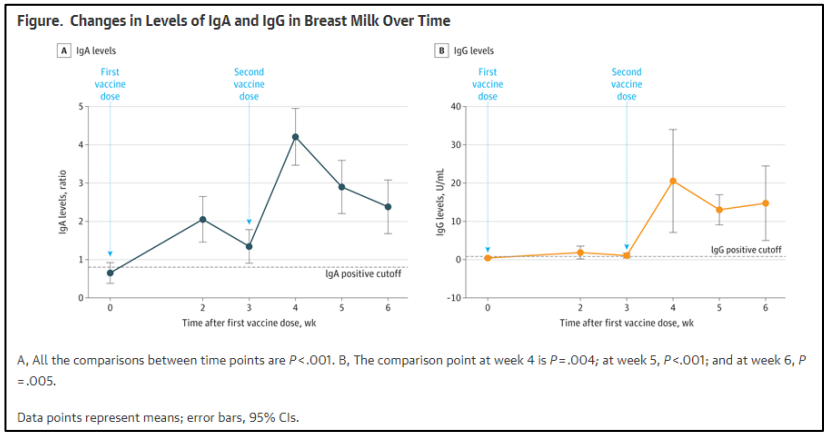
RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 12.04 – 18.04.2021 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Perl SH et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2778766	SARS-CoV-2–Specific Antibodies in Breast Milk After COVID-19 Vaccination of Breastfeeding Women	Presenza di IgA e IgG nel latte materno fino a 6 settimane dopo la vaccinazione con vaccino a mRNA contro SARS-CoV-2.	Eighty-four women completed the study, providing 504 breast milk samples. Women were a mean (SD) age of 34 (4) years and infants 10.32 (7.3) months (Table). Mean levels of anti–SARS-CoV-2-specific IgA antibodies in the breast milk increased rapidly and were significantly elevated at 2 weeks after the first vaccine (2.05 ratio; P < .001), when 61.8% of samples tested positive, increasing to 86.1% at week 4 (1 week after the second vaccine). Mean levels remained elevated for the duration of follow-up, and at week six, 65.7% of samples tested positive. Anti–SARS-CoV-2-specific IgG antibodies remained low for the first 3 weeks, with an increase at week 4 (20.5 U/mL; P = .004), when 91.7% of samples tested positive, increasing to 97% at weeks 5 and 6 (Figure). No mother or infant experienced any serious adverse event during the study period. Forty-seven women (55.9%) reported a vaccine-related adverse event after the first vaccine dose and 52 (61.9%)

			after the second vaccine dose, with local pain being the most common complaint (Table). Four infants developed fever during the study period 7, 12, 15, and 20 days after maternal vaccination. All had symptoms of upper respiratory tract infection including cough and congestion, which resolved without treatment except for 1 infant who was admitted for neonatal fever evaluation due to his age and was treated with antibiotics pending culture results. No other adverse events were reported.  **Figure. Changes in Levels of IgA and IgG in Breast Milk Over Time** A, All the comparisons between time points are $P<.001$. B, The comparison point at week 4 is $P=.004$; at week 5, $P<.001$; and at week 6, $P=.005$. Data points represent means; error bars, 95% CIs.
Haffner MR et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2778455	Postoperative In-Hospital Morbidity and Mortality of Patients With COVID-19 Infection Compared With Patients Without COVID-19 Infection	La mortalità postoperatoria di pazienti con COVID-19 è doppia rispetto ai non infetti in questo studio restrospettivo su oltre 5000 pazienti ; tuttavia non si tiene conto del tipo di procedura e dell'urgenza/elezione.	A total of 5470 surgical patients with positive COVID-19 test results were matched with 5470 surgical patients with negative COVID-19 test results during the same study period. Among all hospitals, there were more than double the number of deaths reported in the cohort of patients with COVID-19 (811 [14.8%]) compared with the cohort of patients without COVID-19 (388 [7.1%]) (P < .001). The rates of complications listed in the Vizient Clinical Data Base (818 [15.0%] vs 760 [13.9%]; P = .11) and median length of stay (10.0 [interquartile range (IQR), 1.3-36.4] vs 10.7 [IQR, 1.0-558.0] days; P = .86) did not differ significantly between the 2 groups. However, hospital-acquired conditions (110 [2.0%] vs 46 [0.8%]; P < .001) and

			patient safety indicators (183 [3.3%] vs 129 [2.4%]; P = .002) were higher in patients with COVID-19. Within each hospital ownership type (public, private, nonprofit), more deaths occurred in the group with COVID-19 compared with the group without COVID-19 in public hospitals (146 [15.8%] vs 46 [4.8%]; P < .001) and nonprofit hospitals (631 [14.7%] vs 326 [7.5%]; P < .001), but not in private hospitals (34 [14.1%] vs 16 [9.4%]; P = .15). Among surgical patients with COVID-19, there were no differences in mortality rates, complications listed in the Vizient Clinical Data Base, hospital-acquired conditions, or patient safety indicators among public, private, or nonprofit hospitals. Table 1. Patient Characteristics, Frequencies, and χ^2 Test *P* Values by COVID-19 Status Table 1. Patient Characteristics, Frequencies, and χ^2 Test *P* Values by COVID-19 Status COVID-19 status, No. (%) Characteristic / Negative (n = 5470) / Positive (n = 5470) / *P* value[a] Patient death Yes 388 (7.1) 811 (14.8) <.001 No 5082 (92.9) 4659 (85.2) Complications Yes 760 (13.9) 818 (15.0) .11 No 4710 (86.1) 4652 (85.0) Hospital-acquired conditions Yes 46 (0.8) 110 (2.0) <.001 No 5424 (99.2) 5360 (98.0) Patient safety indicators Yes 129 (2.4) 183 (3.3) .002 No 5341 (97.6) 5287 (96.7) Length of stay, median (IQR), d 10.7 (1.0-558.0) 10.0 (1.3-36.4) .86 Abbreviation: IQR, interquartile range. [a] Mann-Whitney test *P* value for surgical patients by CC 19 status.
Stanford KA et al JAMA https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2778541	Incorporating HIV Screening With COVID-19 Testing in an Urban Emergency Department During the Pandemic	Lo screening per HIV associato al test per ricerca di SARS-CoV-2 ha determinato un incremento di diagnosi di infezione acuta da HIV in un centro degli USA.	Most sites experienced significant reductions in HIV screens during the pandemic, and overall, the program saw a 49% reduction in testing events from January 1 to April 30, 2020. The ED at UCM, however, maintained HIV screening volumes throughout the pandemic (Figure) and performed 19 111 HIV screens (14 215 in the ED) between January 1 and October 16, 2020, along with 112 242 COVID-19 polymerase chain reaction (PCR) tests (18 830 in the ED). Twelve patients were diagnosed with AHI after the first COVID-19 diagnosis in Cook County on January 24, 2020 (Table). The rate of AHI diagnoses per day was significantly higher during the pandemic

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<td>compared with the prior 4 years (incidence rate ratio, 2.43; 95% CI, 1.22-4.83; P = .01). Other EDs not incorporating HIV screening into COVID-19 testing saw a 25% decrease in AHI diagnoses (incidence rate ratio, 0.75; 95% CI, 0.26-2.14; P = .59) that was not statistically significant.
Patients with AHI comprised 12 of 46 (26.1%) new diagnoses at UCM, the highest proportion on record. Included were 9 men (6 men who have sex with men, 2 heterosexual, and 1 undisclosed) and 3 cisgender women with a median (range) age of 25 (21-28) years. The median (range) viral load was 6 million (115 000 to >6 million) copies/mL. Eleven of 12 patients presented with symptoms consistent with COVID-19. One patient had COVID-19 infection and AHI. All were linked and initiated antiretroviral therapy by a median (range) of 1 (0-38) day from the time of PCR result but 3 (1-41) days from sample collection owing to delays in reflex PCR confirmatory testing, a result of high demands on laboratory personnel and scarcity of supplies (eg, amplification and testing trays) owing to COVID-19 testing volumes.
Table. HIV Screens, New HIV Diagnoses, and Acute HIV Infections Diagnosed in the Emergency Department (ED) at UCM and Other EDs[a]
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<tr><th>Year</th><th>HIV screens in ED at UCM</th><th>New HIV diagnoses in ED at UCM</th><th>AHI diagnoses in ED at UCM</th><th>HIV screens in other x-TLC EDs</th><th>New HIV diagnoses at other x-TLC EDs</th><th>AHI diagnoses at other x-TLC EDs</th></tr>
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Abbreviations: AHI, acute HIV infection; UCM, The University of Chicago Medicine; x-TLC, Expanded HIV Testing and Linkage to Care Program.
[a] Dates of comparison are from January 1, 2016, through October 16, 2020.</td>
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<td>Ramakrishnan S et al

The Lancet</td>
<td>Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial</td>
<td>Trial di fase II che confronta terapia inalatoria con budesonide contro la sola terapia sintomatica (paracetamolo/FANS) in 146</td>
<td>Background : Multiple early reports of patients admitted to hospital with COVID-19 showed that patients with chronic respiratory disease were significantly under-represented in these cohorts. We hypothesised that the widespread use of inhaled glucocorticoids among these patients was responsible for this finding, and tested if</td>
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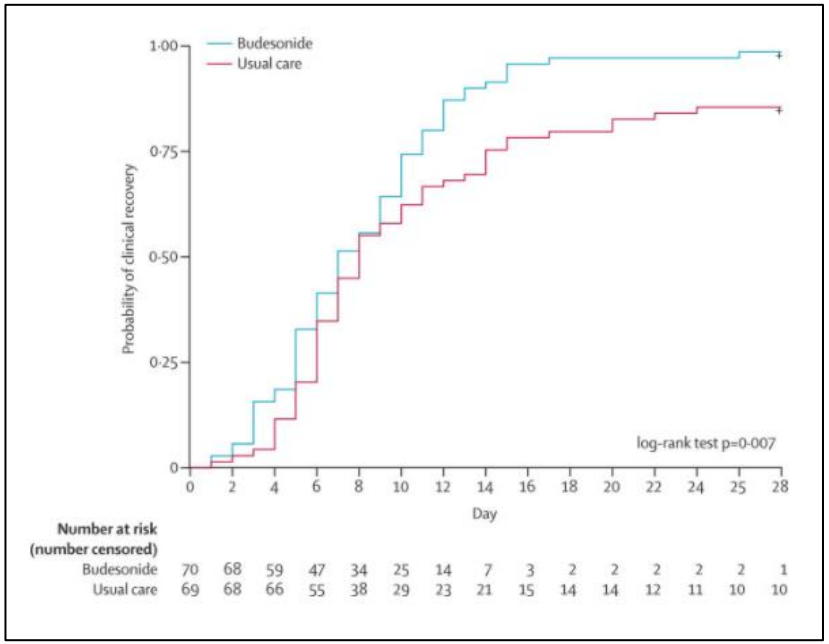
https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00160-0/fulltext		pazienti con COVID-19 lieve, entro sette giorni dall'inizio dei sintomi : si osserva un ridotto ricorso alle cure mediche urgenti (1% contro 14%) e una più rapida risoluzione dei sintomi nel gruppo trattato con budesonide.	inhaled glucocorticoids would be an effective treatment for early COVID-19. Methods : We performed an open-label, parallel-group, phase 2, randomised controlled trial (Steroids in COVID-19; STOIC) of inhaled budesonide, compared with usual care, in adults within 7 days of the onset of mild COVID-19 symptoms. The trial was done in the community in Oxfordshire, UK. Participants were randomly assigned to inhaled budsonide or usual care stratified for age (≤40 years or >40 years), sex (male or female), and number of comorbidities (≤1 and ≥2). Randomisation was done using random sequence generation in block randomisation in a 1:1 ratio. Budesonide dry powder was delivered using a turbohaler at a dose of 800 µg per actuation. Participants were asked to take two inhalations twice a day until symptom resolution. The primary endpoint was COVID-19-related urgent care visit, including emergency department assessment or hospitalisation, analysed for both the per-protocol and intention-to-treat (ITT) populations. The secondary outcomes were self-reported clinical recovery (symptom resolution), viral symptoms measured using the Common Cold Questionnare (CCQ) and the InFLUenza Patient Reported Outcome Questionnaire (FLUPro), body temperature, blood oxygen saturations, and SARS-CoV-2 viral load. The trial was stopped early after independent statistical review concluded that study outcome would not change with further participant enrolment. This trial is registered with ClinicalTrials.gov, NCT04416399. Findings : From July 16 to Dec 9, 2020, 167 participants were recruited and assessed for eligibility. 21 did not meet eligibility criteria and were excluded. 146 participants were randomly assigned—73 to usual care and 73 to budesonide. For the per-protocol population (n=139), the primary outcome occurred in ten

