RICERCA BIBLIOGRAFICA COVID 19

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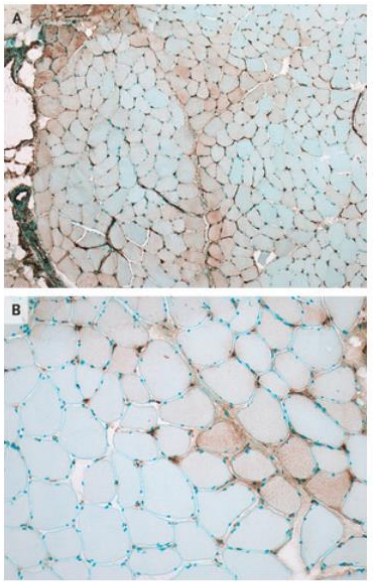
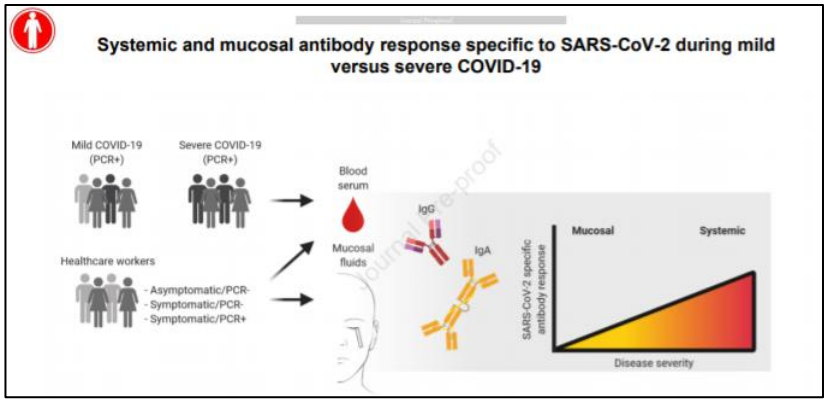
AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
Manzano GS et al NEJM https://www.nejm.org/doi/10.1056/NEJMc2031085	Covid-19–Associated Myopathy Caused by Type I Interferonopathy	Esito di biopsia muscolare su un paziente di 38 anni con COVID-19, mialgie e astenia che dimostra infiammazione perivascolare ed evidenza di produzione di interferon I.	The syndrome of Covid-19 infection includes myalgias and elevated creatine kinase levels in at least a third of patients. Whether the elevation in creatine kinase level is caused by viral infection of muscle, toxic effects of cytokines, or another mechanism is unclear. There are few reports of muscle-biopsy findings in patients with Covid-19. We describe a patient with Covid-19 infection and myopathy who had a muscle-biopsy specimen showing evidence of virus-induced type I interferonopathy.

			Figure 1.  Immunohistochemical Analysis of a Biopsy Specimen from the Left Deltoid Muscle in a Patient with Covid-19.
Cervia C et al Journal of Allergy and Clinical Immunology https://doi.org/10.1016/j.jaci.2020.10.040	Systemic and mucosal antibody responses specific to SARS-CoV-2 during mild versus severe COVID-19.	Studio della entità e deurata della risposta anticorpale sierica e mucosale contro SARS-CoV-2 in due coorti di pazienti con COVID-19 di diversa gravità.	BACKGROUND: Whereas severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-specific antibody tests are increasingly used to estimate the prevalence of SARS-CoV-2 infection, the determinants of these antibody responses remain unclear. OBJECTIVES: To evaluate systemic and mucosal antibody responses toward SARS-CoV-2 in mild versus severe coronavirus disease 2019 (COVID-19) cases. METHODS: Using immunoassays specific for SARS-CoV-2 spike proteins, we determined SARS-CoV-2-specific immunoglobulin A (IgA) and immunoglobulin G (IgG) in sera and mucosal fluids of two cohorts, including SARS-CoV-2 polymerase chain reaction (PCR)(+) patients (n = 64) as well as PCR(+) and PCR(-) healthcare workers (n = 109). RESULTS: SARS-CoV-2-specific serum

			IgA titers in mild COVID-19 cases were often transiently positive, whereas serum IgG titers remained negative or became positive 12-14 days after symptom onset. Conversely, patients with severe COVID-19 showed a highly significant increase of SARS-CoV-2-specific serum IgA and IgG titers after symptom onset. Very high titers of SARS-CoV-2-specific serum IgA correlated with severe acute respiratory distress syndrome (ARDS). Interestingly, some healthcare workers with negative SARS-CoV-2-specific serum antibody titers showed SARS-CoV-2-specific IgA in mucosal fluids with virus-neutralizing capacity in some cases. SARS-CoV-2-specific IgA titers in nasal fluids inversely correlated with age. CONCLUSIONS: Systemic antibody production against SARS-CoV-2 develops mainly in severe COVID-19, with very high IgA titers seen in patients with severe ARDS, whereas mild disease may be associated with transient production of SARS-CoV-2-specific antibodies but stimulate mucosal SARS-CoV-2-specific IgA secretion. 

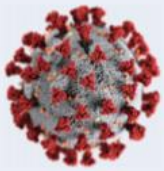
Garrido P et al The American Journal of Emergency Medicine https://doi.org/10.1016/j.ajem.2020.11.011	Clinical value of procalcitonin in critically ill patients infected by SARS-CoV-2.	Studio retrospettivo monocentrico per indagare l'utilità del dosaggio di procalcitonina nei pazienti con COVID-19 : associazione fra elevata PCT all'ingresso e mortalità nei ricoverati in rianimazione.	Background Blood procalcitonin (PCT) levels usually increase during infectious diseases and might be helpful to differentiate bacterial from non-bacterial origin. COVID-19 patients could present co-infections at initial presentation in the Emergency Department and nosocomial infections during stay in the ICU. However, the published literature has not established whether PCT changes could aid in the diagnosis of infectious complication during the COVID-19 pandemic. Methods Retrospective, single-center, cohort study, including COVID-19 patients admitted between March and May 2020. The data were prospectively collected for department purposes; laboratory results were collected automatically at admission and during the whole patient admission. Results 56 patients were analyzed (female 32%, male 68%), 35 were admitted to ICU, and 21 received general ward care. 21 ICU patients underwent mechanical ventilation (88%), and 9 died during admission (26%). Non-survivors had higher initial blood PCT levels than survivors at ICU admission.
Faraone A et al International and Emergency Medicine https://doi.org/10.1007/s11739-020-02562-2	Effectiveness and safety of noninvasive positive pressure ventilation in the treatment of COVID-19-associated acute hypoxemic respiratory failure: a single center, non-ICU setting experience.	Studio retrospettivo sull'effetto della ventilazione non invasiva a pressione positiva su 50 pazienti con COVID-19 e insufficienza respiratoria acuta. Si dimostra a latere un basso rischio infettivo per i curanti.	The role of noninvasive positive pressure ventilation (NIPPV) in COVID-19 patients with acute hypoxemic respiratory failure (AHRF) is uncertain, as no direct evidence exists to support NIPPV use in such patients. We retrospectively assessed the effectiveness and safety of NIPPV in a cohort of COVID-19 patients consecutively admitted to the COVID-19 general wards of a medium-size Italian hospital, from March 6 to May 7, 2020. Healthcare workers (HCWs) caring for COVID-19 patients were monitored, undergoing nasopharyngeal swab for SARS-CoV-2 in case of onset of COVID-19 symptoms, and periodic SARS-CoV-2 screening serology. Overall, 50 patients (mean age 74.6 years) received NIPPV, of which 22 (44%) were successfully weaned, avoiding endotracheal intubation (ETI) and AHRF-related death. Due to limited life expectancy, 25 (50%) of

