RICERCA BIBLIOGRAFICA COVID 19

SETTIMANA 31.05 – 06.06.2021

FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE

DOTT.SSA ELEONORA TADDEI

AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
Turner JS et al Nature https://www.nature.com/articles/s41586-021-03647-4	SARS-CoV-2 infection induces long-lived bone marrow plasma cells in humans	Induzione di una risposta umorale specifica duratura contro SARS-CoV-2, sulla base del fatto che si osservano plasmacellule del midollo osseo in pazienti convalescenti anche a 7-8 mesi dall'infezione.	Long-lived bone marrow plasma cells (BMPCs) are a persistent and essential source of protective antibodies1–7. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) convalescent individuals have a significantly lower risk of reinfection8–10. Nonetheless, it has been reported that anti-SARS-CoV-2 serum antibodies experience rapid decay in the first few months after infection, raising concerns that long-lived BMPCs may not be generated and humoral immunity against this virus may be short-lived11–13. Here we demonstrate that in patients who experienced mild infections (n=77), serum anti-SARS-CoV-2 spike (S) antibodies decline rapidly in the first 4 months after infection and then more gradually over the following 7 months, remaining detectable at least 11 months after infection. Anti-S antibody titers correlated with the frequency of S-specific BMPCs obtained from bone marrow aspirates of 18 SARS-CoV-2 convalescent patients 7 to 8 months after infection. S-specific BMPCs were not detected in aspirates

			from 11 healthy subjects with no history of SARS-CoV-2 infection. We demonstrate that S-binding BMPCs are quiescent, indicating that they are part of a long-lived compartment. Consistently, circulating resting memory B cells directed against the S protein were detected in the convalescent individuals. Overall, we show that SARS-CoV-2 infection induces a robust antigen-specific, long-lived humoral immune response in humans.
Liu Y et al The Lancet https://www.thelancet.com/journals/landig/article/PIIS2589-7500(21)00059-5/fulltext	Associations between changes in population mobility in response to the COVID-19 pandemic and socioeconomic factors at the city level in China and country level worldwide: a retrospective, observational study	Influenza di numerosi fattori fra cui le fasce d'età prevalenti nella popolazione o il livello di istruzione sulla mobilità cittadina in un ampio campione di 358 città cinesi.	Background : Until broad vaccination coverage is reached and effective therapeutics are available, controlling population mobility (ie, changes in the spatial location of a population that affect the spread and distribution of pathogens) is one of the major interventions used to reduce transmission of SARS-CoV-2. However, population mobility differs across locations, which could reduce the effectiveness of pandemic control measures. Here we assess the extent to which socioeconomic factors are associated with reductions in population mobility during the COVID-19 pandemic, at both the city level in China and at the country level worldwide. Methods : In this retrospective, observational study, we obtained anonymised daily mobile phone location data for 358 Chinese cities from Baidu, and for 121 countries from Google COVID-19 Community Mobility Reports. We assessed the intra-city movement intensity, inflow intensity, and outflow intensity of each Chinese city between Jan 25 (when the national emergency response was implemented) and Feb 18, 2020 (when population mobility was lowest) and compared these data to the corresponding lunar calendar period from the previous year (Feb 5 to March 1, 2019). Chinese cities were classified into four socioeconomic index (SEI) groups (high SEI, high–middle SEI, middle SEI, and low SEI) and the association between socioeconomic factors and changes in population mobility were assessed using univariate and

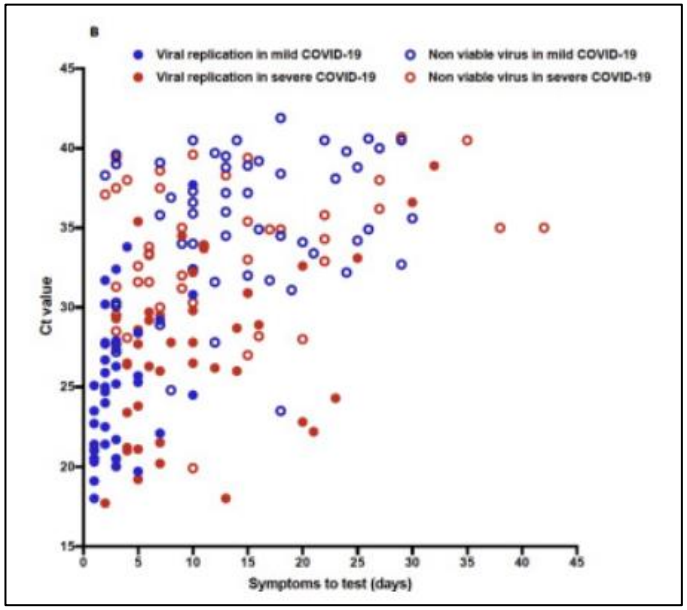
			multivariable linear regression. At the country level, we compared six types of mobility (residential, transit stations, workplaces, retail and recreation, parks, and groceries and pharmacies) 35 days after the implementation of the national emergency response in each country and compared these to data from the same day of the week in the baseline period (Jan 3 to Feb 6, 2020). We assessed associations between changes in the six types of mobility and the country's sociodemographic index using univariate and multivariable linear regression. Findings : The reduction in intra-city movement intensity in China was stronger in cities with a higher SEI than in those with a lower SEI (r=–0·47, p<0·0001). However, reductions in inter-city movement flow (both inflow and outflow intensity) were not associated with SEI and were only associated with government control measures. In the country-level analysis, countries with higher sociodemographic and Universal Health Coverage indexes had greater reductions in population mobility (ie, in transit stations, workplaces, and retail and recreation) following national emergency declarations than those with lower sociodemographic and Universal Health Coverage indexes. A higher sociodemographic index showed a greater reduction in mobility in transit stations (r=–0·27, p=0·0028), workplaces (r=–0·34, p=0·0002), and areas retail and recreation (rxs=–0·30, p=0·0012) than those with a lower sociodemographic index. Interpretation : Although COVID-19 outbreaks are more frequently reported in larger cities, our analysis shows that future policies should prioritise the reduction of risks in areas with a low socioeconomic level—eg, by providing financial assistance and improving public health messaging. However, our study design only

			allows us to assess associations, and a long-term study is needed to decipher causality.
Loenenbach A et al Eurosurveillance https://www.eurosurveillance.org/content/10.2807/1560-7917.ES.2021.26.21.2100433	SARS-CoV-2 variant B.1.1.7 susceptibility and infectiousness of children and adults deduced from investigations of childcare centre outbreaks, Germany, 2021	Secondo questo studio osservazionale condotto in Germania, con la variante « inglese » di SARS-CoV-2 la suscettibilità e l'infettività di adulti e bambini tendono a coincidere.	We investigated three SARS-CoV-2 variant B.1.1.7 childcare centre and related household outbreaks. Despite group cohorting, cases occurred in almost all groups, i.e. also among persons without close contact. Children's secondary attack rates (SAR) were similar to adults (childcare centres: 23% vs 30%; p = 0.15; households: 32% vs 39%; p = 0.27); child- and adult-induced household outbreaks also led to similar SAR. With the advent of B.1.1.7, susceptibility and infectiousness of children and adults seem to converge. Public health measures should be revisited accordingly.
Rennert L et al CID https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab454/6276528	Risk of SARS-CoV-2 reinfection in a university student population	Una pregressa infezione da SARS-CoV-2 conferisce una protezione dell'84% nei confronti della reinfezione in questa ampia casistica di studenti universitari.	We assess protection from previous SARS-CoV-2 infection in a population of 16,101 university students (2,021 with and 14,080 without previous infection). The risk of re-infection during the Spring 2021 semester was 2.2% among previously infected students; estimated protection from previous SARS-CoV-2 infection was 84% (95% CI: 78%-88%).
Vlasova AN et al CID https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab456/6278597	Novel Canine Coronavirus Isolated from a Hospitalized Pneumonia Patient, East Malaysia	Isolamento di un nuovo alfacoronavirus (SARS-CoV-2 è beta) canino-felino da pazienti con polmonite in Malesia.	Background : During the validation of a highly sensitive pan-species coronavirus (CoV) semi-nested RT-PCR assay, we found canine CoV (CCoV) RNA in nasopharyngeal swabs from eight (2.5%) of 301 patients hospitalized with pneumonia during 2017-18 in Sarawak, Malaysia. Most patients were children living in rural areas with frequent exposure to domesticated animals and wildlife. Methods : Specimens were further studied with universal and species-specific CoV and CCoV one-step RT-PCR assays, and viral

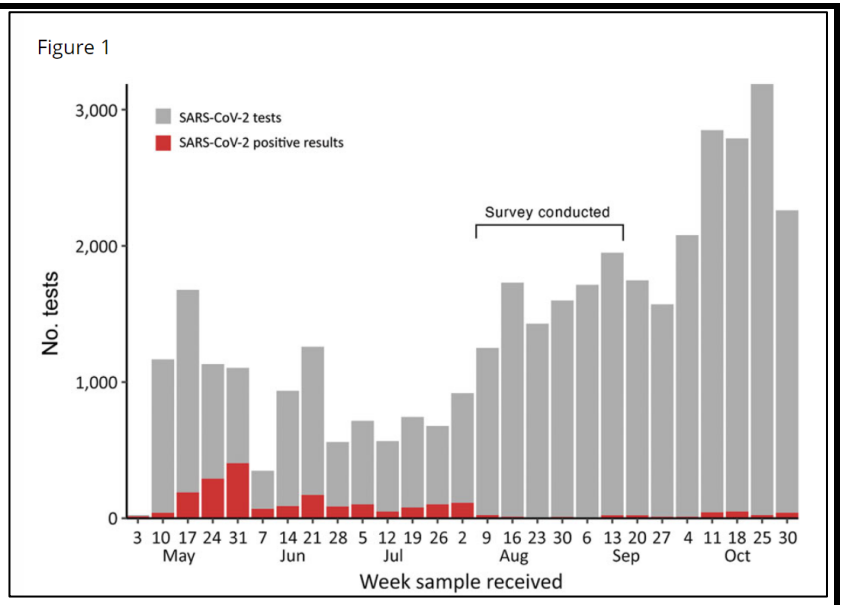
			isolation was performed in A72 canine cells. Complete genome sequencing was conducted using Sanger method. Results : Two of eight specimens contained sufficient amounts of CCoVs as confirmed by less-sensitive single-step RT-PCR assays, and one specimen demonstrated cytopathic effects (CPE) in A72 cells. Complete genome sequencing of the virus causing CPE identified it as a novel canine-feline recombinant alphacoronavirus (genotype II) that we named CCoV-HuPn-2018. Most of CCoV-HuPn-2018 genome is more closely related to a CCoV TN-449, while its S gene shared significantly higher sequence identity with CCoV-UCD-1 (S1 domain) and a feline CoV WSU 79-1683 (S2 domain). CCoV-HuPn-2018 is unique for a 36 nt (12-aa) deletion in the N protein and the presence of full-length and truncated 7b non-structural protein which may have clinical relevance. Conclusions : This is the first report of a novel canine-feline recombinant alphacoronavirus isolated from a human pneumonia patient. If confirmed as a pathogen, it may represent the eighth unique coronavirus known to cause disease in humans. Our findings underscore the public health threat of animal CoVs and a need to conduct better surveillance for them.
Istituto Superiore di Sanità https://www.epicentro.iss.it/vaccini/pdf/report-valutazione-impatto-vaccinazione-covid-19-15-mag-2021.pdf	Impatto della vaccinazione COVID-19 sul rischio di infezione da SARS-CoV-2 e successivo ricovero e decesso in Italia (27.12.2020 - 03.05.2021)	Report sull'effetto dei vaccini contro SARS-CoV-2 (almeno una dose) in Italia in termini di infezioni, ricoveri e decessi.	Questo è il primo report di analisi congiunta dei dati dell'anagrafe nazionale vaccini e della sorveglianza integrata COVID-19. Tale attività è stata possibile attraverso il Decreto-legge 14 gennaio 2021 n. 2, che disciplina i sistemi informativi funzionali all'implementazione del piano strategico dei vaccini per la prevenzione delle infezioni da SARS-CoV-2 (comma 7, art 3). - La gran parte delle persone vaccinate contro COVID-19 (95%) è stata aderente alla schedula vaccinale (seconda dose 21 + 4 giorni per Comirnaty e 28 + 2 giorni per Moderna).