			(14%) of 70 participants in the budesonide group and one (1%) of 69 participant in the usual care group (difference in proportions 0·131, 95% CI 0·043 to 0·218; p=0·004). For the ITT population, the primary outcome occurred in 11 (15%) participants in the usual care group and two (3%) participants in the budesonide group (difference in proportions 0·123, 95% CI 0·033 to 0·213; p=0·009). The number needed to treat with inhaled budesonide to reduce COVID-19 deterioration was eight. Clinical recovery was 1 day shorter in the budesonide group compared with the usual care group (median 7 days [95% CI 6 to 9] in the budesonide group vs 8 days [7 to 11] in the usual care group; log-rank test p=0·007). The mean proportion of days with a fever in the first 14 days was lower in the budesonide group (2%, SD 6) than the usual care group (8%, SD 18; Wilcoxon test p=0·051) and the proportion of participants with at least 1 day of fever was lower in the budesonide group when compared with the usual care group. As-needed antipyretic medication was required for fewer proportion of days in the budesonide group compared with the usual care group (27% [IQR 0–50] vs 50% [15–71]; p=0·025) Fewer participants randomly assigned to budesonide had persistent symptoms at days 14 and 28 compared with participants receiving usual care (difference in proportions 0·204, 95% CI 0·075 to 0·334; p=0·003). The mean total score change in the CCQ and FLUPro over 14 days was significantly better in the budesonide group compared with the usual care group (CCQ mean difference −0·12, 95% CI −0·21 to −0·02 [p=0·016]; FLUPro mean difference −0·10, 95% CI −0·21 to −0·00 [p=0·044]). Blood oxygen saturations and SARS-CoV-2 load, measured by cycle threshold, were not different between the groups. Budesonide was safe, with only five (7%) participants reporting self-limiting adverse events.

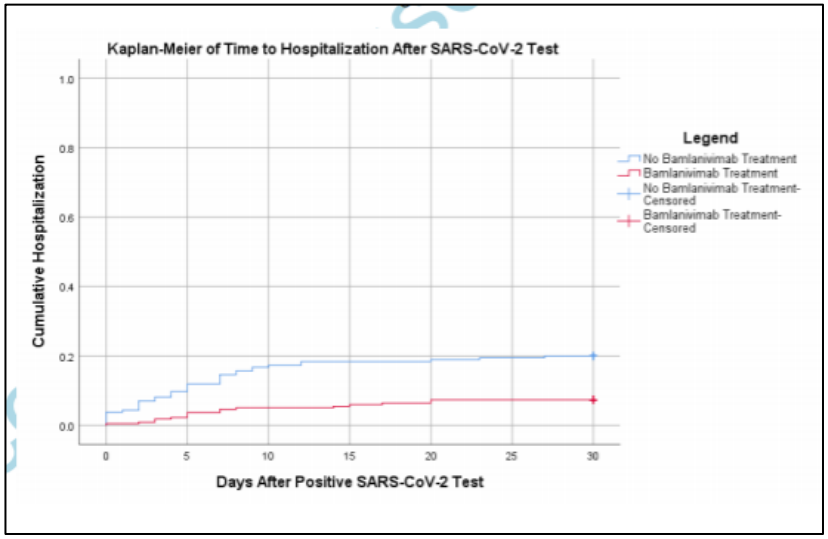
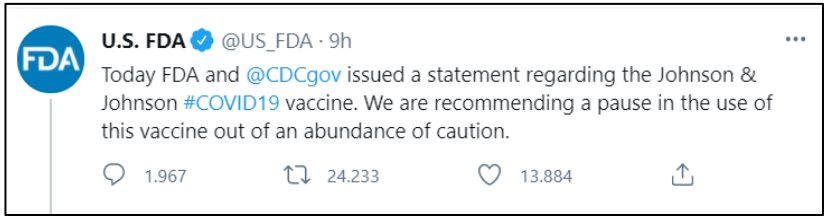
			Interpretation : Early administration of inhaled budesonide reduced the likelihood of needing urgent medical care and reduced time to recovery after early COVID-19. 
Schjørring OL et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2032510?query=featured_home	Lower or Higher Oxygenation Targets for Acute Hypoxemic Respiratory Failure	Utilizzare un target basso di pO2 (60 mmHg) anziché uno più elevato (90 mmHg) in pazienti con insufficienza respiratoria ipossica acuta ricoverati in rianimazione non modifica la mortalità a 90 giorni.	BACKGROUND : Patients with acute hypoxemic respiratory failure in the intensive care unit (ICU) are treated with supplemental oxygen, but the benefits and harms of different oxygenation targets are unclear. We hypothesized that using a lower target for partial pressure of arterial oxygen (Pao2) would result in lower mortality than using a higher target. METHODS : In this multicenter trial, we randomly assigned 2928 adult patients who had recently been admitted to the ICU (≤12 hours before randomization) and who were receiving at least 10 liters of oxygen per minute in an open system or had a fraction of inspired oxygen of at least 0.50 in a closed system to receive oxygen therapy targeting a Pao2 of either 60 mm Hg (lower-oxygenation

			group) or 90 mm Hg (higher-oxygenation group) for a maximum of 90 days. The primary outcome was death within 90 days. RESULTS : At 90 days, 618 of 1441 patients (42.9%) in the lower-oxygenation group and 613 of 1447 patients (42.4%) in the higher-oxygenation group had died (adjusted risk ratio, 1.02; 95% confidence interval, 0.94 to 1.11; P=0.64). At 90 days, there was no significant between-group difference in the percentage of days that patients were alive without life support or in the percentage of days they were alive after hospital discharge. The percentages of patients who had new episodes of shock, myocardial ischemia, ischemic stroke, or intestinal ischemia were similar in the two groups (P=0.24). CONCLUSIONS : Among adult patients with acute hypoxemic respiratory failure in the ICU, a lower oxygenation target did not result in lower mortality than a higher target at 90 days.
Ferreir-Gomes M et al Nature https://www.nature.com/articles/s41467-021-22210-3	SARS-CoV-2 in severe COVID-19 induces a TGF-β-dominated chronic immune response that does not target itself	In 11 pazienti con COVID-19 ricoverati in terapia intensiva, dopo la sieroconversione si osserva una risposta immunitaria dei plasmablasti – produttori di immunoglobuline – tendente alla produzione di IgA2 e non più diretta contro le proteine S e N di SARS-CoV-2. Tale risposta, che contribuisce scarsamente all'immunità, è guidata da TGF-beta che potrebbe essere un bersaglio farmacologico.	The pathogenesis of severe COVID-19 reflects an inefficient immune reaction to SARS-CoV-2. Here we analyze, at the single cell level, plasmablasts egressed into the blood to study the dynamics of adaptive immune response in COVID-19 patients requiring intensive care. Before seroconversion in response to SARS-CoV-2 spike protein, peripheral plasmablasts display a type 1 interferon-induced gene expression signature; however, following seroconversion, plasmablasts lose this signature, express instead gene signatures induced by IL-21 and TGF-β, and produce mostly IgG1 and IgA1. In the sustained immune reaction from COVID-19 patients, plasmablasts shift to the expression of IgA2, thereby reflecting an instruction by TGF-β. Despite their continued presence in the blood, plasmablasts are not found in the lungs of deceased COVID-19 patients, nor does patient IgA2 binds to the dominant antigens of SARS-CoV-2. Our results thus suggest that, in severe COVID-19,

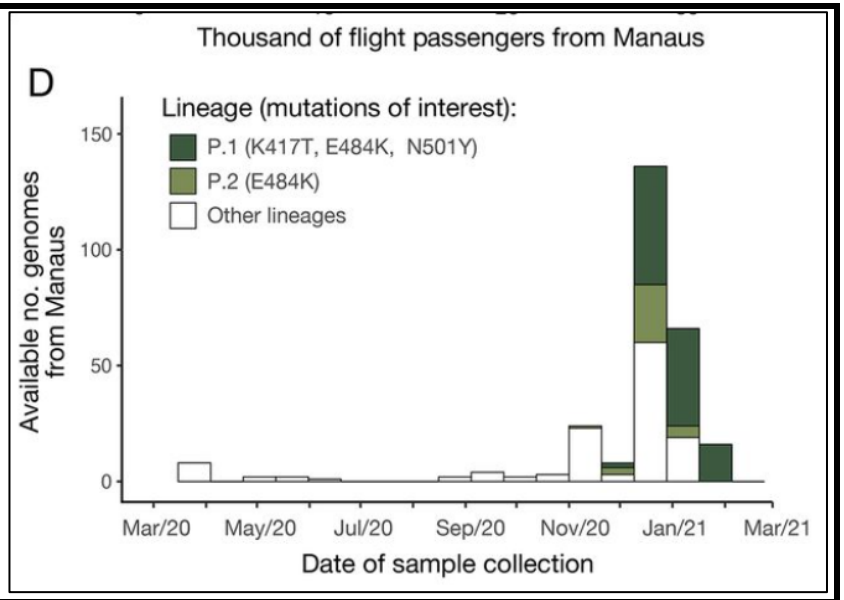
			SARS-CoV-2 triggers a chronic immune reaction that is instructed by TGF-β, and is distracted from itself.
Hall VJ et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00675-9/fulltext	SARS-CoV-2 infection rates of antibody-positive compared with antibody-negative health-care workers in England: a large, multicentre, prospective cohort study (SIREN)	Studio di coorte che segue oltre 25.000 membri del personale ospedaliero in Inghilterra in merito a infezione e reinfezione da SARS-CoV-2 : chi ha avuto un'infezione da SARS-CoV-2 ha riduzione dell'84% del rischio di infettarsi rispetto ai naive (e riduzione del 93% del rischio di infezione sintomatica).	Background : Increased understanding of whether individuals who have recovered from COVID-19 are protected from future SARS-CoV-2 infection is an urgent requirement. We aimed to investigate whether antibodies against SARS-CoV-2 were associated with a decreased risk of symptomatic and asymptomatic reinfection. Methods : A large, multicentre, prospective cohort study was done, with participants recruited from publicly funded hospitals in all regions of England. All health-care workers, support staff, and administrative staff working at hospitals who could remain engaged in follow-up for 12 months were eligible to join The SARS-CoV-2 Immunity and Reinfection Evaluation study. Participants were excluded if they had no PCR tests after enrolment, enrolled after Dec 31, 2020, or had insufficient PCR and antibody data for cohort assignment. Participants attended regular SARS-CoV-2 PCR and antibody testing (every 2–4 weeks) and completed questionnaires every 2 weeks on symptoms and exposures. At enrolment, participants were assigned to either the positive cohort (antibody positive, or previous positive PCR or antibody test) or negative cohort (antibody negative, no previous positive PCR or antibody test). The primary outcome was a reinfection in the positive cohort or a primary infection in the negative cohort, determined by PCR tests. Potential reinfections were clinically reviewed and classified according to case definitions (confirmed, probable, or possible) and symptom-status, depending on the hierarchy of evidence. Primary infections in the negative cohort were defined as a first positive PCR test and seroconversions were excluded when not associated with a