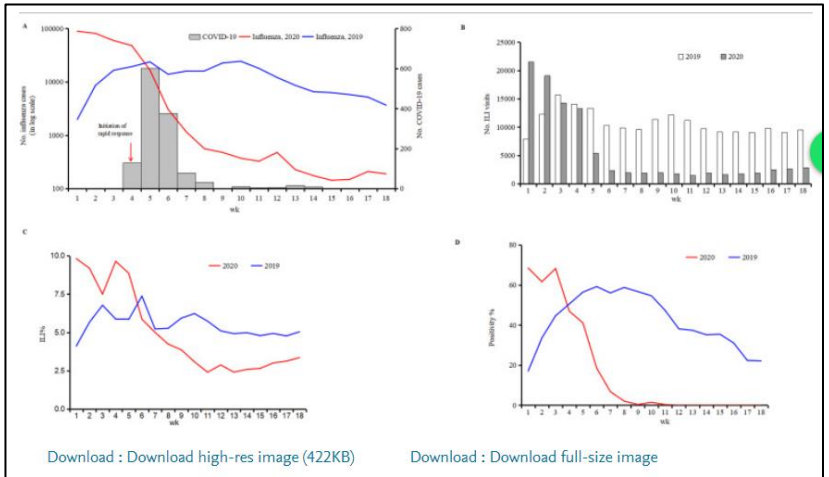
			50 NIPPV-treated patients received a "do not intubate" (DNI) order. Among these, only 6 (24%) were weaned from NIPPV. Of the remaining 25 NIPPV-treated patients without treatment limitations, 16 (64%) were successfully weaned, 9 (36%) underwent delayed ETI and, of these, 3 (33.3%) died. NIPPV success was predicted by the use of corticosteroids (OR 15.4, CI 1.79-132.57, p 0.013) and the increase in the PaO2/FiO2 ratio measured 24-48 h after NIPPV initiation (OR 1.02, CI 1-1.03, p 0.015), while it was inversely correlated with the presence of a DNI order (OR 0.03, CI 0.001-0.57, p 0.020). During the study period, 2 of 124 (1.6%) HCWs caring for COVID-19 patients were diagnosed with SARS-CoV-2 infection. Apart from patients with limited life expectancy, NIPPV was effective in a substantially high percentage of patients with COVID-19-associated AHRF. The risk of SARS-CoV-2 infection among HCWs was low. **Table 2** Clinical features and outcomes of NIPPV-treated patients with or without a DNI order | Variables | Patients with DNI order ($n=25$) | Patients without DNI order ($n=25$) | P value | | --- | --- | --- | --- | | Age, years, mean (SD) | 82.1 (7.6) | 67.1 (8.4) | 0.0001 | | Number of comorbidities, mean (SD) | 3 (1.3) | 1.84 (1.4) | 0.0039 | | SOFA score, mean (SD) | 3.6 (1.4) | 2.6 (0.8) | 0.0032 | | PaO_2/FiO_2 pre-NIPPV (SD) | 127.4 (67.9) | 132.9 (60.2) | 0.7632 | | PaO_2/FiO_2 post-NIPPV (SD) | 127 (80.8) | 169.6 (61.2) | 0.0409 | | NIPPV success, n | 6 (24%) | 16 (64%) | 0.0103 | | Delayed ETI, n | - | 9 (36%) | – | | In-hospital death, n | 22 (88%) | 3 (12%) | <0.0001 |
Savarese G et al European Journal of Heart Failure https://doi.org/10.1002/ejhf.2060	Association between Renin-Angiotensin-Aldosterone system inhibitor use and COVID-19 Hospitalization and death: A 1,4 million patient Nation-Wide registry analysis.	Esito di uno studio di sorveglianza nazionale condotto in Svezia su 1.4 milioni di persone, alla ricerca di una eventuale associazione fra terapia con ACE-inibitori/sartani e ricovero/morte per COVID-19 : nessuna associazione.	AIMS: Renin-angiotensin-aldosterone-system inhibitors (RAASi) improve outcomes in cardiorenal disease but concerns have been raised over increased risk of incident and death from Covid-19. We investigated the association between use of angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) or mineralocorticoid receptor antagonists (MRA) and Covid-19 hospitalization/death in a large nationwide population. METHODS AND RESULTS: Patients with hypertension, heart failure, diabetes, kidney disease, or ischemic heart disease registered in the Swedish

			National Patient Registry until February 1(st) 2020 were included and followed until May 31(st) 2020. Covid-19 cases were defined based on hospitalization/death for Covid-19. Multivariable logistic and Cox regressions were fitted to investigate the association between ACEi/ARB and MRA and risk of hospitalization/death for Covid-19 in the overall population, and of all-cause mortality in Covid-19 cases. We performed consistency analysis to quantify the impact of potential unmeasured confounding. Of 1,387,746 patients (60% receiving ACEi/ARB and 5.8% MRA) 7,146 (0.51%) had incident hospitalization/death from Covid-19. After adjustment for 45 variables, ACEi/ARB use was associated with a reduced risk of hospitalization/death for Covid-19 (Odds Ratio [95% Confidence Interval]: 0.86[0.81-0.91]) in the overall population, and with reduced mortality in Covid-19 cases (Hazard Ratio: 0.89[0.82-0.96]). MRA use was not associated with risk of any outcome. Consistency analysis showed that unmeasured confounding would need to be large for there to be harmful signals associated with RAASi use. CONCLUSIONS: In a 1.4 million nation-wide cohort, use of RAASi was not associated with increased risk of hospitalization for or death from Covid-19.
Shappell CN et al Critical Care Medicine https://journals.lww.com/ccmjournal/Fulltext/2020/12000/Does_Severe_Acute_Respiratory_Syndrome_Coronavirus.1.aspx	Does Severe Acute Respiratory Syndrome Coronavirus 2 Cause Sepsis?	Definire « sepsi » il danno d'organo associato all'infezione grave da SARS-CoV-2, oltre che essere formalmente corretto rispetto alla definizione Sepsis-3, potrebbe favorire una presa in carico	Coronavirus disease 2019 (COVID-19), the disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), poses an unprecedented threat to human health, healthcare systems, and our global economy. Since its emergence, clinicians have attempted to extrapolate the pathophysiology and management strategies for more well-known disease processes such as acute respiratory distress syndrome and other respiratory viruses. One important disease paradigm that has been variably applied to COVID-19, however, is sepsis. Although some experts have unequivocally asserted that multiple organ failure arising from COVID-19 is sepsis

