RICERCA BIBLIOGRAFICA COVID 19

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FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE

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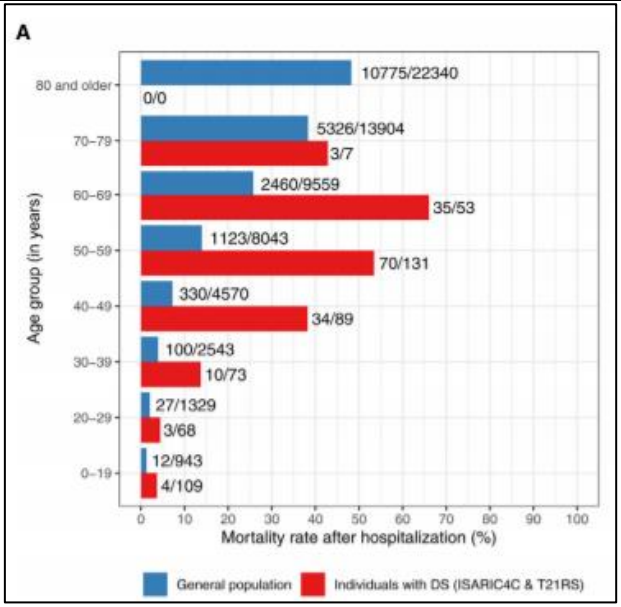
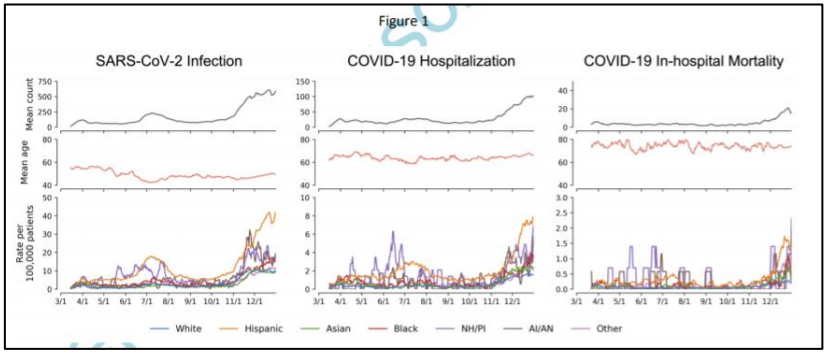
AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
Kaul DR et al American Journal of Transplantation https://onlinelibrary.wiley.com/doi/abs/10.1111/ajt.16532	Donor To Recipient Transmission Of SARS-CoV-2 By Lung Transplantation Despite Negative Donor Upper Respiratory Tract Testing	Trasmissione di infezione da SARS-CoV-2 da un donatore di polmone con tampone nasofaringeo negativo 48 ore prima del prelievo, ma BAL successivamente risultato positivo.	We describe a case of proven transmission of SARS-CoV-2 from lung donor to recipient. The donor had no clinical history or findings suggestive of infection with SARS-CoV-2 and tested negative by reverse transcriptase polymerase chain reaction (RT-PCR) on a nasopharyngeal (NP) swab obtained within 48 hours of procurement. Lower respiratory tract testing was not performed. The recipient developed fever, hypotension and pulmonary infiltrates on post-transplant day 3, and RT-PCR testing for SARS-CoV-2 on an NP swab specimen was non-reactive, but positive on bronchoalveolar lavage (BAL) fluid. One thoracic surgeon present during the transplantation procedure developed COVID-19. Sequence analysis of isolates from donor BAL fluid (obtained at procurement), the recipient, and the infected thoracic surgeon proved donor origin of recipient and health care worker infection. No other organs were procured from this donor. Transplant centers and organ procurement organizations should perform SARS-CoV-2

			testing of lower respiratory tract specimens from potential lung donors, and consider enhanced personal protective equipment for health care workers involved in lung procurement and transplantation.
Huls A et al EClinicalMedicine – The Lancet https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00049-3/fulltext	Medical vulnerability of individuals with down syndrome to severe COVID-19 – data from the trisomy 21 research society and the UK ISARIC4C survey	Esito di una survey sulle caratteristiche e l'outcome di 1046 pazienti con Sindrome di Down e COVID-19 : essi presentano maggiore rischio di complicanze e di morte rispetto alla popolazione adulta generale.	Background : Health conditions, immune dysfunction, and premature aging associated with trisomy 21 (Down syndrome, DS) may impact the clinical course of COVID-19. Methods : The T21RS COVID-19 Initiative launched an international survey for clinicians or caregivers on patients with COVID-19 and DS. Data collected between April and October 2020 (N=1046) were analysed and compared with the UK ISARIC4C survey of hospitalized COVID-19 patients with and without DS. Findings : The mean age of COVID-19 patients with DS in the T21RS survey was 29 years (SD = 18). Similar to the general population, the most frequent signs and symptoms of COVID-19 were fever, cough, and shortness of breath. Joint/muscle pain and vomiting or nausea were less frequent ($p < 0.01$), whereas altered consciousness/confusion were more frequent ($p < 0.01$). Risk factors for hospitalization and mortality were similar to the general population with the addition of congenital heart defects as a risk factor for hospitalization. Mortality rates showed a rapid increase from age 40 and were higher in patients with DS (T21RS DS versus non-DS patients: risk ratio (RR) = 3.5 (95%-CI=2.6;4.4), ISARIC4C DS versus non-DS patients: RR = 2.9 (95%-CI=2.1;3.8)) even after adjusting for known risk factors for COVID-19 mortality. Interpretation : Leading signs/symptoms of COVID-19 and risk factors for severe disease course are similar to the general population. However, individuals with DS present significantly higher rates of medical complications and mortality, especially from age 40.

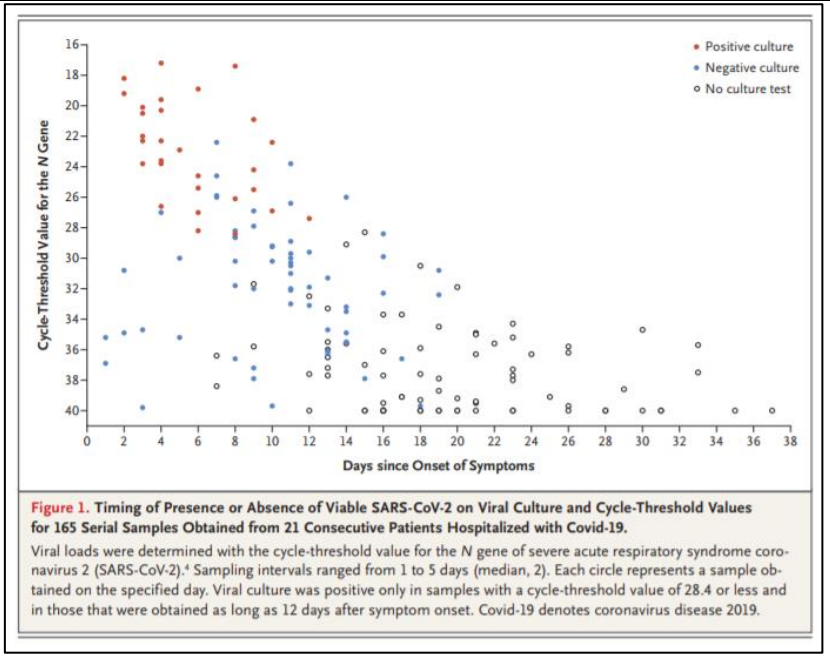
			
Dai CL et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab154/6145124?searchresult=1	Characteristics and Factors Associated with COVID-19 Infection, Hospitalization, and Mortality Across Race and Ethnicity	Studio di coorte retrospettivo su oltre 600.000 pazienti, di cui oltre 50.000 con COVID-19 negli USA, alla ricerca di fattori sociodemografici associati all'infezione e agli outcome : l'etnia ispanica è associata a maggiore tasso di infezione e peggiori outcome.	Background : Data on the characteristics of COVID-19 patients disaggregated by race/ethnicity remain limited. We evaluated the sociodemographic and clinical characteristics of patients across racial/ethnic groups and assessed their associations with COVID-19 outcomes. Methods : This retrospective cohort study examined 629,953 patients tested for SARS-CoV-2 in a large health system spanning California, Oregon, and Washington between March 1 and December 31, 2020. Sociodemographic and clinical characteristics were obtained from electronic health records. Odds of SARS-CoV-2 infection, COVID-19 hospitalization, and in-hospital death were assessed with multivariate logistic regression. Results : 570,298 patients with known race/ethnicity were tested for SARS-CoV-2, of whom 27.8% were non-White minorities. 54,645 individuals tested positive, with minorities representing 50.1%.

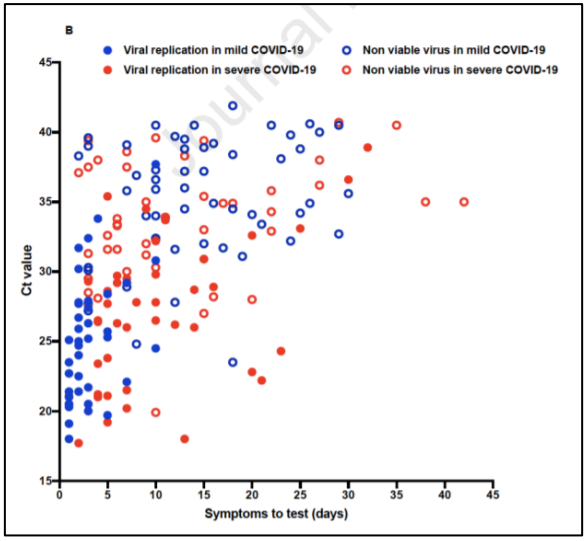
			Hispanics represented 34.3% of infections but only 13.4% of tests. While generally younger than White patients, Hispanics had higher rates of diabetes but fewer other comorbidities. 8,536 patients were hospitalized and 1,246 died, of whom 56.1% and 54.4% were non-White, respectively. Racial/ethnic distributions of outcomes across the health system tracked with state-level statistics. Increased odds of testing positive and hospitalization were associated with all minority races/ethnicities. Hispanic patients also exhibited increased morbidity, and Hispanic race/ethnicity was associated with in-hospital mortality (OR: 1.39 [95% CI: 1.14-1.70]). Conclusion : Major healthcare disparities were evident, especially among Hispanics who tested positive at a higher rate, required excess hospitalization and mechanical ventilation, and had higher odds of in-hospital mortality despite younger age. Targeted, culturally-responsive interventions and equitable vaccine development and distribution are needed to address the increased risk of poorer COVID-19 outcomes among minority populations. 
Hill A et al	Preliminary meta-analysis of randomized trials of ivermectin to treat SARSCoV-2 infection	Metanalisi degli studi a disposizione sull'effetto della terapia con ivermectina per COVID-19. Gli autori concludono che in	Introduction: Ivermectin is a well-established antiparasitic drug licensed since 1981, more recently approved for its anti-inflammatory effects against rosacea. It is being investigated for repurposing against SARS-CoV-2. In-vitro, ivermectin showed some antiviral activity but at higher concentrations than achieved in