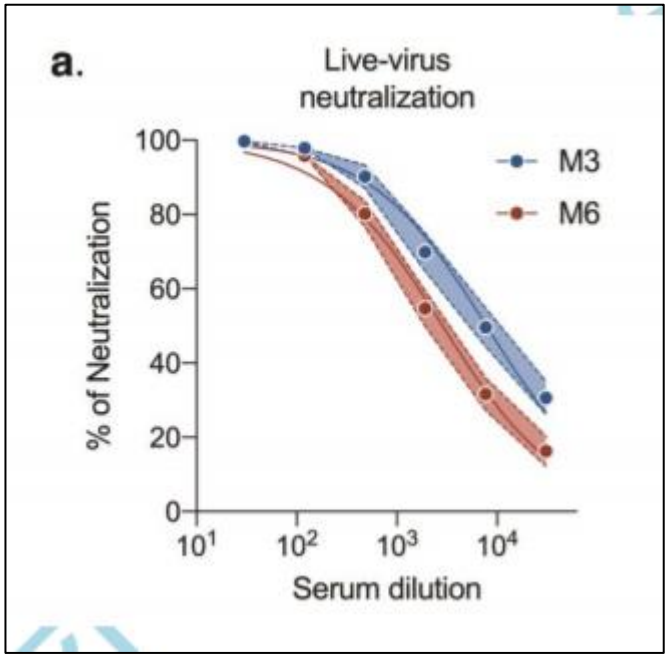
			positive PCR test. A proportional hazards frailty model using a Poisson distribution was used to estimate incidence rate ratios (IRR) to compare infection rates in the two cohorts. Findings : From June 18, 2020, to Dec 31, 2020, 30 625 participants were enrolled into the study. 51 participants withdrew from the study, 4913 were excluded, and 25 661 participants (with linked data on antibody and PCR testing) were included in the analysis. Data were extracted from all sources on Feb 5, 2021, and include data up to and including Jan 11, 2021. 155 infections were detected in the baseline positive cohort of 8278 participants, collectively contributing 2 047 113 person-days of follow-up. This compares with 1704 new PCR positive infections in the negative cohort of 17 383 participants, contributing 2 971 436 person-days of follow-up. The incidence density was 7·6 reinfections per 100 000 person-days in the positive cohort, compared with 57·3 primary infections per 100 000 person-days in the negative cohort, between June, 2020, and January, 2021. The adjusted IRR was 0·159 for all reinfections (95% CI 0·13–0·19) compared with PCR-confirmed primary infections. The median interval between primary infection and reinfection was more than 200 days. Interpretation : A previous history of SARS-CoV-2 infection was associated with an 84% lower risk of infection, with median protective effect observed 7 months following primary infection. This time period is the minimum probable effect because seroconversions were not included. This study shows that previous infection with SARS-CoV-2 induces effective immunity to future infections in most individuals.

Kumar RN et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab305/6224410?searchresult=1	Real-World Experience of Bamlanivimab for COVID-19: A Case-Control Study	Studio retrospettivo caso-controllo su 218 pazienti con COVID-19 trattati con l'anticorpo monoclonale bamlanivimab contro 185 candidati ma non trattati : nel primo gruppo l'ospedalizzazione entro 30 giorni è significativamente ridotta.	Background : COVID-19 has strained healthcare systems with patient hospitalizations and deaths. Anti-spike monoclonal antibodies, including bamlanivimab, have demonstrated reduction in hospitalization rates in clinical trials, yet real-world evidence is lacking. Methods : We conducted a retrospective case-control study across a single healthcare system of non-hospitalized patients, age 18 years or older, with documented positive SARS-CoV-2 testing, risk factors for severe COVID-19, and referrals for bamlanivimab via emergency use authorization. Cases were defined as patients who received bamlanivimab; contemporary controls had a referral order placed but did not receive bamlanivimab. The primary outcome was 30-day hospitalization rate from initial positive SARS-CoV-2 PCR. Descriptive statistics, including Chi-square and Mann-Whitney U test, were performed. Multivariable logistic regression was used for adjusted analysis to evaluate independent associations with 30-day hospitalization. Results : Between November 20, 2020 and January 19, 2021, 218 patients received bamlanivimab (cases) and 185 were referred but did not receive drug (controls). Thirty-day hospitalization rate was significantly lower among patients who received bamlanivimab (7.3% v 20.0%, RR 0.37, 95% CI 0.21-0.64, p<0.001), and the number needed to treat was 8. On logistic regression, odds of hospitalization were increased in patients not receiving bamlanivimab and with a higher number of pre-specified comorbidities (OR 4.19 CI: 1.31-2.16, p<0.001; OR 1.68, CI: 2.12-8.30, p<0.001, respectively). Conclusion : Ambulatory patients with COVID-19 who received bamlanivimab had a lower 30-day hospitalization than control patients in real-world experience. We identified receipt of

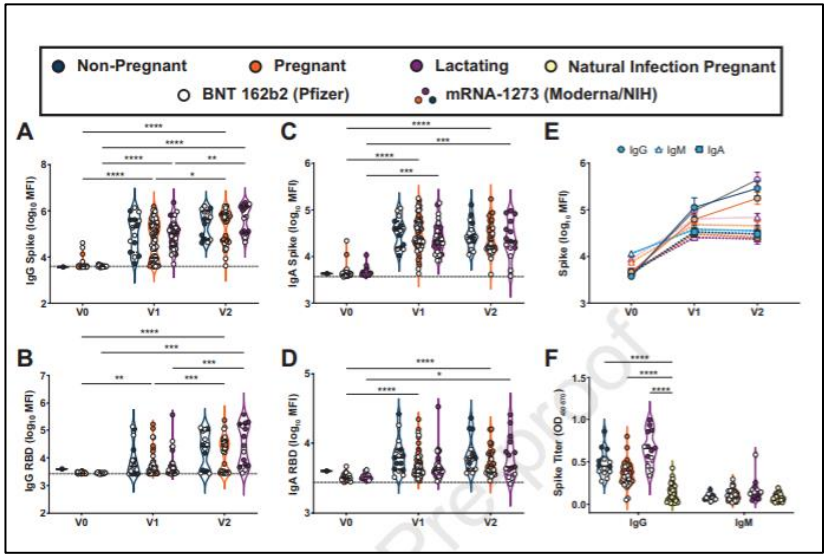
			bamlanivimab and fewer comorbidities as protective factors against hospitalization. 
Mmarks P Food and Drugs Administration's Center for Biologics Evaluation and Research https://www.fda.gov/news-events/press-announcements/joint-cdc-and-fda-statement-johnson-johnson-covid-19-vaccine	Joint CDC and FDA Statement on Johnson & Johnson COVID-19 Vaccine	Sei casi di trombosi venosa cerebrale associata a trombocitopenia successivamente alla somministrazione di vaccino Janssen (Johnson & Johnson, quasi 7 milioni di dosi somministrate negli USA) contro SARS-CoV-2. FDA e CDC stanno valutando i provvedimenti da prendere. Frattanto, viene raccomandata una pausa nelle somministrazioni (twit).	Right now, these adverse events appear to be extremely rare. COVID-19 vaccine safety is a top priority for the federal government, and we take all reports of health problems following COVID-19 vaccination very seriously. People who have received the J&J vaccine who develop severe headache, abdominal pain, leg pain, or shortness of breath within three weeks after vaccination should contact their health care provider. Health care providers are asked to report adverse events to the Vaccine Adverse Event Reporting System at https://vaers.hhs.gov/reportevent.html. 

European Medicines Agency https://www.ema.europa.eu/en/news/covid-19-vaccine-janssen-assessment-very-rare-cases-unusual-blood-clots-low-platelets-continues	COVID-19 Vaccine Janssen: assessment of very rare cases of unusual blood clots with low platelets continues	Aggiornamento sulla procedura di approfondimento da parte dell'EMA dei casi di trombosi venosa riportati negli USA a seguito della somministrazione di vaccino Jannsen contro SARS-CoV-2. La distribuzione in Europa subirà un rallentamento da parte dell'azienda.	As announced last week, EMA's safety committee (PRAC) is reviewing very rare cases of unusual blood clots that occurred in the United States following the use of Janssen's COVID-19 vaccine. The type of blood clot reported, cerebral venous sinus thrombosis (CVST), occurred in most cases in combination with low levels of blood platelets (thrombocytopenia).
Faria NR et al Science https://science.sciencemag.org/content/early/2021/04/13/science.abh2644	Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil	Ricostruzione dell'emergere della variante « brasiliana » di SARS-CoV-2 a Manaus, che viene fatta risalire a metà novembre 2020.	Cases of SARS-CoV-2 infection in Manaus, Brazil, resurged in late 2020, despite previously high levels of infection. Genome sequencing of viruses sampled in Manaus between November 2020 and January 2021 revealed the emergence and circulation of a novel SARS-CoV-2 variant of concern. Lineage P.1, acquired 17 mutations, including a trio in the spike protein (K417T, E484K and N501Y) associated with increased binding to the human ACE2 receptor. Molecular clock analysis shows that P.1 emergence occurred around mid-November 2020 and was preceded by a period of faster molecular evolution. Using a two-category dynamical model that integrates genomic and mortality data, we estimate that P.1 may be 1.7–2.4-fold more transmissible, and that previous (non-P.1) infection provides 54–79% of the protection against infection with P.1 that it provides against non-P.1 lineages. Enhanced global genomic surveillance of variants of concern, which may exhibit increased transmissibility and/or immune evasion, is critical to accelerate pandemic responsiveness.

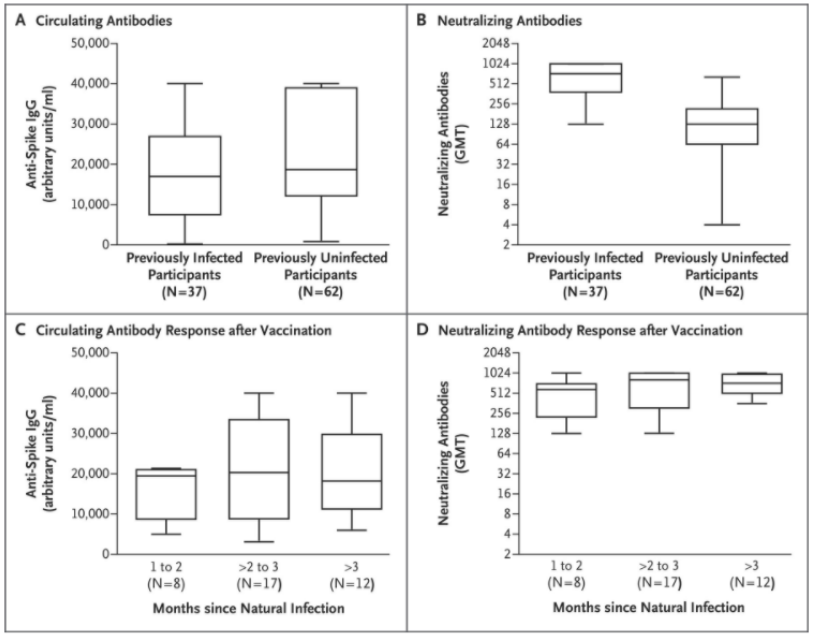
			
Betton M et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab308/6225251?searchresult=1	Sera neutralizing activities against SARS-CoV-2 and multiple variants six month after hospitalization for COVID-19	Saggio dell'attività neutralizzante del siero di pazienti guariti da COVID-19 a distanza di 3 e 6 mesi dalla diagnosi : anche se il titolo di IgG si riduce, l'attività neutralizzante permane invariata (significativamente minore nei confronti della variante « sudafricana » rispetto alle altre) ed è di entità associata alla gravità iniziale dell'infezione stessa.	Background : Humoral response to SARS-CoV-2 occurs within the first weeks after COVID-19. Those antibodies exert a neutralizing activity against SARS-CoV-2, whose evolution overtime after COVID-19 as well as efficiency against novel variants are however poorly characterized. Methods : In this prospective study, sera of 107 patients hospitalized with COVID-19 were collected at 3- and 6-months post-infection. We performed quantitative neutralization experiments on top of high-throughput serological assays evaluating anti-Spike (S) and anti-Nucleocapsid (NP) IgG. Findings : Levels of sero-neutralization and IgG rates against the ancestral strain decreased significantly over time. After 6 months, 2.8% of the patients had a negative serological status for both anti-S and anti-NP IgG. However, all sera had a persistent and effective neutralizing effect against SARS-CoV-2. IgG levels correlated with sero-neutralization and this correlation was stronger for anti-S than

			for anti-NP antibodies. The level of sero-neutralization quantified at 6 months correlated with markers of initial severity, notably admission in intensive care units and the need for mechanical invasive ventilation. In addition, sera collected at 6 months were tested against multiple SARS-CoV-2 variants and showed efficient neutralizing effects against D614G, B.1.1.7 and P.1 variants but a significantly weaker activity against B.1.351 variant. Interpretation : Decrease of IgG rates and serological assays becoming negative did not imply loss of neutralizing capacity. Our results indicate a sustained humoral response against the ancestral strain and the D614G, B.1.1.7 and P.1 variants for at least 6 months in patients previously hospitalized for COVID-19. A weaker protection was however observed for the B.1.351 variant. 