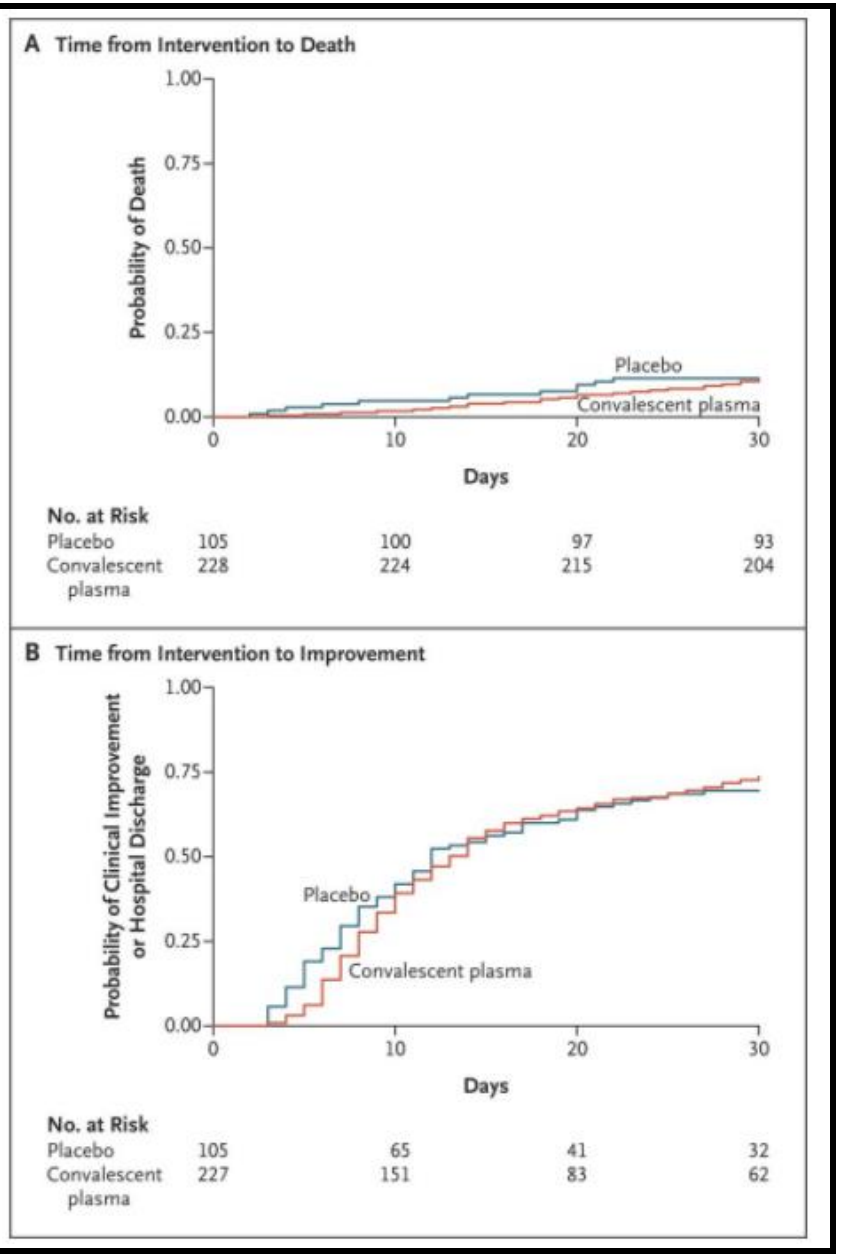
		tempestiva del paziente critico.	(1), other case series of severe COVID-19 infections have not labeled the disease as sepsis despite the fact that patients have proven infection and organ dysfunction and therefore meet the formal definition of sepsis (2,3). We believe it is worth exploring why this is the case, and whether or not it truly serves our patients to think about severe COVID-19 infections as sepsis.
Chirizzi D et al Environment International https://doi.org/10.1016/j.envint.2020.106255	SARS-CoV-2 concentrations and virus-laden aerosol size distributions in outdoor air in north and south of Italy.	La trasmissione di SARS-CoV-2 tramite aerosol all'aria aperta appare molto improbabile sulla base degli esiti di questo studio condotto alla ricerca di particelle virali in due regioni italiane.	The COVID-19 disease spread at different rates in the different countries and in different regions of the same country, as happened in Italy. Transmission by contact or at close range due to large respiratory droplets is widely accepted, however, the role of airborne transmission due to small respiratory droplets emitted by infected individuals (also asymptomatic) is controversial. It was suggested that outdoor airborne transmission could play a role in determining the differences observed in the spread rate. Concentrations of virus-laden aerosol are still poorly known and contrasting results are reported, especially for outdoor environments. Here we investigated outdoor concentrations and size distributions of virus-laden aerosol simultaneously collected during the pandemic, in May 2020, in northern (Veneto) and southern (Apulia) regions of Italy. The two regions exhibited significantly different prevalence of COVID-19. Genetic material of SARS-CoV-2 (RNA) was determined, using both real time RT-PCR and ddPCR, in air samples collected using PM10 samplers and cascade impactors able to separate 12 size ranges from nanoparticles (diameter D < 0.056 microm) up to coarse particles (D > 18 microm). Air samples tested negative for the presence of SARS-CoV-2 at both sites, viral particles concentrations were <0.8 copies m(-3) in PM10 and <0.4 copies m(-3) in each size range investigated. Outdoor air in residential and urban areas was generally not infectious and safe for the public in both northern and southern Italy, with the possible

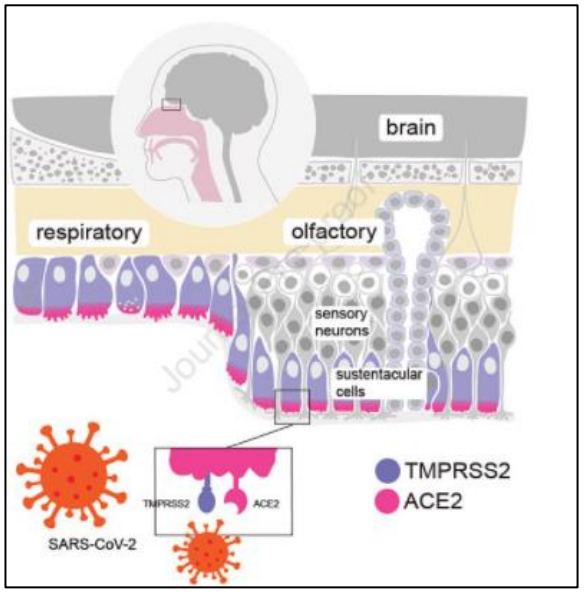
			exclusion of very crowded sites. Therefore, it is likely that outdoor airborne transmission does not explain the difference in the spread of COVID-19 observed in the two Italian regions.
Fattouch K et al The Journal of Thoracic and Cardiovascular Surgery https://doi.org/10.1016/j.jtcvs.2020.09.138	Cardiac surgery outcomes in patients with coronavirus disease 2019 (COVID-19): A case-series report.	Storia di un cluster di infezioni da SARS-CoV-2 in un reparto di Cardiochirurgia : 20 pazienti positivi post-intervento con mortalità del 15%, 12 operatori sanitari colpiti, necessità di fermare l'attività chirurgica.	OBJECTIVE: The impact of coronavirus disease 2019 (COVID-19) on the postoperative course of patients after cardiac surgery is unknown. We experienced a major severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak in our cardiac surgery unit, with several patients who tested positive early after surgery. Here we describe the characteristics, postoperative course, and laboratory findings of these patients, along with the fate of the health care workers. We also discuss how we reorganize and reallocate hospital resources to resume the surgical activity without further positive patients. METHODS: After diagnosis of the first symptomatic patient, surgery was suspended. Nasopharyngeal swabs were performed in all patients and health care workers. Patients who were positive for SARS-CoV-2 were isolated and monitored throughout the in-hospital stay and followed up after discharged until death or clinical recovery. RESULTS: Twenty patients were found to be positive for SARS-CoV-2 sometime after cardiac surgery (mean age 69 +/- 10.4 years; median European System for Cardiac Operative Risk Evaluation II score 3 [interquartile range, 5.1]); the median time from surgery to diagnosis was 15 days (interquartile range, 11). Among the patients, 18 had undergone cardiac surgery and 2 of them transcatheter aortic valve replacement. Overall mortality was 15%. Specific COVID-19-related symptoms were identified in 7 patients (35%). Among the 12 health care workers infected, 1 developed a bilateral mild-grade interstitial pneumonia. CONCLUSIONS: COVID-19 infection after cardiac surgery, regardless the time of the onset, is a serious condition. The

			systemic inflammatory state that follows extracorporeal circulation may mask the typical COVID-19 laboratory findings, making the diagnosis more difficult. A strict reorganization of the hospital resources is necessary to safely resume the cardiac surgical activity. **Cardiac surgery outcomes in patients with COVID-19** **Background**: The impact of COVID-19 in patients referred for cardiac surgery is unknown. There are no firm recommendations available to guide decision making for patients requiring cardiac surgery during pandemic. **Patients**: 20 patients were found positive to Sars-CoV-2 sometimes after urgent cardiac surgery (18 open heart surgery, 2 TAVR) **Results**: 3 patients died; COVID-19 diagnosis after cardiac surgery might be difficult due to the inflammatory state that follows the CPB. Complex hospital resources reorganization is needed to safely resume surgery.   
Cheng W et al Public Health https://doi.org/10.1016/j.puhe.2020.10.011	Successful interruption of seasonal influenza transmission under the COVID-19 rapid response in Zhejiang Province, China.	Studio epidemiologico in cui si osserva che l'introduzione dell'utilizzo universale delle mascherine chirurgiche è associata a significativa riduzione dei casi di sindrome influenzale in una provincia cinese.	OBJECTIVES: The objective of this study was to evaluate whether the non-pharmaceutical interventions (NPIs) introduced to curb the spread of coronavirus disease 2019 (COVID-19) also interrupted the transmission of influenza. STUDY DESIGN: This is a descriptive epidemiological study. METHODS: Data on changes in the number of reported influenza cases, number of influenza-like illness (ILI) visits, ILI percentage and influenza virus positivity were compared between the first 18 weeks of 2020 and the same period of 2019. RESULTS: The changes in the weekly average number of influenza cases were statistically significant between 2020 and 2019 (-4319 vs -525 per week; $P < 0.05$). The slopes of regression lines for the number of ILI visits were also statistically significant between 2020