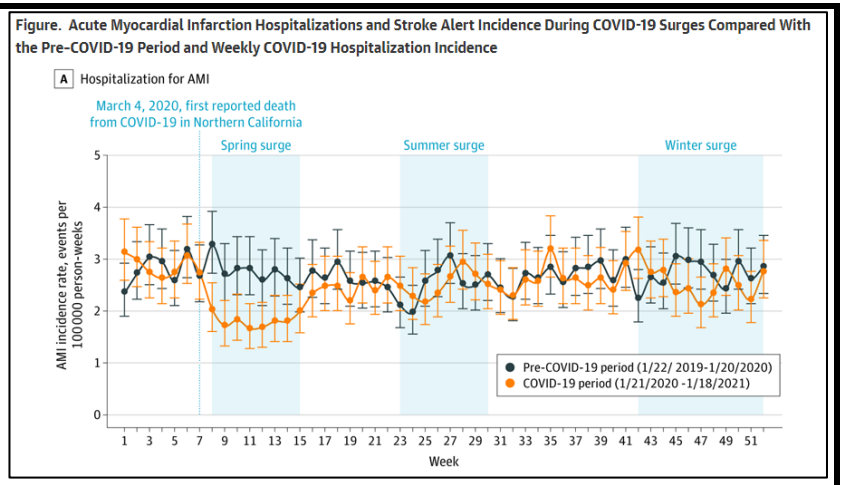
			- L'analisi congiunta ha evidenziato che il rischio di infezione da SARS-CoV-2, ricovero e decesso diminuisce progressivamente dopo le prime due settimane e fino a circa 35 giorni dopo la somministrazione della prima dose. Dopo i 35 giorni si osserva una stabilizzazione della riduzione che è circa dell'80% per il rischio di diagnosi, del 90% per il rischio di ricovero e del 95% per il rischio di decesso. - Questi effetti sono simili sia negli uomini che nelle donne e in persone in diverse fasce di età.
Liu Y et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00662-0	An infectivity-enhancing site on the SARS-CoV-2 spike protein targeted by antibodies	Evidenza della produzione di anticorpi che incrementano la capacità della proteina S di SARS-CoV-2 di legare il recettore ACE2 perché favoriscono la conformazione più adatta del dominio legante il recettore.	Antibodies against the receptor-binding-domain of the SARS-CoV-2 spike protein prevent SARS-CoV-2 infection. However, the effects of antibodies against other spike protein domains are largely unknown. Here, we screened a series of anti-spike monoclonal antibodies from COVID-19 patients, and found that some of antibodies against the N-terminal-domain (NTD) induced the open conformation of receptor binding domain (RBD) and thus enhanced the binding capacity of the spike protein to ACE2 and infectivity of SARS-CoV-2. Mutational analysis revealed that all the infectivity-enhancing antibodies recognized a specific site on the NTD. Structural analysis demonstrated that all the infectivity-enhancing antibodies bound to NTD in a similar manner. The antibodies against this infectivity-enhancing site were detected at high levels in severe patients. Moreover, we identified antibodies against the infectivity-enhancing site in uninfected donors, albeit at a lower frequency. These findings demonstrate that not only neutralizing antibodies but also enhancing antibodies are produced during SARS-CoV-2 infection.

Folgueira MD et al CMI https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(21)00095-1/fulltext	Prolonged SARS-CoV-2 cell culture replication in respiratory samples from patients with severe COVID-19	Le colture cellulari di virus proveniente da pazienti con storia di COVID-19 grave sono positive fino a 32 giorni dall'esordio dei sintomi in questa casistica di 87 persone.	Objectives This study compares the infectivity of SARS-CoV-2 in respiratory samples from patients with mild COVID-19 with those from hospitalized patients with severe bilateral pneumonia. In severe COVID-19, we also analysed the presence of neutralizing activity in paired sera. Methods We performed cell cultures on 193 real-time reverse transcription polymerase chain reaction respiratory samples, positive for SARS-CoV-2, obtained from 189 patients at various times, from clinical diagnosis to follow-up. Eleven samples were obtained from asymptomatic individuals, 91 samples from 91 outpatients with mild forms of COVID-19 and 91 samples from 87 inpatients with severe pneumonia. In these patients, neutralizing activity was analysed in 30 paired sera collected after symptom onset >10 days. Results We detected a cytopathic effect (CPE) in 91/193 (47%) samples. Viral viability was maintained for up to 10 days in patients with mild COVID-19. In patients with severe COVID-19, the virus remained viable for up to 32 days after the onset of symptoms. Patients with severe COVID-19 presented infectious virus at a significantly higher rate in the samples with moderate to low viral load (cycle threshold value ≥ 26): 32/75 (43%) versus 14/63 (22%) for mild cases ($p < 0.01$). We observed a positive CPE despite the presence of clear neutralizing activity (NT50 > 1:1024 in 10% (3/30) of samples. Discussion Patients with severe COVID-19 might shed viable virus during prolonged periods of up to 4 weeks after symptom onset, even when presenting high cycle threshold values in their respiratory

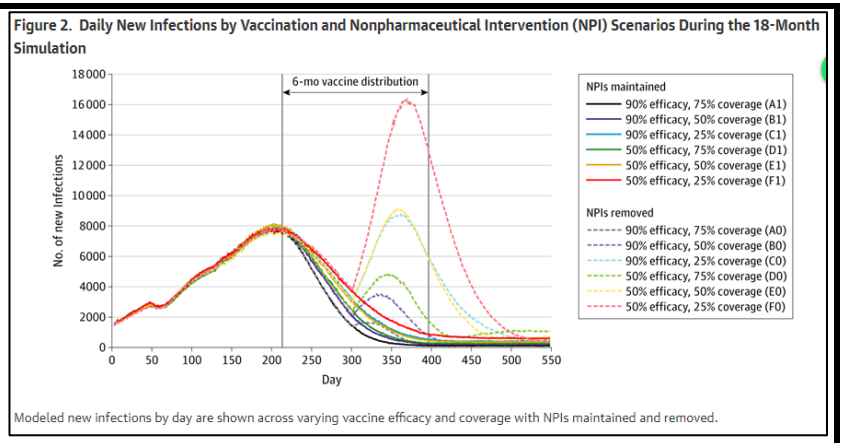
			samples and despite having developed high neutralizing antibody titres. 
Wang EW et al Open Forum Infectious Diseases https://www.ncbi.nlm.nih.gov/research/coronavirus/publication/34056031	SARS-CoV-2 Vaccination During Pregnancy: A Complex Decision.	Revisione delle evidenze in merito alla opportunità di eseguire la vaccinazione contro SARS-CoV-2 in gravidanza.	As the first severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines passed UK and US regulatory milestones in late 2020 and early 2021, multiple professional societies offered recommendations to assist pregnant and breastfeeding people as they choose whether to undergo vaccination. Despite such guidance, the lack of data describing vaccine safety, immunogenicity, and efficacy in pregnant and breastfeeding people has made this decision challenging for many. However, even considering the paucity of data, the known risks of coronavirus disease 2019 during pregnancy likely outweigh the not yet fully elucidated risks of SARS-CoV-2 vaccines, which have reassuring safety and efficacy profiles among nonpregnant people.

Wiens KE et al Emerging Infectious Diseases https://wwwnc.cdc.gov/eid/article/27/6/21-0568_article	Seroprevalence of Severe Acute Respiratory Syndrome Coronavirus 2 IgG in Juba, South Sudan, 2020	La sieroprevalenza di SARS-CoV-2 nella città di Juba in base a questo studio su circa 2200 persone indica che la diffusione reale del virus è stata molto superiore a quella riportata dalle fonti ufficiali del Paese.	Relatively few coronavirus disease cases and deaths have been reported from sub-Saharan Africa, although the extent of its spread remains unclear. During August 10–September 11, 2020, we recruited 2,214 participants for a representative household-based cross-sectional serosurvey in Juba, South Sudan. We found 22.3% of participants had severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor binding domain IgG titers above prepandemic levels. After accounting for waning antibody levels, age, and sex, we estimated that 38.3% (95% credible interval 31.8%–46.5%) of the population had been infected with SARS-CoV-2. At this rate, for each PCR–confirmed SARS-CoV-2 infection reported by the Ministry of Health, 103 (95% credible interval 86–126) infections would have been unreported, meaning SARS-CoV-2 has likely spread extensively within Juba. We also found differences in background reactivity in Juba compared with Boston, Massachusetts, USA, where the immunoassay was validated. Our findings underscore the need to validate serologic tests in sub-Saharan Africa populations.