ResearchSquare – not peer reviewed https://www.researchsquare.com/article/rs-148845/v1		assenza di trial clinici di adeguate dimensioni non vi sono evidenze sufficienti per giudicare questa terapia.	human plasma after normal oral dosing. An animal model demonstrated pathological benefits in COVID19 but no effect on viral RNA. We aimed to assess the available global data from randomized controlled trials (RCTs) of ivermectin in COVID-19. Methods: We conducted a systematic search of PUBMED, EMBASE, MedRxiv and trial registries. We excluded prevention studies and non-randomized or casecontrolled studies. We identified and included 18 RCTs. Data were combined from 2282 patients into a systematic review and meta-analysis. Results: Ivermectin was associated with reduced inflammatory markers (C-Reactive Protein, d-dimer and ferritin) and faster viral clearance by PCR. Viral clearance was treatment dose- and duration-dependent. Ivermectin showed significantly shorter duration of hospitalization compared to control. In six RCTs of moderate or severe infection, there was a 75% reduction in mortality (Relative Risk=0.25 [95%CI 0.12- 0.52]; p=0.0002); 14/650 (2.1%) deaths on ivermectin; 57/597 (9.5%) deaths in controls) with favorable clinical recovery and reduced hospitalization. Discussion: Many studies that were included were not yet published or peerreviewed and meta-analyses are prone to confounding issues. Furthermore, there was a wide variation in standards of care across trials, and ivermectin dose and duration of treatment was heterogeneous. Ivermectin should be validated in larger, appropriately controlled randomized trials before the results are sufficient for review by regulatory authorities.

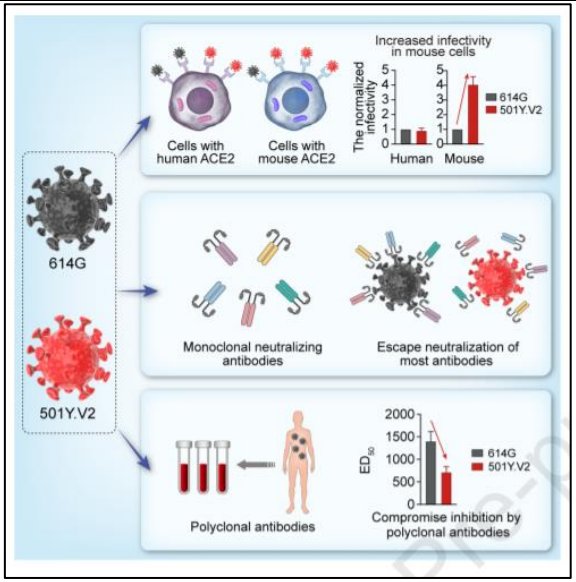
Elezkurtaj S et al Scientific Reports https://www.nature.com/articles/s41598-021-82862-5	Causes of death and comorbidities in hospitalized patients with COVID-19	Esito di 26 autopsie condotte su persone decedute per COVID-19 che avevano una clinica di malattia severa: lo shock settico e l'insufficienza multiorgano emergono come cause di morte, direttamente riconducibili a COVID-19 e non alle comorbidità preesistenti.	Infection by the new corona virus strain SARS-CoV-2 and its related syndrome COVID-19 has been associated with more than two million deaths worldwide. Patients of higher age and with preexisting chronic health conditions are at an increased risk of fatal disease outcome. However, detailed information on causes of death and the contribution of pre-existing health conditions to death yet is missing, which can be reliably established by autopsy only. We performed full body autopsies on 26 patients that had died after SARS-CoV-2 infection and COVID-19 at the Charité University Hospital Berlin, Germany, or at associated teaching hospitals. We systematically evaluated causes of death and pre-existing health conditions. Additionally, clinical records and death certificates were evaluated. We report findings on causes of death and comorbidities of 26 decedents that had clinically presented with severe COVID-19. We found that septic shock and multi organ failure was the most common immediate cause of death, often due to suppurative pulmonary infection. Respiratory failure due to diffuse alveolar damage presented as immediate cause of death in fewer cases. Several comorbidities, such as hypertension, ischemic heart disease, and obesity were present in the vast majority of patients. Our findings reveal that causes of death were directly related to COVID-19 in the majority of decedents, while they appear not to be an immediate result of preexisting health conditions and comorbidities. We therefore suggest that the majority of patients had died of COVID-19 with only contributory implications of preexisting health conditions to the mechanism of death.
Reffo E et al	Inflammatory syndrome in children associated with	Caso clinico di infarto del miocardio in un bambino di 4 anni con sierologia positiva per infezione da	A 4-year-old previously healthy child was admitted for persisting fever, conjunctivitis, and skin rush. Nasopharyngeal swab for SARS-CoV-2 was negative but anti-SARS-CoV-2 IgG was positive (108 U/mL). Laboratory findings showed elevated inflammatory

European Heart Journal https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab077/6145783	COVID-19 complicated by acute myocardial infarction	SARS-CoV-2, trattato con immunoglobuline, steroidi e trombolisi.	markers (CRP 190 mg/L, neutrophilia 16.75 109/L) and absence of any other potential causative organisms.
Min-Chul K et al NEJM https://www.nejm.org/doi/10.1056/NEJMc2027040	Duration of Culturable SARS-CoV-2 in Hospitalized Patients with Covid-19	Su 161 tamponi nasofaringei ottenuti da 21 pazienti ricoverati per COVID-19 in Corea, il virus è osservabile in coltura cellulare entro al massimo 12 giorni dall'esordio dei sintomi, solo in campioni con ciclo soglia della PCR inferiore a 28.4.	The duration of transmissibility of coronavirus disease 2019 (Covid-19) and the associated level of contagion have been uncertain. We cultured severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in serial respiratory samples obtained from hospitalized patients with Covid-19 to assess the duration of shedding of viable virus.

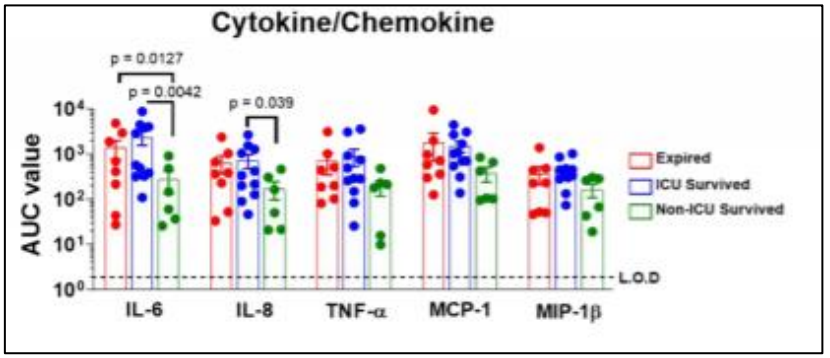
			 **Figure 1. Timing of Presence or Absence of Viable SARS-CoV-2 on Viral Culture and Cycle-Threshold Values for 165 Serial Samples Obtained from 21 Consecutive Patients Hospitalized with Covid-19.** Viral loads were determined with the cycle-threshold value for the *N* gene of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[4] Sampling intervals ranged from 1 to 5 days (median, 2). Each circle represents a sample obtained on the specified day. Viral culture was positive only in samples with a cycle-threshold value of 28.4 or less and in those that were obtained as long as 12 days after symptom onset. Covid-19 denotes coronavirus disease 2019.
Folgueira MD et al Clinical Microbiology and Infection 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	Su 193 tamponi nasofaringei positivi per SARS-CoV-2 eseguiti su 189 pazienti con infezione di gravità variabile : nei casi lievi il virus è visibile in coltura fino a 10 giorni dopo l'esordio dei sintomi, mentre nei casi gravi fino a 32 giorni.	Objectives : This study compares the infectivity of SARS-CoV-2 in respiratory samSuples from patients with mild COVID-19 with those from hospitalised patients with severe bilateral pneumonia. In severe COVID-19, we also analysed the presence of neutralising 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, neutralising activity was analysed in 30 paired sera collected after symptom onset >10 days.

			Results : We detected a cytopathic effect (CPE) in 91 (91/193, 47%) samples. Viral viability was maintained for up to 10 days in the patients with mild COVID-19. In the 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 neutralising activity (NT50 >1:1024 in 10% (3/30) of samples. Conclusions : 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 neutralising antibody titres. 

Li Q et al Cell https://www.cell.com/cell/fulltext/S0092-8674(21)00231-2	No higher infectivity but immune escape of SARS-CoV-2 501Y.V2 variants	SARS-CoV-2 portatore delle mutazioni tipiche della variante « sudafricana » 501Y.V2 non ha maggiore infettività in vitro, ma dimostra minore affinità per anticorpi monoclonali diretti contro la proteina S, siero di pazienti convalescenti e di topi immunizzati rispetto alla variante « classica » 614G.	The 501Y.V2 variants of SARS-CoV-2 containing multiple mutations in Spike are now dominant in South Africa and are rapidly spreading to other countries. Here, experiments with 18 pseudotyped viruses showed that the 501Y.V2 variants do not confer increased infectivity in multiple cell types except for murine ACE2-overexpressing cells, where a substantial increase in infectivity was observed. Notably, the susceptibility of the 501Y.V2 variants to 12 of 17 neutralizing monoclonal antibodies was substantially diminished, and the neutralization ability of the sera from convalescent patients and immunized mice was also reduced for these variants. The neutralization resistance was mainly caused by E484K and N501Y mutations in the receptor-binding domain of Spike. The enhanced infectivity in murine ACE2-overexpressing cells suggests the possibility of spillover of the 501Y.V2 variants to mice. Moreover, the neutralization resistance we detected for the 501Y.V2 variants suggests the potential for compromised efficacy of monoclonal antibodies and vaccines.