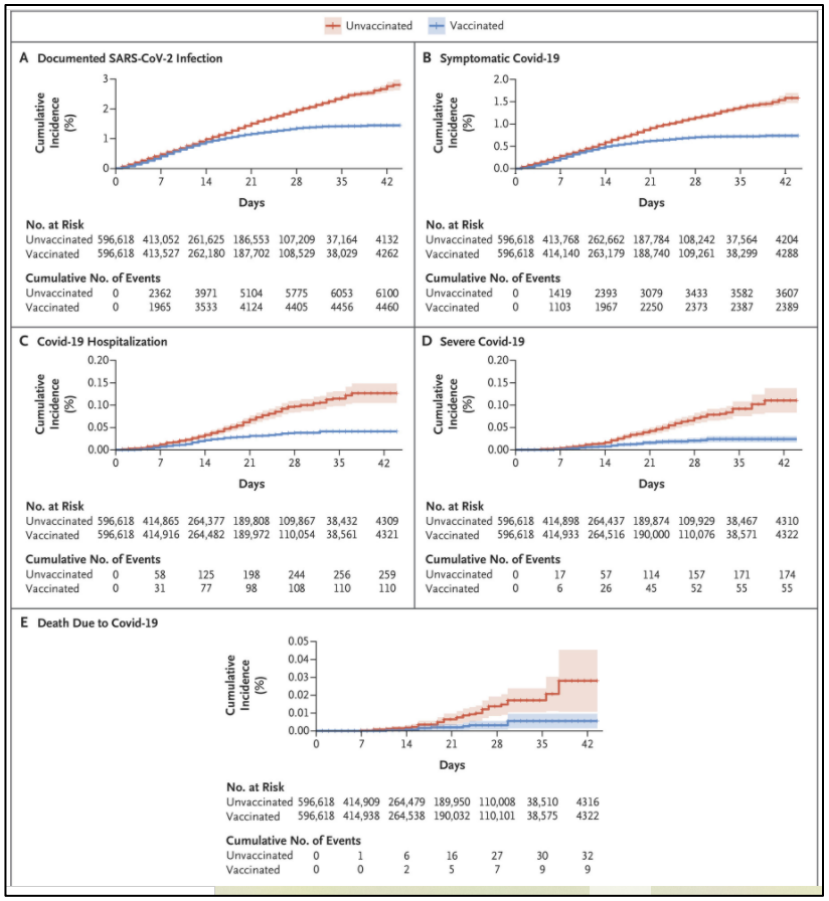
Gray KJ et al American Journal of Obstetrics and Gynecology https://www.ajog.org/article/S0002-9378(21)00187-3/pdf	COVID-19 vaccine response in pregnant and lactating women: a cohort study	Studio di coorte su 84 donne in gravidanza, 31 in allattamento e 16 non gravide sottoposte a vaccino a mRNA (Pfizer/Moderna) contro SARS-CoV-2 : la risposta anticorpale e gli effetti avversi sono comparabili nei tre gruppi, gli anticorpi si ritrovano nel sangue cordonale e nel latte materno.	Background: Pregnant and lactating women were excluded from initial COVID-19 vaccine trials; thus, data to guide vaccine decision-making are lacking. Objectives: To evaluate the immunogenicity and reactogenicity of COVID-19 mRNA vaccination in pregnant and lactating women compared to: (1) non-pregnant controls and (2) natural COVID-19 infection in pregnancy. Study design: 131 reproductive-age vaccine recipients (84 pregnant, 31 lactating, and 16 non-pregnant) were enrolled in a prospective cohort study at two academic medical centers. Titers of SARS-CoV-2 Spike and RBD IgG, IgA and IgM were quantified in participant sera (N=131) and breastmilk (N=31) at baseline, second vaccine dose, 2-6 weeks post second vaccine, and at delivery by Luminex. Umbilical cord sera (N=10) titers were assessed at delivery. Titers were compared to those of pregnant women 4-12 weeks from natural infection (N=37) by ELISA. A pseudovirus neutralization assay was used to quantify neutralizing antibody titers for the subset of women who delivered during the study period. Post-vaccination symptoms were assessed via questionnaire. Kruskal-Wallis tests and a mixed effects model, with correction for multiple comparisons, were used to assess differences between groups. Results: Vaccine-induced antibody titers were equivalent in pregnant and lactating compared to non-pregnant women (median [IQR] 5.59 [4.68-5.89] pregnant, 5.74 [5.06-6.22] lactating, 5.62 [4.77-5.98] non-pregnant, $p = 0.24$). All titers were significantly higher than those induced by SARS-CoV-2 infection during pregnancy ($p < 0.0001$). Vaccine-generated antibodies were present in all umbilical cord blood and breastmilk samples. Neutralizing antibody titers were lower in umbilical cord compared to maternal sera, although this finding did not achieve statistical significance

			(median [IQR] 104.7 [61.2-188.2] maternal sera, 52.3 [11.7-69.6] cord sera, p=0.05). The second vaccine dose (boost dose) increased SARS-CoV-2-specific IgG, but not IgA, in maternal blood and breastmilk. No differences were noted in reactogenicity across the groups. Conclusions: COVID-19 mRNA vaccines generated robust humoral immunity in pregnant and lactating women, with immunogenicity and reactogenicity similar to that observed in non-pregnant women. Vaccine-induced immune responses were significantly greater than the response to natural infection. Immune transfer to neonates occurred via placenta and breastmilk. 
Qiu X et al Clinical Microbiology and Infection	The role of asymptomatic and pre-symptomatic infection in SARS-CoV-2 transmission—a living systematic review	Rrevisione delle evidenze in merito alla contagiosità degli asintomatici per infezione da SARS-CoV-2.	Background : Reports suggest that asymptomatic individuals (those with no symptoms at all throughout infection) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are infectious, but the extent of transmission based on symptom status requires further study.

https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00038-0/fulltext			Purpose : This living review aims to critically appraise available data about secondary attack rates from people with asymptomatic, pre-symptomatic and symptomatic SARS-CoV-2 infection. Data sources : Medline, EMBASE, China Academic Journals full-text database (CNKI), and pre-print servers were searched from 30 December 2019 to 3 July 2020 using relevant MESH terms. Study selection : Studies that report on contact tracing of index cases with SARS-CoV-2 infection in either English or Chinese were included. Data extraction : Two authors independently extracted data and assessed study quality and risk of bias. We calculated the secondary attack rate as the number of contacts with SARS-CoV-2, divided by the number of contacts tested. Data synthesis : Of 927 studies identified, 80 were included. Summary secondary attack rate estimates were 1% (95% CI 0%–2%) with a prediction interval of 0%–10% for asymptomatic index cases in ten studies, 7% (95% CI 3%–11%) with a prediction interval of 1%–40% for pre-symptomatic cases in 11 studies and 6% (95% CI 5%–8%) with a prediction interval of 5%–38% for symptomatic index cases in 40 studies. The highest secondary attack rates were found in contacts who lived in the same household as the index case. Other activities associated with transmission were group activities such as sharing meals or playing board games with the index case, regardless of the disease status of the index case. Limitations : We excluded some studies because the index case or number of contacts were unclear. Conclusion : Asymptomatic patients can transmit SARS-CoV-2 to others, but our findings indicate that such individuals are responsible for fewer secondary infections than people with symptoms.

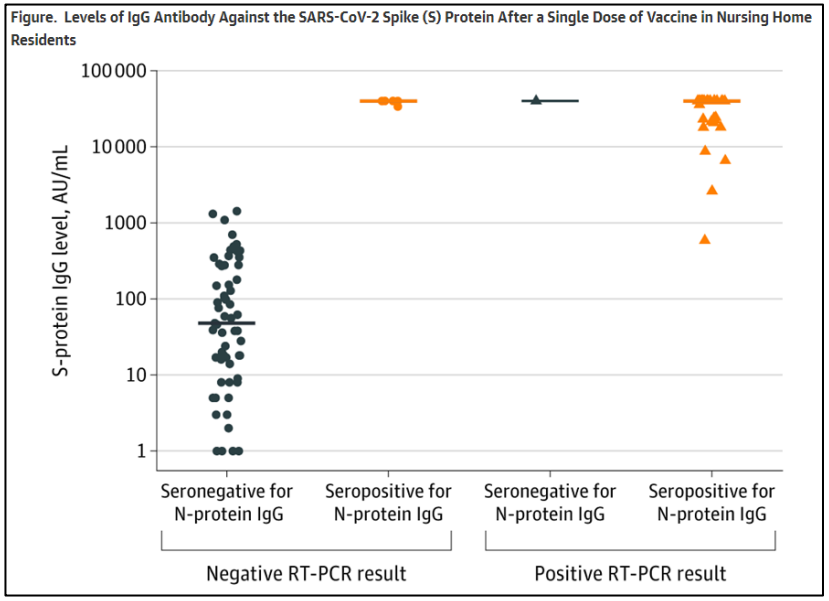
Anichini G et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2103825?query=featured_home	SARS-CoV-2 Antibody Response in Persons with Past Natural Infection	Il titolo neutralizzante di anticorpi contro SARS-CoV-2 presente nel siero di pazienti con storia di COVID-19 dopo una dose di vaccino a mRNA è superiore a quello presente dopo due dosi nel siero di pazienti naive per l'infezione.	Whether or not persons who have already been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) should be vaccinated is unclear. Only a few studies have shown that vaccinees who were previously infected with SARS-CoV-2 had a significantly higher antibody response than previously uninfected vaccinees. In an observational cohort study, we enrolled 100 health care workers, including 38 (9 men and 29 women) with a documented history of SARS-CoV-2 infection (mean duration between infection and vaccination, 111 days). The mean age of these previously infected participants was 35.1 years (95% confidence interval [CI], 31.7 to 38.6). Our study also included 62 participants (25 men and 37 women) who had not been previously infected. The mean age of those participants was 44.7 years (95% CI, 41.0 to 47.6). 

