masked to treatment. The primary safety endpoints included solicited local and systemic adverse events in the 7 days after each dose and unsolicited adverse events up to 12 months after dosing. Here, data are reported up until day 57. Primary immunogenicity endpoints were antigen-specific IgG ELISA and SARS-CoV-2 microneutralisation assays assessed at 28 days after each dose. The study is ongoing and registered with ClinicalTrials.gov, NCT04495933. Findings Between June 23, 2020, and Aug 17, 2020, of 314 healthy volunteers screened, 120 were randomly assigned (n=24 per group), and 114 (95%) completed the study up to day 57 (mean age 32·5 years [SD 10·4], 65 [54%] male, 55 [46%] female). Severe solicited reactions were infrequent and occurred at similar rates in participants receiving placebo (two [8%] of 24) and the SARS-CoV-2 sclamp vaccine at any dose (three [3%] of 96). Both solicited reactions and unsolicited adverse events occurred at a similar frequency in participants receiving placebo and the SARS-CoV-2 sclamp vaccine. Solicited reactions occurred in 19 (79%) of 24 participants receiving placebo and 86 (90%) of 96 receiving the SARS-CoV-2 sclamp vaccine at any dose. Unsolicited adverse events occurred in seven (29%) of 24 participants receiving placebo and 35 (36%) of 96 participants receiving the SARS-CoV-2 sclamp vaccine at any dose. Vaccination with SARS-CoV-2 sclamp elicited a similar antigen-specific response irrespective of dose: 4 weeks after the

			initial dose (day 29) with 5 μg dose (geometric mean titre [GMT] 6400, 95% CI 3683–11 122), with 15 μg dose (7492, 4959–11 319), and the two 45 μg dose cohorts (8770, 5526–13 920 in the two-dose 45 μg cohort; 8793, 5570–13 881 in the single-dose 45 μg cohort); 4 weeks after the second dose (day 57) with two 5 μg doses (102 400, 64 857–161 676), with two 15 μg doses (74 725, 51 300–108 847), with two 45 μg doses (79 586, 55 430–114 268), only a single 45 μg dose (4795, 2858–8043). At day 57, 67 (99%) of 68 participants who received two doses of sclamp vaccine at any concentration produced a neutralising immune response, compared with six (25%) of 24 who received a single 45 μg dose and none of 22 who received placebo. Participants receiving two doses of sclamp vaccine elicited similar neutralisation titres, irrespective of dose: two 5 μg doses (GMT 228, 95% CI 146–356), two 15 μg doses (230, 170–312), and two 45 μg doses (239, 187–307). Interpretation This first-in-human trial shows that a subunit vaccine comprising mammalian cell culture-derived, MF59-adjuvanted, molecular clamp-stabilised recombinant spike protein elicits strong immune responses with a promising safety profile. However, the glycoprotein 41 peptide present in the clamp created HIV diagnostic assay interference, a possible barrier to widespread use highlighting the criticality of potential non-spike directed immunogenicity during vaccine development. Studies are ongoing with alternative molecular clamp trimerisation domains to ameliorate this response.

			
European Medicines Agency https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-ema-finds-possible-link-very-rare-cases-unusual-blood-clots-low-blood	COVID-19 Vaccine Janssen: EMA finds possible link to very rare cases of unusual blood clots with low blood platelets	Sulla base di 8 casi di trombosi e trombocitopenia associati temporalmente alla somministrazione di vaccino Janssen contro SARS-CoV-2, l'EMA riconosce il possibile nesso causale. Il rapporto rischio-beneficio a livello di popolazione rimane a favore dell'utilizzo del vaccino.	At its meeting of 20 April 2021, EMA's safety committee (PRAC) concluded that a warning about unusual blood clots with low blood platelets should be added to the product information for COVID-19 Vaccine Janssen. PRAC also concluded that these events should be listed as very rare side effects of the vaccine.

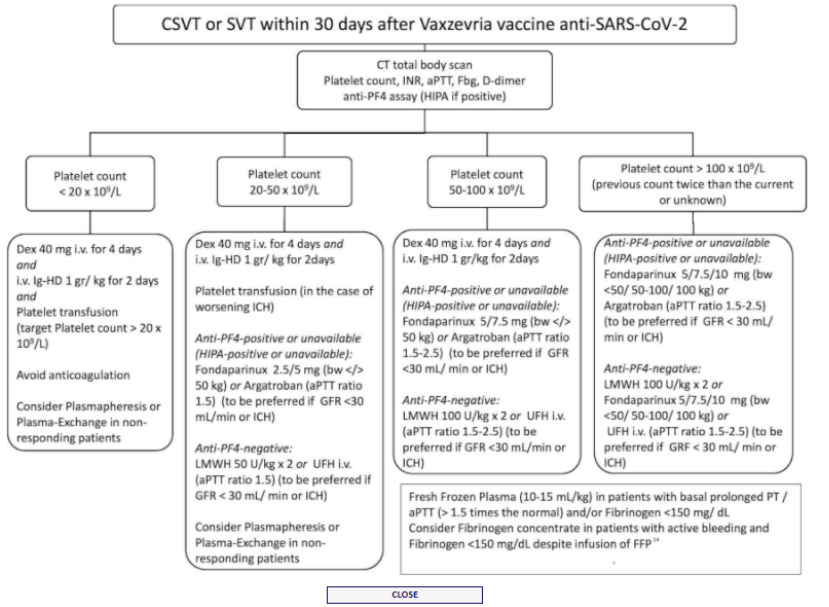
Di Domenico L et al Eurosurveillance https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.15.2100272	Impact of January 2021 curfew measures on SARS-CoV-2 B.1.1.7 circulation in France separator	Secondo questo modello, il solo lockdown con coprifuoco serale imposto in Francia negli scorsi mesi non limita la circolazione di SARS-CoV-2 in assenza delle altre misure di distanziamento sociale.	The new B.1.1.7 variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (20I/501Y.V1, also called variant of concern (VOC) 202012/01) initially detected in the United Kingdom [1,2] has rapidly expanded its geographical range across European countries [3]. A large-scale genome sequencing initiative was conducted in France on 7–8 January (Flash1 survey [4], the first of a set of surveys), reporting that 3.3% of all SARS-CoV-2 detections were B.1.1.7 viruses. To limit SARS-CoV-2 spread, strengthened social distancing measures were implemented in the country in the month of January. Starting from a curfew at 20:00 in place since mid-December, the national authorities set a curfew at 18:00 from 2 January in several departments with deteriorating indicators. This was extended nationwide on 16 January, with renewed recommendations on teleworking and preventive measures. On 31 January, stricter controls of the compliance with the measures and closure of large commercial centres were applied. The presence of the B.1.1.7 variant on the territory, however, poses critical challenges to epidemic control. Its higher transmissibility represents a strong selective advantage that makes it prone to rapidly becoming the dominant strain. Social distancing has a differential impact on the variant and the historical strains, not visible before the implementation of surveillance that monitored variant frequency over time. Assessing the impact of implemented measures on the two strains through modelling is key for epidemic management.
Taquet M et al Preprint, not peer reviewed	Cerebral venous thrombosis: a retrospective cohort study of 513,284 confirmed COVID-19 cases and a comparison	In questo studio retrospettivo in corso di revisione l'incidenza di trombosi venosa cerebrale dopo infezione da SARS-	Using an electronic health records network we estimated the absolute incidence of cerebral venous thrombosis (CVT) in the two weeks following COVID-19 diagnosis(N=513,284),or influenza (N=172,742),or receipt of the BNT162b2 or mRNA-1273 COVID-

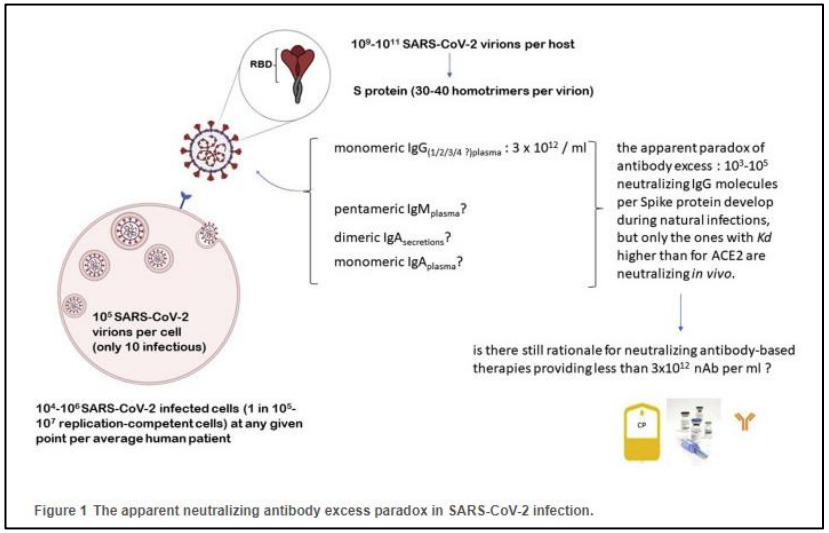
https://osf.io/a9jdq/	with 489,871 people receiving a COVID-19 mRNA vaccine	CoV-2 è maggiore che dopo l'influenza e dopo la somministrazione di vaccini a mRNA (Pfizer, Moderna) o a vettore adenovirale (Vaxzevria).	19 vaccines(N=489,871).Theincidence of portal vein thrombosis (PVT) was also assessed in these groups, as well as the baseline CVT incidence over a two-week period. The incidence of CVT after COVID-19 diagnosis was 39.0 per million people (95% CI, 25.2–60.2). This was higher than the CVT incidence after influenza (0.0 per million people, 95% CI 0.0–22.2, adjusted RR=6.73, P=.003) or after receiving BNT162b2 or mRNA-1273 vaccine (4.1 per million people, 95% CI 1.1–14.9, adjusted RR=6.36, P<.001). The relative risks were similar if a broader definition of CVT was used. For PVT, the incidence was 436.4 per million people (382.9-497.4) after COVID-19, 98.4 (61.4-157.6) after influenza, and 44.9 (29.7-68.0) after BNT162b2 or mRNA-1273. The incidence of CVT following COVID-19 was higher than the incidence observed across the entire health records network (0.41 per million people over any 2-week period). Laboratory test results, availablein a subset of the COVID-19 patients, provide preliminary evidence suggestive of raised D-dimer, lowered fibrinogen, and an increased rate of thrombocytopenia in the CVT and PVT groups. Mortality was 20% and 18.8% respectively. These data show that the incidence of CVT issignificantly increased after COVID-19,and greater than that observed with BNT162b2 and mRNA-1273 COVID-19 vaccines. The risk of CVT following COVID-19 is also higher than the latest estimate from the European Medicines Agency for theincidence associated withChAdOx1 nCoV-19 vaccine (5.0 per million people, 95% CI 4.3–5.8). Although requiring replication and corroboration, the present data highlight the risk of serious thrombotic events in COVID-19, and can help contextualizethe risks and benefits of vaccinationin this regard.