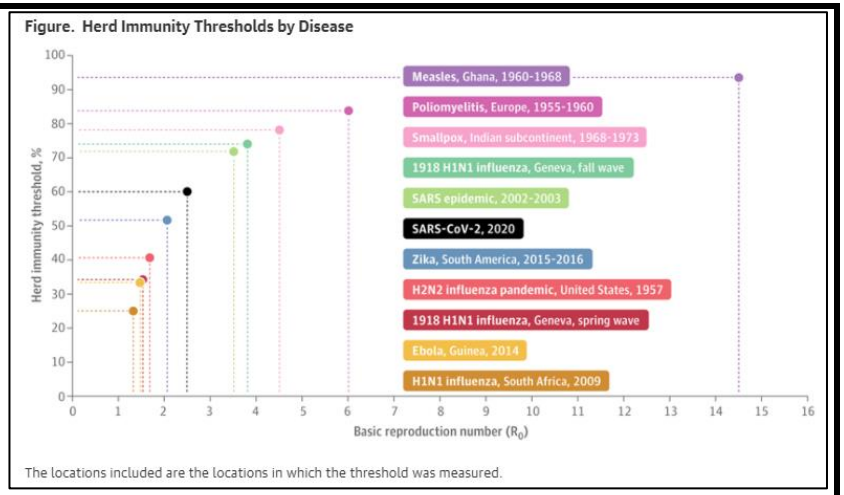
			and 2019 (-911 vs -98 per week; P < 0.05). CONCLUSIONS: This study found that the prevalence of influenza was substantially decreased when NPIs were implemented for the containment of COVID-19.  Download : Download high-res image (422KB) Download : Download full-size image Fig. 1. Influenza-like illness (ILI) sentinel surveillance results in Zhejiang Province during the first 18 weeks of 2020 and 2019. (A) Reported influenza and COVID-19 cases; (B) the number of ILI visits in all sentinel hospitals; (C) ILI percentage; (D) influenza positivity of the samples tested.
Dorfman et al JAMA https://jamanetwork.com/channels/health-forum/fullarticle/2768376	Mask Exemptions During the COVID-19 Pandemic—A New Frontier for Clinicians	Come affrontare la richiesta di « esenzione dalla mascherina » da parte dei pazienti : aspetti medici e legali (USA).	Masking or face covering amid the global coronavirus disease 2019 (COVID-19) pandemic has emerged as a highly polarizing practice, with surprising partisan divisions. While masking remains contentious, there is bipartisan agreement among policy makers that medical exemptions for masking are necessary and appropriate. Yet there is a dearth of guidance for clinicians on how to approach a request for an exemption. We analyze the medical and legal standards to guide this debate.

Simonovich VA et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2031304?query-featured_coronavirus=	A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia	Deludenti risultati di un trial clinico randomizzato, in doppio cieco, su 333 pazienti trattati con plasma di soggetti guariti oppure con placebo per polmonite COVID-19 relata: nessuna differenza negli outcome clinici e nella mortalità.	BACKGROUND : Convalescent plasma is frequently administered to patients with Covid-19 and has been reported, largely on the basis of observational data, to improve clinical outcomes. Minimal data are available from adequately powered randomized, controlled trials. METHODS : We randomly assigned hospitalized adult patients with severe Covid-19 pneumonia in a 2:1 ratio to receive convalescent plasma or placebo. The primary outcome was the patient's clinical status 30 days after the intervention, as measured on a six-point ordinal scale ranging from total recovery to death. RESULTS : A total of 228 patients were assigned to receive convalescent plasma and 105 to receive placebo. The median time from the onset of symptoms to enrollment in the trial was 8 days (interquartile range, 5 to 10), and hypoxemia was the most frequent severity criterion for enrollment. The infused convalescent plasma had a median titer of 1:3200 of total SARS-CoV-2 antibodies (interquartile range, 1:800 to 1:3200]. No patients were lost to follow-up. At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group in the distribution of clinical outcomes according to the ordinal scale (odds ratio, 0.83 (95% confidence interval [CI], 0.52 to 1.35; P=0.46). Overall mortality was 10.96% in the convalescent plasma group and 11.43% in the placebo group, for a risk difference of −0.46 percentage points (95% CI, −7.8 to 6.8). Total SARS-CoV-2 antibody titers tended to be higher in the convalescent plasma group at day 2 after the intervention. Adverse events and serious adverse events were similar in the two groups. CONCLUSIONS : No significant differences were observed in clinical status or overall mortality between patients treated with convalescent plasma and those who received placebo.


A Time from Intervention to Death
Probability of Death
1.00
0.75
0.50
0.25
0.00
Placebo
Convalescent plasma
0
10
20
30
Days
No. at Risk
Placebo 105 100 97 93
Convalescent plasma 228 224 215 204
B Time from Intervention to Improvement
Probability of Clinical Improvement or Hospital Discharge
1.00
0.75
0.50
0.25
0.00
Placebo
Convalescent plasma
0
10
20
30
Days
No. at Risk
Placebo 105 65 41 32
Convalescent plasma 227 151 83 62

Fodoulina L et al iScience https://www.cell.com/iscience/pdf/S2589-0042(20)31036-1.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS2589004220310361%3Fshowall%3Dtrue	SARS-CoV-2 receptors and entry genes are expressed in the human olfactory neuroepithelium and brain	Le cellule sustentaculari (*di supporto* ai neuroni) del bulbo olfattivo possiedono il recettore ACE2 e potrebbero costituire la via di ingresso di SARS-CoV-2 nel sistema nervoso centrale.	Reports indicate an association between COVID-19 and anosmia, as well as the presence of SARS-CoV-2 virions in the olfactory bulb. To test whether the olfactory neuroepithelium may represent a target of the virus, we generated RNA-seq libraries from human olfactory neuroepithelia, in which we found substantial expression of the genes coding for the virus receptor angiotensin-converting enzyme-2 (ACE2), and for the virus internalization enhancer TMPRSS2. We analyzed a human olfactory single-cell RNA-seq dataset and determined that sustentacular cells, which maintain the integrity of olfactory sensory neurons, express ACE2 and TMPRSS2. ACE2 protein was highly expressed in a subset of sustentacular cells in human and mouse olfactory tissues. Finally, we found ACE2 transcripts in specific brain cell types, both in mice and humans. Sustentacular cells thus represent a potential entry door for SARS-CoV-2 in a neuronal sensory system that is in direct connection with the brain. 

Omer SB et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2772167	Herd Immunity and Implications for SARS-CoV-2 Control	L'immunità di gregge ottenuta tramite l'infezione naturale non appare una valida strategia per controllare la diffusione di SARS-CoV-2 nella popolazione mondiale.	Herd immunity, also known as indirect protection, community immunity, or community protection, refers to the protection of susceptible individuals against an infection when a sufficiently large proportion of immune individuals exist in a population. In other words, herd immunity is the inability of infected individuals to propagate an epidemic outbreak due to lack of contact with sufficient numbers of susceptible individuals. It stems from the individual immunity that may be gained through natural infection or through vaccination. The term herd immunity was initially introduced more than a century ago. In the latter half of the 20th century, the use of the term became more prevalent with the expansion of immunization programs and the need for describing targets for immunization coverage, discussions on disease eradication, and cost-effectiveness analyses of vaccination programs. Eradication of smallpox and sustained reductions in disease incidence in adults and those who are not vaccinated following routine childhood immunization with conjugated Haemophilus influenzae type B and pneumococcal vaccines are successful examples of the effects of vaccine-induced herd immunity.