			
Ma S et al Nature https://www.nature.com/articles/s41392-021-00521-7	Efficacy and safety of systematic corticosteroids among severe COVID-19 patients: a systematic review and meta-analysis of randomized controlled trials	Metanalisi dei trial clinic randomizzati sull'effetto degli steroidi sulla sopravvivenza e altri outcome avversi nei pazienti con COVID-19. Il beneficio viene meno se non si includono i risultati del RECOVERY.	The benefits and harms of corticosteroids for patients with severe coronavirus disease 2019 (COVID-19) remain unclear. We systematically searched PubMed, Embase, and Cochrane Central Register of Controlled Trials from December 31, 2019 to October 1, 2020 to identify randomized controlled trials (RCTs) that evaluated corticosteroids in severe COVID-19 patients. The primary outcome was all-cause mortality at the longest follow-up. Secondary outcomes included a composite disease progression (progression to intubation, ventilation, extracorporeal membrane oxygenation, ICU transfer, or death among those not ventilated at enrollment) and incidence of serious adverse events. A random-effects model was applied to calculate risk ratio (RR) with 95% confidence intervals (CIs). We used the Grading of Recommendations Assessment, Development, and Evaluation approach to evaluate the certainty of the evidence. Seven RCTs involving 6250 patients were included, of

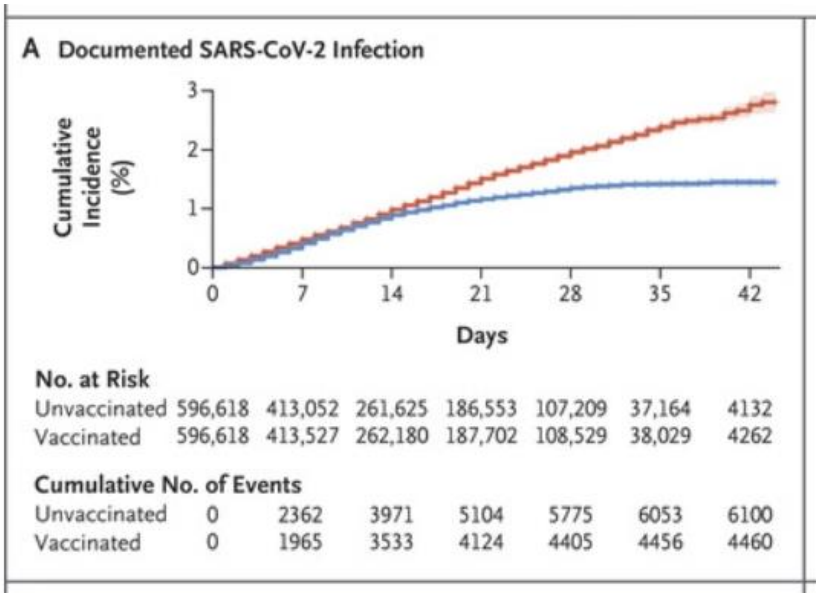
			which the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial comprised nearly 78% of all included subjects. Results showed that corticosteroids were associated with a decreased all-cause mortality (27.3 vs. 31.1%; RR: 0.85; 95% CI: 0.73–0.99; P = 0.04; low-certainty evidence). Trial sequential analysis suggested that more trials were still required to confirm the results. However, such survival benefit was absent if RECOVERY trial was excluded (RR: 0.83; 95% CI: 0.65–1.06; P = 0.13). Furthermore, corticosteroids decreased the occurrence of composite disease progression (30.6 vs. 33.3%; RR: 0.77; 95% CI: 0.64–0.92; P = 0.005), but not increased the incidence of serious adverse events (3.5 vs. 3.4%; RR: 1.16; 95% CI: 0.39–3.43; P = 0.79).
FDA Briefing Document https://www.fda.gov/media/146217/download	Janssen Ad26.COV2.S Vaccine for the Prevention of COVID-19	Documento sottoposto a FDA per l'autorizzazione in emergenza del vaccino Janssen a vettore adenovirale contro SARS-CoV-2.	On February 4, 2021, Janssen Biotech, Inc. (the Sponsor) submitted an Emergency Use Authorization (EUA) request to FDA for an investigational vaccine intended to prevent COVID19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The vaccine, known as Ad26.COV2.S, is a replication-incompetent adenovirus type 26 (Ad26) vectored vaccine encoding a stabilized variant of the SARS-CoV-2 S protein. The proposed use under an EUA is for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 18 years of age and older. The proposed dosing regimen is a single intramuscular injection at the dose level of 5×1010 viral particles (vp).
Tang J et al Nature	Antibody affinity maturation and plasma IgA associate with clinical outcome in hospitalized COVID-19 patients.	Analisi dell'immunità in 25 pazienti ricoverati per COVID-19 : si osservano maggiori livelli di citochine proinfiammatorie e di IgA	Hospitalized COVID-19 patients often present with a large spectrum of clinical symptoms. There is a critical need to better understand the immune responses to SARS-CoV-2 that lead to either resolution or exacerbation of the clinical disease. Here, we examine longitudinal plasma samples from hospitalized COVID-19 patients with differential clinical outcome. We perform immune-repertoire

https://doi.org/10.1038/s41467-021-21463-2		contro la proteina spike nei casi fatali.	analysis including cytokine, hACE2-receptor inhibition, neutralization titers, antibody epitope repertoire, antibody kinetics, antibody isotype and antibody affinity maturation against the SARS-CoV-2 prefusion spike protein. Fatal cases demonstrate high plasma levels of IL-6, IL-8, TNFalpha, and MCP-1, and sustained high percentage of IgA-binding antibodies to prefusion spike compared with non-ICU survivors. Disease resolution in non-ICU and ICU patients associates with antibody binding to the receptor binding motif and fusion peptide, and antibody affinity maturation to SARS-CoV-2 prefusion spike protein. Here, we provide insight into the immune parameters associated with clinical disease severity and disease-resolution outcome in hospitalized patients that could inform development of vaccine/therapeutics against COVID-19. 
Versyck M et al Journal of Mycology and Medicine	Invasive pulmonary aspergillosis in COVID-19 critically ill patients: Results of a French monocentric cohort.	Studio retrospettivo monocentrico su pazienti con ARDS secondaria a COVID-19 : prevalenza di aspergillosi polmonare del 3.7%, in linea con altre popolazioni di ARDS.	INTRODUCTION: Coronavirus disease 2019 or COVID-19 is a new infectious disease responsible for potentially severe respiratory impairment associated with initial immunosuppression. Similarly to influenza, several authors have described a higher risk of fungal infection after COVID-19, in particular for invasive pulmonary aspergillosis. The main objective here is to define the prevalence of invasive pulmonary aspergillosis (IPA) in a cohort of COVID-19

			patients with moderate to severe acute respiratory disease syndrome (ARDS). MATERIAL AND METHODS: We conducted a large monocentric retrospective study investigating all the ventilated COVID-19 patients with ARDS hospitalized at Valenciennes' general hospital, France, between March 15, 2020 and April 30, 2020. In the center a systematic IPA screening strategy was carried out for all ARDS patients, with weekly tests of serum galactomannan and beta-D-glucan. Bronchoalveolar lavage with culture and chest CT scan were performed when the serum assays were positives. RESULTS: A total of 54 patients were studied. Their median age was 65 years, and 37 of the patients (71%) were male. Two patients had chronic immunosuppression and among all the patients, only 2 non-immunocompromised presented a putative IPA during their stay. CONCLUSION: The prevalence of IPA in this cohort of COVID-19 patients (3.7%) is not higher than what is described in the other ARDS populations in the literature. These results are however different from the previous publications on COVID-19 patients and must therefore be confirmed by larger and multicentric studies.
Rollins N et al The Lancet https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(20)30538-6/fulltext	A public health approach for deciding policy on infant feeding and mother–infant contact in the context of COVID-19	Stima del peso in termini di mortalità infantile, molto rilevante, di politiche che scoraggino l'allattamento al seno nei Paesi in via di sviluppo.	The COVID-19 pandemic has raised concern about the possibility and effects of mother–infant transmission of SARS-CoV-2 through breastfeeding and close contact. The insufficient available evidence has resulted in differing recommendations by health professional associations and national health authorities. We present an approach for deciding public health policy on infant feeding and mother–infant contact in the context of COVID-19, or for future emerging viruses, that balances the risks that are associated with viral infection against child survival, lifelong health, and development, and also maternal health. Using the Lives Saved Tool, we used available data to show how different public health approaches might affect infant mortality. Based on existing

			evidence, including population and survival estimates, the number of infant deaths in low-income and middle-income countries due to COVID-19 (2020–21) might range between 1800 and 2800. By contrast, if mothers with confirmed SARS-CoV-2 infection are recommended to separate from their newborn babies and avoid or stop breastfeeding, additional deaths among infants would range between 188 000 and 273 000.
Khan F et al Thorax https://doi.org/10.1136/thoraxjnl-2020-215266	Systematic review and meta-analysis of anakinra, sarilumab, siltuximab and tocilizumab for COVID-19.	Revisione sistematica e metanalisi delle evidenze sui farmaci immunomodulatori per il trattamento di COVID-19 : solo per tocilizumab sono disponibili sufficienti dati per eseguire una metanalisi, da cui emerge un beneficio sulla mortalità.	BACKGROUND: There is accumulating evidence for an overly activated immune response in severe COVID-19, with several studies exploring the therapeutic role of immunomodulation. Through systematic review and meta-analysis, we assess the effectiveness of specific interleukin inhibitors for the treatment of COVID-19. METHODS: Electronic databases were searched on 7 January 2021 to identify studies of immunomodulatory agents (anakinra, sarilumab, siltuximab and tocilizumab) for the treatment of COVID-19. The primary outcomes were severity on an Ordinal Scale measured at day 15 from intervention and days to hospital discharge. Key secondary endpoints included overall mortality. RESULTS: 71 studies totalling 22 058 patients were included, 6 were randomised trials. Most studies explored outcomes in patients who received tocilizumab (60/71). In prospective studies, tocilizumab was associated with improved unadjusted survival (risk ratio 0.83, 95% CI 0.72 to 0.96, I(2)=0.0%), but conclusive benefit was not demonstrated for other outcomes. In retrospective studies, tocilizumab was associated with less severe outcomes on an Ordinal Scale (generalised OR 1.34, 95% CI 1.10 to 1.64, I(2)=98%) and adjusted mortality risk (HR 0.52, 95% CI 0.41 to 0.66, I(2)=76.6%). The mean difference in duration of hospitalisation was 0.36 days (95% CI -0.07 to 0.80, I(2)=93.8%). There was substantial heterogeneity in retrospective studies, and estimates should be

			interpreted cautiously. Other immunomodulatory agents showed similar effects to tocilizumab, but insufficient data precluded meta-analysis by agent. CONCLUSION: Tocilizumab was associated with a lower relative risk of mortality in prospective studies, but effects were inconclusive for other outcomes. Current evidence for the efficacy of anakinra, siltuximab or sarilumab in COVID-19 is insufficient, with further studies urgently needed for conclusive findings.
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	Efficacia del vaccino BNT162b2 (Pfizer) contro SARS-CoV-2 somministrato in Israele.	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);