Risma K et al Journal of Allergy and Clinical Immunology https://pubmed.ncbi.nlm.nih.gov/33857566/	Potential Mechanisms of Anaphylaxis to COVID-19 mRNA Vaccines.	La componente dei vaccini a mRNA probabilmente alla base delle rare reazioni anafilattiche riportate è il polietilenglicole (PEG).	Anaphylaxis to vaccines is historically a rare event. The Coronavirus Disease 2019 (COVID-19) pandemic drove the need for rapid vaccine production applying a novel antigen delivery system: mRNA vaccines packaged in lipid nanoparticles (LNP). Unexpectedly, public vaccine administration led to a small number of severe allergic reactions with resultant substantial public concern, especially within atopic individuals. We reviewed the constituents of the mRNA LNP vaccine and considered several contributors to these reactions: 1) contact system activation by nucleic acid, 2) complement recognition of the vaccine activating allergic effector cells, 3) pre-existing antibody recognition of polyethylene glycol (PEG), a LNP surface hydrophilic polymer, and 4) direct mast cell activation, coupled with potential genetic or environmental predispositions to hypersensitivity. Unfortunately, measurement of anti-PEG antibodies in vitro is not clinically available, and the predictive value of skin testing to PEG components as a COVID-19 mRNA vaccine-specific anaphylaxis marker is unknown. Even less is known regarding the applicability of vaccine use for testing (in vitro/vivo) to ascertain pathogenesis or predict reactivity risk. Expedient and thorough research-based evaluation of patients who have suffered anaphylactic vaccine reactions and prospective clinical trials in putative at-risk individuals are needed to address these concerns during a public health crisis.
Bulterys PL et al Journal of Clinical Microbiology	Impact of COVID-19 shelter-in-place order on transmission of gastrointestinal pathogens in Northern California.	Marcata riduzione delle infezioni gastrointestinali virali (adenovirus F40/41, astrovirus, norovirus, rotavirus, sapovirus) e di alcune batteriche (ma non quelle primariamente food-borne) in California dopo	In response to the COVID -19 pandemic, California was the first state to impose a strict shelter-in-place (SIP) order in March 2020. Although enforced social distancing early in the pandemic delayed the spread of COVID-19, little is known about its potential impact on the incidence of other communicable infectious diseases. Such a natural experiment involving the society-wide cessation of human interaction outside the household is unique in modern history and

https://jcm.asm.org/content/jcm/early/2021/04/12/JCM.00449-21.full.pdf		l'inizio del lock-down di marzo 2020 rispetto ai due anni precedenti.	could provide useful insight regarding transmission patterns of other pathogens circulating in the community. The objective of this study was to determine the impact of California's SIP order on the gastrointestinal pathogen landscape dynamics in Northern California.
Wu T et al Journal of Asthma https://doi.org/10.1080/02770903.2021.1917603	Asthma does not influence the severity of COVID-19: a Meta-analysis.	Metanalisi che mostra come l'asma non appaia un fattore di rischio per COVID-19 grave.	OBJECTIVE: Previous studies have reported a correlation between coronavirus disease-2019 (COVID-19) and asthma. However, data on whether asthma constitutes a risk factor for COVID-19 and the prevalence of asthma in COVID-19 cases still remains scant. Here, we interrogated and analysed the association between COVID-19 and asthma. METHODS: In this study, we systematically searched PubMed, Embase, and Web of Science databases for studies published between January 1, to August 28, 2020. We included studies that reported the epidemiological and clinical features of COVID-19 and its prevalence in asthma patients. We excluded reviews, animal trails, single case reports, small case series and studies evaluating other coronavirus-related illnesses. Raw data from the studies were pooled into a meta-analysis. RESULTS: We analysed findings from 18 studies, including asthma patients with COVID-19. The pooled prevalence of asthma in COVID-19 cases was 0.08 (95% CI, 0.06-0.11), with an overall I(2) of 99.07%, $p < 0.005$. The data indicated that asthma did not increase the risk of developing severe COVID-19 (odds ratio [OR] 1.04 (95% CI, 0.75-1.46) p = 0.28; I(2)=20%). In addition, there was no significant difference in the incidence of asthma with analyse age in COVID-19 infections [OR] 0.7795% CI, 0.59-1.00) p = 0.24; I(2)=29%). CONCLUSION: Taken together, our data suggested that asthma is not a significant risk factor for the development of severe COVID-19.

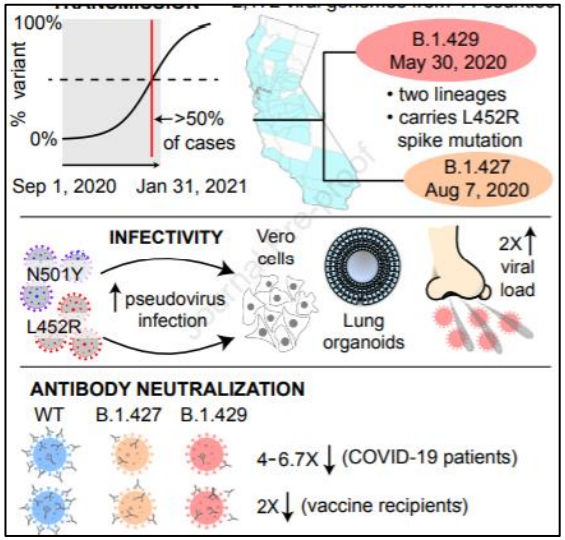
Agenzia Italiana del Farmaco https://www.aifa.gov.it/-/vaccino-contro-il-covid-19-janssen-ema-evidenzia-un-possibile-legame-con-casi-molto-rari-di-trombi-inusuali-con-basso-livello-di-piastrine	Vaccino contro il COVID-19 Janssen: EMA evidenzia un possibile legame con casi molto rari di trombi inusuali con basso livello di piastrine	Comunicato AIFA che riporta il pronunciamento di EMA sul rischio di trombosi e piatrinopenia legati al vaccino Janssen, tutti in persone di età inferiore a 60 anni; si conclude per un beneficio persistente a favore dell'utilizzo del vaccino nella popolazione.	EMA conferma che il rapporto beneficio-rischio complessivo rimane positivo. Nella riunione del 20 aprile 2021, il Comitato per la Sicurezza dell'EMA (PRAC) ha concluso che alle informazioni sul prodotto per il vaccino COVID-19 Janssen deve essere aggiunta un'avvertenza inerente trombi inusuali associati a livelli bassi di piastrine. Il PRAC ha anche concluso che questi eventi dovrebbero essere elencati tra gli effetti indesiderati molto rari del vaccino.
Gresele P et al Blood transfusion http://www.bloodtransfusion.it/articolosing.aspx?id=001156	Management of cerebral and splanchnic vein thrombosis associated with thrombocytopenia in subjects previously vaccinated with Vaxzevria (AstraZeneca): a position statement from the Italian Society for the Study of Haemostasis and Thrombosis (SISET)	Algoritmo di trattamento di trombosi/trombocitopenia a seguito di somministrazione di vaccino Vaxzevria contro SARS-CoV-2.	ChAdOx1 nCOV-19 (Vaxzevria) is a vaccine against SARS-CoV-2 infection (COVID-19) developed by Oxford University and AstraZeneca that uses a replication-deficient chimpanzee adenoviral vector (ChAdOx1) containing the SARS-CoV-2 structural surface glycoprotein antigen (spike protein; nCoV-19) gene. Over the last few weeks, there have been several reports of thromboembolic events in subjects who had been administered Vaxzevria in the previous weeks. This led several European countries to decide to suspend its administration or, more recently, to limit it to subjects over 60 years of age.