			
Solomon MD et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2780794	Changes in Patterns of Hospital Visits for Acute Myocardial Infarction or Ischemic Stroke During COVID-19 Surges	Durante le ondeate di COVID-19 successive alla prima le ospedalizzazioni per infarto del miocardio e icuts, indici del ricorso alle cure mediche urgenti, non sono significativamente diminuite rispetto all'atteso secondo questo studio condotto in California.	In contrast to the initial COVID-19 surge during March to April 2020 in the US and to recent data from the UK, no significant declines in AMI hospitalization or stroke alerts were observed during the largest and most recent surge during October 2020 to January 2021 in KPNC. A modest decline was observed for stroke alerts during the summer COVID-19 surge but quickly rebounded.

			
Patel MD et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780539	Association of Simulated COVID-19 Vaccination and Nonpharmaceutical Interventions With Infections, Hospitalizations, and Mortality	Secondo questo modello, alla rimozione delle misure non farmacologiche di prevenzione di SARS-CoV-2, sarebbe più vantaggioso vaccinare un maggior numero di persone (75%) con un vaccino meno efficace (50%) che un minor numero (50%) con un vaccino più efficace (90%) al fine di prevenire la diffusione del virus.	Importance Vaccination against SARS-CoV-2 has the potential to significantly reduce transmission and COVID-19 morbidity and mortality. The relative importance of vaccination strategies and nonpharmaceutical interventions (NPIs) is not well understood. Objective To assess the association of simulated COVID-19 vaccine efficacy and coverage scenarios with and without NPIs with infections, hospitalizations, and deaths. Design, Setting, and Participants An established agent-based decision analytical model was used to simulate COVID-19 transmission and progression from March 24, 2020, to September 23, 2021. The model simulated COVID-19 spread in North Carolina, a US state of 10.5 million people. A network of 1 017 720 agents was constructed from US Census data to represent the statewide population. Exposures Scenarios of vaccine efficacy (50% and 90%), vaccine coverage (25%, 50%, and 75% at the end of a 6-month distribution period), and NPIs (reduced mobility, school closings, and use of face masks) maintained and removed during vaccine distribution.

			Main Outcomes and Measures Risks of infection from the start of vaccine distribution and risk differences comparing scenarios. Outcome means and SDs were calculated across replications. Results In the worst-case vaccination scenario (50% efficacy, 25% coverage), a mean (SD) of 2 231 134 (117 867) new infections occurred after vaccination began with NPIs removed, and a mean (SD) of 799 949 (60 279) new infections occurred with NPIs maintained during 11 months. In contrast, in the best-case scenario (90% efficacy, 75% coverage), a mean (SD) of 527 409 (40 637) new infections occurred with NPIs removed and a mean (SD) of 450 575 (32 716) new infections occurred with NPIs maintained. With NPIs removed, lower efficacy (50%) and higher coverage (75%) reduced infection risk by a greater magnitude than higher efficacy (90%) and lower coverage (25%) compared with the worst-case scenario (mean [SD] absolute risk reduction, 13% [1%] and 8% [1%], respectively). Conclusions and Relevance Simulation outcomes suggest that removing NPIs while vaccines are distributed may result in substantial increases in infections, hospitalizations, and deaths. Furthermore, as NPIs are removed, higher vaccination coverage with less efficacious vaccines can contribute to a larger reduction in risk of SARS-CoV-2 infection compared with more efficacious vaccines at lower coverage. These findings highlight the need for well-resourced and coordinated efforts to achieve high vaccine coverage and continued adherence to NPIs before many prepandemic activities can be resumed.

			
Fahmy O et al Critical Care Explorations https://journals.lww.com/ccejournal/Fulltext/2021/05000/Is_Microthrombosis_the_Main_Pathology_in.29.aspx	Is Microthrombosis the Main Pathology in Coronavirus Disease 2019 Severity?—A Systematic Review of the Postmortem Pathologic Findings	Revisione dell'esito di 691 autopsie su persone decedute per COVID-19 : il reperto più osservato è il danno alveolarea diffuso (DAD), con presenza di microtrombi e angiogenesi polmonare.	Objectives: This systematic review attempts to retrieve and report the findings of postmortem studies including the histopathologic data of deceased coronavirus disease 2019 patients and to review the manifestations of coronavirus disease 2019–associated thrombotic pathologies reported in the recent literature. Data Sources: PubMed, Excerpta Medica Database, and Cochrane library between December 1, 2019, and August 26, 2020. Study Selection: Investigators screened 360 unique references, retrieved published autopsy series, and report on the postmortem histopathologic information on patients who had died of coronavirus disease 2019. Data Extraction: Investigators independently abstracted all available data including study design, participant demographics, key histopathologic findings, disease severity markers, duration of hospital stay, and cause of death. Data Synthesis: From the 65 eligible studies, 691 total completed autopsies were included in evidence synthesis. Histopathologic evaluation of the lungs revealed presence of diffuse alveolar damage in 323 of 443 patients and pulmonary microthrombi in 242 of 326 patients. Deep venous thrombosis and pulmonary embolism

			were found in 41% and ~15%, respectively, of the cadavers examined for thromboembolic events. d-dimer levels were generally higher in patients with severe clinical course of coronavirus disease 2019. Plasma levels of ferritin, lactate dehydrogenase, interleukin-6, and C-reactive protein were higher in nonsurvivors when compared with survivors. Overall, microthrombi and extensive angiogenesis of lung vasculature were the most common pathologic findings in the lungs and microthrombi in most of the assessed organ-tissue. Conclusions: Diffuse alveolar damage was the most predominant feature in the lungs of coronavirus disease 2019 patients who underwent postmortem assessment. Widespread pulmonary microthrombosis and extensive pulmonary angiogenesis, in addition to frequent pulmonary and extrapulmonary microthrombotic and thromboembolic findings in patients with coronavirus disease 2019, appear to be consistent with the disease-specific hypercoagulability. Further discovery efforts in assessing the link between coronavirus disease 2019, hypercoagulable state, and immunothrombosis are warranted. In the interim, increased attention to anticoagulant treatment approaches in coronavirus disease 2019 patients is needed.
Lambermont B et al Critical Care Explorations https://journals.lww.com/ccejournal/Fulltext/2021/05000/Outcome_Improvement_Between_the_First_Two_Waves_of.27.aspx	Outcome Improvement Between the First Two Waves of the Coronavirus Disease 2019 Pandemic in a Single Tertiary-Care Hospital in Belgium	La mortalità a 30 giorni dei pazienti ricoverati per COVID-19 durante la seconda ondata pandemica (ottobre-novembre 2020) è stata significativamente inferiore rispetto alla prima (marzo-maggio 2020) in un ospedale di terzo livello in Belgio.	Objectives: To compare patient management and outcome during the first and second waves of the coronavirus 2019 pandemic. Design: Single-center prospective cohort study. Setting: Tertiary-care University Hospital. Patients: All adult patients admitted in either the first (from March 15 to May 15, 2020) or second (from October 1 to November 30, 2020) wave of coronavirus disease 2019. Interventions: None.

			Measurements and Main Results: Primary outcome was 30-day mortality. During the second wave of the coronavirus disease 2019 pandemic, 33 patients (4.8%) were transferred due to overcrowding and excluded from analysis. There were 341 (first wave of the coronavirus disease 2019 pandemic) and 695 (second wave of the coronavirus disease 2019 pandemic) coronavirus disease 2019 patients admitted to the hospital, with median age first wave of the coronavirus disease 2019 pandemic as 68 (57–80) and second wave of the coronavirus disease 2019 pandemic as 71 (60–80) ($p = 0.15$), and similar admission severity. For the first wave of the coronavirus disease 2019 pandemic versus second wave of the coronavirus disease 2019 pandemic, 30-day mortality was 74/341 (22%) and 98/662 (15%) ($p = 0.007$). In the ward, 11/341 (3.2%) and 404/662 (61%) received dexamethasone ($p < 0.001$); 6/341 (2%) and 79/662 (12%) received high-flow nasal oxygen ($p < 0.0001$); 2/341 (0.6%) and 88/662 (13.3%) received remdesivir ($p < 0.0001$); 249/341 (73%) and 0/662 (0%) received hydroxychloroquine ($p < 0.0001$); and 87/341 (26%) and 128/662 (19%) ($p = 0.024$) patients were transferred to ICU. On ICU admission, median Sequential Organ Failure Assessment was 6 (3–7) and 4 (3–6) ($p = 0.02$). High-flow nasal oxygen was given to 16/87 (18%) and 102/128 (80%) ($p < 0.001$); 69/87 (79%) and 56/128 (44%) received mechanical ventilation ($p < 0.001$) with durations 17 days (10–26 d) and 10 days (5–17 d) ($p = 0.01$). Median ICU length of stay was 14 days (5–27 d) and 6 days (3–11 d) ($p < 0.001$). Finally, 16/87 (18%) and 8/128 (6%) received renal replacement therapy ($p = 0.0055$); and 64/87 (74%) and 51/128 (40%) needed vasopressor support ($p < 0.001$). Conclusions: The main therapeutic changes between the first wave of the coronavirus disease 2019 pandemic and the second wave of the coronavirus disease 2019 pandemic were use of steroids,

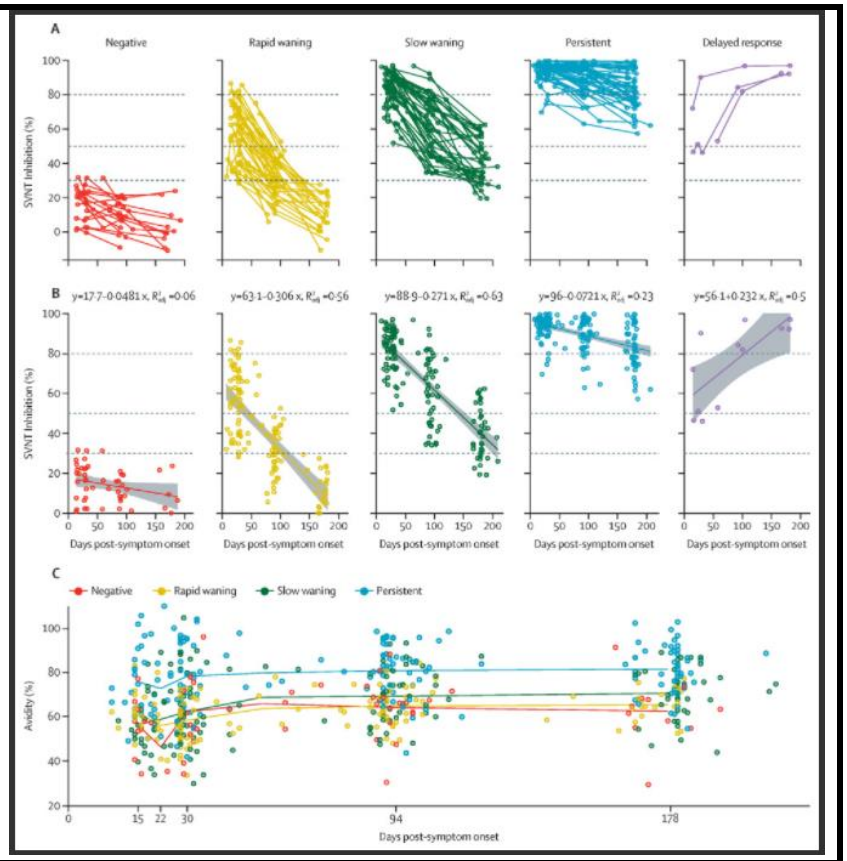
<table>
<tr><td></td><td></td><td></td><td>unrestrictive use of high-flow nasal oxygen for hypoxemic patients, and transfer of patients to other geographic areas in the case of ICU overcrowding. These changes were associated with a decrease in 30-day mortality, ICU admission, and organ support.</td></tr>
<tr><td>Callaway E et al