			
Hubiche T et al JAMA https://jamanetwork.com/journals/jamadermatology/fullarticle/2773121	Clinical, Laboratory, and Interferon-Alpha Response Characteristics of Patients With Chilblain-like Lesions During the COVID-19 Pandemic	Studio retrospettivo condotto su 40 pazienti che si presentavano con lesioni delle estremità tipo « geloni » che sono state associate a COVID-19.	Importance: Chilblain-like lesions have been reported during the coronavirus 2019 (COVID-19) pandemic. The pathophysiology of such manifestations remains largely unknown. Objective: To perform a systematic clinical, histologic, and biologic assessment in a cohort of patients with chilblain-like lesions occurring during the COVID-19 pandemic. Design, Setting, and Participants: In this prospective case series carried out with a COVID-19 multidisciplinary consultation group at the University Hospital of Nice, France, 40 consecutive patients presenting with chilblain-like lesions were included. Main Outcomes and Measures: Patients underwent a thorough general and dermatologic examination, including skin biopsies, vascular investigations, biologic analyses, interferon-alpha (IFN-α) stimulation and detection, and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) and serologic analysis. Results: Overall, 40 consecutive patients with chilblain-like lesions were included. Most patients were young, with a median (range)

			age of 22 (12-67) years; 19 were male and 21 were female. The clinical presentation was highly reproducible with chilblain-like lesions mostly on the toes. Bullous and necrotic evolution was observed in 11 patients. Acrocyanosis or cold toes were reported in 19 (47.5%) cases. Criteria compatible with COVID-19 cases were noted in 11 (27.5%) within 6 weeks prior to the eruption. The real-time PCR (rt-PCR) testing results were negative in all cases. Overall, SARS-CoV-2 serology results were positive in 12 patients (30%). D-dimer concentration levels were elevated in 24 (60.0%) cases. Cryoglobulinemia and parvovirus B19 serologic results were negative for all tested patients. The major histologic findings were features of lymphocytic inflammation and vascular damage with thickening of venule walls and pericyte hyperplasia. A significant increase of IFN-α production after in vitro stimulation was observed in the chilblain population compared with patients with mild-severe acute COVID-19. Conclusions and Relevance: Taken together, our results suggest that chilblain-like lesions observed during the COVID-19 pandemic represent manifestations of a viral-induced type I interferonopathy.
Spellberg B et al JAMA https://r.search.yahoo.com/_ylt=AwrJQ5uIHcBfgmAAINrc5olQ;_ylu=Y29sbwNpcjIEcG9zAzEEdnRpZAMEc2VjA3Ny/RV=2/RE=1606454792/RO=10/RU=https%3a%2f%2fjamanetwork	Antibodies, Immunity, and COVID-19	Riflessione sull'immunità contro SARS-CoV-2 alla luce delle conoscenze su altre malattie virali, rilevanza dell'immunità di gregge e ruolo dell'immunità anticorpale.	Widespread availability ofcommercial assays that detect anti–severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) antibodies has enabled researchers to examine naturally acquired immunity to coronavirus disease 2019 (COVID- 19) at the population level. Several studies have found that the SARS-CoV-2 seroprevalence (the percentage of the population with serum containing antibodies that recognize the virus) has remained below 20% even in the most adversely affected areas globally, such as Spain and Italy

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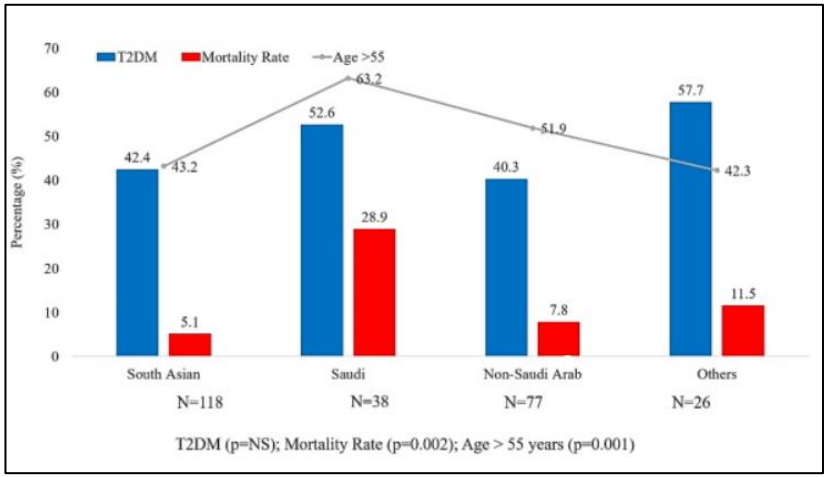
Mitjià O et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2021801	A Cluster-Randomized Trial of Hydroxychloroquine for Prevention of Covid-19	Trial clinico sull'utilizzo di idrossiclorochina come profilassi post-esposizione dell'infezione da SARS-CoV-2 in 2314 contatti di 672 persone positive : nessuna efficacia dimostrata.	BACKGROUND : Current strategies for preventing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection are limited to nonpharmacologic interventions. Hydroxychloroquine has been proposed as a postexposure therapy to prevent coronavirus disease 2019 (Covid-19), but definitive evidence is lacking. METHODS : We conducted an open-label, cluster-randomized trial involving asymptomatic contacts of patients with polymerase-chain-reaction (PCR)–confirmed Covid-19 in Catalonia, Spain. We Randomly assigned clusters of contacts to the hydroxychloroquine group (which received the drug at a dose of 800 mg once, followed by 400 mg daily for 6 days) or to the usual-care group (which received no specific therapy). The primary outcome was PCR-confirmed, symptomatic Covid-19 within 14 days. The secondary outcome was SARS-CoV-2 infection, defined by symptoms compatible with Covid-19 or a positive PCR test regardless of symptoms. Adverse events were assessed for up to 28 days. RESULTS : The analysis included 2314 healthy contacts of 672 index case patients with Covid-19 who were identified between March 17 and April 28, 2020. A total of 1116 contacts were randomly assigned to receive hydroxychloroquine and 1198 to receive usual care. Results were similar in the hydroxychloroquine and usual-care

			groups with respect to the incidence of PCR-confirmed, symptomatic Covid-19 (5.7% and 6.2%, respectively; risk ratio, 0.86 [95% confidence interval, 0.52 to 1.42]). In addition, hydroxychloroquine was not associated with a lower incidence of SARS-CoV-2 transmission than usual care (18.7% and 17.8%, respectively). The incidence of adverse events was higher in the hydroxychloroquine group than in the usual-care group (56.1% vs. 5.9%), but no treatment-related serious adverse events were reported. CONCLUSIONS : Postexposure therapy with hydroxychloroquine did not prevent SARS-CoV-2 infection or symptomatic Covid-19 in healthy persons exposed to a PCR-positive case patient.
The Lancet Editorial Board The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32472-7/fulltext	COVID-19 vaccines: no time for complacency	Ancora molto rimane da fare nella lotta contro SARS-CoV-2, anche se nel 2020 sono stati raggiunti grandi risultati con lo sforzo dell'intera comunità scientifica.	"Yes. Yes. Yes." That was the response of John Bell, Regius Professor of Medicine at the University of Oxford, when asked whether we could be confident that life will be returning to normal by spring. He was being interviewed by the BBC shortly after the announcement last week by Pfizer and BioNTech that their COVID-19 vaccine candidate had 90% efficacy in clinical trials. Similar announcements about the Russian Sputnik V and Moderna vaccines followed soon after. The prospect of preventing illness and death, and avoiding the harm and misery of extended restrictions, is a cause for optimism. But although it is right to be hopeful and encouraged, we are far from ending COVID-19 as a public health issue.
Ortega MC et al The Lancet https://www.thelancet.com/journals/laneur/article	Lessons from individuals with Down syndrome during COVID-19	Coinvolgimento delle persone con Sindrome di Down nella pandemia di COVID-19.	The COVID-19 pandemic presents particular challenges for people with intellectual disability. Individuals with Down syndrome, the most common form of intellectual disability, exhibit a higher prevalence of respiratory tract infections, immune dysfunction, chronic inflammation, early ageing, and comorbidities associated with COVID-19 risk leading to poorer clinical outcomes, but it is currently unknown to what extent they are more vulnerable to