			
Amorim MR et al Emerging Infectious Diseases https://wwwnc.cdc.gov/eid/article/27/6/21-0558_article	Respiratory Viral Shedding in Healthcare Workers Reinfected with SARS-CoV-2, Brazil, 2020	Quattro casi di reinfezione da SARS-CoV-2 in operatori sanitari Brasiliani con documentato shedding virale : i dispositivi di protezione rimangono fondamentali.	We documented 4 cases of severe acute respiratory syndrome coronavirus 2 reinfection by non–variant of concern strains among healthcare workers in Campinas, Brazil. We isolated infectious particles from nasopharyngeal secretions during both infection episodes. Improved and continued protection measures are necessary to mitigate the risk for reinfection among healthcare workers.
Focosi D et al Clinical Microbiology and Infection https://www.clinicalmicrobiologyandinfection.com/	Patient-blood management for COVID19 convalescent plasma therapy: should donor-recipient differences in concentration and affinity of neutralizing antibodies drive use?	Indicazioni per ottimizzare l'utilizzo di plasma di soggetti convalescenti (il cosiddetto patient-blood management) per il trattamento di COVID-19 nell'ambito di trial clinici.	Background : COVID19 convalescent plasma (CCP) is being extensively investigated as a treatment, with mixed results to date. Overall, there has been a generalized lack of appropriateness in prescriptions, which is termed patient-blood management in the field of transfusion medicine. Objectives : We aimed at dissecting study design variables which could affect clinical outcome after CCP therapy. We focus here on

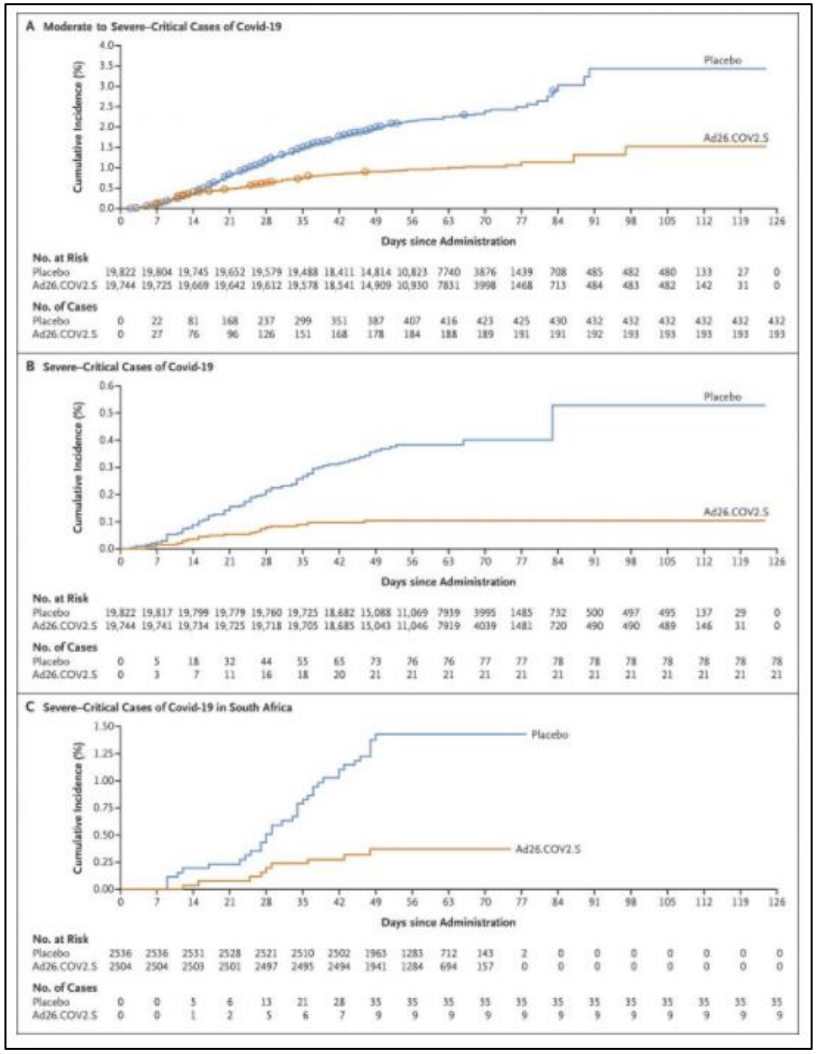
article/S1198-743X(21)00171-3/fulltext			variables such as pretransfusion antibody testing in recipients, dose adjustements, and antibody affinity measurements. Sources : We searched PubMed and preprint servers for relevant preclinical and clinical studies discussing each of these variables in the field of CCP therapy. Content : We show evidences on how neglecting those variables has affected the outcomes of the vast majority of CCP clinical trials to date. Implications : A better understanding of such variables will improve the design of the next generation of CCP clinical trials. This will likely lead to better clinical outcomes and minimize risks from subneutralizing neutralizing antibody doses.  Figure 1 The apparent neutralizing antibody excess paradox in SARS-CoV-2 infection.
Domingo P et a Clinical Microbiology and Infection	Not all COVID-19 pandemic waves are alike	Confronto fra le caratteristiche dei pazienti con COVID-19 della prima e seconda « ondata » (spartiacque agosto 2020) a Barcellona : nella prima la	Objective : We aimed to assess differences in patients' profiles in the first two surges of the SARS-CoV-2 pandemic in Barcelona, Spain. Methods : We prospectively collected data from all adult patients with SARS-CoV-2 infection diagnosed at the Hospital de la Santa

https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00188-9/fulltext		mortalità era più che doppia.	Creu i Sant Pau, Barcelona, Spain. All the patients were diagnosed through nasopharyngeal swab PCR. The first surge spanned from March 1 to August 13, 2020, while surge two encompasses August 14 to December 8, 2020. Results : There were 2479 and 852 patients with microbiologically proved SARS-CoV-2 infection in surge one and two, respectively. Patients from surge two were significantly younger (median age: 52 [IQR: 35] vs. 59 [40] years, respectively, P < 0.001), had fewer comorbidities (379/852, 44.5% vs. 1237/2479, 49.9%, P = 0.007), and a shorter interval between onset of symptoms-diagnosis (median: 3 [5] vs. 4 [5] days, P < 0.001). All-cause in-hospital mortality significantly decreased both for the whole population (24/852, 2.8% vs. 218/2479, 8.8%, P < 0.001) and hospitalized patients (20/302, 6.6% vs. 206/1570, 13.1%, P = 0.012). At adjusted logistic regression analysis, predictors of in-hospital mortality were older age (per year, adjusted odds ratio [aOR] 1.079, 95% CI: 1.063-1.094), male sex (aOR 1.476, 95% CI: 1.079-2.018), having comorbidities (aOR 1.414, 95% CI: 0.934-2.141), ICU admission (aOR 3.812, 95% CI: 1.875-7.751), mechanical ventilation (aOR 2.076, 95% CI: 0.968-4.454), and COVID-19 during surge one (with respect to surge two) (aOR 2.176, CI: 95% 1.286-3.680). Conclusions : First wave SARS-CoV-2-infected patients had a more than two-fold higher in-hospital mortality than second-wave patients. The causes are likely multifactorial.
Adarsh B et al Infectious Diseases Society of America	Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	Linee guida IDSA aggiornate a metà aprile 2021 sul trattamento di COVID-19.	Background: There are many pharmacologic therapies that are being used or considered for treatment of coronavirus disease 2019 (COVID-19). There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature.

https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v4.2.02.pdf			Objective: There are many pharmacologic therapies that are being used or considered for treatment of COVID-19. There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature. Methods: In March 2020, the Infectious Diseases Society of America (IDSA) formed a multidisciplinary guideline panel of infectious disease clinicians, pharmacists, and methodologists with varied areas of expertise. The process followed a rapid recommendation checklist. The panel prioritized questions and outcomes. Then a systematic review of the peerreviewed and grey literature was conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence and make recommendations. Results: On April 11, 2020, IDSA released online initial treatment recommendations and narrative summaries of other treatments under evaluation. Since that time, the guideline panel and methodologists have continued to monitor the literature and issue updates and addendums to these guidelines in response to evolving research. Conclusions: Since the inception of its work, the panel has expressed the overarching goal that patients be recruited into ongoing trials, which would provide much needed evidence on the efficacy and safety of various therapies for COVID-19, given that we could not make a determination whether the benefits outweigh harms for most treatments.
Deng X et al Cell	Transmission, infectivity, and neutralization of a spike L452R SARS-CoV-2 variant	La variante « californiana » B.1.427/B.1.429 di SARS-CoV-2 presenta una aumentata trasmissibilità (19-24% in più) rispetto a quelle più antiche e viene	We identified an emerging SARS-CoV-2 variant by viral whole-genome sequencing of 2,172 nasal/nasopharyngeal swab samples from 44 counties in California, a state in the Western United States. Named B.1.427/B.1.429 to denote its 2 lineages, the variant emerged in May 2020 and increased from 0% to >50% of sequenced