Dagan N et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2101765?query=featured_home	BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting	Confronto fra oltre 500.000 persone vaccinate contro SARS-CoV-2 in Israele (Pfizer) e altrettanti controlli non vaccinati : dati molto incoraggianti sulla prevenzione di infezione, malattia sintomatica, ospedalizzazione, malattia grave e morte.	BACKGROUND : As mass vaccination campaigns against coronavirus disease 2019 (Covid-19) commence worldwide, vaccine effectiveness needs to be assessed for a range of outcomes across diverse populations in a noncontrolled setting. In this study, data from Israel's largest health care organization were used to evaluate the effectiveness of the BNT162b2 mRNA vaccine. METHODS : All persons who were newly vaccinated during the period from December 20, 2020, to February 1, 2021, were matched to unvaccinated controls in a 1:1 ratio according to demographic and clinical characteristics. Study outcomes included documented infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), symptomatic Covid-19, Covid-19–related hospitalization, severe illness, and death. We estimated vaccine effectiveness for each outcome as one minus the risk ratio, using the Kaplan–Meier estimator. RESULTS : Each study group included 596,618 persons. Estimated vaccine effectiveness for the study outcomes at days 14 through 20 after the first dose and at 7 or more days after the second dose was as follows: for documented infection, 46% (95% confidence interval [CI], 40 to 51) and 92% (95% CI, 88 to 95); for symptomatic Covid-19, 57% (95% CI, 50 to 63) and 94% (95% CI, 87 to 98); for hospitalization, 74% (95% CI, 56 to 86) and 87% (95% CI, 55 to 100); and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection and symptomatic Covid-19 was consistent across age groups, with potentially slightly lower effectiveness in persons with multiple coexisting conditions.

			CONCLUSIONS : This study in a nationwide mass vaccination setting suggests that the BNT162b2 mRNA vaccine is effective for a wide range of Covid-19–related outcomes, a finding consistent with that of the randomized trial. 
Muir K et al NEJM	Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination	Caso clinico drammatico di coagulazione intravascolare disseminata, trombocitopenia e riscontro di anticorpi anti-PF4 in una	Thrombosis and thrombocytopenia have been reported after vaccination with the ChAdOx1 nCoV-19 vaccine (Oxford–AstraZeneca), a recombinant chimpanzee adenoviral vector encoding the spike glycoprotein of the severe acute respiratory

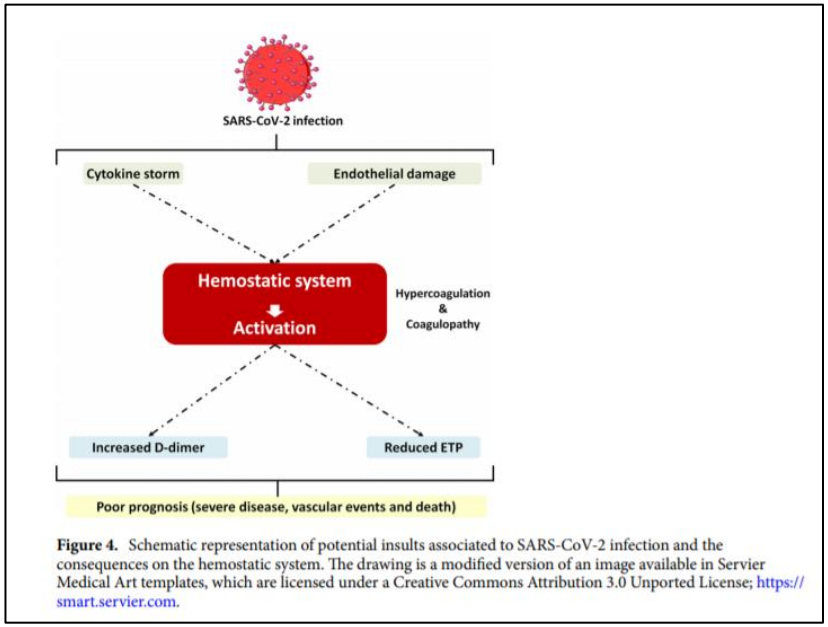
https://www.nejm.org/doi/full/10.1056/NEJMc2105869?query=featured_home		donna di 48 anni vaccinata 14 giorni prima dell'evento con vaccino a vettore adenovirale Janssen contro SARS-CoV-2.	syndrome coronavirus 2 (SARS-CoV-2).1,2 To date, such reactions have not been associated with other vaccines against coronavirus 2019 (Covid-19). We describe a case of extensive thrombosis associated with severe thrombocytopenia and disseminated intravascular coagulation that resembled autoimmune heparin-induced thrombocytopenia3 in a patient who had received the Ad26.COV2.S vaccine (Johnson & Johnson/Janssen), a recombinant adenovirus serotype 26 vector encoding the SARS-CoV-2 spike glycoprotein.
Frampton D et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00170-5/fulltext	Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study	Studio di coorte su 341 pazienti ricoverati per COVID-19 a Londra tra novembre e dicembre 2020, sottoposti a sequenziamento di SARS-CoV-2 isolato dai loro campioni per confrontare la gravità di infezione da variante « inglese » rispetto agli altri ceppi : non si dimostra una maggiore gravità. Questo studio è in contrasto con altri precedenti, rispetto ai quali ha però alcuni punti di forza come l'effettivo sequenziamento di SARS-CoV-2 per identificare le varianti.	Background : Emergence of variants with specific mutations in key epitopes in the spike protein of SARS-CoV-2 raises concerns pertinent to mass vaccination campaigns and use of monoclonal antibodies. We aimed to describe the emergence of the B.1.1.7 variant of concern (VOC), including virological characteristics and clinical severity in contemporaneous patients with and without the variant. Methods : In this cohort study, samples positive for SARS-CoV-2 on PCR that were collected from Nov 9, 2020, for patients acutely admitted to one of two hospitals on or before Dec 20, 2020, in London, UK, were sequenced and analysed for the presence of VOC-defining mutations. We fitted Poisson regression models to investigate the association between B.1.1.7 infection and severe disease (defined as point 6 or higher on the WHO ordinal scale within 14 days of symptoms or positive test) and death within 28 days of a positive test and did supplementary genomic analyses in a cohort of chronically shedding patients and in a cohort of remdesivir-treated patients. Viral load was compared by proxy, using PCR cycle threshold values and sequencing read depths. Findings : Of 496 patients with samples positive for SARS-CoV-2 on PCR and who met inclusion criteria, 341 had samples that could be

			sequenced. 198 (58%) of 341 had B.1.1.7 infection and 143 (42%) had non-B.1.1.7 infection. We found no evidence of an association between severe disease and death and lineage (B.1.1.7 vs non-B.1.1.7) in unadjusted analyses (prevalence ratio [PR] 0·97 [95% CI 0·72–1·31]), or in analyses adjusted for hospital, sex, age, comorbidities, and ethnicity (adjusted PR 1·02 [0·76–1·38]). We detected no B.1.1.7 VOC-defining mutations in 123 chronically shedding immunocompromised patients or in 32 remdesivir-treated patients. Viral load by proxy was higher in B.1.1.7 samples than in non-B.1.1.7 samples, as measured by cycle threshold value (mean 28·8 [SD 4·7] vs 32·0 [4·8]; p=0·0085) and genomic read depth (1280 [1004] vs 831 [682]; p=0·0011). Interpretation : Emerging evidence exists of increased transmissibility of B.1.1.7, and we found increased virus load by proxy for B.1.1.7 in our data. We did not identify an association of the variant with severe disease in this hospitalised cohort.
Ong SWX et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00201-2/fulltext	Lack of detail in population-level data impedes analysis of SARS-CoV-2 variants of concern and clinical outcomes	Commento allo studio precedente e opinioni degli autori su come interpretare l'effetto clinico delle varianti di SARS-CoV-2, in considerazione delle lacune spesso presenti nei dati a disposizione.	Genetic drift and selection pressures (in particular with passive antibody treatments and vaccination) will continue to engender changes in SARS-CoV-2 and might result in the emergence of variants of high consequence—variants that are more virulent, escape from host immunity, or are resistant to treatment. Active, timely, and broad-based genomic surveillance is crucial for their early detection. But careful epidemiologic and clinical assessment, coupled with a healthy scepticism, is important when assessing claims of the effect of these variants.
Ufficio Registri di Monitoraggio AIFA https://www.aifa.gov.it/documents/20142/147552	Report n.1 Monitoraggio Anticorpi Monoclonali per COVID-19	Dati dal registro AIFA sulla prescrizione di anticorpi monoclonali per COVID-19 : al 9 aprile inseriti 1423 pazienti.	Dati relativi alla settimana 2 – 8 aprile 2021 (estrazione dati 9 aprile 2021)

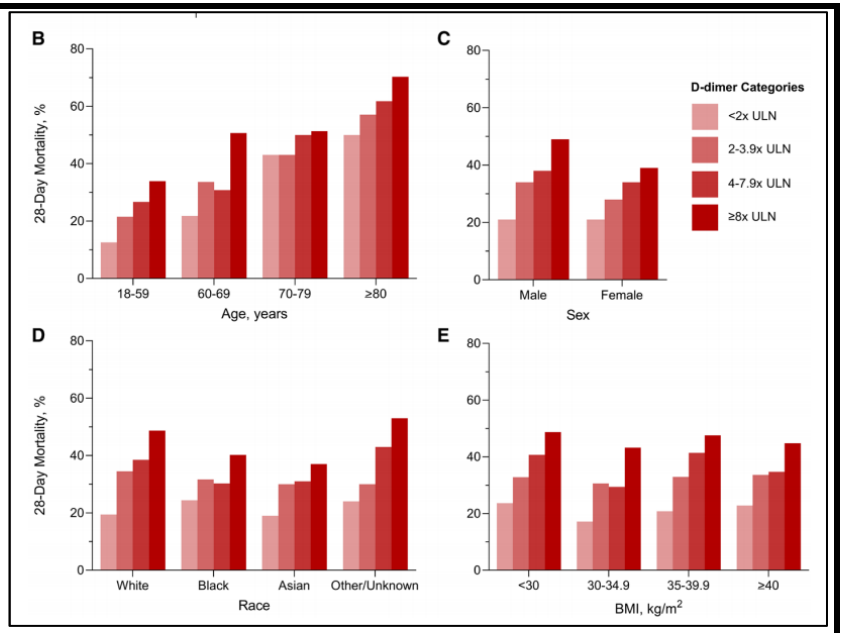
6/report_n.1_monitoraggio_monoclonali_09.04.2021.pdf			
Blain H et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2778926	Spike Antibody Levels of Nursing Home Residents With or Without Prior COVID-19 3 Weeks After a Single BNT162b2 Vaccine Dose	Il livello di IgG anti-proteina S di SARS-CoV-2 è significativamente più elevato dopo una sola dose di vaccino a mRNA in soggetti anziani residenti in case di riposo con storia di infezione (tampone o sierologia positiva) rispetto ai naive. Questo conferma negli anziani quanto già osservato in soggetti più giovani.	Recent studies have suggested that, to reach immunity, immunocompetent SARS-CoV-2 seropositive adults may only require 1 dose rather than 2 doses of a messenger RNA vaccine1,2; however, these studies did not include older adults. Older adults living in nursing homes are at higher risk for severe COVID-19, and the immune response to the vaccine may differ from that of younger, healthier adults. We compared IgG antibody levels after a single dose of BNT162b2 (Pfizer-BioNTech) vaccine in nursing home residents with or without prior COVID-19.  Figure. Levels of IgG Antibody Against the SARS-CoV-2 Spike (S) Protein After a Single Dose of Vaccine in Nursing Home Residents S-protein IgG level, AU/mL 100 000 10 000 1000 100 10 1 Seronegative for N-protein IgG Seropositive for N-protein IgG Seronegative for N-protein IgG Seropositive for N-protein IgG Negative RT-PCR result Positive RT-PCR result