Nature

https://www.nature.com/articles/d41586-021-01483-0</td><td>Coronavirus variants get Greek names — but will scientists use them?</td><td>Non più nomi geografici o sigle poco comprensibili, il WHO introduce una denominazione delle varianti di SARS-CoV-2 basata sull’ordine alfabetico greco.</td><td>When researchers in South Africa spotted a highly mutated strain of coronavirus driving the country’s second wave in late 2020, they called it variant 501Y.V2. Naming schemes developed by other scientists have called it B.1.351, 20H/501Y.V2 and GH/501Y.V2. But many media outlets — and some scientists — describe the same virus as ‘the South African variant’.
To quell such confusion and avoid geographical stigmas, everyone should now just call it ‘Beta’, according to a naming scheme announced on 31 May by the World Health Organization (WHO) in Geneva.
VARIANTS OF CONCERN
<table><tr><th>WHO label</th><th>Pango lineage</th><th>GISAID clade</th><th>Nextstrain clade</th><th>Earliest documented samples</th><th>Date of designation</th></tr><tr><td>Alpha</td><td>B.1.1.7</td><td>GRY</td><td>20I/S:501Y.V1</td><td>UK, Sept 2020</td><td>Dec 2020</td></tr><tr><td>Beta</td><td>B.1.351</td><td>GH/501Y.V2</td><td>20H/S:501Y.V2</td><td>South Africa, May 2020</td><td>Dec 2020</td></tr><tr><td>Gamma</td><td>P.1</td><td>GR/501Y.V3</td><td>20J/S:501Y.V3</td><td>Brazil, Nov 2020</td><td>Jan 2021</td></tr><tr><td>Delta</td><td>B.1.617.2</td><td>G/452R.V3</td><td>21A/S:478K</td><td>India, Oct 2020</td><td>May 2021</td></tr></table></td></tr>
<tr><td>World Health Organization</td><td>Tracking SARS-CoV-2 variants</td><td>Nuova nomenclatura WHO delle varianti di SARS-CoV-2.</td><td>WHO and its international networks of experts are monitoring changes to the virus so that if significant mutations are identified, we can inform countries and the public about any changes needed to react to the variant, and prevent its spread. Globally, systems have been established and are being strengthened to detect</td></tr>
</table>

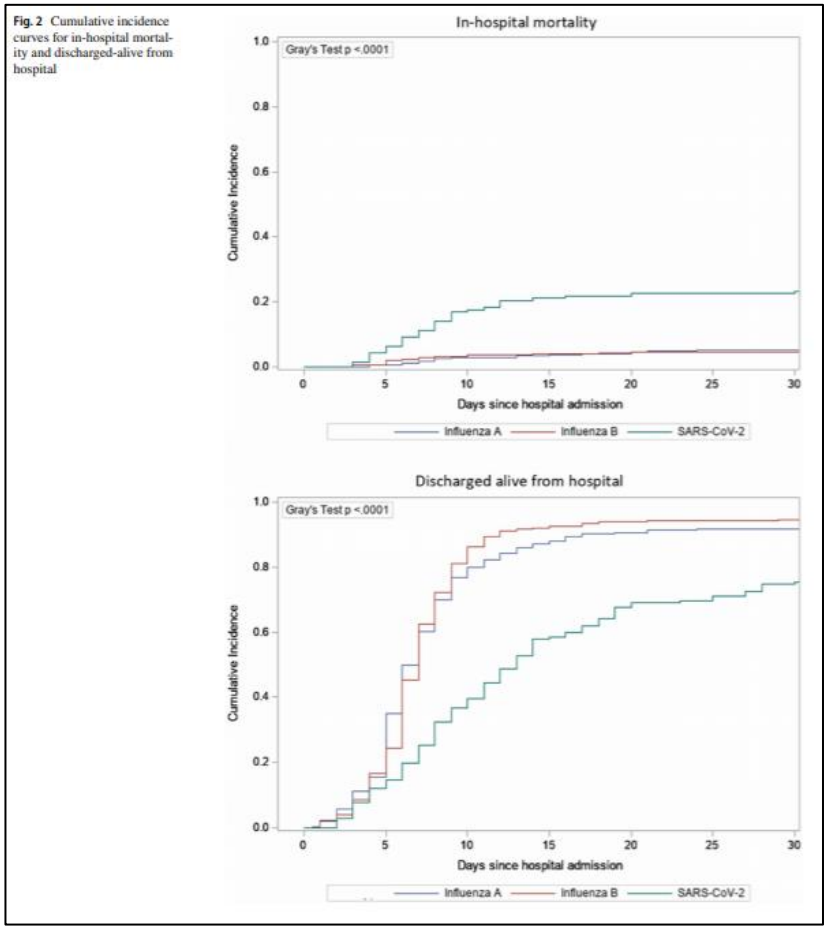
https://www.who.int/en/activities/tracking-SARS-CoV-2-variants/			"signals" of potential VOIs or VOCs and assess these based on the risk posed to global public health. National authorities may choose to designate other variants of local interest/concern. Current strategies and measures recommended by WHO continue to work against virus variants identified since the start of the pandemic
Chia WN et al The Lancet https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(21)00025-2/fulltext	Dynamics of SARS-CoV-2 neutralising antibody responses and duration of immunity: a longitudinal study	Una coorte di 164 pazienti guariti da COVID-19 è stata seguita nel tempo per predire la durata della risposta anticorpo-mediata: gli autori concludono che tale valutazione deve essere fatta caso per caso.	Background : Studies have found different waning rates of neutralising antibodies compared with binding antibodies against SARS-CoV-2. The impact of neutralising antibody waning rate at the individual patient level on the longevity of immunity remains unknown. We aimed to investigate the peak levels and dynamics of neutralising antibody waning and IgG avidity maturation over time, and correlate this with clinical parameters, cytokines, and T-cell responses. Methods : We did a longitudinal study of patients who had recovered from COVID-19 up to day 180 post-symptom onset by monitoring changes in neutralising antibody levels using a previously validated surrogate virus neutralisation test. Changes in antibody avidities and other immune markers at different convalescent stages were determined and correlated with clinical features. Using a machine learning algorithm, temporal change in neutralising antibody levels was classified into five groups and used to predict the longevity of neutralising antibody-mediated immunity. Findings : We approached 517 patients for participation in the study, of whom 288 consented for outpatient follow-up and collection of serial blood samples. 164 patients were followed up and had adequate blood samples collected for analysis, with a total of 546 serum samples collected, including 128 blood samples taken up to 180 days post-symptom onset. We identified five distinctive

			patterns of neutralising antibody dynamics as follows: negative, individuals who did not, at our intervals of sampling, develop neutralising antibodies at the 30% inhibition level (19 [12%] of 164 patients); rapid waning, individuals who had varying levels of neutralising antibodies from around 20 days after symptom onset, but seroreverted in less than 180 days (44 [27%] of 164 patients); slow waning, individuals who remained neutralising antibody-positive at 180 days post-symptom onset (46 [28%] of 164 patients); persistent, although with varying peak neutralising antibody levels, these individuals had minimal neutralising antibody decay (52 [32%] of 164 patients); and delayed response, a small group that showed an unexpected increase of neutralising antibodies during late convalescence (at 90 or 180 days after symptom onset; three [2%] of 164 patients). Persistence of neutralising antibodies was associated with disease severity and sustained level of pro-inflammatory cytokines, chemokines, and growth factors. By contrast, T-cell responses were similar among the different neutralising antibody dynamics groups. On the basis of the different decay dynamics, we established a prediction algorithm that revealed a wide range of neutralising antibody longevity, varying from around 40 days to many decades. Interpretation : Neutralising antibody response dynamics in patients who have recovered from COVID-19 vary greatly, and prediction of immune longevity can only be accurately determined at the individual level. Our findings emphasise the importance of public health and social measures in the ongoing pandemic outbreak response, and might have implications for longevity of immunity after vaccination.

			
Ranjbar K et al BMC Infectious Diseases https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8035859/	Methylprednisolone or dexamethasone, which one is superior corticosteroid in the treatment of hospitalized COVID-19 patients: a triple-blinded randomized controlled trial	Piccolo trial clinico su 86 pazienti ricoverati per COVID-19 e randomizzati in cieco a ricevere metilprednisolone 2 mg/Kg/die (dimezzato a scalare dal 5 giorno) o desametasone 6 mg/die (dosaggio riportato erroneamente come 6	Background : Although almost a year has passed since the Coronavirus disease 2019 (COVID-19) outbreak and promising reports of vaccines have been presented, we still have a long way until these measures are available for all. Furthermore, the most appropriate corticosteroid and dose in the treatment of COVID-19 have remained uncertain. We conducted a study to assess the effectiveness of methylprednisolone treatment versus dexamethasone for hospitalized COVID-19 patients.