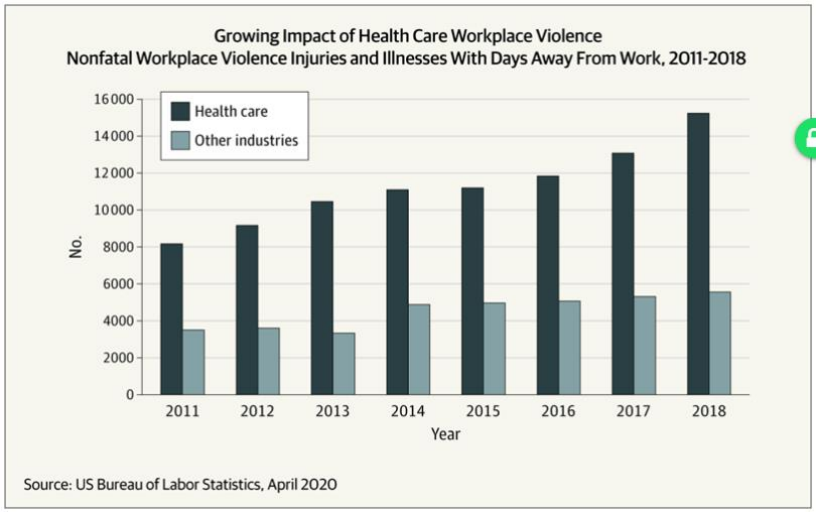
https://www.cell.com/cell/fulltext/S0092-8674(21)00505-5		neutralizzata fino a 7 volte meno dal plasma di soggetti guariti.	cases from September 2020 to January 2021, showing 18.6-24% increased transmissibility relative to wild-type circulating strains. The variant carries 3 mutations in the spike protein, including an L452R substitution. We found 2-fold increased B.1.427/B.1.429 viral shedding in vivo and increased L452R pseudovirus infection of cell cultures and lung organoids, albeit decreased relative to pseudoviruses carrying the N501Y mutation common to variants B.1.1.7, B.1.351, and P.1. Antibody neutralization assays revealed 4.0 to 6.7-fold and 2.0-fold decreases in neutralizing titers from convalescent patients and vaccine recipients, respectively. The increased prevalence of a more transmissible variant in California exhibiting decreased antibody neutralization warrants further investigation. 
Sadoff J et al NEJM	Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19	Trial clinico di fase III su efficacia e sicurezza del vaccino Janssen contro SARS-CoV-2 : protezione del	BACKGROUND : The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding full-length severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein in a prefusion-stabilized conformation.

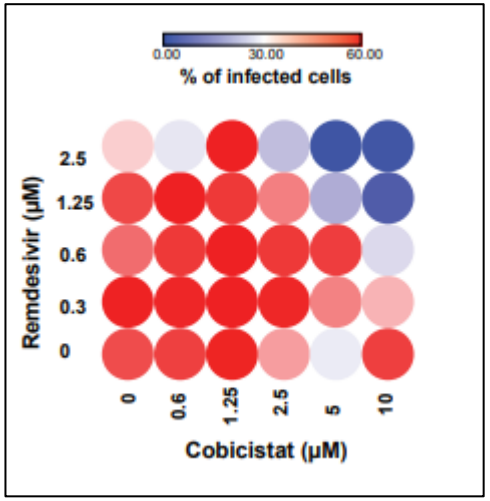
https://www.nejm.org/doi/full/10.1056/NEJMoa2101544?query=featured_home		66% dalla malattia da moderata a grave/critica, e delll'85% contro la malattia da grave a critica dopo 28 giorni dalla singola dose.	METHODS : In an international, randomized, double-blind, placebo-controlled, phase 3 trial, we randomly assigned adult participants in a 1:1 ratio to receive a single dose of Ad26.COV2.S (5×1010 viral particles) or placebo. The primary end points were vaccine efficacy against moderate to severe–critical coronavirus disease 2019 (Covid-19) with an onset at least 14 days and at least 28 days after administration among participants in the per-protocol population who had tested negative for SARS-CoV-2. Safety was also assessed. RESULTS : The per-protocol population included 19,630 SARS-CoV-2–negative participants who received Ad26.COV2.S and 19,691 who received placebo. Ad26.COV2.S protected against moderate to severe–critical Covid-19 with onset at least 14 days after administration (116 cases in the vaccine group vs. 348 in the placebo group; efficacy, 66.9%; adjusted 95% confidence interval [CI], 59.0 to 73.4) and at least 28 days after administration (66 vs. 193 cases; efficacy, 66.1%; adjusted 95% CI, 55.0 to 74.8). Vaccine efficacy was higher against severe–critical Covid-19 (76.7% [adjusted 95% CI, 54.6 to 89.1] for onset at ≥14 days and 85.4% [adjusted 95% CI, 54.2 to 96.9] for onset at ≥28 days). Despite 86 of 91 cases (94.5%) in South Africa with sequenced virus having the 20H/501Y.V2 variant, vaccine efficacy was 52.0% and 64.0% against moderate to severe–critical Covid-19 with onset at least 14 days and at least 28 days after administration, respectively, and efficacy against severe– critical Covid-19 was 73.1% and 81.7%, respectively. Reactogenicity was higher with Ad26.COV2.S than with placebo but was generally mild to moderate and transient. The incidence of serious adverse events was balanced between the two groups. Three deaths occurred in the vaccine group (none were Covid-19–related), and 16 in the placebo group (5 were Covid-19–related).

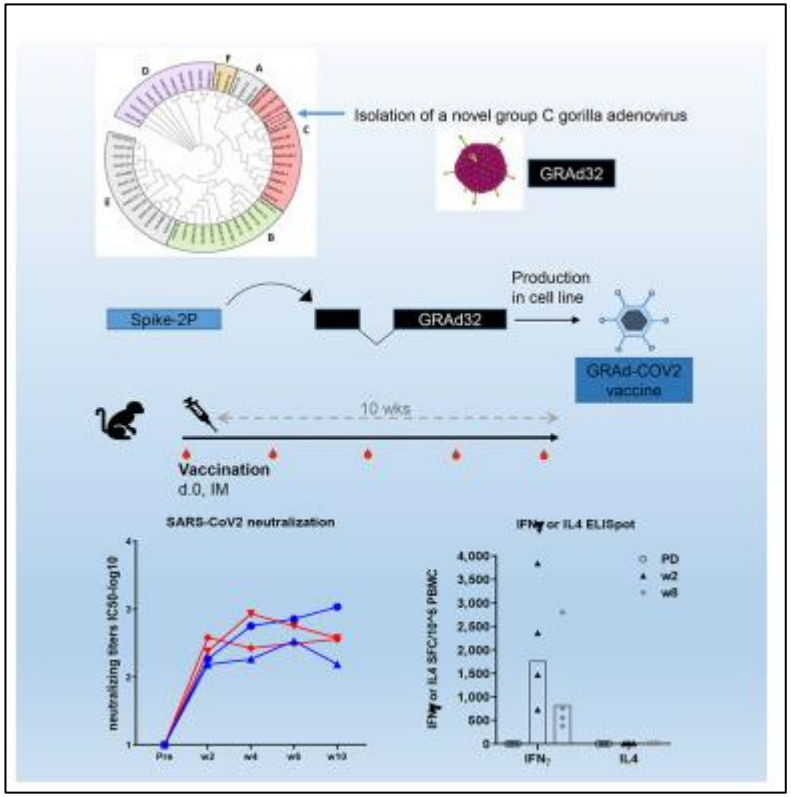
			CONCLUSIONS : A single dose of Ad26.COV2.S protected against symptomatic Covid-19 and asymptomatic SARS-CoV-2 infection and was effective against severe–critical disease, including hospitalization and death. Safety appeared to be similar to that in other phase 3 trials of Covid-19 vaccines. 

Shimabukuro TT et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2104983?query=featured_home	Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons	Dati sulla sicurezza dei vaccini a mRNA contro SARS-CoV-2 in gravidanza.	BACKGROUND : Many pregnant persons in the United States are receiving messenger RNA (mRNA) coronavirus disease 2019 (Covid-19) vaccines, but data are limited on their safety in pregnancy. METHODS : From December 14, 2020, to February 28, 2021, we used data from the “v-safe after vaccination health checker” surveillance system, the v-safe pregnancy registry, and the Vaccine Adverse Event Reporting System (VAERS) to characterize the initial safety of mRNA Covid-19 vaccines in pregnant persons. RESULTS : A total of 35,691 v-safe participants 16 to 54 years of age identified as pregnant. Injection-site pain was reported more frequently among pregnant persons than among nonpregnant women, whereas headache, myalgia, chills, and fever were reported less frequently. Among 3958 participants enrolled in the v-safe pregnancy registry, 827 had a completed pregnancy, of which 115 (13.9%) resulted in a pregnancy loss and 712 (86.1%) resulted in a live birth (mostly among participants with vaccination in the third trimester). Adverse neonatal outcomes included preterm birth (in 9.4%) and small size for gestational age (in 3.2%); no neonatal deaths were reported. Although not directly comparable, calculated proportions of adverse pregnancy and neonatal outcomes in persons vaccinated against Covid-19 who had a completed pregnancy were similar to incidences reported in studies involving pregnant women that were conducted before the Covid-19 pandemic. Among 221 pregnancy-related adverse events reported to the VAERS, the most frequently reported event was spontaneous abortion (46 cases). CONCLUSIONS : Preliminary findings did not show obvious safety signals among pregnant persons who received mRNA Covid-19 vaccines. However, more longitudinal follow-up, including follow-up

			of large numbers of women vaccinated earlier in pregnancy, is necessary to inform maternal, pregnancy, and infant outcomes.
Hacisuleyman E et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2105000?query=featured_home	Vaccine Breakthrough Infections with SARS-CoV-2 Variants	Due casi di infezione sintomatica in donne vaccinate e con risposta anticorpale presente, sostenuti da virus con mutazioni E484K nel primo caso e T95I, del142–144, e D614G nel secondo.	Emerging variants of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are of clinical concern. In a cohort of 417 persons who had received the second dose of BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna) vaccine at least 2 weeks previously, we identified 2 women with vaccine breakthrough infection. Despite evidence of vaccine efficacy in both women, symptoms of coronavirus disease 2019 developed, and they tested positive for SARS-CoV-2 by polymerase-chain-reaction testing. Viral sequencing revealed variants of likely clinical importance, including E484K in 1 woman and three mutations (T95I, del142–144, and D614G) in both. These observations indicate a potential risk of illness after successful vaccination and subsequent infection with variant virus, and they provide support for continued efforts to prevent and diagnose infection and to characterize variants in vaccinated persons.
Larkin H JAMA https://jamanetwork.com/journals/jama/fullarticle/2779310?guestAccessKey=409a05fb-c41c-4734-93ff-f567e7846b79&utm_source=silverchair&utm_me	Navigating Attacks Against Health Care Workers in the COVID-19 Era	Dati sulla violenza contro gli operatori sanitari negli USA durante la pandemia di COVID-19.	Violence against US health care workers has been on the rise for at least a decade. According to US Bureau of Labor Statistics data, the incidence of violence–related health care worker injuries has increased by 67%, from 6.4 per 10 000 full-time workers in 2011 to 10.7 per 10 000 in 2018. Also in 2018, health care and social service workers were 5 times more likely to experience workplace violence than all workers, comprising a whopping 73% of all nonfatal workplace injuries and illnesses requiring days away from work.