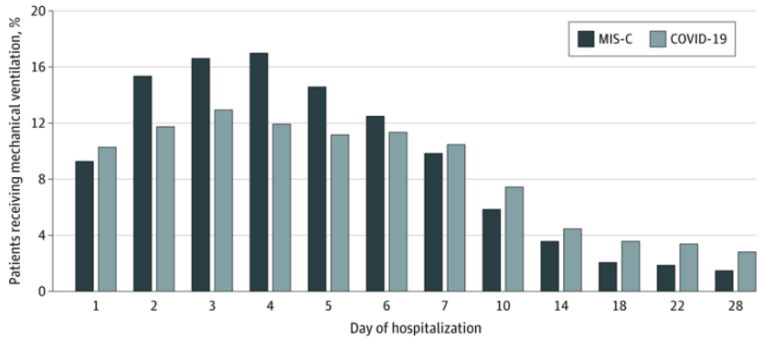
			and for severe disease, 62% (95% CI, 39 to 80) and 92% (95% CI, 75 to 100), respectively. Estimated effectiveness in preventing death from Covid-19 was 72% (95% CI, 19 to 100) for days 14 through 20 after the first dose. Estimated effectiveness in specific subpopulations assessed for documented infection 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. 
Al- Samkari H et al Annals of Internal Medicine	Thrombosis, Bleeding, and the Observational Effect of Early Therapeutic Anticoagulation on Survival	Studio di coorte multicentrico su 3239 pazienti critici con COVID-19 ricoverati in terapia	Background: Hypercoagulability may be a key mechanism of death in patients with coronavirus disease 2019 (COVID-19). Objective: To evaluate the incidence of venous thromboembolism (VTE) and major bleeding in critically ill patients with COVID-19 and

https://www.acpjournals.org/doi/10.7326/M20-6739	in Critically Ill Patients With COVID-19	intensiva : l'utilizzo précoce di anticoagulante a dosaggio terapeutico non ha effetto sulla mortalità. Si registrano complicanze emorragiche nel 2.8% dei pazienti, dei quali la gran parte (66.7%) era sottoposta a dosaggio terapeutico di anticoagulante.	examine the observational effect of early therapeutic anticoagulation on survival. Design: In a multicenter cohort study of 3239 critically ill adults with COVID-19, the incidence of VTE and major bleeding within 14 days after intensive care unit (ICU) admission was evaluated. A target trial emulation in which patients were categorized according to receipt or no receipt of therapeutic anticoagulation in the first 2 days of ICU admission was done to examine the observational effect of early therapeutic anticoagulation on survival. A Cox model with inverse probability weighting to adjust for confounding was used. Setting: 67 hospitals in the United States. Participants: Adults with COVID-19 admitted to a participating ICU. Measurements: Time to death, censored at hospital discharge, or date of last follow-up. Results: Among the 3239 patients included, the median age was 61 years (interquartile range, 53 to 71 years), and 2088 (64.5%) were men. A total of 204 patients (6.3%) developed VTE, and 90 patients (2.8%) developed a major bleeding event. Independent predictors of VTE were male sex and higher D-dimer level on ICU admission. Among the 2809 patients included in the target trial emulation, 384 (11.9%) received early therapeutic anticoagulation. In the primary analysis, during a median follow-up of 27 days, patients who received early therapeutic anticoagulation had a similar risk for death as those who did not (hazard ratio, 1.12 [95% CI, 0.92 to 1.35]). Limitation: Observational design. Conclusion: Among critically ill adults with COVID-19, early therapeutic anticoagulation did not affect survival in the target trial emulation.

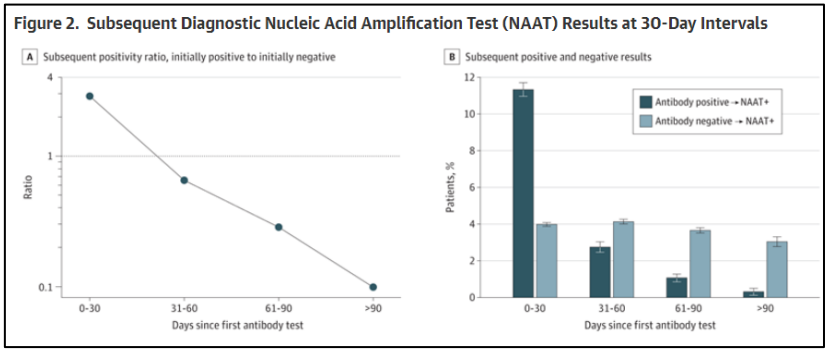
Patell R et al Thrombosis and Haemosthasis https://www.thieme-connect.de/products/ejournals/abstract/10.1055/s-0040-1721664	Pharmacologic Thromboprophylaxis and Thrombosis in Hospitalized Patients with COVID-19: A Pooled Analysis	Analisi delle evidenze a disposizione sull'effetto dell'utilizzo di anticoagulante a dosaggio terapeutico sui pazienti con COVID-19 : minore incidenza di trombosi nei pazienti scoagulati, mentre non si osservano differenze significative di incidenza di trombosi e sanguinamento tra dosaggio intermedio e dosaggio terapeutico di anticoagulante.	Background Coronavirus disease 2019 (COVID-19) increases thrombosis in hospitalized patients prompting adoption of different thromboprophylaxis strategies. Safety and efficacy of escalated-dose pharmacologic thromboprophylaxis are not established. Objectives To determine the pooled incidence of thrombosis/bleeding in hospitalized patients with COVID-19 for standard-dose, intermediate-dose, therapeutic anticoagulation, and no pharmacologic thromboprophylaxis. Methods MEDLINE, EMBASE, and Cochrane CENTRAL were searched up to August 29, 2020 for studies reporting pharmacologic thromboprophylaxis and thrombosis or bleeding. Pooled event rates were calculated using a random-effects model. Results Thirty-five observational studies were included. The pooled incidence rates of total venous thromboembolism (N = 4,685) were: no prophylaxis 41.9% (95% confidence interval [CI]: 28.1–57.2, I 2 = 76%), standard-dose prophylaxis 19.8% (95% CI: 13.2–28.6, I 2 = 95%), intermediate-dose prophylaxis 11.9% (95% CI: 4.3–28.6, I 2 = 91%), and therapeutic-dose anticoagulants 10.5% (95% CI: 4.2–23.8, I 2 = 82%, p = 0.003). The pooled incidence rates of arterial thrombosis (N = 1,464) were: no prophylaxis 11.3% (95% CI: 5.2–23.0, I 2 = 0%), standard-dose prophylaxis 2.5% (95% CI: 1.4–4.3, I 2 = 45%), intermediate-dose prophylaxis 2.1% (95% CI: 0.5–7.7, I 2 = 45%), and therapeutic-dose anticoagulants 1.3% (95% CI: 0.2–8.8, I 2 = 0, p = 0.009). The pooled bleeding event rates (N = 6,393) were nonsignificantly higher in therapeutic-dose anticoagulants compared with standard-dose prophylaxis, (6.3 vs. 1.7%, p = 0.083). Conclusion Thrombosis rates were lower in hospitalized COVID-19 patients who received pharmacologic thromboprophylaxis. Thrombosis and bleeding rates for patients receiving intermediate-dose thromboprophylaxis or therapeutic anticoagulation were

			similar to those who received standard-dose pharmacologic thromboprophylaxis.
May M et al Antimicrobial Agents and Chemotherapy https://aac.asm.org/content/early/2021/01/20/AAC.02167-20	Limited Utility of Procalcitonin in Identifying Community-Associated Bacterial Infections in Patients Presenting with Coronavirus Disease 2019	Il dosaggio di procalcitonina è utile, se negativo, per escludere coinfezioni batteriche anche in COVID-19.	The role of procalcitonin in identifying community-associated bacterial infections among patients with coronavirus disease 2019 is not yet established. In 2443 patients with 148 bacterial co-infections, mean procalcitonin levels were significantly higher with any bacterial infection (13.16 ± 51.19 ng/mL, p=0.0091) and with bacteremia (34.25 ± 85.01 ng/mL, p=0.0125) than without infection (2.00 ±15.26 ng/mL). Procalcitonin (cutoff 0.25 or 0.50 ng/mL) did not reliably identify bacterial co-infections, but may be useful in excluding bacterial infection.
Feldstein LR et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2777026	Characteristics and Outcomes of US Children and Adolescents With Multisystem Inflammatory Syndrome in Children (MIS-C) Compared With Severe Acute COVID-19	Case series di 1116 pazienti di età inferiore a 21 anni ospedalizzati per COVID-19 : sono fattori associati alla MISC (sindrome infiammatoria multisistemica del bambino) l'etnia afroamericana, l'età 6-12 anni e caratteristiche di maggiore gravità.	Importance Refinement of criteria for multisystem inflammatory syndrome in children (MIS-C) may inform efforts to improve health outcomes. Objective To compare clinical characteristics and outcomes of children and adolescents with MIS-C vs those with severe coronavirus disease 2019 (COVID-19). Setting, Design, and Participants Case series of 1116 patients aged younger than 21 years hospitalized between March 15 and October 31, 2020, at 66 US hospitals in 31 states. Final date of follow-up was January 5, 2021. Patients with MIS-C had fever, inflammation, multisystem involvement, and positive severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcriptase–polymerase chain reaction (RT-PCR) or antibody test results or recent exposure with no alternate diagnosis. Patients with COVID-