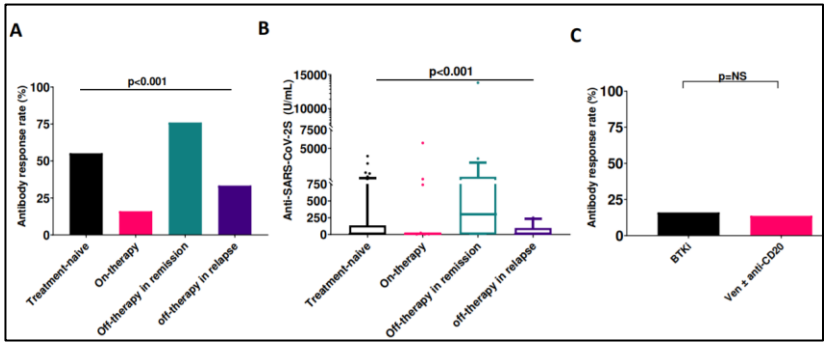
Scully M et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2105385?query=featured_home	Pathologic Antibodies to Platelet Factor 4 after ChAdOx1 nCoV-19 Vaccination	Un'altra casistica di 23 pazienti con trombocitopenia e trombosi (e 1 caso di diatesi emorragica) in seguito ad assunzione di vaccino Astrazeneca/Vaxzevria contro SARS-CoV-2 : 21/23 avevano anticorpi anti-fattore piastrinico 4.	BACKGROUND : The mainstay of control of the coronavirus disease 2019 (Covid-19) pandemic is vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Within a year, several vaccines have been developed and millions of doses delivered. Reporting of adverse events is a critical postmarketing activity. METHODS : We report findings in 23 patients who presented with thrombosis and thrombocytopenia 6 to 24 days after receiving the first dose of the ChAdOx1 nCoV-19 vaccine (AstraZeneca). On the basis of their clinical and laboratory features, we identify a novel underlying mechanism and address the therapeutic implications. RESULTS : In the absence of previous prothrombotic medical conditions, 22 patients presented with acute thrombocytopenia and thrombosis, primarily cerebral venous thrombosis, and 1 patient presented with isolated thrombocytopenia and a hemorrhagic phenotype. All the patients had low or normal fibrinogen levels and elevated d-dimer levels at presentation. No evidence of thrombophilia or causative precipitants was identified. Testing for antibodies to platelet factor 4 (PF4) was positive in 21 patients, negative in 1 patient, and equivocal in 1 patient. On the basis of the pathophysiological features observed in these patients, we recommend that treatment with platelet transfusions be avoided because of the risk of progression in thrombotic symptoms and that the administration of a nonheparin anticoagulant agent and intravenous immune globulin be considered for the first occurrence of these symptoms. CONCLUSIONS : Vaccination against SARS-CoV-2 remains critical for control of the Covid-19 pandemic. A pathogenic PF4-dependent syndrome, unrelated to the use of heparin therapy, can occur after the administration of the ChAdOx1 nCoV-19 vaccine. Rapid

			identification of this rare syndrome is important because of the therapeutic implications.
De la MorenaBarrio ME et al Scientific Reports https://www.nature.com/articles/s41598-021-85906-y	Prognostic value of thrombin generation parameters in hospitalized COVID-19 patients	Confronto fra 127 pazienti ricoverati per COVID-19, 24 ricoverati per polmonite non associata a SARS-CoV-2 e 12 sani, di cui si studia la produzione di trombina in relazione alla gravità clinica: una minore produzione, come possibile effetto di coagulopatia in atto, è associata insieme all'elevazione dei D-dimeri a prognosi peggiore nei pazienti con COVID-19.	SARS-CoV-2 infection increases the risk of thrombosis by different mechanisms not fully characterized. Although still debated, an increase in D-dimer has been proposed as a first-line hemostasis test associated with thromboembolic risk and unfavorable prognosis. We aim to systematically and comprehensively evaluate the association between thrombin generation parameters and the inflammatory and hypercoagulable state, as well as their prognostic value in COVID-19 patients. A total of 127 hospitalized patients with confirmed COVID-19, 24 hospitalized patients with SARS-CoV-2-negative pneumonia and 12 healthy subjects were included. Clinical characteristics, thrombin generation triggered by tissue factor with and without soluble thrombomodulin, and also by silica, as well as other biochemical parameters were assessed. Despite the frequent use of heparin, COVID-19 patients had similar thrombin generation to healthy controls. In COVID-19 patients, the thrombin generation lag-time positively correlated with markers of cell lysis (LDH), inflammation (CRP, IL-6) and coagulation (D-dimer), while the endogenous thrombin potential (ETP) inversely correlated with D-dimer and LDH, and positively correlated with fibrinogen levels. Patients with more prolonged lag-time and decreased ETP had higher peak ISTH-DIC scores, and had more severe disease (vascular events and death). The ROC curve and Kaplan Meier estimate indicated that the D-dimer/ETP ratio was associated with in-hospital mortality (HR 2.5; p = 0.006), and with the occurrence of major adverse events (composite end-point of vascular events and death) (HR 2.38; p = 0.004). The thrombin generation ETP and lag-time

			variables correlate with thromboinflammatory markers, and the D-dimer/ETP ratio can predict major adverse events in COVID-19.  **Figure 4.** Schematic representation of potential insults associated to SARS-CoV-2 infection and the consequences on the hemostatic system. The drawing is a modified version of an image available in Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.
Short S et al Critical Care Medicine https://journals.lww.com/ccmjournal/Fulltext/2021/05000/d_dimer_and_Death_in_Critically_Ill_Patients_With.19.aspx?context=FeaturedArticles&collectionId=3	d-dimer and Death in Critically Ill Patients With Coronavirus Disease 2019	In questo studio di coorte multicentrico su oltre 3400 pazienti ricoverati in terapia intensiva per COVID-19 si osserva una associazione fra livelli maggiori di D-dimeri circolanti e rischio di morte a 28 giorni.	OBJECTIVES: Hypercoagulability may be a key mechanism for acute organ injury and death in patients with severe coronavirus disease 2019, but the relationship between elevated plasma levels of d-dimer, a biomarker of coagulation activation, and mortality has not been rigorously studied. We examined the independent association between d-dimer and death in critically ill patients with coronavirus disease 2019. DESIGN: Multicenter cohort study. SETTING: ICUs at 68 hospitals across the United States. PATIENTS: Critically ill adults with coronavirus disease 2019 admitted to ICUs between March 4, 2020, and May 25, 2020, with a measured d-dimer concentration on ICU day 1 or 2. INTERVENTIONS: None.

			MEASUREMENTS AND MAIN RESULTS: The primary exposure was the highest normalized d-dimer level (assessed in four categories: < 2×, 2–3.9×, 4–7.9×, and ≥ 8× the upper limit of normal) on ICU day 1 or 2. The primary endpoint was 28-day mortality. Multivariable logistic regression was used to adjust for confounders. Among 3,418 patients (63.1% male; median age 62 yr [interquartile range, 52–71 yr]), 3,352 (93.6%) had a d-dimer concentration above the upper limit of normal. A total of 1,180 patients (34.5%) died within 28 days. Patients in the highest compared with lowest d-dimer category had a 3.11-fold higher odds of death (95% CI, 2.56–3.77) in univariate analyses, decreasing to a 1.81-fold increased odds of death (95% CI, 1.43–2.28) after multivariable adjustment for demographics, comorbidities, and illness severity. Further adjustment for therapeutic anticoagulation did not meaningfully attenuate this relationship (odds ratio, 1.73; 95% CI, 1.36–2.19). CONCLUSIONS: In a large multicenter cohort study of critically ill patients with coronavirus disease 2019, higher d-dimer levels were independently associated with a greater risk of death.

			
Herishanu Y et al Blood https://ashpublications.org/blood/article/doi/10.1182/blood.2021011568/475742/Efficacy-of-the-BNT162b2-mRNA-COVID-19-Vaccine-in?searchresult=1	Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia	Confronto fra 52 pazienti con leucemia linfatica cronica vaccinati con vaccino Pfizer contro SARS-CoV-2 e 52 controlli non affetti da LLC: la risposta anticorpale è significativamente meno presente negli affetti da leucemia, soprattutto in coloro con malattia attiva e in trattamento.	Patients with chronic lymphocytic leukemia (CLL) have an increased risk for severe COVID-19 disease and mortality. The goal of this study (NCT04746092) was to determine the efficacy of COVID-19 vaccine in patients with CLL. We evaluated humoral immune responses to BNT162b2 mRNA COVID-19 vaccine in patients with CLL and compared responses with those obtained in age-matched healthy controls. Patients received two vaccine doses, 21 days apart, and antibody titers were measured using Elecsys® Anti-SARS-CoV-2S assay after administration of the second dose. In a total of 167 patients with CLL the antibody response rate was 39.5%. A comparison between 52 patients with CLL and 52 sex- and aged-matched healthy controls, revealed a significantly reduced response rate among patients (52% vs 100%, respectively; adjusted odds ratio=0.010, 95% CI 0.001-0.162; p<0.001). Response rate was highest in patients who obtained clinical remission after treatment

			(79.2%), followed by 55.2% in treatment-naïve and 16% only in patients under treatment at the time of vaccination. In patients treated with either BTK inhibitors or venetoclax ± anti-CD20 antibody, response rates were considerably low (16.0% and 13.6%, respectively). None of the patients exposed to anti-CD20 antibodies <12 months prior to vaccination responded. In a multivariate analysis, the independent predictors of response were younger age, females, lack of currently active treatment, IgG levels ≥550 mg/dL and IgM levels ≥40mg/dL. In conclusion, antibody-mediated response to BNT162b2 mRNA COVID-19 vaccine in patients with CLL is markedly impaired and affected by disease activity and treatment. 
Sadoff J et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2106075?query=featured_home	Thrombotic Thrombocytopenia after Ad26.COV2.S Vaccination — Response from the Manufacturer	I produttori del vaccino Janssen sostengono la differenza fra il vettore virale di Vaxzevria/Astrazeneca (di scimpanzé) e il proprio (umano), che farebbe prevedere un minore rischio trombotico.	The Ad26.COV2.S vaccine uses a human Ad26–based vector, whereas the ChAdOx1 nCoV-19 vaccine uses a chimpanzee adenovirus–based vector (references S3 and S4). Ad26 is from Ad species D and can engage CD46 as its cellular receptor, whereas ChAdOx1 nCoV-19 is from Ad species E and uses the Coxsackie and adenovirus receptor (CAR) and possibly other molecules as its cellular receptors; these two vectors thus use different host cell receptors and are likely to have different phylogenetic and biologic characteristics. In addition, the Ad26.COV2.S vaccine transgene codes for a membrane-bound SARS-CoV-2 S protein (prefusion

			conformation–stabilized by two proline substitutions) that does not shed S1, most likely as a consequence of knocking out the furin cleavage site (reference S5), which is different from the unmodified S protein encoded by the ChAdOx1 nCoV-19 vaccine. Therefore, these two adenoviral vector Covid-19 vaccines may have quite different biologic effects. More evidence is needed to clarify the observation of thrombotic thrombocytopenia in persons receiving a vaccine against Covid-19.
Tang J et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab317/6228549?searchresult=1	Impact of convalescent plasma therapy on SARS CoV-2 antibody profile in COVID-19 patients	Lo studio degli anticorpi contro SARS-CoV-2 in 16 pazienti con COVID-19, di cui 8 trattati con plasma di convalescenti, mostra che il titolo neutralizzante e l'avidità degli anticorpi non si modificano dopo il trattamento. Inoltre nei pazienti con esito infausto il titolo neutralizzante va riducendosi prima del decesso.	Convalescent plasma (CP) have been used for treatment of COVID-19, but their effectiveness varies significantly. Moreover, the impact of CP treatment on the composition of SARS-CoV-2 antibodies in COVID-19 patients and antibody markers that differentiate between those who survive and those who succumb to the COVID-19 disease are not well understood. Herein, we performed longitudinal analysis of antibody profile on 115 sequential plasma samples from 16 hospitalized COVID-19 patients treated with either CP or standard of care, only half of them survived. Differential antibody kinetics was observed for antibody binding, IgM/IgG/IgA distribution, and affinity maturation in 'survived' vs. 'fatal' COVID-19 patients. Surprisingly, CP treatment did not predict survival. Strikingly, marked decline in neutralization titers was observed in the fatal patients prior to death, and convalescent plasma treatment did not reverse this trend. Furthermore, irrespective of CP treatment, higher antibody affinity to the SARS-CoV-2 prefusion spike was associated with survival outcome, while sustained elevated IgA response was associated with fatal outcome in these COVID-19 patients. These findings propose that treatment of COVID-19 patients with convalescent plasma should be carefully targeted, and effectiveness of treatment may depend on the clinical and