dium=email&utm_campaign=article_alert-jama&utm_content=olf&utm_term=042121			
Shytai IL et al bioRXiv –preprint, not peer reviewed https://www.biorxiv.org/content/10.1101/2021.03.09.434219v1	The FDA-approved drug cobicistat synergizes with remdesivir to inhibit SARS-CoV-2 replication	Il booster cobicistat ha un'attività antivirale contro SARS-CoV-2 bloccando la fusione del virus con la membrana delle cellule e mostra sinergismo in vitro con l'inibitore della polimerasi virale remdesivir.	Combinations of direct-acting antivirals are needed to minimize drug-resistance mutations and stably suppress replication of RNA viruses. Currently, there are limited therapeutic options against the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) and testing of a number of drug regimens has led to conflicting results. Here we show that cobicistat, which is an-FDA approved drug-booster that blocks the activity of the drug metabolizing proteins Cytochrome P450-3As (CYP3As) and P-glycoprotein (P-gp), inhibits SARS-CoV-2 replication. Cell-to-cell membrane fusion assays indicated that the antiviral effect of cobicistat is exerted through inhibition of spike protein-mediated membrane fusion. In line with this, incubation with low micromolar concentrations of cobicistat decreased viral replication in three different cell lines including cells of lung and gut origin. When cobicistat was used in combination with the putative CYP3A target and nucleoside analog remdesivir, a synergistic effect on the inhibition of viral replication was observed in cell lines and in a primary human colon organoid. The cobicistat/remdesivir combination was able to potently abate viral

			replication to levels comparable to mock-infected cells leading to an almost complete rescue of infected cell viability. These data highlight cobicistat as a therapeutic candidate for treating SARS-CoV-2 infection and as a potential building block of combination therapies for COVID-19. 
Capone S et al Molecular Therapy https://www.cell.com/molecular-therapy-family/molecular-therapy/fulltext/S1525-0016(21)00210-0	Immunogenicity of a new gorilla adenovirus vaccine candidate for COVID-19	Messa a punto di un nuovo vaccino a vettore adenovirale (di macaco) attualmente in fase preclinica.	The COVID-19 pandemic caused by the emergent SARS-CoV-2 coronavirus threatens global public health and there is an urgent need to develop safe and effective vaccines. Here we report the generation and the preclinical evaluation of a novel replication-defective gorilla adenovirus-vectored vaccine encoding the pre-fusion stabilized Spike (S) protein of SARS-CoV2. We show that our vaccine candidate, GRAd-COV2, is highly immunogenic both in mice and macaques, eliciting both functional antibodies which neutralize SARS-CoV-2 infection and block Spike protein binding to the ACE2 receptor, and a robust, Th1-dominated cellular response. We show here that the pre-fusion stabilized Spike antigen is superior to the wild type in inducing ACE2-interfering, SARS-CoV2 neutralizing antibodies. To face the unprecedented need for vaccine

			manufacturing at massive scale, different GRAd genome deletions were compared to select the vector backbone showing the highest productivity in stirred tank bioreactors. This preliminary dataset identified GRAd-COV2 as a potential COVID-19 vaccine candidate, supporting the translation of GRAd-COV2 vaccine in a currently ongoing Phase I clinical trial (NCT04528641). 
Riley S et al Science	Resurgence of SARS-CoV-2: detection by community viral surveillance	Proposta di campionamento sulla popolazione per intercettare proattivamente le fasi di ripresa della pandemia di COVID-19	Surveillance of the SARS-CoV-2 epidemic has mainly relied on case reporting which is biased by health service performance, test availability and test-seeking behaviors. We report a community-wide national representative surveillance program in England involving self-administered swab results from 594,000 individuals

https://science.sciencemag.org/content/early/2021/04/22/science.abf0874		anziché seguire soltanto la segnalazione dei casi diagnosticati.	tested for SARS-CoV-2, regardless of symptoms, from May to beginning of September 2020. The epidemic declined between May and July 2020 but then increased gradually from mid-August, accelerating into early September 2020 at the start of the second wave. When compared to cases detected through routine surveillance, we report here a longer period of decline and a younger age distribution. Representative community sampling for SARS-CoV-2 can substantially improve situational awareness and feed into the public health response even at low prevalence.
Al-Aly Z et al Nature https://www.nature.com/articles/s41586-021-03553-9	High-dimensional characterization of post-acute sequalae of COVID-19	Amplissimo studio che dimostra un elevato impatto delle sequele dell'infezione da SARS-CoV-2 sul recupero dei pazienti con storia di COVID-19, tanto maggiore quanto più grave è stata la fase acuta.	The acute clinical manifestations of COVID-19 are well characterized1,2; however, its post-acute sequalae have not been comprehensively described. Here, we use the national healthcare databases of the US Department of Veterans Affairs to systematically and comprehensively identify 6-month incident sequalae including diagnoses, medication use, and laboratory abnormalities in 30-day survivors of COVID-19. We show that beyond the first 30 days of illness, people with COVID-19 exhibit higher risk of death and health resource utilization. Our high dimensional approach identifies incident sequalae in the respiratory system and several others including nervous system and neurocognitive disorders, mental health disorders, metabolic disorders, cardiovascular disorders, gastrointestinal disorders, malaise, fatigue, musculoskeletal pain, and anemia. We show increased incident use of several therapeutics including pain medications (opioids and non-opioids), antidepressants, anxiolytics, antihypertensives, and oral hypoglycemics and evidence of laboratory abnormalities in multiple organ systems. Analysis of an array of pre-specified outcomes reveals a risk gradient that increased across severity of the acute COVID-19 infection (non-hospitalized, hospitalized, admitted to intensive care). The findings

			show that beyond the acute illness, substantial burden of health loss — spanning pulmonary and several extrapulmonary organ systems — is experienced by COVID-19 survivors. The results provide a roadmap to inform health system planning and development of multidisciplinary care strategies to reduce chronic health loss among COVID-19 survivors.
Lebreton G et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00096-5/fulltext	Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study	L'esperienza del centro nella gestione di pazienti in ECMO è un fattore indipendente che influisce sulla mortalità a 90 giorni in questi pazienti critici con COVID-19.	Background In the Île-de-France region (henceforth termed Greater Paris), extracorporeal membrane oxygenation (ECMO) for severe acute respiratory distress syndrome (ARDS) was considered early in the COVID-19 pandemic. We report ECMO network organisation and outcomes during the first wave of the pandemic. Methods In this multicentre cohort study, we present an analysis of all adult patients with laboratory-confirmed SARS-CoV-2 infection and severe ARDS requiring ECMO who were admitted to 17 Greater Paris intensive care units between March 8 and June 3, 2020. Central regulation for ECMO indications and pooling of resources were organised for the Greater Paris intensive care units, with six mobile ECMO teams available for the region. Details of complications (including ECMO-related complications, renal replacement therapy, and pulmonary embolism), clinical outcomes, survival status at 90 days after ECMO initiation, and causes of death are reported. Multivariable analysis was used to identify pre-ECMO variables independently associated with 90-day survival after ECMO. Findings The 302 patients included who underwent ECMO had a median age of 52 years (IQR 45−58) and Simplified Acute Physiology Score-II of 40 (31−56), and 235 (78%) of whom were men. 165 (55%) were

			transferred after cannulation by a mobile ECMO team. Before ECMO, 285 (94%) patients were prone positioned, median driving pressure was 18 cm H2O (14−21), and median ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen was 61 mm Hg (IQR 54−70). During ECMO, 115 (43%) of 270 patients had a major bleeding event, 27 of whom had intracranial haemorrhage; 130 (43%) of 301 patients received renal replacement therapy; and 53 (18%) of 294 had a pulmonary embolism. 138 (46%) patients were alive 90 days after ECMO. The most common causes of death were multiorgan failure (53 [18%] patients) and septic shock (47 [16%] patients). Shorter time between intubation and ECMO (odds ratio 0·91 [95% CI 0·84−0·99] per day decrease), younger age (2·89 [1·41−5·93] for ≤48 years and 2·01 [1·01−3·99] for 49–56 years vs ≥57 years), higher pre-ECMO renal component of the Sequential Organ Failure Assessment score (0·67, 0·55−0·83 per point increase), and treatment in centres managing at least 30 venovenous ECMO cases annually (2·98 [1·46–6·04]) were independently associated with improved 90-day survival. There was no significant difference in survival between patients who had mobile and on-site ECMO initiation. Interpretation Beyond associations with similar factors to those reported on ECMO for non-COVID-19 ARDS, 90-day survival among ECMO-assisted patients with COVID-19 was strongly associated with a centre's experience in venovenous ECMO during the previous year. Early ECMO management in centres with a high venovenous ECMO case volume should be advocated, by applying centralisation and regulation of ECMO indications, which should also help to prevent a shortage of resources.