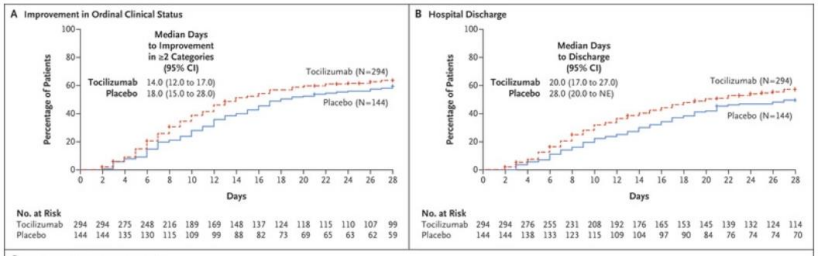
			19 had positive RT-PCR test results and severe organ system involvement. Exposure SARS-CoV-2. Main Outcomes and Measures Presenting symptoms, organ system complications, laboratory biomarkers, interventions, and clinical outcomes. Multivariable regression was used to compute adjusted risk ratios (aRRs) of factors associated with MIS-C vs COVID-19. Results Of 1116 patients (median age, 9.7 years; 45% female), 539 (48%) were diagnosed with MIS-C and 577 (52%) with COVID-19. Compared with patients with COVID-19, patients with MIS-C were more likely to be 6 to 12 years old (40.8% vs 19.4%; absolute risk difference [RD], 21.4% [95% CI, 16.1%-26.7%]; aRR, 1.51 [95% CI, 1.33-1.72] vs 0-5 years) and non-Hispanic Black (32.3% vs 21.5%; RD, 10.8% [95% CI, 5.6%-16.0%]; aRR, 1.43 [95% CI, 1.17-1.76] vs White). Compared with patients with COVID-19, patients with MIS-C were more likely to have cardiorespiratory involvement (56.0% vs 8.8%; RD, 47.2% [95% CI, 42.4%-52.0%]; aRR, 2.99 [95% CI, 2.55-3.50] vs respiratory involvement), cardiovascular without respiratory involvement (10.6% vs 2.9%; RD, 7.7% [95% CI, 4.7%-10.6%]; aRR, 2.49 [95% CI, 2.05-3.02] vs respiratory involvement), and mucocutaneous without cardiorespiratory involvement (7.1% vs 2.3%; RD, 4.8% [95% CI, 2.3%-7.3%]; aRR, 2.29 [95% CI, 1.84-2.85] vs respiratory involvement). Patients with MIS-C had higher neutrophil to lymphocyte ratio (median, 6.4 vs 2.7, P < .001), higher C-reactive protein level (median, 152 mg/L vs 33 mg/L; P < .001), and lower platelet count (<150 ×103 cells/μL [212/523 {41%} vs 84/486 {17%}, P < .001]). A total of 398 patients (73.8%) with MIS-C and 253 (43.8%) with COVID-19 were admitted to the intensive care unit, and 10 (1.9%) with MIS-C and 8 (1.4%) with COVID-19 died during hospitalization. Among patients with MIS-C with reduced left

			ventricular systolic function (172/503, 34.2%) and coronary artery aneurysm (57/424, 13.4%), an estimated 91.0% (95% CI, 86.0%-94.7%) and 79.1% (95% CI, 67.1%-89.1%), respectively, normalized within 30 days. Conclusions and Relevance This case series of patients with MIS-C and with COVID-19 identified patterns of clinical presentation and organ system involvement. These patterns may help differentiate between MIS-C and COVID-19. **Figure 3. Clinical Outcomes by Day of Hospitalization for Patients With MIS-C and Severe COVID-19** A Mechanical ventilator support and death  Hospitalized patients MIS-C 529 510 495 437 399 345 285 148 83 48 36 24 Severe COVID-19 563 428 319 276 236 202 172 118 74 51 43 35 Receiving mechanical ventilation MIS-C 49 81 88 90 77 66 52 31 19 11 10 8 Severe COVID-19 58 66 73 67 63 64 59 42 25 20 19 16 Cumulative deaths MIS-C 0 1 2 3 4 5 5 6 7 8 8 8 Severe COVID-19 0 3 3 3 3 3 3 4 4 4 4 4
Harvey RA et al JAMA https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2776810	Association of SARS-CoV-2 Seropositive Antibody Test With Risk of Future Infection	In una coorte di oltre 2 milioni di pazienti, essere sieropositivi per SARS-CoV-2 implica un rischio aumentato di avere un tampone nasofaringeo per SARS-CoV-2 positivo nei primi 30 giorni (shedding),	Importance Understanding the effect of serum antibodies to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) on susceptibility to infection is important for identifying at-risk populations and could have implications for vaccine deployment. Objective The study purpose was to evaluate evidence of SARS-CoV-2 infection based on diagnostic nucleic acid amplification test (NAAT) among patients with positive vs negative test results for

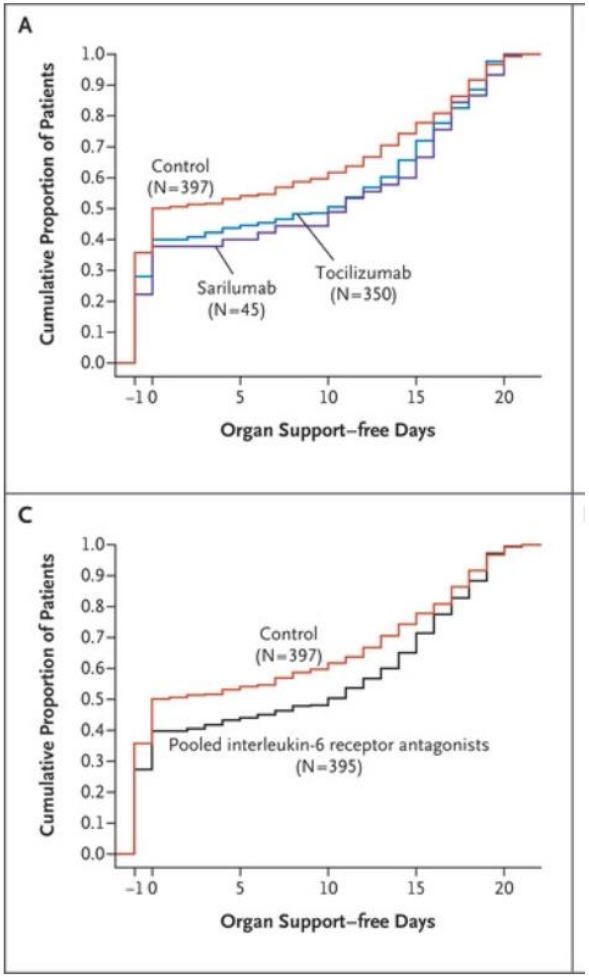
		ma poi una riduzione del rischio nel periodo successivo osservato fino a 90 giorni.	antibodies in an observational descriptive cohort study of clinical laboratory and linked claims data. Design, Setting, and Participants The study created cohorts from a deidentified data set composed of commercial laboratory tests, medical and pharmacy claims, electronic health records, and hospital chargemaster data. Patients were categorized as antibody-positive or antibody-negative according to their first SARS-CoV-2 antibody test in the database. Main Outcomes and Measures Primary end points were post-index diagnostic NAAT results, with infection defined as a positive diagnostic test post-index, measured in 30-day intervals (0-30, 31-60, 61-90, >90 days). Additional measures included demographic, geographic, and clinical characteristics at the time of the index antibody test, including recorded signs and symptoms or prior evidence of coronavirus 2019 (COVID) diagnoses or positive NAAT results and recorded comorbidities. Results The cohort included 3 257 478 unique patients with an index antibody test; 56% were female with a median (SD) age of 48 (20) years. Of these, 2 876 773 (88.3%) had a negative index antibody result, and 378 606 (11.6%) had a positive index antibody result. Patients with a negative antibody test result were older than those with a positive result (mean age 48 vs 44 years). Of index-positive patients, 18.4% converted to seronegative over the follow-up period. During the follow-up periods, the ratio (95% CI) of positive NAAT results among individuals who had a positive antibody test at index vs those with a negative antibody test at index was 2.85 (95% CI, 2.73-2.97) at 0 to 30 days, 0.67 (95% CI, 0.6-0.74) at 31 to 60 days, 0.29 (95% CI, 0.24-0.35) at 61 to 90 days, and 0.10 (95% CI, 0.05-0.19) at more than 90 days.

			Conclusions and Relevance In this cohort study, patients with positive antibody test results were initially more likely to have positive NAAT results, consistent with prolonged RNA shedding, but became markedly less likely to have positive NAAT results over time, suggesting that seropositivity is associated with protection from infection. The duration of protection is unknown, and protection may wane over time. 
Katz MH et al JAMA https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2776809	How to Advise Persons Who Are Antibody Positive for SARS-CoV-2 About Future Infection Risk	Come rispondere ai pazienti che chiedono se il fatto di avere anticorpi contro SARS-CoV-2 li protegga dalla reinfezione e per quanto tempo: non è chiaro.	Underlying the question of whether the presence of antibodies provides protection against future infections are 3 questions: are antibodies protective, how good are the available tests for accurately detecting antibodies, and how long does protection last? To address the first question, we know that most patients who recover from COVID-19 have antibodies and that reinfection (as opposed to extended symptoms or ongoing viral shedding) is rare, at least at this date. However, even if antibodies are protective, there remains a question of how accurate commercial tests are for detecting antibodies.
Rosas IO et al NEJM	Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia	Trial clinico di fase 3 su pazienti con polmonite da SARS-CoV-2 trattati con tocilizumab 8 mg/Kg EV	BACKGROUND : Coronavirus disease 2019 (Covid-19) is associated with immune dysregulation and hyperinflammation, including elevated interleukin-6 levels. The use of tocilizumab, a monoclonal antibody against the interleukin-6 receptor, has resulted in better

https://www.nejm.org/doi/full/10.1056/NEJMoa2028700?query=featured_home		contro placebo più standard of care: non si dimostra un beneficio del tocilizumab sulla mortalità o sul miglioramento clinico a 28 giorni. La percentuale di pazienti trattati con steroidi è molto bassa, minore nel gruppo tocilizumab. Il trial è stato finanziato dalla stessa La Roche che produce il farmaco !	outcomes in patients with severe Covid-19 pneumonia in case reports and retrospective observational cohort studies. Data are needed from randomized, placebo-controlled trials. METHODS : In this phase 3 trial, we randomly assigned patients who were hospitalized with severe Covid-19 pneumonia in a 2:1 ratio receive a single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight) or placebo. Approximately one quarter of the participants received a second dose of tocilizumab or placebo 8 to 24 hours after the first dose. The primary outcome was clinical status at day 28 on an ordinal scale ranging from 1 (discharged or ready for discharge) to 7 (death) in the modified intention-to-treat population, which included all the patients who had received at least one dose of tocilizumab or placebo. RESULTS : Of the 452 patients who underwent randomization, 438 (294 in the tocilizumab group and 144 in the placebo group) were included in the primary and secondary analyses. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% confidence interval [CI], 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI, 1.0 to 4.0) in the placebo group (between-group difference, −1.0; 95% CI, −2.5 to 0; P=0.31 by the van Elteren test). In the safety population, serious adverse events occurred in 103 of 295 patients (34.9%) in the tocilizumab group and in 55 of 143 patients (38.5%) in the placebo group. Mortality at day 28 was 19.7% in the tocilizumab group and 19.4% in the placebo group (weighted difference, 0.3 percentage points (95% CI, –7.6 to 8.2; nominal P=0.94). CONCLUSIONS : In this randomized trial involving hospitalized patients with severe Covid-19 pneumonia, the use of tocilizumab did not result in significantly better clinical status or lower mortality than placebo at 28 days.