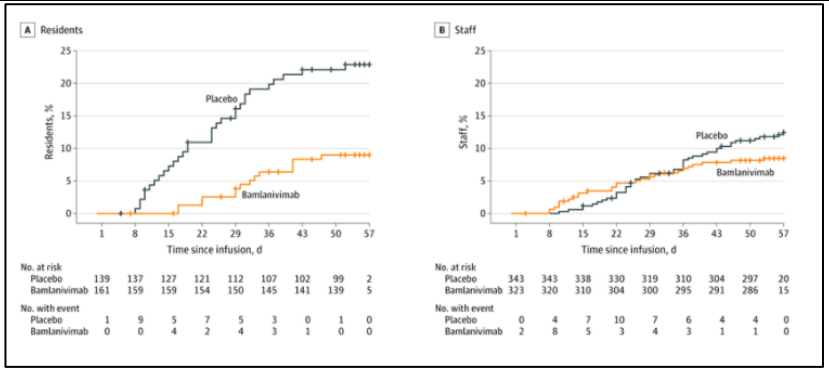
		mg/Kg/die nell'abstract ma chiarito nel testo) : il primo gruppo ha migliore status al giorno 5 e 10, minore ricorso alla ventilazione meccanica e minore durata di ospedalizzazione. La mortalità è molto alta (18% e 38% rispettivamente nei due gruppi, con un trend verso la significatività). La dose relativa di metilprednisolone è maggiore di quella di desametasone, questo potrebbe spiegare l'effetto oltre alla maggiore penetrazione del primo steroide nei polmoni.	Methods : In this prospective triple-blinded randomized controlled trial, we enrolled 86 hospitalized COVID-19 patients from August to November 2020, in Shiraz, Iran. The patients were randomly allocated into two groups to receive either methylprednisolone (2 mg/kg/day; intervention group) or dexamethasone (6 mg/kg/day; control group). Data were assessed based on a 9-point WHO ordinal scale extending from uninfected (point 0) to death (point 8). Results : There were no significant differences between the groups on admission. However, the intervention group demonstrated significantly better clinical status compared to the control group at day 5 (4.02 vs. 5.21, p = 0.002) and day 10 (2.90 vs. 4.71, p = 0.001) of admission. There was also a significant difference in the overall mean score between the intervention group and the control group, (3.909 vs. 4.873 respectively, p = 0.004). The mean length of hospital stay was 7.43 ± 3.64 and 10.52 ± 5.47 days in the intervention and control groups, respectively (p = 0.015). The need for a ventilator was significantly lower in the intervention group than in the control group (18.2% vs 38.1% p = 0.040). Conclusion : In hospitalized hypoxic COVID-19 patients, methylprednisolone demonstrated better results compared to dexamethasone.
Takuva S et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2107920?query=featured_home	Thromboembolic Events in the South African Ad26.COV2.S Vaccine Study	Gli eventi tromboembolici registrati temporalmente dopo la vaccinazione contro SARS-CoV-2 con vaccino Janssen in questo studio sono avvenuti in persone con fattori di rischio preesistenti in questa casistica di oltre 280.000 persone ; nessun caso di	Here, we report interim safety data from the first 288,368 participants who were vaccinated with Ad26.COV2.S in the Sisonke study — an open label, single-group, phase 3b implementation study to monitor the effectiveness of the single-dose Ad26.COV2.S vaccine among 500,000 health care workers in South Africa (ClinicalTrials.gov number, NCT04838795. opens in new tab). Enrollment in the study began on February 17, 2021, and as of April 12, 2021, a total of 288,368 health care workers had received the

		trombocitopenia trombotica indotta da vaccino.	Ad26.COV2.S vaccine, among whom 5898 (2%) reported adverse events.
Erich P et al Infection https://link.springer.com/article/10.1007/s15010-021-01610-z?utm_source=sn&utm_medium=referral&utm_content=RM&utm_campaign=BSLB_1_CA01_BSLB_AWA_CA01_GL_LSGR_PubH_Coronavirus_Landing Page	COVID-19 is not "just another flu": a real-life comparison of severe COVID-19 and influenza in hospitalized patients in Vienna, Austria	Il ricovero per COVID-19 presenta maggiore durata, maggiore incidenza di complicanze e maggiore mortalità rispetto a quello per influenza in questo studio retrospettivo su 142 pazienti con COVID-19 a confronto con 266 pazienti con influenza ricoverati in Austria.	Background : COVID-19 is regularly compared to influenza. Mortality and case-fatality rates vary widely depending on incidence of COVID-19 and the testing policy in affected countries. To date, data comparing hospitalized patients with COVID-19 and influenza is scarce. Methods : Data from patients with COVID-19 were compared to patients infected with influenza A (InfA) and B (InfB) virus during the 2017/18 and 2018/19 seasons. All patients were ≥ 18 years old, had PCR-confirmed infection and needed hospital treatment. Demographic data, medical history, length-of-stay (LOS), complications including in-hospital mortality were analyzed. Results : In total, 142 patients with COVID-19 were compared to 266 patients with InfA and 300 with InfB. Differences in median age (COVID-19 70.5 years vs InfA 70 years and InfB 77 years, $p < 0.001$) and laboratory results were observed. COVID-19 patients had fewer comorbidities, but complications (respiratory insufficiency, pneumonia, acute kidney injury, acute heart failure and death) occurred more frequently. Median length-of-stay (LOS) was longer in COVID-19 patients (12 days vs InfA 7 days vs. InfB 7 days, $p < 0.001$). There was a fourfold higher in-hospital mortality in COVID-19 patients (23.2%) when compared with InfA (5.6%) or InfB (4.7%; $p < 0.001$). Conclusion : In hospitalized patients, COVID-19 is associated with longer LOS, a higher number of complications and higher in-hospital mortality compared to influenza, even in a population with fewer co-morbidities. This data, a high reproduction number and limited

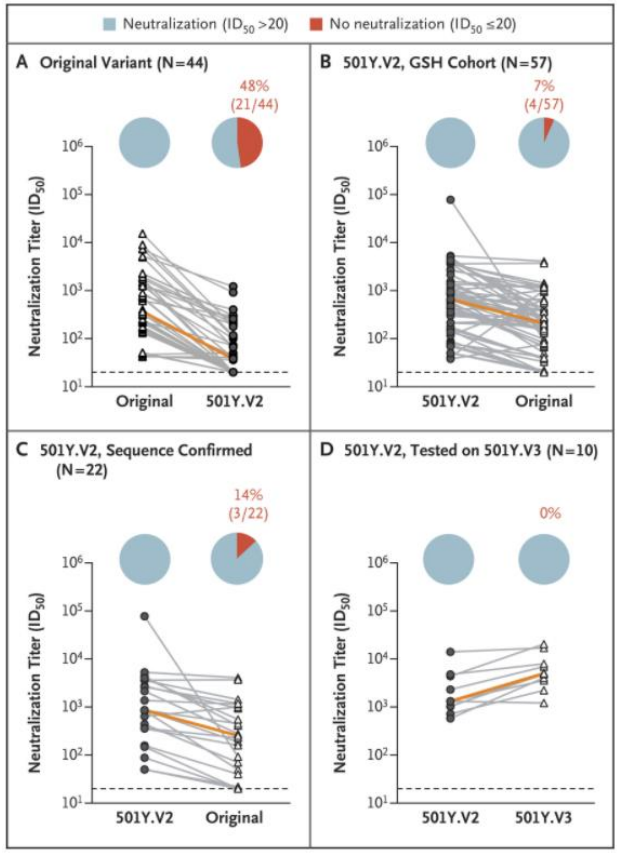
			treatment options, alongside excess mortality during the SARS-CoV-2 pandemic, support the containment strategies implemented by most authorities.  **Fig. 2** Cumulative incidence curves for in-hospital mortality and discharged-alive from hospital
Stepehnson J et al JAMA	Children and Teens Struggling with Mental Health During COVID-19 Pandemic	Riassunto di un report della fondazione Kaiser sulla salute mentale di bambini e adolescenti negli USA durante il periodo	A number of factors potentially contribute to worsening mental health outcomes in children and adolescents, the KFF brief explains, including school closures, social distancing, and stay-at-home orders, which could lead to loneliness and isolation. Among parents, pandemic-related stresses and difficulties, such as job insecurity

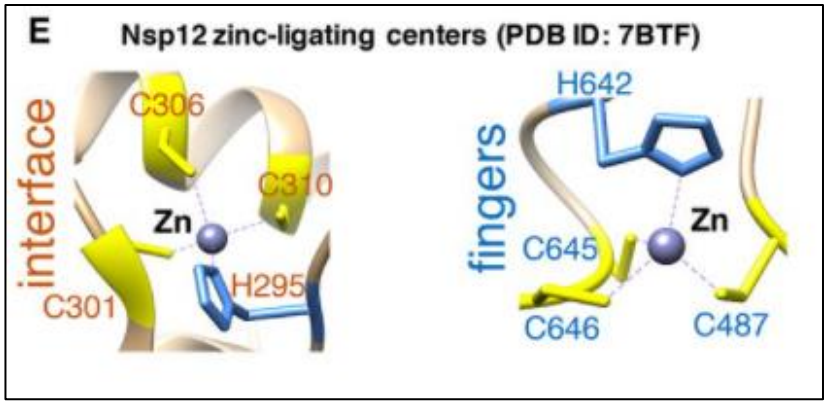
https://jamanetwork.com/journals/jama-health-forum/fullarticle/2780778		pandemico a confronto con gli anni precedenti.	and loss, may contribute to poor mental health, which itself might be a contributing factor to negative mental health outcomes for their children.
Cohen MS et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2780870?resultClick=1	Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial	Trial clinico di fase 3 su 966 partecipanti fra personale e ospiti di case di riposo, in cui si osserva che la terapia con bamlanivimab riduce l'incidenza di COVID-19 (malattia) rispetto al placebo. Studio condotto prima dell'avvento massiccio delle varianti.	Importance Preventive interventions are needed to protect residents and staff of skilled nursing and assisted living facilities from COVID-19 during outbreaks in their facilities. Bamlanivimab, a neutralizing monoclonal antibody against SARS-CoV-2, may confer rapid protection from SARS-CoV-2 infection and COVID-19. Objective To determine the effect of bamlanivimab on the incidence of COVID-19 among residents and staff of skilled nursing and assisted living facilities. Design, Setting, and Participants Randomized, double-blind, single-dose, phase 3 trial that enrolled residents and staff of 74 skilled nursing and assisted living facilities in the United States with at least 1 confirmed SARS-CoV-2 index case. A total of 1175 participants enrolled in the study from August 2 to November 20, 2020. Database lock was triggered on January 13, 2021, when all participants reached study day 57. Interventions Participants were randomized to receive a single intravenous infusion of bamlanivimab, 4200 mg (n = 588), or placebo (n = 587). Main Outcomes and Measures The primary outcome was incidence of COVID-19, defined as the detection of SARS-CoV-2 by reverse transcriptase–polymerase chain reaction and mild or worse disease severity within 21 days of detection, within 8 weeks of randomization. Key secondary outcomes included incidence of moderate or worse COVID-19 severity and incidence of SARS-CoV-2 infection.