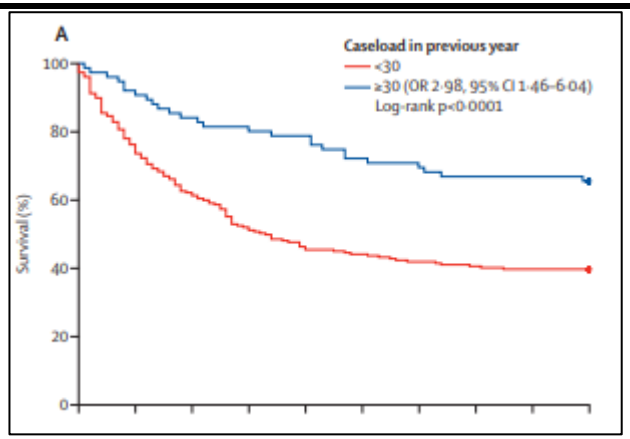
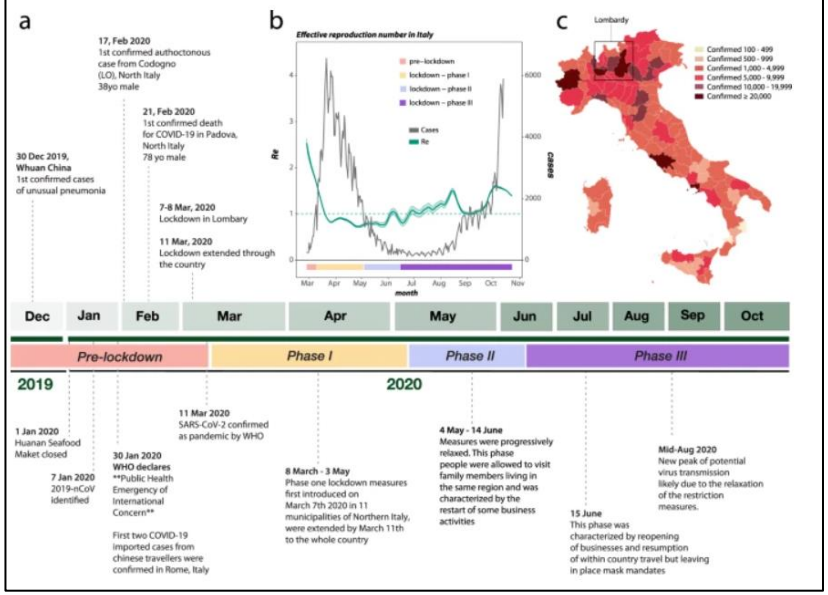
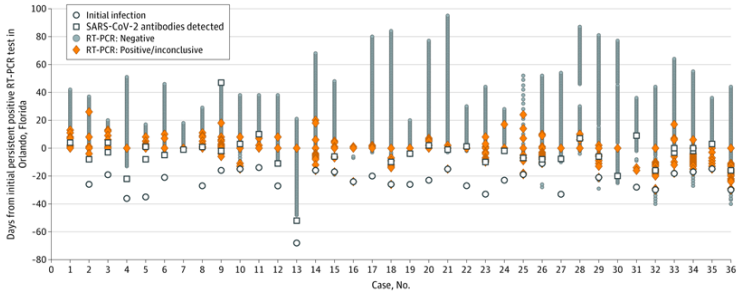
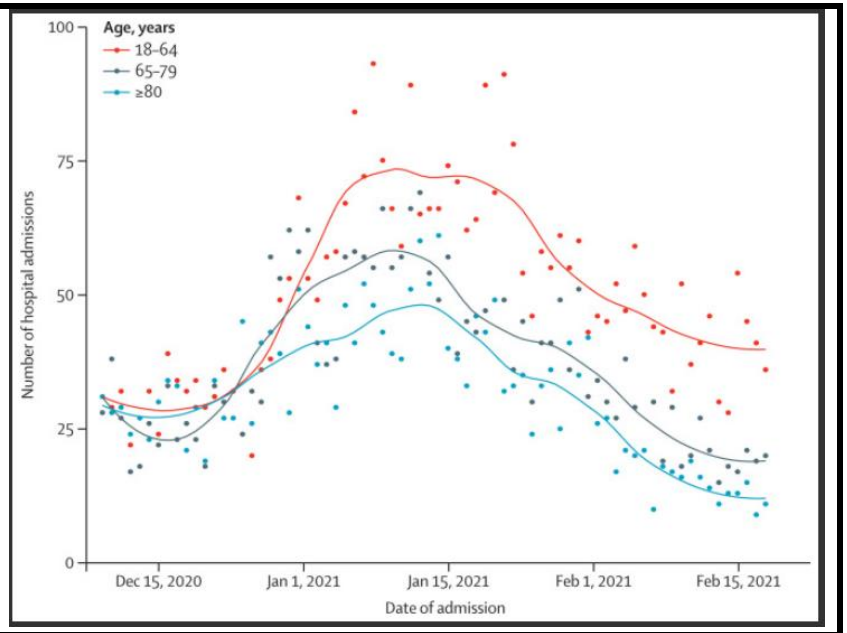
			
Giovanetti M et al Communications biology https://www.nature.com/articles/s42003-021-02025-0	SARS-CoV-2 shifting transmission dynamics and hidden reservoirs potentially limit efficacy of public health interventions in Italy	Secondo il modello presentato in questo studio e basato sulla situazione italiana, alcuni reservoir di infezione da SARS-CoV-2, che convergono per via degli spostamenti di persone, potrebbero sostenere la diffusione della pandemia e dovrebbero essere presi di mira da misure ad hoc (vaccinazione), mantenendo valide le misure di distanziamento già in atto.	We investigated SARS-CoV-2 transmission dynamics in Italy, one of the countries hit hardest by the pandemic, using phylodynamic analysis of viral genetic and epidemiological data. We observed the co-circulation of multiple SARS-CoV-2 lineages over time, which were linked to multiple importations and characterized by large transmission clusters concomitant with a high number of infections. Subsequent implementation of a three-phase nationwide lockdown strategy greatly reduced infection numbers and hospitalizations. Yet we present evidence of sustained viral spread among sporadic clusters acting as “hidden reservoirs” during summer 2020. Mathematical modelling shows that increased mobility among residents eventually catalyzed the coalescence of such clusters, thus driving up the number of infections and initiating a new epidemic wave. Our results suggest that the efficacy of public health interventions is, ultimately, limited by the size and structure of epidemic reservoirs, which may warrant prioritization during vaccine deployment.

			Fig. 1: History of SARS-CoV-2 epidemic in Italy. 
Mack CD et al JAMA https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2779287?resultClick=1	SARS-CoV-2 Transmission Risk Among National Basketball Association Players, Staff, and Vendors Exposed to Individuals With Positive Test Results After COVID-19 Recovery During the 2020 Regular and Postseason	Nessun caso di infezione secondaria fra i contatti (ravvicinati) di 36 giocatori dell'NBA con storia di infezione da SARS-CoV-2 e tampone persistentemente positivo, per i quali l'indicazione all'isolamento era stata sospesa sulla base del criterio temporale dei CDC (10 dall'esordio dei sintomi, con almeno 24 ore di asintomaticità).	Importance Clinical data are lacking regarding the risk of viral transmission from individuals who have positive reverse-transcription–polymerase chain reaction (RT-PCR) SARS-CoV-2 test results after recovery from COVID-19. Objective To describe case characteristics, including viral dynamics and transmission of infection, for individuals who have clinically recovered from SARS-CoV-2 infection but continued to have positive test results following discontinuation of isolation precautions. Design, Setting, and Participants This retrospective cohort study used data collected from June 11, 2020, to October 19, 2020, as part of the National Basketball Association (NBA) closed campus occupational health program in Orlando, Florida, which required daily RT-PCR testing and ad hoc serological testing for SARS-CoV-2 IgG antibodies. Nearly 4000 NBA players, staff, and vendors

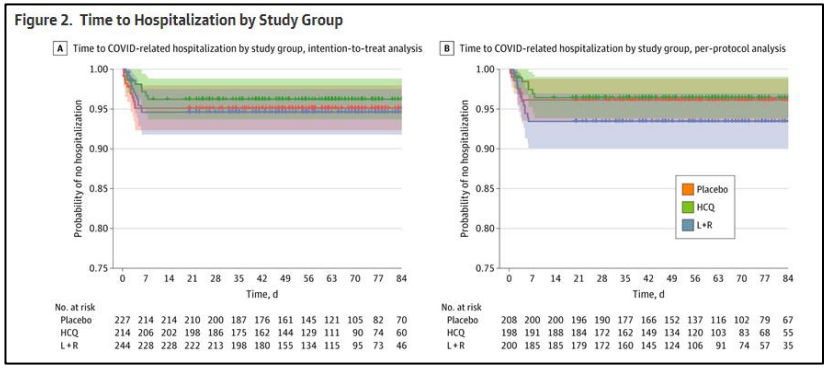
			participated in the NBA's regular and postseason occupational health program in Orlando. Persistent positive cases were those who recovered from a documented SARS-CoV-2 infection, satisfied US Centers for Disease Control and Prevention criteria for discontinuation of isolation precautions, and had at least 1 postinfection positive RT-PCR test(s) result. Exposures Person-days of participation in indoor, unmasked activities that involved direct exposure between persistent positive cases and noninfected individuals. Main Outcomes and Measures Transmission of SARS-CoV-2 following interaction with persistent positive individuals, as measured by the number of new COVID-19 cases in the Orlando campus program. Results Among 3648 individuals who participated, 36 (1%) were persistent positive cases, most of whom were younger than 30 years (24 [67%]) and male (34 [94%]). Antibodies were detected in 33 individuals (91.7%); all remained asymptomatic following the index persistent positive RT-PCR result. Cycle threshold values for persistent positive RT-PCR test results were typically above the Roche cobas SARS-CoV-2 limit of detection. Cases were monitored for up to 100 days (mean [SD], 51 [23.9] days), during which there were at least 1480 person-days of direct exposure activities, with no transmission events or secondary infections of SARS-CoV-2 detected (0 new cases). Conclusions and Relevance In this retrospective cohort study of the 2020 NBA closed campus occupational health program, recovered individuals who continued to test positive for SARS-CoV-2 following discontinuation of isolation were not infectious to others. These findings support time-based US Centers of Disease Control and Prevention recommendations for ending isolation.