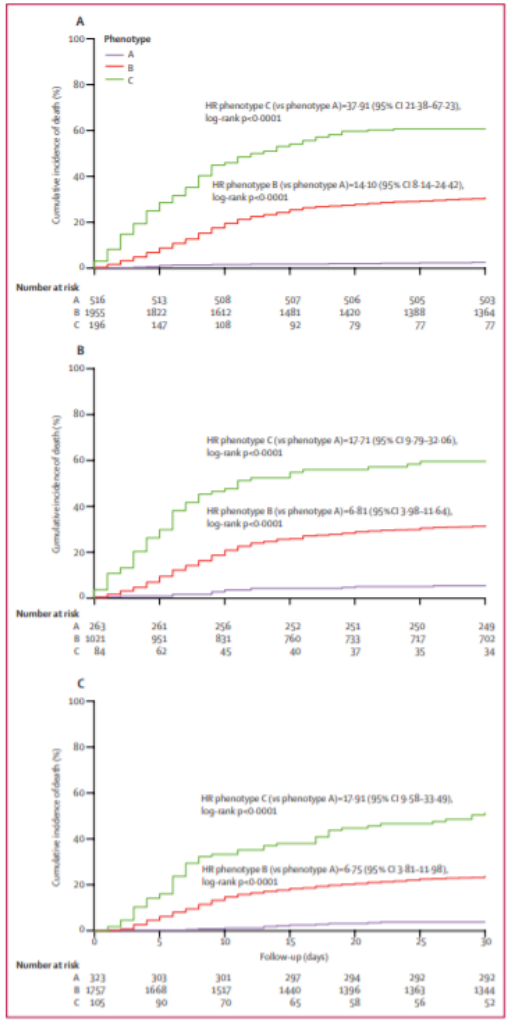
			
The REMAP-CAP Investigators NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2100433?query=featured_home	Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19	Trial clinico su pazienti ricoverati in rianimazione per COVID-19 e assegnati a terapia con tocilizumab, sarilumab o solo standard of care : si osserva un beneficio sulla sopravvivenza e sullo svezzamento dal supporto intensivo (in accordo con i risultati del trial RECOVERY).	BACKGROUND : The efficacy of interleukin-6 receptor antagonists in critically ill patients with coronavirus disease 2019 (Covid-19) is unclear. METHODS : We evaluated tocilizumab and sarilumab in an ongoing international, multifactorial, adaptive platform trial. Adult patients with Covid-19, within 24 hours after starting organ support in the intensive care unit (ICU), were randomly assigned to receive tocilizumab (8 mg per kilogram of body weight), sarilumab (400 mg), or standard care (control). The primary outcome was respiratory and cardiovascular organ support–free days, on an ordinal scale combining in-hospital death (assigned a value of −1) and days free of organ support to day 21. The trial uses a Bayesian statistical model with predefined criteria for superiority, efficacy, equivalence, or futility. An odds ratio greater than 1 represented improved survival, more organ support–free days, or both. RESULTS : Both tocilizumab and sarilumab met the predefined criteria for efficacy. At that time, 353 patients had been assigned to tocilizumab, 48 to sarilumab, and 402 to control. The median number of organ support–free days was 10 (interquartile range, −1 to 16) in the tocilizumab group, 11 (interquartile range, 0 to 16) in the sarilumab group, and 0 (interquartile range, −1 to 15) in the control group. The median adjusted cumulative odds ratios were 1.64 (95% credible interval, 1.25 to 2.14) for tocilizumab and 1.76 (95% credible interval, 1.17 to 2.91) for sarilumab as compared with

			control, yielding posterior probabilities of superiority to control of more than 99.9% and of 99.5%, respectively. An analysis of 90-day survival showed improved survival in the pooled interleukin-6 receptor antagonist groups, yielding a hazard ratio for the comparison with the control group of 1.61 (95% credible interval, 1.25 to 2.08) and a posterior probability of superiority of more than 99.9%. All secondary analyses supported efficacy of these interleukin-6 receptor antagonists. CONCLUSIONS : In critically ill patients with Covid-19 receiving organ support in ICUs, treatment with the interleukin-6 receptor antagonists tocilizumab and sarilumab improved outcomes, including survival.

			
Rubin EJ et al NEJM	Interleukin-6 Receptor Inhibition in Covid-19 — Cooling the Inflammatory Soup	Commento ai lavori precedenti, che tenta di rendere ragione dei risultati apparentemente contraddittori e conclude che il timing della terapia con inibitori di interleukina	With coronavirus disease 2019 (Covid-19), the role of localized inflammation was evident early on, because severe symptoms developed in many patients late after infection, when the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load was decreasing. One of the prime candidates for mediating inflammation in Covid-19 has been interleukin-6, a cytokine

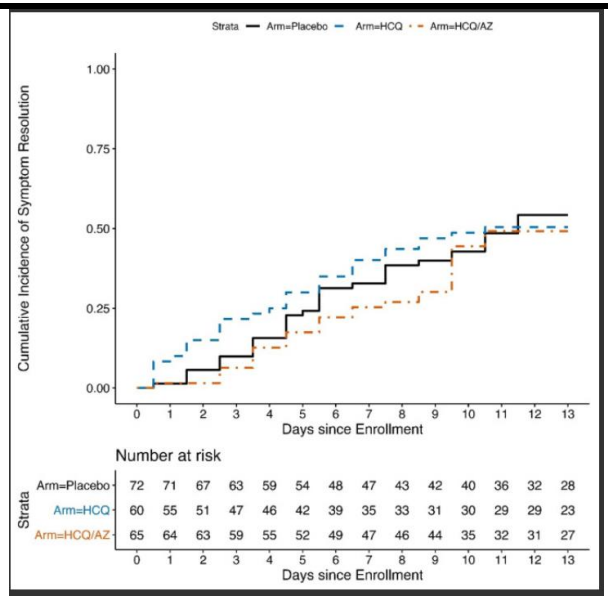
https://www.nejm.org/doi/full/10.1056/NEJMe2103108		6 è probabilmente un aspetto cruciale, ma ancora non si hanno sufficienti conoscenze per utilizzare in modo ottimale questi farmaci.	produced by macrophages that induces a proinflammatory response and is often elevated in patients with Covid-19. One of the attractions of interleukin-6 is that there are already approved agents that block either the cytokine or its receptor. In fact, enthusiasm for this therapy was so high that interleukin-6 blockade was being widely used in the United States before we had any evidence of its efficacy. However, in the absence of potent antivirals to block SARS-CoV-2 replication, it was unclear whether this strategy was safe. The results of two trials now appear in the Journal, with apparently contradictory results.
Gutièrrez-Gutièrrez B et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(21)00019-0/fulltext	Identification and validation of clinical phenotypes with prognostic implications in patients admitted to hospital with COVID-19: a multicentre cohort study	Proposta di tre fenotipi clinici (A,B,C) di pazienti con COVID-19 di gravità crescente, ai quali è associata mortalità crescente. L'assegnazione a un fenotipo tramite il modello proposto dagli autori può essere d'aiuto nel monitorare i pazienti più a rischio.	Background : The clinical presentation of COVID-19 in patients admitted to hospital is heterogeneous. We aimed to determine whether clinical phenotypes of patients with COVID-19 can be derived from clinical data, to assess the reproducibility of these phenotypes and correlation with prognosis, and to derive and validate a simplified probabilistic model for phenotype assignment. Phenotype identification was not primarily intended as a predictive tool for mortality. Methods : In this study, we used data from two cohorts: the COVID-19@Spain cohort, a retrospective cohort including 4035 consecutive adult patients admitted to 127 hospitals in Spain with COVID-19 between Feb 2 and March 17, 2020, and the COVID-19@HULP cohort, including 2226 consecutive adult patients admitted to a teaching hospital in Madrid between Feb 25 and April 19, 2020. The COVID-19@Spain cohort was divided into a derivation cohort, comprising 2667 randomly selected patients, and an internal validation cohort, comprising the remaining 1368 patients. The COVID-19@HULP cohort was used as an external validation cohort. A probabilistic model for phenotype assignment was derived in the derivation cohort using multinomial logistic regression and validated

			in the internal validation cohort. The model was also applied to the external validation cohort. 30-day mortality and other prognostic variables were assessed in the derived phenotypes and in the phenotypes assigned by the probabilistic model. Findings : Three distinct phenotypes were derived in the derivation cohort (n=2667)—phenotype A (516 [19%] patients), phenotype B (1955 [73%]) and phenotype C (196 [7%])—and reproduced in the internal validation cohort (n=1368)—phenotype A (233 [17%] patients), phenotype B (1019 [74%]), and phenotype C (116 [8%]). Patients with phenotype A were younger, were less frequently male, had mild viral symptoms, and had normal inflammatory parameters. Patients with phenotype B included more patients with obesity, lymphocytopenia, and moderately elevated inflammatory parameters. Patients with phenotype C included older patients with more comorbidities and even higher inflammatory parameters than phenotype B. We developed a simplified probabilistic model (validated in the internal validation cohort) for phenotype assignment, including 16 variables. In the derivation cohort, 30-day mortality rates were 2·5% (95% CI 1·4–4·3) for patients with phenotype A, 30·5% (28·5–32·6) for patients with phenotype B, and 60·7% (53·7–67·2) for patients with phenotype C (log-rank test p<0·0001). The predicted phenotypes in the internal validation cohort and external validation cohort showed similar mortality rates to the assigned phenotypes (internal validation cohort: 5·3% [95% CI 3·4–8·1] for phenotype A, 31·3% [28·5–34·2] for phenotype B, and 59·5% [48·8–69·3] for phenotype C; external validation cohort: 3·7% [2·0–6·4] for phenotype A, 23·7% [21·8–25·7] for phenotype B, and 51·4% [41·9–60·7] for phenotype C). Interpretation : Patients admitted to hospital with COVID-19 can be classified into three phenotypes that correlate with mortality. We

			developed and validated a simplified tool for the probabilistic assignment of patients into phenotypes. These results might help to better classify patients for clinical management, but the pathophysiological mechanisms of the phenotypes must be investigated. 