			Results The prevention population comprised a total of 966 participants (666 staff and 300 residents) who were negative at baseline for SARS-CoV-2 infection and serology (mean age, 53.0 [range, 18-104] years; 722 [74.7%] women). Bamlanivimab significantly reduced the incidence of COVID-19 in the prevention population compared with placebo (8.5% vs 15.2%; odds ratio, 0.43 [95% CI, 0.28-0.68]; P < .001; absolute risk difference, −6.6 [95% CI, −10.7 to −2.6] percentage points). Five deaths attributed to COVID-19 were reported by day 57; all occurred in the placebo group. Among 1175 participants who received study product (safety population), the rate of participants with adverse events was 20.1% in the bamlanivimab group and 18.9% in the placebo group. The most common adverse events were urinary tract infection (reported by 12 participants [2%] who received bamlanivimab and 14 [2.4%] who received placebo) and hypertension (reported by 7 participants [1.2%] who received bamlanivimab and 10 [1.7%] who received placebo). Conclusions and Relevance Among residents and staff in skilled nursing and assisted living facilities, treatment during August-November 2020 with bamlanivimab monotherapy reduced the incidence of COVID-19 infection. Further research is needed to assess preventive efficacy with current patterns of viral strains with combination monoclonal antibody therapy.

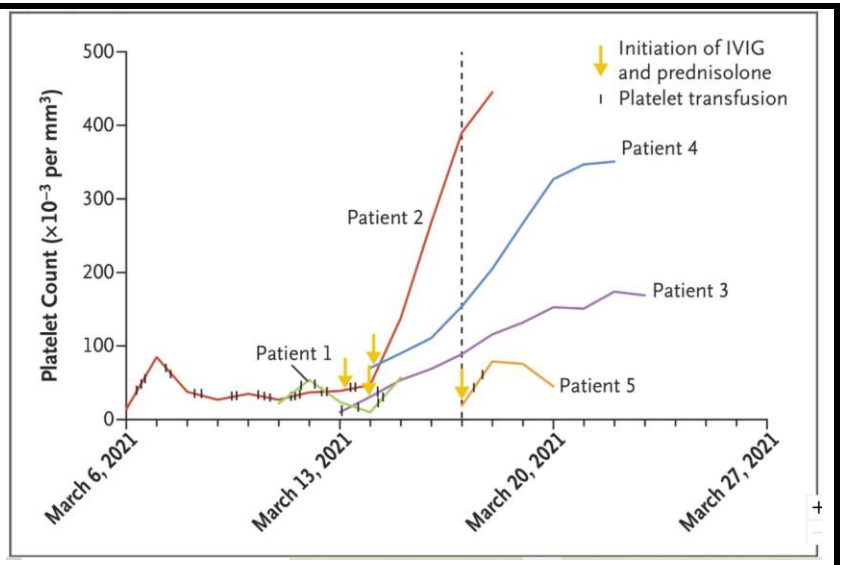
			
Talbot HK et al CID https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab123/6288408	Coronavirus disease 2019 (COVID-19) Versus Influenza in Hospitalized Adult Patients in the United States: Differences in Demographic and Severity Indicators.	Ancora uno studio che confronta influenza stagionale e COVID-19 ed evidenzia come le due malattie siano molto diverse in termini di complicanze, mortalità e durata di ricovero.	Background : Novel coronavirus disease 2019 (COVID-19) is frequently compared with influenza. The Hospitalized Adult Influenza Vaccine Effectiveness Network (HAIVEN) conducts studies on the etiology and characteristics of U.S. hospitalized adults with influenza. It began enrolling patients with COVID-19 hospitalizations in March 2020. Patients with influenza were compared with those with COVID-19 in the first months of the U.S. epidemic. Methods : Adults aged ≥ 18 years admitted to hospitals in 4 sites with acute respiratory illness were tested by real-time reverse transcription polymerase chain reaction for influenza and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus causing COVID-19. Demographic and illness characteristics were collected for influenza illnesses during 3 seasons 2016–2019. Similar data were collected on COVID-19 cases admitted before June 19, 2020. Results : Age groups hospitalized with COVID-19 (n = 914) were similar to those admitted with influenza (n = 1937); 80% of patients with influenza and 75% of patients with COVID-19 were aged ≥50 years. Deaths from COVID-19 that occurred in younger patients were less often related to underlying conditions. White non-Hispanic persons were overrepresented in influenza (64%)

			compared with COVID-19 hospitalizations (37%). Greater severity and complications occurred with COVID-19 including more ICU admissions (AOR = 15.3 [95% CI: 11.6, 20.3]), ventilator use (AOR = 15.6 [95% CI: 10.7, 22.8]), 7 additional days of hospital stay in those discharged alive, and death during hospitalization (AOR = 19.8 [95% CI: 12.0, 32.7]). Conclusions : While COVID-19 can cause a respiratory illness like influenza, it is associated with significantly greater severity of illness, longer hospital stays, and higher in-hospital deaths.
Moyo-Gwete T et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMc2104192?query=featured_home	Cross-Reactive Neutralizing Antibody Responses Elicited by SARS-CoV-2 501Y.V2 (B.1.351)	Il plasma di soggetti con storia di infezione da SARS-CoV-2 acquisita in Sudafrica nel periodo in cui la variante B.1.351 era già prevalente cross-reagisce anche con la variante « brasiliana ».	Overall, we found that 501Y.V2 elicits robust neutralizing antibody responses against both the original variant and 501Y.V3 (P.1), which indicates high levels of cross-reactivity. Our data indicate that vaccines built on the spike protein of 501Y.V2 may be promising candidates for the elicitation of cross-reactive neutralizing antibody responses to SARS-CoV-2.

			
Maio N et al Science https://science.sciencemag.org/content/early/2021/06/02/science.abi5224	Fe-S cofactors in the SARS-CoV-2 RNA-dependent RNA polymerase are potential antiviral targets	Potenziale target di terapia contro SARS-CoV-2 nei cofattori necessari per l'attività della RNA polimerasi RNA-dipendente del virus.	Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causal agent of coronavirus disease 2019 (COVID-19), uses an RNA-dependent RNA polymerase (RdRp) for the replication of its genome and the transcription of its genes. We found that the catalytic subunit of the RdRp, nsp12, ligates two iron-sulfur metal cofactors in sites that were modeled as zinc centers in the available cryo-electron microscopy structures of the RdRp complex. These metal binding sites are essential for replication and for interaction with the viral helicase. Oxidation of the clusters by the stable nitroxide

			TEMPOL caused their disassembly, potently inhibited the RdRp, and blocked SARS-CoV-2 replication in cell culture. These iron-sulfur clusters thus serve as cofactors for the SARS-CoV-2 RdRp and are targets for therapy of COVID-19. 
Ahn JY et al MedRXiv – preprint https://doi.org/10.1101/2021.05.26.21257700;	Safety and immunogenicity of a recombinant DNA COVID-19 vaccine containing the coding regions of the spike and nucleocapsid proteins: Preliminary results from an open-label, phase 1 trial in healthy adults aged 19–55 years	Efficacia e sicurezza di due vaccini ricombinanti contro SARS-COV-2 contenenti la sequenza della proteina S e, nel secondo caso, della porzione legante il recettore della proteina S e della proteina nucleocapsidica	Background We investigated the safety and immunogenicity of two recombinant COVID-19 DNA vaccine candidates in first-in-human trials. GX-19 contains plasmid DNA encoding SARS-CoV-2 spike protein, and GX-19N contains plasmid DNA encoding SARS-CoV-2 receptor binding domain (RBD) foldon and nucleocapsid protein (NP) as well as plasmid DNA encoding SARS-CoV-2 spike protein. Methods Two open-label phase 1 trials of GX-19 and GX-19N safety and immunogenicity were performed in healthy adults aged 19–55 years. GX-19 trial participants received two vaccine injections (1·5 mg or 3·0 mg, 1:1 ratio) four weeks apart. GX-19N trial participants received two 3·0 mg vaccine injections four weeks apart. Findings Between June 17 and July 30 and December 28 and 31, 2020, 40 and 21 participants were enrolled in the GX-19 and GX-19N trials, respectively. Thirty-two participants (52·5%) reported 80 treatment-emergent adverse events (AE) after vaccination. All solicited AEs were mild except one case of moderate fatigue