			Figure. Test Results Among 36 Individuals Who Recovered From COVID-19 With Persistent Positive SARS-CoV-2 Reverse-Transcription-Polymerase Chain Reaction (RT-PCR) Tests  The longitudinal pattern of test results across recovered individuals who continued to test positive differed greatly with some individuals who experienced large stretches of negative test results without any positive test results, while others had more frequent intermittent positive tests. Recovered persistent/recurrent positive designation was based on clinician diagnosis using standardized operational definitions. The *index date* (day 0) was defined as the date of the first positive or inconclusive RT-PCR test result occurred after isolation had been discontinued. The RT-PCR test results shown were run primarily on the Roche cobas platform; results from the Hologic Panther platform was used before arrival in Orlando, Florida, and in 1 rare occasion in Orlando when the Roche cobas platform was not available (this applies only to case number 25).
Vasileiou E et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00677-2/fulltext	Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study	Riduzione delle ospedalizzazioni per SARS-CoV-2 dopo la vaccinazione con almeno una dose nella popolazione scozzese.	Background The BNT162b2 mRNA (Pfizer–BioNTech) and ChAdOx1 nCoV-19 (Oxford–AstraZeneca) COVID-19 vaccines have shown high efficacy against disease in phase 3 clinical trials and are now being used in national vaccination programmes in the UK and several other countries. Studying the real-world effects of these vaccines is an urgent requirement. The aim of our study was to investigate the association between the mass roll-out of the first doses of these COVID-19 vaccines and hospital admissions for COVID-19. Methods We did a prospective cohort study using the Early Pandemic Evaluation and Enhanced Surveillance of COVID-19—EAVE II—database comprising linked vaccination, primary care, real-time reverse transcription-PCR testing, and hospital admission patient records for 5·4 million people in Scotland (about 99% of the population) registered at 940 general practices. Individuals who had previously tested positive were excluded from the analysis. A time-

			dependent Cox model and Poisson regression models with inverse propensity weights were fitted to estimate effectiveness against COVID-19 hospital admission (defined as 1–adjusted rate ratio) following the first dose of vaccine. Findings Between Dec 8, 2020, and Feb 22, 2021, a total of 1 331 993 people were vaccinated over the study period. The mean age of those vaccinated was 65·0 years (SD 16·2). The first dose of the BNT162b2 mRNA vaccine was associated with a vaccine effect of 91% (95% CI 85–94) for reduced COVID-19 hospital admission at 28–34 days post-vaccination. Vaccine effect at the same time interval for the ChAdOx1 vaccine was 88% (95% CI 75–94). Results of combined vaccine effects against hospital admission due to COVID-19 were similar when restricting the analysis to those aged 80 years and older (83%, 95% CI 72–89 at 28–34 days post-vaccination). Interpretation Mass roll-out of the first doses of the BNT162b2 mRNA and ChAdOx1 vaccines was associated with substantial reductions in the risk of hospital admission due to COVID-19 in Scotland. There remains the possibility that some of the observed effects might have been due to residual confounding.

			
Rreis G et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779044	Effect of Early Treatment With Hydroxychloroquine or Lopinavir and Ritonavir on Risk of Hospitalization Among Patients With COVID-19 The TOGETHER Randomized Clinical Trial	Trial clinico randomizzato condotto in Brasile su pazienti sintomatici per COVID-19 e interrotto per futilità dopo i risultati dell'analisi ad interim : né idrossiclorochina né lopinavir/ritonavir somministrati precocemente rispetto all'esordio di malattia (la gran parte comunque dopo 5 giorni) riducono le ospedalizzazioni per COVID-19 rispetto al placebo.	Importance Data on the efficacy of hydroxychloroquine or lopinavir-ritonavir for the treatment of high-risk outpatients with COVID-19 in developing countries are needed. Objective To determine whether hydroxychloroquine or lopinavir-ritonavir reduces hospitalization among high-risk patients with early symptomatic COVID-19 in an outpatient setting. Design, Setting, and Participants This randomized clinical trial was conducted in Brazil. Recently symptomatic adults diagnosed with respiratory symptoms from SARS-CoV-2 infection were enrolled between June 2 and September 30, 2020. The planned sample size was 1476 patients, with interim analyses planned after 500 patients were enrolled. The trial was stopped after the interim analysis for futility with a sample size of 685 patients. Statistical analysis was performed in December 2020.

			Interventions Patients were randomly assigned to hydroxychloroquine (800 mg loading dose, then 400 mg daily for 9 days), lopinavir-ritonavir (loading dose of 800 mg and 200 mg, respectively, every 12 hours followed by 400 mg and 100 mg, respectively, every 12 hours for the next 9 days), or placebo. Main Outcomes and Measures The primary outcomes were COVID-19–associated hospitalization and death assessed at 90 days after randomization. COVID-19–associated hospitalization was analyzed with a Cox proportional hazards model. The trial included the following secondary outcomes: all-cause hospitalization, viral clearance, symptom resolution, and adverse events. Results Of 685 participants, 632 (92.3%) self-identified as mixed-race, 377 (55.0%) were women, and the median (range) age was 53 (18-94) years. A total of 214 participants were randomized to hydroxychloroquine; 244, lopinavir-ritonavir; and 227, placebo. At first interim analysis, the data safety monitoring board recommended stopping enrollment of both hydroxychloroquine and lopinavir-ritonavir groups because of futility. The proportion of patients hospitalized for COVID-19 was 3.7% (8 participants) in the hydroxychloroquine group, 5.7% (14 participants) in the lopinavir-ritonavir group, and 4.8% (11 participants) in the placebo group. We found no significant differences between interventions for COVID-19–associated hospitalization (hydroxychloroquine: hazard ratio [HR], 0.76 [95% CI, 0.30-1.88]; lopinavir-ritonavir: HR, 1.16 [95% CI, 0.53-2.56] as well as for the secondary outcome of viral clearance through day 14 (hydroxychloroquine: odds ratio [OR], 0.91 [95% CI, 0.82-1.02]; lopinavir-ritonavir: OR, 1.04 [95% CI, 0.94-1.16]). At the end of the trial, there were 3 fatalities recorded, 1 in the placebo group and 2 in the lopinavir-ritonavir intervention group.

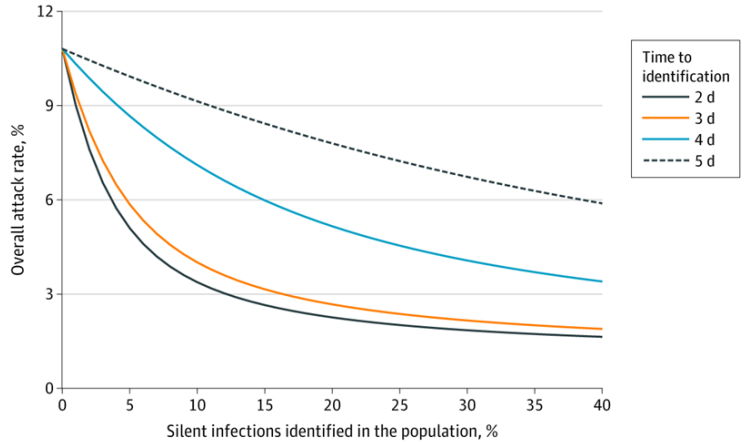
			Conclusions and Relevance In this randomized clinical trial, neither hydroxychloroquine nor lopinavir-ritonavir showed any significant benefit for decreasing COVID-19–associated hospitalization or other secondary clinical outcomes. This trial suggests that expedient clinical trials can be implemented in low-income settings even during the COVID-19 pandemic.  Figure 2. Time to Hospitalization by Study Group A Time to COVID-related hospitalization by study group, intention-to-treat analysis B Time to COVID-related hospitalization by study group, per-protocol analysis Probability of no hospitalization 1.00 0.95 0.90 0.85 0.80 0.75 0 7 14 21 28 35 42 49 56 63 70 77 84 Time, d Placebo HCQ L+R No. at risk Placebo 227 214 214 210 200 187 176 161 145 121 105 82 70 HCQ 214 206 202 198 186 175 162 144 129 111 90 74 60 L+R 244 228 228 222 213 198 180 155 134 115 95 73 46 No. at risk Placebo 208 200 200 196 190 177 166 152 137 116 102 79 67 HCQ 198 191 188 184 172 162 149 134 120 103 83 68 55 L+R 200 185 185 179 172 160 145 124 106 91 74 57 35
Rubin GA et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779053	Cardiac Corrected QT Interval Changes Among Patients Treated for COVID-19 Infection During the Early Phase of the Pandemic	Studio di coorte su 561 adulti testati per SARS-CoV-2, sottoposti a elettrocardiogramma ed eventualmente trattati con idrossiclorochina e/o azitromicina o nessuna delle due in un centro degli USA : la diagnosi di COVID-19 è indipendentemente associata a un prolungamento dell'intervallo QT.	Importance Critical illness, a marked inflammatory response, and viruses such as SARS-CoV-2 may prolong corrected QT interval (QTc). Objective To evaluate baseline QTc interval on 12-lead electrocardiograms (ECGs) and ensuing changes among patients with and without COVID-19. Design, Setting, and Participants This cohort study included 3050 patients aged 18 years and older who underwent SARS-CoV-2 testing and had ECGs at Columbia University Irving Medical Center from March 1 through May 1, 2020. Patients were analyzed by treatment group over 5 days, as follows: hydroxychloroquine with azithromycin, hydroxychloroquine alone, azithromycin alone, and neither hydroxychloroquine nor azithromycin. ECGs were manually analyzed by electrophysiologists masked to COVID-19 status.