/PIIS1474-4422(20)30401-4/fulltext			severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.According to a survey, done by the Trisomy 21 Research Society, the number of SARS-CoV-2 infections in people with trisomy 21 substantially dropped after the first wave of infection between March and May 2020, and even after the resurgence of coronavirus infections in September 2020.
Smith MJ et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)32337-0/fulltext	Emergency use authorisation for COVID-19 vaccines: lessons from Ebola	In che misura è etico autorizzare l'approvazione in emergenza di un vaccino per COVID-19 ? Accessibilità dei dati a disposizione, un rapporto rischio-beneficio favorevole e una rigorosa definizione di tale rapporto, sistema imparziale di monitoraggio appaiono requisiti fondamentali.	Emergency use authorisations—a regulatory mechanism that enables the public to gain access to promising investigational medical products when those products have not yet received regulatory approval and licensure3—have previously been used for unlicensed vaccines in public health emergencies and can be ethically justified provided that certain conditions are met.
Sheshah E et al Diabetes Research and Clinical Practice https://www.sciencedirect.com/science/article/pii/S0168822720307956	Prevalence of Diabetes, Management and Outcomes among Covid-19 Adult Patients Admitted in a Specialized Tertiary Hospital in Riyadh, Saudi Arabia	Studio retrospettivo sulle caratteristiche di 300 pazienti ricoverati per infezione da SARS-CoV-2 in Arabia Saudita : età superiore a 50 anni, insufficienza cardiaca e insufficienza rénale acuta sono associate a esito infausto.	This retrospective study aimed to characterize comorbidities and associated with mortality among hospitalized adults with Covid-19 managed as per the Saudi Ministry of Health protocol in a specialized tertiary hospital in Riyadh, Saudi Arabia. Medical records of 300 adult patients with PCR-confirmed SARS-CoV2 infection and admitted in King Salman Hospital (KSH) from May 1 to July 31 2020 were included. Medical history, management and outcomes were noted. Males significantly outnumber females (259 versus 41). South Asians comprise 41% of all admitted patients. Mortality rate was 10% and highest among Saudi males (28.9%). Type 2 diabetes mellitus (T2DM) was the most common comorbidity (45.7%). Almost all patients (99%) had pneumonia. Patients >50 years were three times more likely to die (confidence interval, CI 1.3-6.9; p=0.01) from Covid-19. Congestive heart failure (odds ratio OR 19.4,

			CI-1.5-260.0; p=0.02) and acute kidney injury (OR 11.7, CI-4.7-28.6; p<0.001) were significantly associated with higher mortality. Dexamethasone use significantly improved the final outcome based on net reclassification improvement (NRI) and integrated discrimination improvement (IDI) (p<0.05). In this single-center study, T2DM was very common among hospitalized Covid-19 patients. Patients >50 years, those with congestive heart failure and acute kidney injury are at higher risk for worse Covid-19 outcome. 
Bhimraj A et al IDSA https://www.idsociety.org/practice-guideline/covid-19-guideline-treatment-and-management/#toc-6	Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19	Aggiornamento al 22.11.2020 delle linee guida della Società Americana di Malattie Infettive (IDSA), con chiusura all'utilizzo di tocilizumab e indicazione a uso di remdesivir per 5 giorni nei pazienti in ossigenoterapia.	Background: There are many pharmacologic therapies that are being used or considered for treatment of coronavirus disease 2019 (COVID-19). There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature. Objective: There are many pharmacologic therapies that are being used or considered for treatment of coronavirus disease 2019 (COVID-19). There is a need for frequently updated practice guidelines on their use, based on critical evaluation of rapidly emerging literature.

			Methods: In March 2020, the Infectious Diseases Society of America (IDSA) formed a multidisciplinary guideline panel of infectious disease clinicians, pharmacists, and methodologists with varied areas of expertise. The process followed a rapid recommendation checklist. The panel prioritized questions and outcomes. Then a systematic review of the peer-reviewed and grey literature was conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to assess the certainty of evidence and make recommendations. Results: On April 11, 2020, IDSA released online initial treatment recommendations and narrative summaries of other treatments under evaluation. Since that time, the guideline panel and methodologists have continued to monitor the literature and issue updates and addendums to these guidelines in response to evolving research. Conclusions: Since the inception of its work, the panel has expressed the overarching goal that patients be recruited into ongoing trials, which would provide much needed evidence on the efficacy and safety of various therapies for COVID-19, given that we could not make a determination whether the benefits outweigh harms for most treatments.
Zhang Y et al Frontiers in Immunology https://doi.org/10.3389/fimmu.2020.577442	Immunomodulation for Severe COVID-19 Pneumonia: The State of the Art	Revisione delle evidenze attuali riguardo l'immunoterapia per COVID-19.	COVID-19 has become a worldwide pandemic caused by the novel coronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Severe cases of COVID-19 have accounted for 10-20% of all infections, leading to more than 500,000 deaths. Increasing evidence has suggested that the inflammatory cytokine storm originating from the anti-SARS-CoV-2 immune response plays an important role in the pathogenesis of critically ill patients with COVID-19, which leads to mixed antagonistic response syndrome (MARS). In the early stage of severe COVID-19, systemic

			inflammatory response syndrome causes acute respiratory distress syndrome, multiple organ dysfunction syndrome, and even multiple organ failure. In the late stage of severe disease, increased production of anti-inflammatory cytokines drives the immune response to become dominated by compensatory anti-inflammatory response syndrome, which leads to immune exhaustion and susceptibility to secondary infections. Therefore, precise immunomodulation will be beneficial for patients with severe COVID-19, and immunosuppressive or immune enhancement therapy will depend on the disease course and immune status. This review summarizes the current understanding of the immunopathogenesis of severe COVID-19, especially the role of the inflammatory cytokine storm in disease progression. Immune indicators and immunotherapy strategies for severe COVID-19 are reviewed and the potential implications discussed.
Bai X et al Medical Hypotheses https://www.sciencedirect.com/science/article/pii/S0306987720332850?via%3Dihub	Hypothesis: Alpha-1-antitrypsin is a promising treatment option for COVID-19.	Speculazione sul ruolo di alfa 1 antitripsina come terapia contro SARS-CoV-2.	No definitive treatment for COVID-19 exists although promising results have been reported with remdesivir and glucocorticoids. Short of a truly effective preventive or curative vaccine against SARS-CoV-2, it is becoming increasingly clear that multiple pathophysiologic processes seen with COVID-19 as well as SARS-CoV-2 itself should be targeted. Because alpha-1-antitrypsin (AAT) embraces a panoply of biologic activities that may antagonize several pathophysiologic mechanisms induced by SARS-CoV-2, we hypothesize that this naturally occurring molecule is a promising agent to ameliorate COVID-19. We posit at least seven different mechanisms by which AAT may alleviate COVID-19. First, AAT is a serine protease inhibitor (SERPIN) shown to inhibit TMPRSS-2, the host serine protease that cleaves the spike protein of SARS-CoV-2, a necessary preparatory step for the virus to bind its cell surface receptor ACE2 to gain intracellular entry. Second, AAT has anti-viral

			activity against other RNA viruses HIV and influenza as well as induces autophagy, a known host effector mechanism against MERS-CoV, a related coronavirus that causes the Middle East Respiratory Syndrome. Third, AAT has potent anti-inflammatory properties, in part through inhibiting both nuclear factor-kappa B (NFkappaB) activation and ADAM17 (also known as tumor necrosis factor-alpha converting enzyme), and thus may dampen the hyper-inflammatory response of COVID-19. Fourth, AAT inhibits neutrophil elastase, a serine protease that helps recruit potentially injurious neutrophils and implicated in acute lung injury. AAT inhibition of ADAM17 also prevents shedding of ACE2 and hence may preserve ACE2 inhibition of bradykinin, reducing the ability of bradykinin to cause a capillary leak in COVID-19. Fifth, AAT inhibits thrombin, and venous thromboembolism and in situ microthrombi and macrothrombi are increasingly implicated in COVID-19. Sixth, AAT inhibition of elastase can antagonize the formation of neutrophil extracellular traps (NETs), a complex extracellular structure comprised of neutrophil-derived DNA, histones, and proteases, and implicated in the immunothrombosis of COVID-19; indeed, AAT has been shown to change the shape and adherence of non-COVID-19-related NETs. Seventh, AAT inhibition of endothelial cell apoptosis may limit the endothelial injury linked to severe COVID-19-associated acute lung injury, multi-organ dysfunction, and pre-eclampsia-like syndrome seen in gravid women. Furthermore, because both NETs formation and the presence of anti-phospholipid antibodies are increased in both COVID-19 and non-COVID pre-eclampsia, it suggests a similar vascular pathogenesis in both disorders. As a final point, AAT has an excellent safety profile when administered to patients with AAT deficiency and is dosed intravenously once weekly but also comes in an inhaled

			preparation. Thus, AAT is an appealing drug candidate to treat COVID-19 and should be studied.