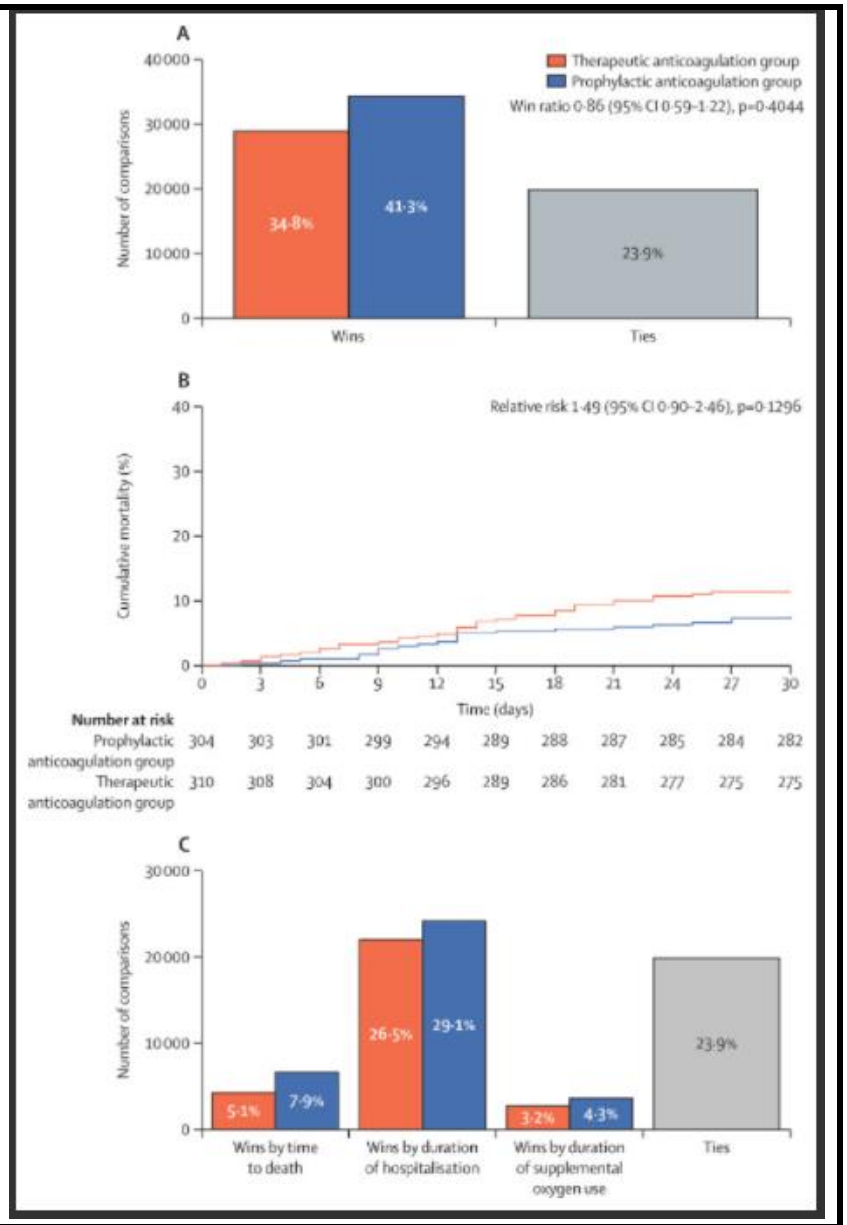
			reported in the 1·5 mg GX-19 group. Binding antibody responses increased after vaccination in all groups. The geometric mean titers (GMTs) of spike-binding antibodies on day 57 were 85·74, 144·20, and 201·59 in the 1·5 mg, 3·0 mg GX-19 groups and the 3·0 mg GX-19N group, respectively. In GX-19N group, neutralizing antibody response (50% neutralizing titer using FRNT) significantly increased after vaccination, but GMT of neutralizing antibody on day 57 (37.26) was lower than those from human convalescent serum (288.78). GX-19N induced stronger T cell responses than GX-19. The magnitude of GX-19N-induced T cell responses was comparable to those observed in the convalescent PBMCs. GX-19N induced both SARS-CoV-2 spike- and NP-specific T cell responses, and the amino acid sequences of 15-mer peptides containing NP-specific T cell epitopes identified in GX-19N-vaccinated participants were identical with those of diverse SARS-CoV-2 variants Interpretation GX-19N is safe, tolerated and induces humoral and broad SARS-CoV-2-specific T cell response which may enable cross-reactivity to emerging SARS-CoV-2 variants.
Schultz nh ET al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2104882?query=featured_home	Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination	Cinque casi di trombosi e trombocitopenia fra operatori sanitari giovani recentemente vaccinati (<10 giorni) con vaccino AstraZeneca/Vaxzevria contro SARS-CoV-2, con elevati livelli di anticorpi anti-fattore piastrinico 4 (PF4). Deceduti 3/5, nessuna precedente esposizione a eparina.	We report findings in five patients who presented with venous thrombosis and thrombocytopenia 7 to 10 days after receiving the first dose of the ChAdOx1 nCoV-19 adenoviral vector vaccine against coronavirus disease 2019 (Covid-19). The patients were health care workers who were 32 to 54 years of age. All the patients had high levels of antibodies to platelet factor 4–polyanion complexes; however, they had had no previous exposure to heparin. Because the five cases occurred in a population of more than 130,000 vaccinated persons, we propose that they represent a rare vaccine-related variant of spontaneous heparin-induced thrombocytopenia that we refer to as vaccine-induced immune thrombotic thrombocytopenia.

			
Greinacher A et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2104840?query=featured_home	Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination	Descrizione di 11 casi di trombosi e trombocitopenia esorditi entro 16 giorni da vaccinazione con AstraZeneca/Vvaxzevria contro SARS-CoV-2 in persone di età 29-45 anni, di cui 9 donne, fra Germania e Austria. Deceduti 6/11. Tutti i pazienti sono risultati positivi per anticorpi anti PF4, in assenza di precedente esposizione a eparina.	BACKGROUND Several cases of unusual thrombotic events and thrombocytopenia have developed after vaccination with the recombinant adenoviral vector encoding the spike protein antigen of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (ChAdOx1 nCov-19, AstraZeneca). More data were needed on the pathogenesis of this unusual clotting disorder. METHODS We assessed the clinical and laboratory features of 11 patients in Germany and Austria in whom thrombosis or thrombocytopenia had developed after vaccination with ChAdOx1 nCov-19. We used a standard enzyme-linked immunosorbent assay to detect platelet factor 4 (PF4)–heparin antibodies and a modified (PF4-enhanced) platelet-activation test to detect platelet-activating antibodies under various reaction conditions. Included in this testing were samples from patients who had blood samples referred for

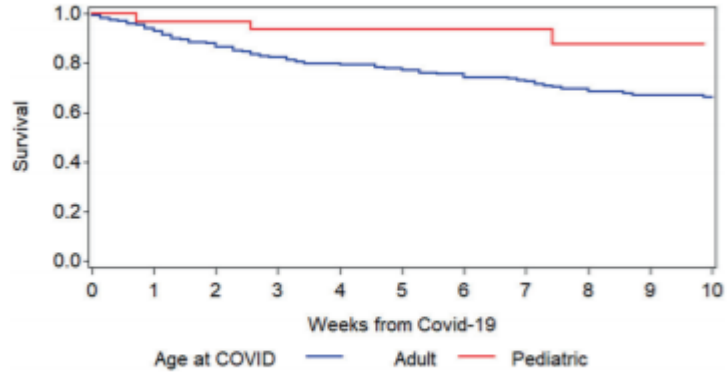
			investigation of vaccine-associated thrombotic events, with 28 testing positive on a screening PF4–heparin immunoassay. RESULTS Of the 11 original patients, 9 were women, with a median age of 36 years (range, 22 to 49). Beginning 5 to 16 days after vaccination, the patients presented with one or more thrombotic events, with the exception of 1 patient, who presented with fatal intracranial hemorrhage. Of the patients with one or more thrombotic events, 9 had cerebral venous thrombosis, 3 had splanchnic-vein thrombosis, 3 had pulmonary embolism, and 4 had other thromboses; of these patients, 6 died. Five patients had disseminated intravascular coagulation. None of the patients had received heparin before symptom onset. All 28 patients who tested positive for antibodies against PF4–heparin tested positive on the platelet-activation assay in the presence of PF4 independent of heparin. Platelet activation was inhibited by high levels of heparin, Fc receptor–blocking monoclonal antibody, and immune globulin (10 mg per milliliter). Additional studies with PF4 or PF4–heparin affinity purified antibodies in 2 patients confirmed PF4-dependent platelet activation. CONCLUSIONS Vaccination with ChAdOx1 nCov-19 can result in the rare development of immune thrombotic thrombocytopenia mediated by platelet-activating antibodies against PF4, which clinically mimics autoimmune heparin-induced thrombocytopenia.
Lopes RD et al The Lancet	Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer	Trial clinico multicentrico condotto in Brasile per confrontare l'effetto di anticoagulante a dose terapeutica (rivaroxaban nei pazienti stabili, enoxaparina	Background : COVID-19 is associated with a prothrombotic state leading to adverse clinical outcomes. Whether therapeutic anticoagulation improves outcomes in patients hospitalised with COVID-19 is unknown. We aimed to compare the efficacy and safety

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01203-4/fulltext	concentration (ACTION): an open-label, multicentre, randomised, controlled trial	o eparina EV nei pazienti instabili) oppure a dose profilattica nei pazienti ricoverati con COVID-19 con livelli di D-dimero superiori al limite di normalità del laboratorio di riferimento: il dosaggio terapeutico non migliora l'outcome ed è associato a maggiori effetti avversi (sanguinamento).	of therapeutic versus prophylactic anticoagulation in this population. Methods : We did a pragmatic, open-label (with blinded adjudication), multicentre, randomised, controlled trial, at 31 sites in Brazil. Patients (aged ≥18 years) hospitalised with COVID-19 and elevated D-dimer concentration, and who had COVID-19 symptoms for up to 14 days before randomisation, were randomly assigned (1:1) to receive either therapeutic or prophylactic anticoagulation. Therapeutic anticoagulation was in-hospital oral rivaroxaban (20 mg or 15 mg daily) for stable patients, or initial subcutaneous enoxaparin (1 mg/kg twice per day) or intravenous unfractionated heparin (to achieve a 0·3–0·7 IU/mL anti-Xa concentration) for clinically unstable patients, followed by rivaroxaban to day 30. Prophylactic anticoagulation was standard in-hospital enoxaparin or unfractionated heparin. The primary efficacy outcome was a hierarchical analysis of time to death, duration of hospitalisation, or duration of supplemental oxygen to day 30, analysed with the win ratio method (a ratio >1 reflects a better outcome in the therapeutic anticoagulation group) in the intention-to-treat population. The primary safety outcome was major or clinically relevant non-major bleeding through 30 days. This study is registered with ClinicalTrials.gov (NCT04394377) and is completed. Findings : From June 24, 2020, to Feb 26, 2021, 3331 patients were screened and 615 were randomly allocated (311 [50%] to the therapeutic anticoagulation group and 304 [50%] to the prophylactic anticoagulation group). 576 (94%) were clinically stable and 39 (6%) clinically unstable. One patient, in the therapeutic group, was lost to follow-up because of withdrawal of consent and was not included in the primary analysis. The primary efficacy outcome was not different between patients assigned therapeutic

			or prophylactic anticoagulation, with 28 899 (34·8%) wins in the therapeutic group and 34 288 (41·3%) in the prophylactic group (win ratio 0·86 [95% CI 0·59–1·22], p=0·40). Consistent results were seen in clinically stable and clinically unstable patients. The primary safety outcome of major or clinically relevant non-major bleeding occurred in 26 (8%) patients assigned therapeutic anticoagulation and seven (2%) assigned prophylactic anticoagulation (relative risk 3·64 [95% CI 1·61–8·27], p=0·0010). Allergic reaction to the study medication occurred in two (1%) patients in the therapeutic anticoagulation group and three (1%) in the prophylactic anticoagulation group. Interpretation : In patients hospitalised with COVID-19 and elevated D-dimer concentration, in-hospital therapeutic anticoagulation with rivaroxaban or enoxaparin followed by rivaroxaban to day 30 did not improve clinical outcomes and increased bleeding compared with prophylactic anticoagulation. Therefore, use of therapeutic-dose rivaroxaban, and other direct oral anticoagulants, should be avoided in these patients in the absence of an evidence-based indication for oral anticoagulation.