			Multivariable modeling evaluated clinical associations with QTc prolongation from baseline. Exposures COVID-19, hydroxychloroquine, azithromycin. Main Outcomes and Measures Mean QTc prolongation, percentage of patients with QTc of 500 milliseconds or greater. Results A total of 965 patients had more than 2 ECGs and were included in the study, with 561 (58.1%) men, 198 (26.2%) Black patients, and 191 (19.8%) aged 80 years and older. There were 733 patients (76.0%) with COVID-19 and 232 patients (24.0%) without COVID-19. COVID-19 infection was associated with significant mean QTc prolongation from baseline by both 5-day and 2-day multivariable models (5-day, patients with COVID-19: 20.81 [95% CI, 15.29 to 26.33] milliseconds; P < .001; patients without COVID-19: −2.01 [95% CI, −17.31 to 21.32] milliseconds; P = .93; 2-day, patients with COVID-19: 17.40 [95% CI, 12.65 to 22.16] milliseconds; P < .001; patients without COVID-19: 0.11 [95% CI, −12.60 to 12.81] milliseconds; P = .99). COVID-19 infection was independently associated with a modeled mean 27.32 (95% CI, 4.63-43.21) millisecond increase in QTc at 5 days compared with COVID-19–negative status (mean QTc, with COVID-19: 450.45 [95% CI, 441.6 to 459.3] milliseconds; without COVID-19: 423.13 [95% CI, 403.25 to 443.01] milliseconds; P = .01). More patients with COVID-19 not receiving hydroxychloroquine and azithromycin had QTc of 500 milliseconds or greater compared with patients without COVID-19 (34 of 136 [25.0%] vs 17 of 158 [10.8%], P = .002). Multivariable analysis revealed that age 80 years and older compared with those younger than 50 years (mean difference in QTc, 11.91 [SE, 4.69; 95% CI, 2.73 to 21.09]; P = .01), severe chronic kidney disease compared with no chronic kidney disease (mean difference in QTc, 12.20 [SE, 5.26; 95% CI, 1.89 to 22.51; P = .02]), elevated high-sensitivity

			troponin levels (mean difference in QTc, 5.05 [SE, 1.19; 95% CI, 2.72 to 7.38]; P < .001), and elevated lactate dehydrogenase levels (mean difference in QTc, 5.31 [SE, 2.68; 95% CI, 0.06 to 10.57]; P = .04) were associated with QTc prolongation. Torsades de pointes occurred in 1 patient (0.1%) with COVID-19. Conclusions and Relevance In this cohort study, COVID-19 infection was independently associated with significant mean QTc prolongation at days 5 and 2 of hospitalization compared with day 0. More patients with COVID-19 had QTc of 500 milliseconds or greater compared with patients without COVID-19.
Etheridge SP et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779057	COVID-19 Infection and Corrected QT Interval Prolongation—Collateral Damage From Our Newest Enemy	Commento all'articolo precendente che discute le cosiddette « canalopatie virali », alterazioni dell'attività dei canali ionici osservate in corso di infezione virale, spiegate dalla capacità di alcuni virus di alterare l'espressione dei canali stessi.	Unimagined a few short months ago, SARS-CoV-2 has spread rapidly across the globe to cause a worldwide pandemic, unparalleled since the 1918 H1N1 influenza pandemic. Deaths in the United States due to COVID-19 surpassed 500 000 in February 2021. The extraordinary efficiency in person-to-person transmission and the relatively high level of morbidity and mortality represent the perfect storm of an emerging infectious disease.1 New York City was among the original US epicenters of the COVID-19 pandemic.
Tu TM et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779040	Acute Ischemic Stroke During the Convalescent Phase of Asymptomatic COVID-2019 Infection in Men	Case series di 18 adulti con ictus ischemico a distanza mediana di 54 giorni da un test sierologico positivo per SARS-CoV-2, con infezione asintomatica.	Importance Acute ischemic stroke (AIS) is a known neurological complication in patients with respiratory symptoms of COVID-19 infection. However, AIS has not been described as a late sequelae in patients without respiratory symptoms of COVID-19. Objective To assess AIS experienced by adults 50 years or younger in the convalescent phase of asymptomatic COVID-19 infection. Design, Setting, and Participants This case series prospectively identified consecutive male patients who received care for AIS from public health hospitals in Singapore between May 21, 2020, and October 14, 2020. All of these patients had laboratory-confirmed asymptomatic COVID-19 infection based on a positive SARS-CoV-2

			serological (antibodies) test result. These patients were individuals from South Asian countries (India and Bangladesh) who were working in Singapore and living in dormitories. The total number of COVID-19 cases (54 485) in the worker dormitory population was the population at risk. Patients with ongoing respiratory symptoms or positive SARS-CoV-2 serological test results confirmed through reverse transcriptase–polymerase chain reaction nasopharyngeal swabs were excluded. Main Outcomes and Measures Clinical course, imaging, and laboratory findings were retrieved from the electronic medical records of each participating hospital. The incidence rate of AIS in the case series was compared with that of a historical age-, sex-, and ethnicity-matched national cohort. Results A total of 18 male patients, with a median (range) age of 41 (35-50) years and South Asian ethnicity, were included. The median (range) time from a positive serological test result to AIS was 54.5 (0-130) days. The median (range) National Institutes of Health Stroke Scale score was 5 (1-25). Ten patients (56%) presented with a large vessel occlusion, of whom 6 patients underwent intravenous thrombolysis and/or endovascular therapy. Only 3 patients (17%) had a possible cardiac source of embolus. The estimated annual incidence rate of AIS was 82.6 cases per 100 000 people in this study compared with 38.2 cases per 100 000 people in the historical age-, sex-, and ethnicity-matched cohort (rate ratio, 2.16; 95% CI, 1.36-3.48; P < .001). Conclusions and Relevance This case series suggests that the risk for AIS is higher in adults 50 years or younger during the convalescent period of a COVID-19 infection without respiratory symptoms. Acute ischemic stroke could be part of the next wave of complications of COVID-19, and stroke units should be on alert and

			use serological testing, especially in younger patients or in the absence of traditional risk factors.
Moghadas SM et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2779052?resultClick=1	Simulated Identification of Silent COVID-19 Infections Among Children and Estimated Future Infection Rates With Vaccination	Modello di diffusione di SARS-CoV-2 in cui i bambini non vengono vaccinati : se non si ricercano attivamente le infezioni asintomatiche in questa fascia d'età, la sola vaccinazione degli adulti non ferma la diffusione del virus.	Importance A significant proportion of COVID-19 transmission occurs silently during the presymptomatic and asymptomatic stages of infection. Children, although important drivers of silent transmission, are not included in the current COVID-19 vaccination campaigns. Objective To estimate the benefits of identifying silent infections among children as a proxy for their vaccination. Design, Setting, and Participants This study used an age-structured disease transmission model, parameterized with census data and estimates from published literature, to simulate the estimated synergistic effect of interventions in reducing attack rates during the course of 1 year among a synthetic population representative of the US demographic composition. The population included 6 age groups of 0 to 4, 5 to 10, 11 to 18, 19 to 49, 50 to 64, and 65 years or older based on US census data. Data were analyzed from December 12, 2020, to February 26, 2021. Exposures In addition to the isolation of symptomatic cases within 24 hours of symptom onset, vaccination of adults was implemented to reach a 40% to 60% coverage during 1 year with an efficacy of 95% against symptomatic and severe COVID-19. Main Outcomes and Measures The combinations of proportion and speed for detecting silent infections among children that would suppress future attack rates to less than 5%. Results In the base-case scenarios with an effective reproduction number Re = 1.2, a targeted approach that identifies 11% of silent infections among children within 2 days and 14% within 3 days after

			infection would bring attack rates to less than 5% with 40% vaccination coverage of adults. If silent infections among children remained undetected, achieving the same attack rates would require an unrealistically high vaccination coverage (≥81%) of this age group, in addition to 40% vaccination coverage of adults. The estimated effect of identifying silent infections was robust in sensitivity analyses with respect to vaccine efficacy against infection and reduced susceptibility of children to infection. Conclusions and Relevance In this simulation modeling study of a synthetic US population, in the absence of vaccine availability for children, a targeted approach to rapidly identify silent COVID-19 infections in this age group was estimated to significantly mitigate disease burden. These findings suggest that without measures to interrupt transmission chains from silent infections, vaccination of adults is unlikely to contain the outbreaks in the near term. **Figure 1. Estimated Mean Attack Rates Without Vaccination and With Identification of Silent Infections in the Population**  Color curves represent attack rates when different proportions of silent infections are identified in the population, corresponding to different time delays after infection.