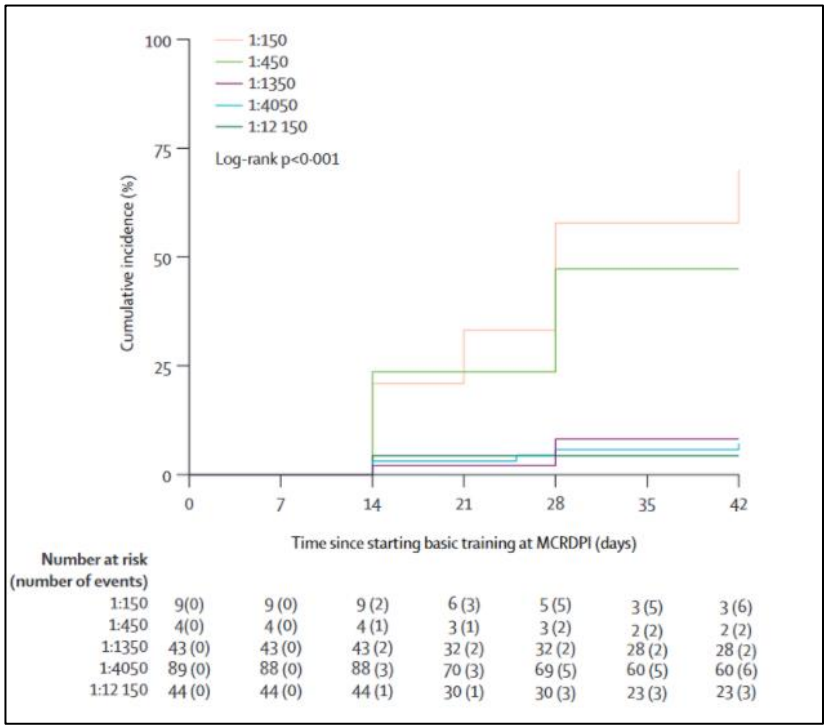
			immunological status of COVID-19 patients as well as the quality of the antibodies in the convalescent plasma.
Alrubayyi A et al Nature https://www.nature.com/articles/s41577-021-00551-w	Seeing SARS-CoV-2 variants through the eyes of T cells	Commento a un articolo pre-print non revisionato in cui si osserva come le mutazioni della proteina spike tipiche delle varianti di SARS-CoV-2 non abbiano effetto significativo sull'affinità con i recetti T-cellulari rispetto al virus ancestrale, salvo come sempre la variante "sudafricana".	Both CD4+ and CD8+ T cells from COVID-19 convalescent donors were found to recognize the ancestral reference strain and the variant proteome-wide sequences with similar efficiency. In mRNA vaccine recipients also, CD4+ and CD8+ T cell responses to the ancestral and variant peptide pools were similar, with the exception of the B.1.351 variant, for which mildly decreased T cell reactivity to S protein peptides was observed. Analysis of defined T cell epitopes showed that 93% of CD4+ T cell epitopes and 97% of CD8+ T cell epitopes are conserved in the analysed variants. Single point mutations in the T cell epitopes were predicted to have no negative effect on HLA binding capacity, which provides a molecular basis for the marginal impact of the mutations on T cell responses in the study group.
Grasselli G et al Chest https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/33857475	Hospital-acquired infections in critically-ill COVID-19 patients.	Studio retrospettivo multicentrico su 774 pazienti ricoverati per COVID-19, di cui si ricercano i fattori di rischio per infezioni nosocomiali: la ventilazione con pressione positiva e l'utilizzo di antibiotici ad ampio spettro all'ingresso sono associati ad infezioni batteriche.	BACKGROUND: Few small studies have described hospital-acquired infections (HAIs) during COVID-19. RESEARCH QUESTION: What patient characteristics in critically ill patients with COVID-19 are associated with HAIs and how do HAIs associate with outcomes in these patients? STUDY DESIGN AND METHODS: Multicenter retrospective analysis of prospectively collected data including adult patients with severe COVID-19, admitted to 8 Italian hub hospitals from February 20, 2020, to May 20, 2020. Descriptive statistics, univariable and multivariable Weibull regression models were used to assess incidence, microbial etiology, resistance patterns, risk factors (i.e., demographics, comorbidities, exposure to medication), and impact on outcomes (i.e., ICU survival, length of ICU and hospital stay and duration of mechanical ventilation) of

			microbiologically-confirmed HAIs. RESULTS: Of the 774 included patients, 359 (46%) patients developed 759 HAIs (44.7 infections/1000 ICU patient-days, 35% multi-drug resistant (MDR) bacteria). Ventilator-associated pneumonia (VAP) (389, 50%), bloodstream infections (183, 34%), and catheter related blood stream infections (74, 10%) were the most frequent HAIs, with 26.0 (23.6-28.8) VAPs/1000 patient intubation-days, 11.7(10.1-13.5) BSIs/1000 ICU patient-days, and 4.7 (3.8-5.9) CRBSIs/1000 patient-days. Gram-negative bacteria (especially Enterobacterales) and Staphylococcus aureus caused 64% and 28% of VAPs. Variables independently associated with infection were age, PEEP and treatment with broad-spectrum antibiotic at admission. 234 patients (30%) died in ICU (15.3 deaths/1000 ICU patient-days). Patients with HAIs complicated by septic shock had almost doubled mortality (52% vs. 29%), while non-complicated infections did not affect mortality. HAIs prolonged mechanical ventilation (24(14-39) vs. 9(5-13) days; p<0.001), ICU and hospital stay (24(16-41) vs. 9(6-14) days, p=0.003; and (42(25-59) vs. 23(13-34) days, p<0.001). INTERPRETATION: Critically-ill COVID-19 patients are at high risk for HAIs, especially VAPs and BSIs due to MDR organisms. HAIs prolong mechanical ventilation and hospitalization, and HAIs complicated by septic-shock almost doubled mortality.
Rief W JAMA https://jamanetwork.com/channels/health-forum/fullarticle/2779081	Fear of Adverse Effects and COVID-19 Vaccine Hesitancy	Alcuni consigli su come affrontare i dubbi e i timori legati alla vaccinazione contro SARS-CoV-2 da parte dei pazienti.	Health care decisions, including whether to take part in vaccination against COVID-19, are based on the comparison of the potential costs of participation with the expected benefits. Costs can span a variety of factors, but fear of adverse effects has featured prominently in recent surveys. As extensive research of our groups and others on nocebo effects has shown,1 it is—ironically—this very same fear that can amplify and even induce adverse effects. Therefore, addressing concerns by providing evidence-based

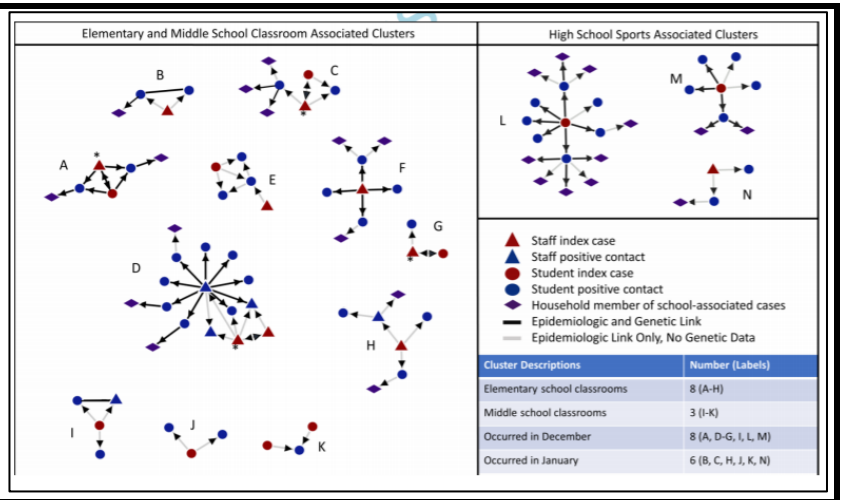
			information as part of larger information campaigns and individual conversations is key to increasing vaccine uptake. We present a number of strategies that can be adopted to target a fear of adverse effects.
Ledford H Nature https://www.nature.com/articles/d41586-021-00998-w	COVID vaccines and blood clots: five key questions	Riflessioni sugli effetti avversi tromboembolici associati ai vaccini contro SARS-CoV-2 e domande aperte.	ome of that confusion stems from an urgent need to act quickly on the basis of messy, incomplete and capricious real-world data. As regulators are forced to make decisions, scientists are still racing to investigate the rare clotting disorder and its link to the vaccines. Here are some of the key questions that they are hoping to answer : What could the connection be between blood clots and vaccines? Are other COVID-19 vaccines linked to blood-clotting disorders? How rare are the blood clots in vaccinated people? Are certain groups of people more at risk? What impact will fears over potential side effects have on global vaccination efforts?
Braun KM et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab281/6226897?searchresult=1	Viral sequencing reveals US healthcare personnel rarely become infected with SARS-CoV-2 through patient contact	In questo studio retrospettivo su 95 operatori sanitari con infezione da SARS-CoV-2 e 137 pazienti individuati come possibile fonte, si osserva in realtà che solo in 4/95 casi, sulla base del sequenziamento di SARS-CoV-2, il virus dell'operatore sanitario e quello del paziente "indiziato" coincidevano: l'infezione acquisita in comunità appare più frequente almeno in questa casistica.	Background : Healthcare personnel (HCP) are at increased risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). We posit current infection control guidelines generally protect HCP from SARS-CoV-2 infection in a healthcare setting. Methods : In this retrospective case series, we use viral genomics to investigate the likely source of SARS-CoV-2 infection in HCP at a major academic medical institution in the Upper Midwest of the United States between 25 March - 27 December, 2020. We obtain limited epidemiological data through informal interviews and review of the electronic health record. We combine epidemiological information with healthcare-associated viral sequences and with viral sequences collected in the broader community to infer the most likely source of infection in HCP. Results : We investigated SARS-CoV-2 infection clusters involving 95 HCP and 137 possible patient contact sequences. The majority of