A
Therapeutic anticoagulation group
Prophylactic anticoagulation group
Win ratio 0·86 (95% CI 0·59–1·22), p=0·4044
Number of comparisons
40000
30000
20000
10000
0
34·8%
41·3%
23·9%
Wins
Ties
B
Relative risk 1·49 (95% CI 0·90–2·46), p=0·1296
Cumulative mortality (%)
40
30
20
10
0
0 3 6 9 12 15 18 21 24 27 30
Time (days)
Number at risk
Prophylactic anticoagulation group 304 303 301 299 294 289 288 287 285 284 282
Therapeutic anticoagulation group 310 308 304 300 296 289 286 281 277 275 275
C
Number of comparisons
30000
20000
10000
0
5·1%
7·9%
26·5%
29·1%
3·2%
4·3%
23·9%
Wins by time to death
Wins by duration of hospitalisation
Wins by duration of supplemental oxygen use
Ties

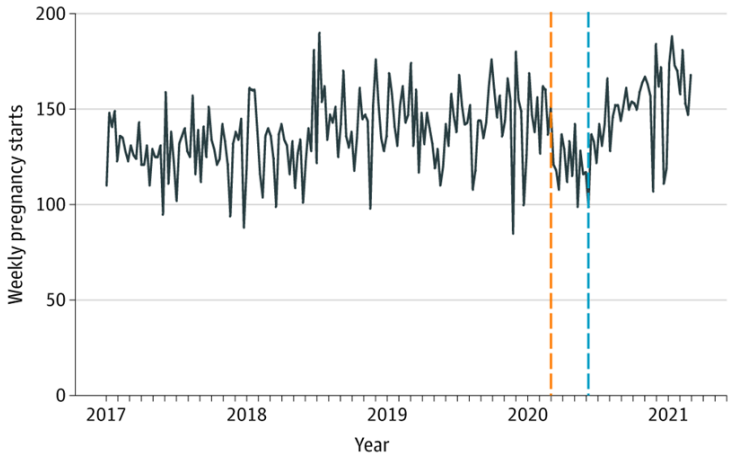
Lesho E et al CID https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab507/6292251	Emergence of the E484K Mutation in SARS-CoV-2 Lineage B.1.1.345 in Upstate New York	15 casi di pazienti infettati con una variante di SARS-CoV-2 portatrice della sostituzione E484K a New York.	A SARS-CoV-2 B.1.1.345 variant carrying the E484K mutation was detected in four patients with no apparent epidemiological association from a hospital network in upstate New York. Subsequent analysis identified an additional eleven B.1.1.345 variants from this region between December 2020 and February 2021.
Ljungman P et al Leukemia https://www.nature.com/articles/s41375-021-01302-5	COVID-19 and stem cell transplantation; results from an EBMT and GETH multicenter prospective survey	Su quasi 400 pazienti sottoposti a trapianto autologo o allgenico di cellule staminali ematopoietiche e con storia di COVID-19, 83.5% ha sviluppato una polmonite e 22.5% ha avuto necessità di ricovero in rianimazione.	This study reports on 382 COVID-19 patients having undergone allogeneic (n = 236) or autologous (n = 146) hematopoietic cell transplantation (HCT) reported to the European Society for Blood and Marrow Transplantation (EBMT) or to the Spanish Group of Hematopoietic Stem Cell Transplantation (GETH). The median age was 54.1 years (1.0–80.3) for allogeneic, and 60.6 years (7.7–81.6) for autologous HCT patients. The median time from HCT to COVID-19 was 15.8 months (0.2–292.7) in allogeneic and 24.6 months (−0.9 to 350.3) in autologous recipients. 83.5% developed lower respiratory tract disease and 22.5% were admitted to an ICU. Overall survival at 6 weeks from diagnosis was 77.9% and 72.1% in allogeneic and autologous recipients, respectively. Children had a survival of 93.4%. In multivariate analysis, older age ($p = 0.02$), need for ICU ($p < 0.0001$) and moderate/high immunodeficiency index ($p = 0.04$) increased the risk while better performance status ($p = 0.001$) decreased the risk for mortality. Other factors such as underlying diagnosis, time from HCT, GVHD, or ongoing immunosuppression did not significantly impact overall survival. We conclude that HCT patients are at high risk of developing LRTD, require admission to ICU, and have increased mortality in COVID-19.

			 **Fig. 2** Survival after diagnosis of COVID-19 in adults and children.
Tardif J et al The Lancet https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00222-8/fulltext	Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial	Trial clinico multicentrico su pazienti a rischio, non ospedalizzati, con COVID-19 trattati con colchicina che sembra conferire un beneficio rispetto all'outcome composito decesso/ospedalizzazione rispetto al placebo.	Background Evidence suggests a role for excessive inflammation in COVID-19 complications. Colchicine is an oral anti-inflammatory medication beneficial in gout, pericarditis, and coronary disease. We aimed to investigate the effect of colchicine on the composite of COVID-19-related death or hospital admission. Methods The present study is a phase 3, randomised, double-blind, adaptive, placebo-controlled, multicentre trial. The study was done in Brazil, Canada, Greece, South Africa, Spain, and the USA, and was led by the Montreal Heart Institute. Patients with COVID-19 diagnosed by PCR testing or clinical criteria who were not being treated in hospital were eligible if they were at least 40 years old and had at least one high-risk characteristic. The randomisation list was computer-generated by an unmasked biostatistician, and masked randomisation was centralised and done electronically through an automated interactive web-response system. The allocation sequence was unstratified and used a 1:1 ratio with a blocking

			schema and block sizes of six. Patients were randomly assigned to receive orally administered colchicine (0·5 mg twice per day for 3 days and then once per day for 27 days thereafter) or matching placebo. The primary efficacy endpoint was the composite of death or hospital admission for COVID-19. Vital status at the end of the study was available for 97·9% of patients. The analyses were done according to the intention-to-treat principle. The COLCORONA trial is registered with ClinicalTrials.gov (NCT04322682) and is now closed to new participants. Findings Trial enrolment began in March 23, 2020, and was completed in Dec 22, 2020. A total of 4488 patients (53·9% women; median age 54·0 years, IQR 47·0–61·0) were enrolled and 2235 patients were randomly assigned to colchicine and 2253 to placebo. The primary endpoint occurred in 104 (4·7%) of 2235 patients in the colchicine group and 131 (5·8%) of 2253 patients in the placebo group (odds ratio [OR] 0·79, 95·1% CI 0·61–1·03; p=0·081). Among the 4159 patients with PCR-confirmed COVID-19, the primary endpoint occurred in 96 (4·6%) of 2075 patients in the colchicine group and 126 (6·0%) of 2084 patients in the placebo group (OR 0·75, 0·57–0·99; p=0·042). Serious adverse events were reported in 108 (4·9%) of 2195 patients in the colchicine group and 139 (6·3%) of 2217 patients in the placebo group (p=0·051); pneumonia occurred in 63 (2·9%) of 2195 patients in the colchicine group and 92 (4·1%) of 2217 patients in the placebo group (p=0·021). Diarrhoea was reported in 300 (13·7%) of 2195 patients in the colchicine group and 161 (7·3%) of 2217 patients in the placebo group (p<0·0001). Interpretation In community-treated patients including those without a mandatory diagnostic test, the effect of colchicine on COVID-19-related clinical

			events was not statistically significant. Among patients with PCR-confirmed COVID-19, colchicine led to a lower rate of the composite of death or hospital admission than placebo. Given the absence of orally administered therapies to prevent COVID-19 complications in community-treated patients and the benefit of colchicine in patients with PCR-proven COVID-19, this safe and inexpensive anti-inflammatory agent could be considered for use in those at risk of complications. Notwithstanding these considerations, replication in other studies of PCR-positive community-treated patients is recommended.
Stout MJ et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2780572?resultClick=1	Use of Electronic Medical Records to Estimate Changes in Pregnancy and Birth Rates During the COVID-19 Pandemic	Minore numero di nuove gravidanze rispetto all'atteso dopo l'inizio delle misure di contenimento di COVID-19 negli USA e prevista risalita dall'estate 2021.	Importance The influence of the COVID-19 pandemic on fertility rates has been suggested in the lay press and anticipated based on documented decreases in fertility and pregnancy rates during previous major societal and economic shifts. Anticipatory planning for birth rates is important for health care systems and government agencies to accurately estimate size of economy and model working and/or aging populations. Objective To use projection modeling based on electronic health care records in a large US university medical center to estimate changes in pregnancy and birth rates prior to and after the COVID-19 pandemic societal lockdowns. Design, Setting, and Participants This cohort study included all pregnancy episodes within a single US academic health care system retrospectively from 2017 and modeled prospectively to 2021. Data were analyzed September 2021. Exposures Pre– and post–COVID-19 pandemic societal shutdown measures. Main Outcomes and Measures The primary outcome was number of new pregnancy episodes initiated within the health care system and use of those episodes to project birth volumes. Interrupted

			time series analysis was used to assess the degree to which COVID-19 societal changes may have factored into pregnancy episode volume. Potential reasons for the changes in volumes were compared with historical pregnancy volumes, including delays in starting prenatal care, interruptions in reproductive endocrinology and infertility services, and preterm birth rates. Results This cohort study documented a steadily increasing number of pregnancy episodes over the study period, from 4100 pregnancies in 2017 to 4620 in 2020 (28 284 total pregnancies; median maternal [interquartile range] age, 30 [27-34] years; 18 728 [66.2%] White women, 3794 [13.4%] Black women; 2177 [7.7%] Asian women). A 14% reduction in pregnancy episode initiation was observed after the societal shutdown of the COVID-19 pandemic (risk ratio, 0.86; 95% CI, 0.79-0.92; P < .001). This decrease appeared to be due to a decrease in conceptions that followed the March 15 mandated COVID-19 pandemic societal shutdown. Prospective modeling of pregnancies currently suggests that a birth volume surge can be anticipated in summer 2021. Conclusions and Relevance This cohort study using electronic medical record surveillance found an initial decline in births associated with the COVID-19 pandemic societal changes and an anticipated increase in birth volume. Future studies can further explore how pregnancy episode volume changes can be monitored and birth rates projected in real-time during major societal events.

			Figure 1. Trajectory of Weekly Volumes of New Pregnancy Episodes From 2017 to March 2021  The orange vertical dashed line indicates when the state-mandated stay-at-home order was placed, and the blue dashed line marks when the stay-at-home order was lifted.