Manisty C et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00501-8/fulltext	Antibody response to first BNT162b2 dose in previously SARS-CoV-2-infected individuals		We reasoned that previous infection could be analogous to immune priming. As such, a first prime vaccine dose would effectively act as boost, so a second dose might not be needed. To test this, we undertook a nested case-control analysis of 51 participants of COVIDsortium, an ongoing longitudinal observational study of health-care workers (HCWs) in London who underwent weekly PCR and quantitative serology testing from the day of the first UK lockdown on March 23, 2020, and for 16 weeks onwards. 24 of 51 HCWs had a previous laboratory-confirmed mild or asymptomatic SARS-CoV-2 infection, as confirmed by positive detection of antibodies against the SARS-CoV-2 nucleocapsid (Elecsys Anti-SARS-CoV-2 N ECLIA, Roche Diagnostics, Burgess Hill, UK) or the receptor binding domain of the SARS-CoV-2 S1 subunit of the spike protein (anti-S; Elecsys anti-SARS-CoV-2 spike ECLIA, Roche Diagnostics), whereas 27 HCWs remained seronegative. A median of 12·5 sampling timepoints per participant permitted the identification of peak antibody titres in seropositive individuals while avoiding false negatives.
Johnston C et al EClinicalMedicine – The Lancet https://www.thelancet.com/journals/eclinm/article/PIIS2589-5370(21)00053-5/fulltext	Hydroxychloroquine with or without azithromycin for treatment of early SARS-CoV-2 infection among high-risk outpatient adults: A randomized clinical trial	Trial clinico randomizzato su 219 pazienti non ricoverati affetti da COVID-19 trattati con idrossiclorochina con aggiunta o meno di azitromicina oppure placebo : interrotto precocemente per futilità, i trattamenti proposti non hanno influenza sulla durata dei sintomi e non appaiono utili nei pazienti non ospedalizzati.	Background : Treatment options for outpatients with COVID-19 could reduce morbidity and prevent SARS-CoV-2 transmission. Methods : In this randomized, double-blind, three-arm (1:1:1) placebo-equivalent controlled trial conducted remotely throughout the United States, adult outpatients with laboratory-confirmed SARS-CoV-2 infection were recruited. Participants were randomly assigned to receive hydroxychloroquine (HCQ) (400 mg BID x1day, followed by 200 mg BID x9days) with or without azithromycin (AZ) (500 mg, then 250 mg daily x4days) or placebo-equivalent (ascorbic acid (HCQ) and folic acid (AZ)), stratified by risk for progression to severe COVID-19 (high-risk vs. low-risk). Self-collected nasal swabs for SARS-CoV-2 PCR, FLUPro symptom surveys, EKGs and vital signs were collected daily. Primary endpoints were: (a) 14-day

			progression to lower respiratory tract infection (LRTI), 28-day COVID-19 related hospitalization, or death; (b) 14-day time to viral clearance; secondary endpoints included time to symptom resolution (ClinicalTrials.gov: NCT04354428). Due to the low rate of clinical outcomes, the study was terminated for operational futility. Findings : Between 15th April and 27th July 2020, 231 participants were enrolled and 219 initiated medication a median of 5.9 days after symptom onset. Among 129 high-risk participants, incident LRTI occurred in six (4.7%) participants (two control, four HCQ/AZ) and COVID-19 related hospitalization in seven (5.4%) (four control, one HCQ, two HCQ/AZ); no LRTI and two (2%) hospitalizations occurred in the 102 low-risk participants (one HCQ, one HCQ/AZ). There were no deaths. Among 152 participants with viral shedding at enrollment, median time to clearance was 5 days (95% CI=4–6) in HCQ, 6 days (95% CI=4–8) in HCQ/AZ, and 8 days (95% CI=6–10) in control. Viral clearance was faster in HCQ (HR=1.62, 95% CI=1.01–2.60, p = 0.047) but not HCQ/AZ (HR=1.25, p = 0.39) compared to control. Among 197 participants who met the COVID-19 definition at enrollment, time to symptom resolution did not differ by group (HCQ: HR=1.02, 95% CI-0.63–1.64, p = 0.95, HCQ/AZ: HR=0.91, 95% CI=0.57–1.45, p = 0.70). Interpretation : Neither HCQ nor HCQ/AZ shortened the clinical course of outpatients with COVID-19, and HCQ, but not HCQ/AZ, had only a modest effect on SARS-CoV-2 viral shedding. HCQ and HCQ/AZ are not effective therapies for outpatient treatment of SARV-CoV-2 infection.

			
Janiaud P et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2777060	Association of Convalescent Plasma Treatment With Clinical Outcomes in Patients With COVID-19 A Systematic Review and Meta-analysis	Revisione sistematica e metanalisi sulla terapia con plasma di soggetti guariti in COVID-19 : per il momento non c'è evidenza di beneficio sulla mortalità o sugli altri outcome clinici.	Importance Convalescent plasma is a proposed treatment for COVID-19. Objective To assess clinical outcomes with convalescent plasma treatment vs placebo or standard of care in peer-reviewed and preprint publications or press releases of randomized clinical trials (RCTs). Data Sources PubMed, the Cochrane COVID-19 trial registry, and the Living Overview of Evidence platform were searched until January 29, 2021. Study Selection The RCTs selected compared any type of convalescent plasma vs placebo or standard of care for patients with confirmed or suspected COVID-19 in any treatment setting. Data Extraction and Synthesis Two reviewers independently extracted data on relevant clinical outcomes, trial characteristics, and patient characteristics and used the Cochrane Risk of Bias Assessment Tool. The primary analysis included peer-reviewed

			publications of RCTs only, whereas the secondary analysis included all publicly available RCT data (peer-reviewed publications, preprints, and press releases). Inverse variance–weighted meta-analyses were conducted to summarize the treatment effects. The certainty of the evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation. Main Outcomes and Measures All-cause mortality, length of hospital stay, clinical improvement, clinical deterioration, mechanical ventilation use, and serious adverse events. Results A total of 1060 patients from 4 peer-reviewed RCTs and 10 722 patients from 6 other publicly available RCTs were included. The summary risk ratio (RR) for all-cause mortality with convalescent plasma in the 4 peer-reviewed RCTs was 0.93 (95% CI, 0.63 to 1.38), the absolute risk difference was −1.21% (95% CI, −5.29% to 2.88%), and there was low certainty of the evidence due to imprecision. Across all 10 RCTs, the summary RR was 1.02 (95% CI, 0.92 to 1.12) and there was moderate certainty of the evidence due to inclusion of unpublished data. Among the peer-reviewed RCTs, the summary hazard ratio was 1.17 (95% CI, 0.07 to 20.34) for length of hospital stay, the summary RR was 0.76 (95% CI, 0.20 to 2.87) for mechanical ventilation use (the absolute risk difference for mechanical ventilation use was −2.56% [95% CI, −13.16% to 8.05%]), and there was low certainty of the evidence due to imprecision for both outcomes. Limited data on clinical improvement, clinical deterioration, and serious adverse events showed no significant differences. Conclusions and Relevance Treatment with convalescent plasma compared with placebo or standard of care was not significantly associated with a decrease in all-cause mortality or with any benefit

			for other clinical outcomes. The certainty of the evidence was low to moderate for all-cause mortality and low for other outcome.
Creech CB et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2777059	SARS-CoV-2 Vaccines	Riassunto delle caratteristiche dei vaccini contro SARS-CoV-2 approvati per l'uso o in fase avanzata di sperimentazione.	Shortly after SARS-CoV emerged at the turn of the 21st century, the spike (S) protein (particularly in its prefusion [native] conformation) was identified as the immunodominant antigen of the virus. Evaluation of patients with SARS-CoV-2 revealed that binding and neutralizing antibodies primarily target the receptor-binding domain of the S1 subunit. Once this putative vaccine target was identified, the next challenge was how to best generate an effective immune response to SARS-CoV-2. The characteristics of this response would include production of neutralizing antibodies, generation of a T-cell response, and avoidance of immune-enhanced disease (vaccine-induced response that led to paradoxically increased disease severity on viral challenge).

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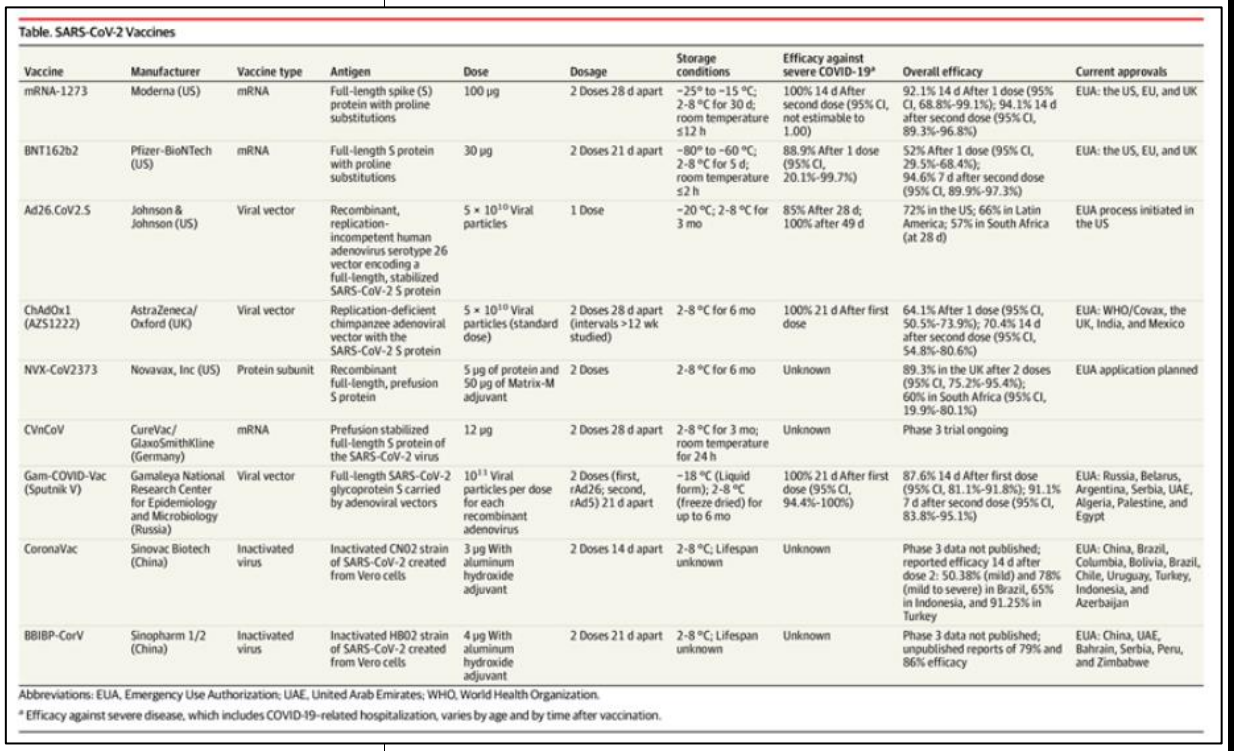