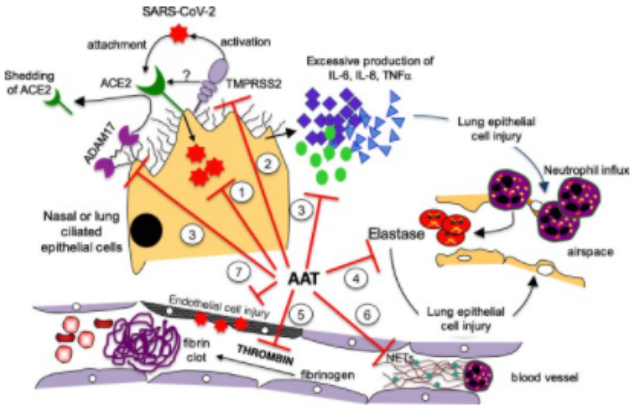


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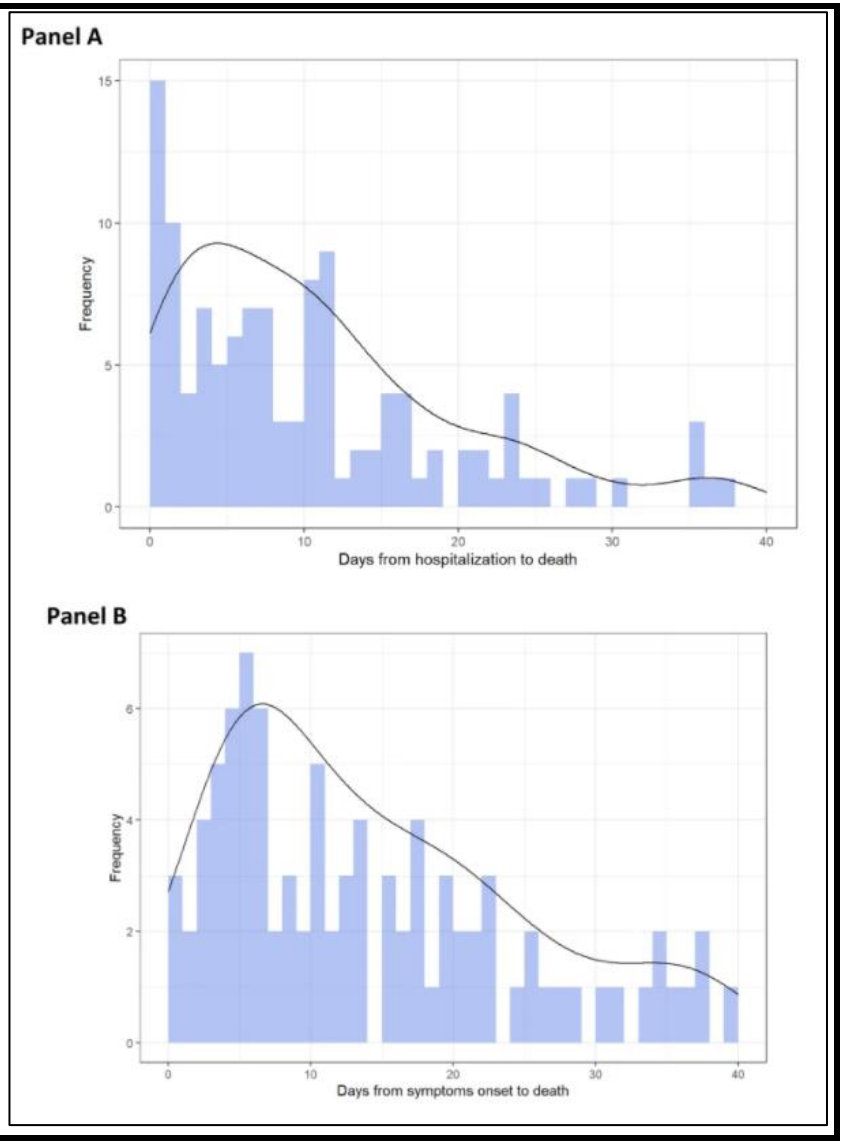
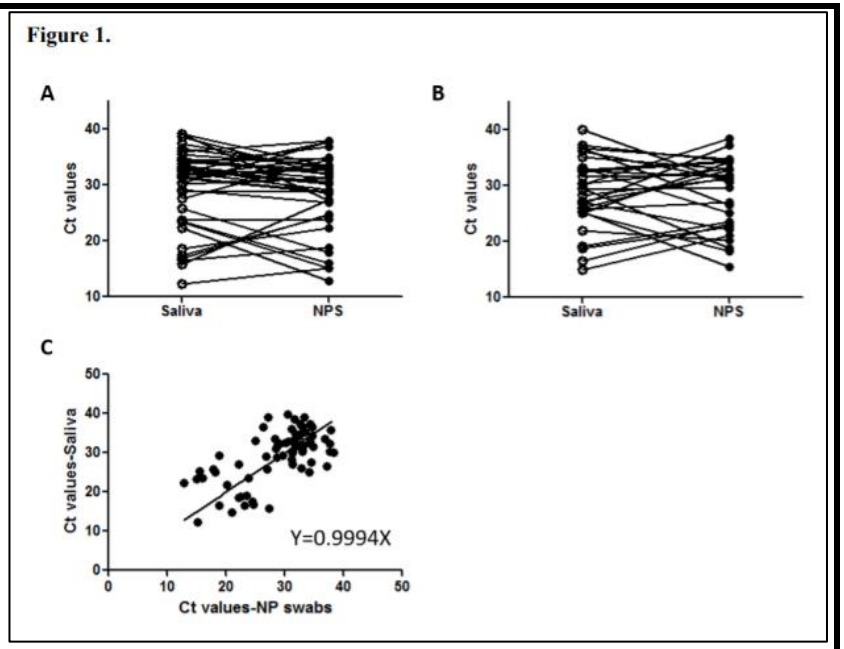
Fig. 1. Hypothesized mechanisms by alpha-1-antitrypsin (AAT) may be therapeutically efficacious against COVID-19. We hypothesize that AAT is a promising therapeutic against COVID-19 *via* at least seven mechanisms (see accompanying text for full description). In brief, we posit that AAT will: *(1)* augment host immunity against SARS-CoV-2 by enhancing autophagy, *(2)* inhibit TMPRSS-2 activity, mitigating a key and necessary step prior to SARS-CoV-2 entry into cells, *(3)* antagonize inflammation, *(4)* inhibit neutrophil elastase and ameliorate acute lung injury, *(5)* inhibit thrombin, retarding microthrombi formation, *(6)* inhibit neutrophil extracellular traps (NETs) adherence, limiting immunothrombosis seen with COVID-19, and *(7)* protect against endothelial cell apoptosis, curbing COVID-19-associated endothelial injury. Whereas TMPRSS-2 may also process ACE2 to facilitate binding and entry of SARS-CoV, it is not known whether such activity also enhances SARS-CoV-2 binding to ACE2; this uncertainly is denoted by the question mark. ACE2 = receptor for SARS-CoV-2; TMPRSS-2 = serine protease necessary to "activate" SARS-CoV-2; T-shaped "arrows" = inhibition; red heptagon = SARS-CoV-2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