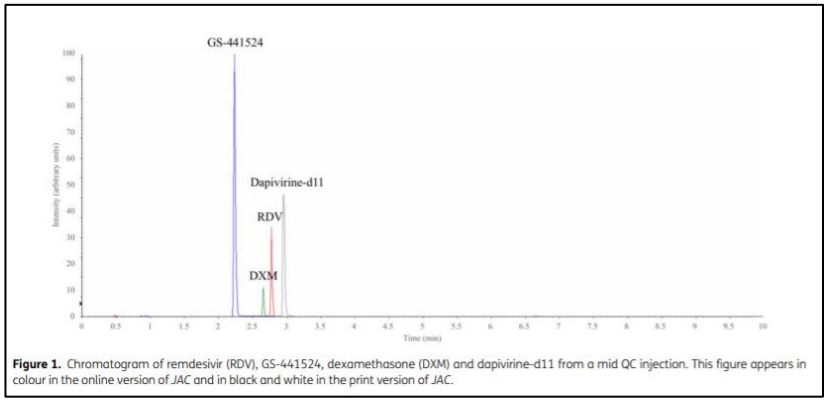
			HCP infections could not be linked to a patient or co-worker (55/95; 57.9%) and were genetically similar to viruses circulating concurrently in the community. We found 10.5% of infections could be traced to a coworker (10/95). Strikingly, only 4.2% of HCP infections could be traced to a patient source (4/95). Conclusions : Infections among HCP add further strain to the healthcare system and put patients, HCP, and communities at risk. We found no evidence for healthcare-associated transmission in the majority of HCP infections evaluated here. Though we cannot rule out the possibility of cryptic healthcare-associated transmission, it appears that HCP most commonly becomes infected with SARS-CoV-2 via community exposure. This emphasizes the ongoing importance of mask-wearing, physical distancing, robust testing programs, and rapid distribution of vaccines.
Letizia AG et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00158-2/fulltext	SARS-CoV-2 seropositivity and subsequent infection risk in healthy young adults: a prospective cohort study	Studio di coorte prospettico di 6 settimane su 3076 giovani adulti (Marines) di cui si osserva il rischio di infezione da SARS-CoV-2 in base allo stato sierologico di partenza: una infezione pregressa conferisce una protezione dell'84% contro la reinfezione, con rischio maggiore in chi ha minore titolo di IgG e anticorpi neutralizzanti.	Background : Whether young adults who are infected with SARS-CoV-2 are at risk of subsequent infection is uncertain. We investigated the risk of subsequent SARS-CoV-2 infection among young adults seropositive for a previous infection. Methods : This analysis was performed as part of the prospective COVID-19 Health Action Response for Marines study (CHARM). CHARM included predominantly male US Marine recruits, aged 18–20 years, following a 2-week unsupervised quarantine at home. After the home quarantine period, upon arrival at a Marine-supervised 2-week quarantine facility (college campus or hotel), participants were enrolled and were assessed for baseline SARS-CoV-2 IgG seropositivity, defined as a dilution of 1:150 or more on receptor-binding domain and full-length spike protein ELISA. Participants also completed a questionnaire consisting of demographic information, risk factors, reporting of 14 specific COVID-19-related symptoms or any other unspecified symptom,

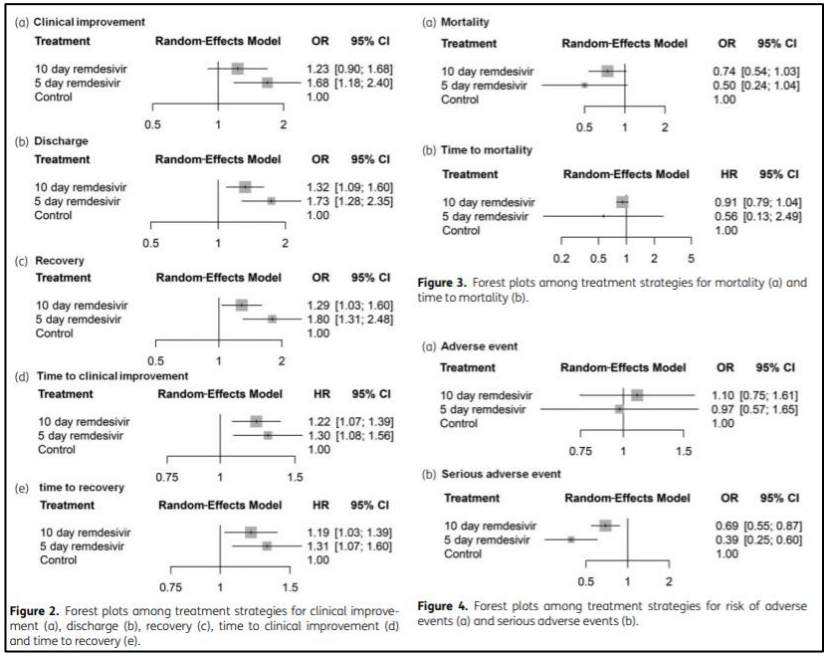
			and brief medical history. SARS-CoV-2 infection was assessed by PCR at weeks 0, 1, and 2 of quarantine and participants completed a follow-up questionnaire, which included questions about the same COVID-19-related symptoms since the last study visit. Participants were excluded at this stage if they had a positive PCR test during quarantine. Participants who had three negative swab PCR results during quarantine and a baseline serum serology test at the beginning of the supervised quarantine that identified them as seronegative or seropositive for SARS-CoV-2 then went on to basic training at Marine Corps Recruit Depot—Parris Island. Three PCR tests were done at weeks 2, 4, and 6 in both seropositive and seronegative groups, along with the follow-up symptom questionnaire and baseline neutralising antibody titres on all subsequently infected seropositive and selected seropositive uninfected participants (prospective study period). Findings : Between May 11, 2020, and Nov 2, 2020, we enrolled 3249 participants, of whom 3168 (98%) continued into the 2-week quarantine period. 3076 (95%) participants, 2825 (92%) of whom were men, were then followed up during the prospective study period after quarantine for 6 weeks. Among 189 seropositive participants, 19 (10%) had at least one positive PCR test for SARS-CoV-2 during the 6-week follow-up (1·1 cases per person-year). In contrast, 1079 (48%) of 2247 seronegative participants tested positive (6·2 cases per person-year). The incidence rate ratio was 0·18 (95% CI 0·11–0·28; p<0·001). Among seropositive recruits, infection was more likely with lower baseline full-length spike protein IgG titres than in those with higher baseline full-length spike protein IgG titres (hazard ratio 0·45 [95% CI 0·32–0·65]; p<0·001). Infected seropositive participants had viral loads that were about 10-times lower than those of infected seronegative participants

			(ORF1ab gene cycle threshold difference 3·95 [95% CI 1·23–6·67]; p=0·004). Among seropositive participants, baseline neutralising titres were detected in 45 (83%) of 54 uninfected and in six (32%) of 19 infected participants during the 6 weeks of observation (ID50 difference p<0·0001). Interpretation : Seropositive young adults had about one-fifth the risk of subsequent infection compared with seronegative individuals. Although antibodies induced by initial infection are largely protective, they do not guarantee effective SARS-CoV-2 neutralisation activity or immunity against subsequent infection. These findings might be relevant for optimisation of mass vaccination strategies. 

Gettings JR et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab332/6232104?searchresult=1	SARS-CoV-2 transmission in a Georgia school district — United States, December 2020–January 2021	Studio dei casi secondari di infezione da SARS-CoV-2 in una scuola americana nel periodo dicembre 2020-gennaio 2021: 86 casi indice, 59/679 contatti sono divenuti casi secondari, di cui oltre la metà asintomatici. I contesti cui si fa risalire la gran parte dei contagi sono gli sport al chiuso, le riunioni al chiuso e le lezioni di scuola elementare.	Background : To inform prevention strategies, we assessed the extent of SARS-CoV-2 transmission and settings in which transmission occurred in a Georgia public school district. Methods : During December 1, 2020–January 22, 2021, SARS-CoV-2–infected index cases and their close contacts in schools were identified by school and public health officials. For in-school contacts, we assessed symptoms and offered SARS-CoV-2 RT-PCR testing; performed epidemiologic investigations and whole-genome sequencing to identify in-school transmission; and calculated secondary attack rate (SAR) by school setting (e.g., sports, elementary school classroom), index case role (i.e., staff, student), and index case symptomatic status. Results : We identified 86 index cases and 1,119 contacts, 688 (63.1%) of whom received testing. Fifty-nine (8.7%) of 679 contacts tested positive; 15 (17.4%) of 86 index cases resulted in ≥2 positive contacts. Among 55 persons testing positive with available symptom data, 31 (56.4%) were asymptomatic. Highest SAR were in indoor, high-contact sports settings (23.8%, 95% confidence interval [CI] 12.7, 33.3), staff meetings/lunches (18.2%, CI 4.5–31.8), and elementary school classrooms (9.5%, CI 6.5–12.5). SAR was higher for staff (13.1%, CI 9.0–17.2) versus student index cases (5.8%, CI 3.6–8.0) and for symptomatic (10.9%, CI 8.1–13.9) versus asymptomatic index cases (3.0%, CI 1.0–5.5). Conclusions : Indoor sports may pose a risk to the safe operation of in-person learning. Preventing infection in staff members, through measures that include COVID-19 vaccination, is critical to reducing in-school transmission. Because many positive contacts were asymptomatic, contact tracing should be paired with testing, regardless of symptoms.

			
Reckers A et al Journal of Antimicrobial Chemotherapy https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkab094/6231591?searchresult=1	A combined assay for quantifying remdesivir and its metabolite, along with dexamethasone, in serum	Quantificazione rapida tramite cromatografia liquida e spettrometria di massa dei livelli di remdesivir e desametasone nel siero di pazienti trattati per COVID-19, utilizzabile al fine di ottimizzare le dosi.	Background : As global confirmed cases and deaths from coronavirus disease 2019 (COVID-19) surpass 100 and 2.2 million, respectively, quantifying the effects of the widespread treatment of remdesivir (GS-5734, Veklury) and the steroid dexamethasone is becoming increasingly important. Limited pharmacokinetic studies indicate that remdesivir concentrations in serum decrease quickly after dosing, so its primary serum metabolite GS-441524 may have more analytical utility. Objectives : We developed and validated a method to quantify remdesivir, its metabolite GS-441524 and dexamethasone in human serum. Methods : We used LC-MS/MS and applied the method to 23 serum samples from seven patients with severe COVID-19. Results : The method has limits of detection of 0.0375 ng/mL for remdesivir, 0.375 ng/mL for GS-441524 and 3.75 ng/mL for dexamethasone. We found low intra-patient variability, but significant inter-patient variability, in remdesivir, GS-441524 and dexamethasone levels.

			Conclusions : The significant inter-patient variability highlights the importance of therapeutic drug monitoring of COVID-19 patients and possible dose adjustment to achieve efficacy.  **Figure 1.** Chromatogram of remdesivir (RDV), GS-441524, dexamethasone (DXM) and dapivirine-d11 from a mid QC injection. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.
Lai C et al Journal of Antimicrobial Chemotherapy https://academic.oup.com/jac/advance-article/doi/10.1093/jac/dkab093/6184581?searchresult=1	Clinical efficacy and safety of remdesivir in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials	Revisione sistematica e metanalisi sull'effetto del remdesivir (per 5 o 10 giorni) sugli outcome di COVID-19: beneficio sul miglioramento clinico e la durata del trattamento, non sulla mortalità.	Objectives : We performed a systematic review and network meta-analysis of randomized controlled trials (RCTs) to provide updated information regarding the clinical efficacy of remdesivir in treating coronavirus disease 2019 (COVID-19). Methods : PubMed, Embase, Cochrane Library, clinical trial registries of ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform were searched for relevant articles published up to 18 November 2020. Results : Five RCTs, including 13 544 patients, were included in this meta-analysis. Among them, 3839 and 391 patients were assigned to the 10 day and 5 day remdesivir regimens, respectively. Patients receiving 5 day remdesivir therapy presented greater clinical improvement than those in the control group [OR = 1.68 (95% CI 1.18–2.40)], with no significant difference observed between the 10 day and placebo groups [OR = 1.23 (95% CI 0.90–1.68)]. Patients receiving remdesivir revealed a greater likelihood of discharge [10 day remdesivir versus control: OR = 1.32 (95% CI 1.09–1.60); 5 day remdesivir versus control: OR = 1.73 (95% CI 1.28–2.35)] and

			recovery [10 day remdesivir versus control: OR = 1.29 (95% CI 1.03–1.60); 5 day remdesivir versus control: OR = 1.80 (95% CI 1.31–2.48)] than those in the control group. In contrast, no mortality benefit was observed following remdesivir therapy. Furthermore, no significant association was observed between remdesivir treatment and an increased risk of adverse events. Conclusions : Remdesivir can help improve the clinical outcome of hospitalized patients with COVID-19 and a 5 day regimen, instead of a 10 day regimen, may be sufficient for treatment. Moreover, remdesivir appears as tolerable as other comparators or placebo.  **Figure 2.** Forest plots among treatment strategies for clinical improvement (a), discharge (b), recovery (c), time to clinical improvement (d) and time to recovery (e). **Figure 3.** Forest plots among treatment strategies for mortality (a) and time to mortality (b). **Figure 4.** Forest plots among treatment strategies for risk of adverse events (a) and serious adverse events (b).