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<td>Zhou B et al

Nature

https://www.nature.com/articles/s41586-021-03361-1</td>
<td>SARS-CoV-2 spike D614G change enhances replication and transmission</td>
<td>Dimostrazione che la « vecchia » variante di SARS-CoV-2 portatrice della sostituzione D614G, ormai prevalente a livello mondiale, ha un vantaggio di affinità nei confronti del recettore ACE2 e di capacità replicativa.</td>
<td>During the evolution of SARS-CoV-2 in humans a D614G substitution in the spike (S) protein emerged and became the predominant circulating variant (S-614G) of the COVID-19 pandemic. However, whether the increasing prevalence of the S-614G variant represents a fitness advantage that improves replication and/or transmission in humans or is merely due to founder effects remains elusive. Here, we generated isogenic SARS-CoV-2 variants and demonstrate that the S-614G variant has (i) enhanced binding to human host cell surface receptor angiotensin-converting enzyme 2 (ACE2), (ii) increased replication in primary human bronchial and nasal airway epithelial cultures as well as in a novel human ACE2 knock-in mouse</td>
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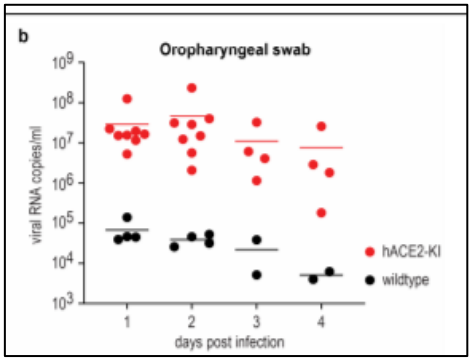
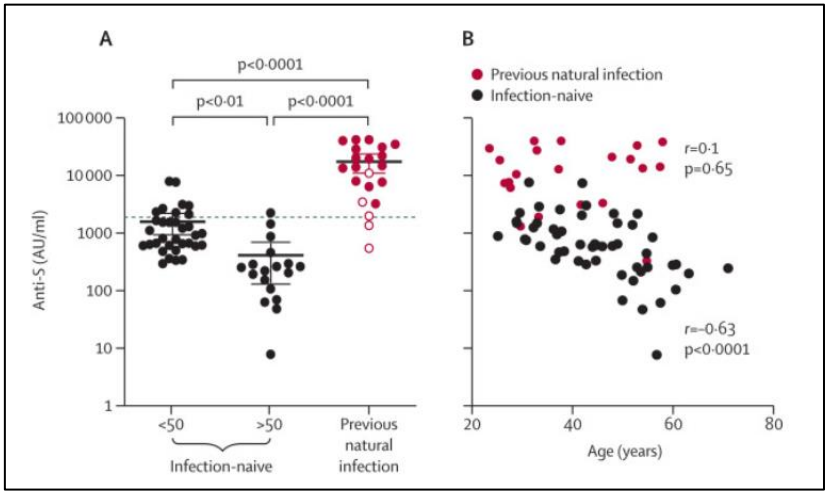
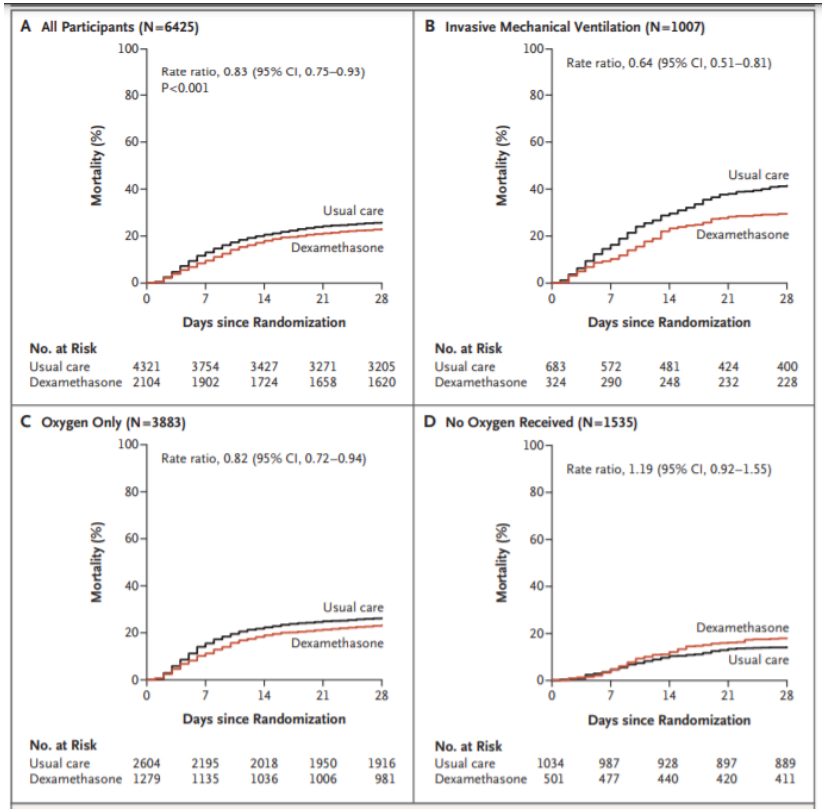
			model, and (iii) markedly increased replication and transmissibility in hamster and ferret models of SARS-CoV-2 infection. Collectively, our data show that while the S-614G substitution results in subtle increases in binding and replication in vitro, it provides a real competitive advantage in vivo, particularly during the transmission bottle neck, providing an explanation for the global predominance of S-614G variant among the SARS-CoV-2 viruses currently circulating. 
Prendecki M et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00502-X/fulltext	Effect of previous SARS-CoV-2 infection on humoral and T-cell responses to single-dose BNT162b2 vaccine	Di 72 operatori sanitari sottoposti a vaccino Pfizer, dei quali 21 con storia di infezione pregressa, questi ultimi dimostrano maggiore risposta immunitaria umorale e cellulare dopo una sola dose. Inoltre, gli individui di età superiore a 50 anni hanno una risposta meno elevata e meritano, secondo gli autori, la priorità insieme ai soggetti naive.	The rapid implementation of SARS-CoV-2 vaccination is now a global health-care priority. Successful phase 3 trial outcomes have been reported for numerous vaccines that induce robust humoral and cellular immune responses against the SARS-CoV-2 spike protein. To gain rapid control of accelerating cases and maximise public health impact, the UK Government has adopted the strategy of delaying second vaccination to 12 weeks. This policy has generated controversy, particularly among health-care workers (HCWs), the majority of whom have received BNT162b2 mRNA vaccine. Limited data on immune responses to single-dose vaccination with BNT162b2 are available, and vaccine responses following previous natural infection have not been assessed in clinical trials. We have therefore investigated immunological responses to single-dose

			BNT162b2 using a combination of serology, live virus neutralisation, and T-cell enzyme-linked immunospot (ELISpot) assays. 
Hayde Z et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab183/6150026?searchresult=1	Difference in SARS-CoV-2 attack rate between children and adults may reflect bias	Riflessioni sulla stima del tasso d'attacco dell'infezione da SARS-CoV-2 fra adulti e bambini : possibile influenza di un bias diagnostico.	The epidemiology of coronavirus disease 2019 (COVID-19) in children has been challenging to establish, owing to the high prevalence of asymptomatic infection in this population. Lower secondary attack rates in children compared to adults have been observed in household contact studies, but there is evidence this may reflect lower testing in children and reduced exposure, rather than a genuine difference in biological susceptibility. Additionally, children may shed infectious virus for a shorter period than adults and their antibody response may be less broad, with implications for both polymerase chain reaction and serological testing. Improvements in study design, data collection, and data interpretation are required to better understand the epidemiology of COVID-19 in children.

The RECOVERY Collaborative Group NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2021436?query=featured_coronavirus	Dexamethasone in Hospitalized Patients with Covid-19	Ulteriori risultati del trial RECOVERY in merito alla terapia con desametasone 6 mg EV/OS contro standard of care : si dimostra un beneficio sulla mortalità a 28 giorni nei pazienti ventilati e in quelli sottoposti a ossigenoterapia in genere, non in quelli che non necessitano di ossigeno supplementare. Riguardo la distanza dall'esordio dei sintomi, si dimostra un beneficio per chi riceve desametasone a partire da 7 giorni dopo.	BACKGROUND : Coronavirus disease 2019 (Covid-19) is associated with diffuse lung damage. Glucocorticoids may modulate inflammation-mediated lung injury and thereby reduce progression to respiratory failure and death. METHODS : In this controlled, open-label trial comparing a range of possible treatments in patients who were hospitalized with Covid-19, we randomly assigned patients to receive oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days or to receive usual care alone. The primary outcome was 28-day mortality. Here, we report the final results of this assessment. RESULTS : A total of 2104 patients were assigned to receive dexamethasone and 4321 to receive usual care. Overall, 482 patients (22.9%) in the dexamethasone group and 1110 patients (25.7%) in the usual care group died within 28 days after randomization (age-adjusted rate ratio, 0.83; 95% confidence interval [CI], 0.75 to 0.93; P<0.001). The proportional and absolute between-group differences in mortality varied considerably according to the level of respiratory support that the patients were receiving at the time of randomization. In the dexamethasone group, the incidence of death was lower than that in the usual care group among patients receiving invasive mechanical ventilation (29.3% vs. 41.4%; rate ratio, 0.64; 95% CI, 0.51 to 0.81) and among those receiving oxygen without invasive mechanical ventilation (23.3% vs. 26.2%; rate ratio, 0.82; 95% CI, 0.72 to 0.94) but not among those who were receiving no respiratory support at randomization (17.8% vs. 14.0%; rate ratio, 1.19; 95% CI, 0.92 to 1.55). CONCLUSIONS : In patients hospitalized with Covid-19, the use of dexamethasone resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen

			alone at randomization but not among those receiving no respiratory support.  **Figure 2. Mortality at 28 Days in All Patients and According to Respiratory Support at Randomization.** Shown are Kaplan–Meier survival curves for 28-day mortality among all the patients in the trial (primary outcome) (Panel A) and in three respiratory-support subgroups according to whether the patients were undergoing invasive mechanical ventilation (Panel B), receiving oxygen (with or without noninvasive ventilation) and without invasive mechanical ventilation (Panel C), or receiving no supplemental oxygen (Panel D) at the time of randomization. The Kaplan–Meier curves have not been adjusted for age. The rate ratios have been adjusted for the age of the patients in three categories (<70 years, 70 to 79 years, and ≥80 years). Estimates of the rate ratios and 95% confidence intervals in Panels B, C, and D were derived from a single age-adjusted regression model involving an interaction term between treatment assignment and level of respiratory support at randomization.
Eyal N et al Clinical Infectious Diseases	How to test SARS-CoV-2 vaccines ethically even after one is available	Come continuare a condurre trial clinici sui vacicni contro SARS-CoV-2 nonostante alcuni vaccini	Although vaccines against SARS-CoV-2 have now been found safe and efficacious, there remains an urgent global health need to test both these vaccines and additional vaccines against the same virus. Under variable conditions, either standard or unusual designs would

https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciab182/6152007?searchresult=1		siano già stati approvati e siano disponibili per la popolazione.	for both familiar and often-missed reasons make continued testing possible and ethical.