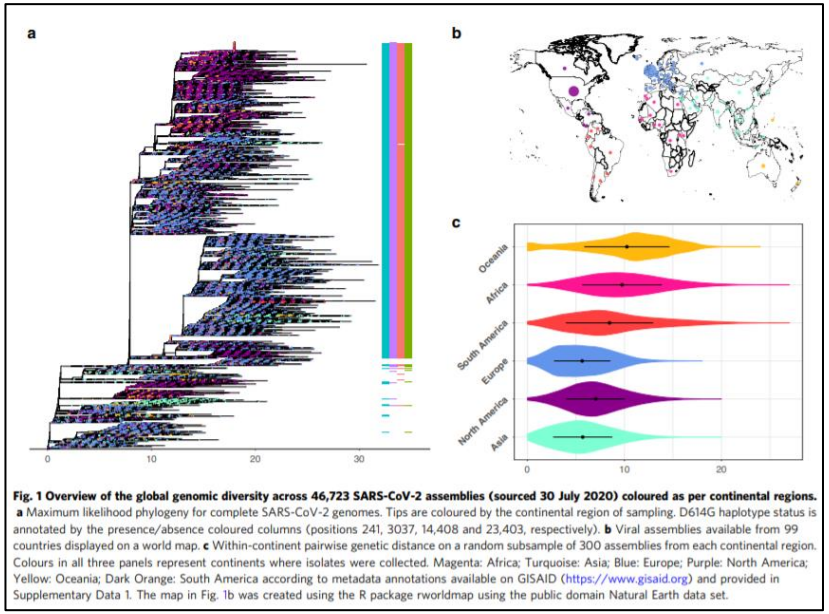
Bellan M et al Scientific Reports https://doi.org/10.1038/s41598-020-77698-4	Fatality rate and predictors of mortality in an Italian cohort of hospitalized COVID-19 patients	Età, diagnosi di neoplasia e rapporto paO2/FiO2 sono associati alla mortalità per COVID-19 in questo studio retrospettivo su 486 pazienti ospedalizzati in nord Italia ad aprile-marzo 2020.	Clinical features and natural history of coronavirus disease 2019 (COVID-19) differ widely among different countries and during different phases of the pandemia. Here, we aimed to evaluate the case fatality rate (CFR) and to identify predictors of mortality in a cohort of COVID-19 patients admitted to three hospitals of Northern Italy between March 1 and April 28, 2020. All these patients had a confirmed diagnosis of SARS-CoV-2 infection by molecular methods. During the study period 504/1697 patients died; thus, overall CFR was 29.7%. We looked for predictors of mortality in a subgroup of 486 patients (239 males, 59%; median age 71 years) for whom sufficient clinical data were available at data cut-off. Among the demographic and clinical variables considered, age, a diagnosis of cancer, obesity and current smoking independently predicted mortality. When laboratory data were added to the model in a further subgroup of patients, age, the diagnosis of cancer, and the baseline PaO2/FiO2 ratio were identified as independent predictors of mortality. In conclusion, the CFR of hospitalized patients in Northern Italy during the ascending phase of the COVID-19 pandemic approached 30%. The identification of mortality predictors might contribute to better stratification of individual patient risk.

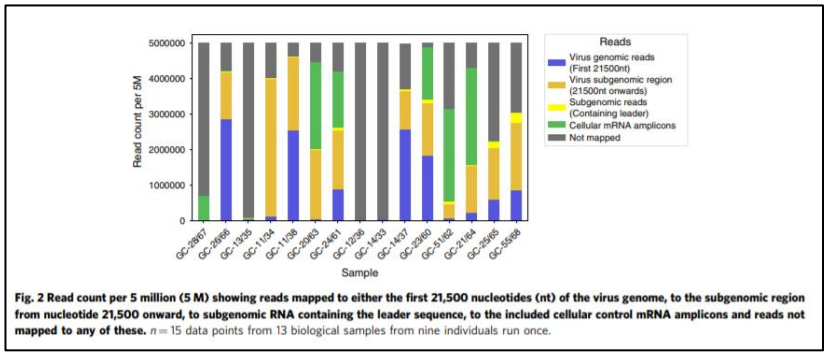
			 Panel A Frequency Days from hospitalization to death Panel B Frequency Days from symptoms onset to death

Yee R et al Journal of Clinical Microbiology https://doi.org/10.1128/JCM.02686-20	Saliva is a Promising Alternative Specimen for the Detection of SARS-CoV-2 in Children and Adults.	Comparazione di tampone nasofaringeo e campioni salivari di 300 pazienti adulti e pediatrici : performance identica nei pazienti adulti sintomatici, con i vantaggi della raccolta salivare, rendono quest'ultima una valida alternativa al tampone nasofaringeo.	Testing efforts for SARS-CoV-2 have been burdened by the scarcity of testing materials and personal protective equipment for health care workers. The simple and painless process of saliva collection allows for widespread testing, but enthusiasm is hampered by variable performance compared to nasopharyngeal swab (NPS) samples. We prospectively collected paired NPS and saliva samples from a total of 300 unique adult and pediatric patients. SARS-CoV-2 RNA was detected in 32.2% (97/300) of the individuals using the TaqPath COVID-19 Combo Kit (Thermo Fisher). Performance of saliva and NPS were compared against the total number of positives regardless of specimen type. The overall concordance for saliva and NPS was 91.0% (273/300) and 94.7% (284/300), respectively. The positive percent agreement (PPA) for saliva and NPS was 81.4% (79/97) and 89.7% (87/97), respectively. Saliva detected 10 positive cases that were negative by NPS. In symptomatic and asymptomatic pediatric patients not previously diagnosed with COVID-19, the performances of saliva and NPS were comparable (PPA: 82.4% vs 85.3%). The overall PPA for adults were 83.3% and 90.7% for saliva and NPS, respectively, with saliva detecting 4 cases less than NPS. However, saliva performance in symptomatic adults was identical to NPS (PPA of 93.8%). With lower cost and self-collection capabilities, saliva can be an appropriate alternative sample choice to NPS for detection of SARS-CoV-2 in children and adults.

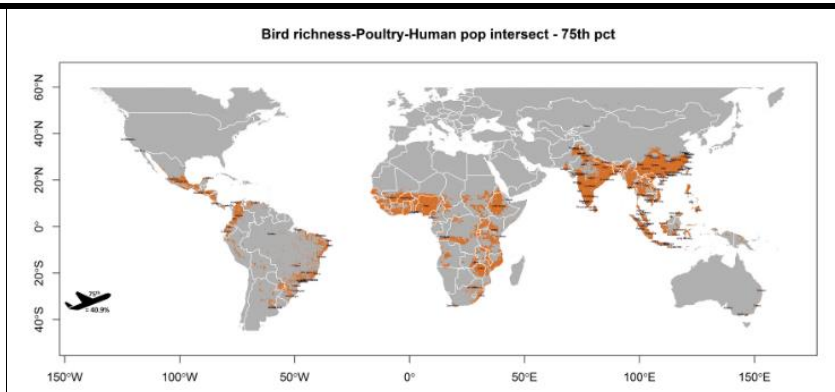
			
Hussain A et al Asian Cardiovascular and Thoracic Annals https://doi.org/10.1177/0218492320977633	Sternal wound infections during the COVID-19 pandemic: an unexpected benefit.	Analisi retrospettiva delle caratteristiche di 2600 pazienti sottoposti a cardiochirurgia in un centro del Regno Unito, in cui si osserva che durante la pandemia da COVID-19 si è ridotta la prevalenza di infezioni della ferita sternotomica, forse a causa di una rigorosa applicazione di procedure di isolamento e asepsi.	BACKGROUND: The novel coronavirus, now termed SARS-CoV-2, has had a significant impact on cardiac surgical services globally. Although drastically reduced, our institution has maintained a significant level of cardiac surgical activity during the pandemic. Rigorous COVID-19 guidelines have been instituted to mitigate the risk of viral transmission. We observed a reduction in sternal wound infections since the institution of new perioperative surgical guidelines. METHODS: We performed a retrospective analysis of all patients who underwent cardiac surgery at our institution since a national lockdown was declared in March 2020. A retrospective analysis of all patients who underwent cardiac surgery in the 12 months preceding the national lockdown, as a baseline cohort group, was also performed. RESULTS: A total of 2600 patients (493 during the COVID-19 pandemic) were included in this study. Urgent/emergency procedures accounted for more than 60% of

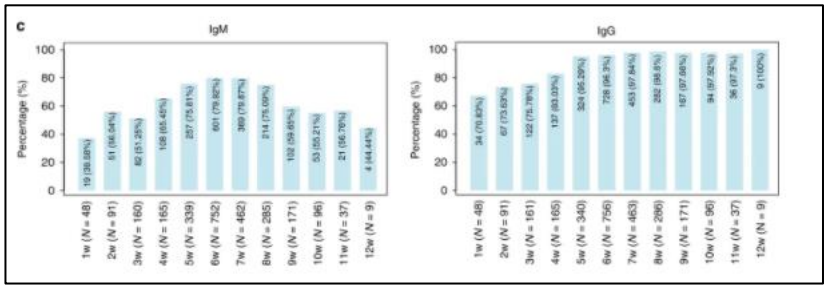
			procedures performed during the lockdown compared to 39% previously. During the COVID-19 pandemic, there were 4 sternal wound infections with an overall incidence of 0.8%. In comparison, the incidence of sternal wound infections was significantly higher at 3.0% in the 12-month period prior to lockdown with 63 sternal wound infections (p = 0.006). CONCLUSION: This report suggests a significant role of iatrogenic causes in sternal wound infections prior to the pandemic. The strict implementation of guidelines in the perioperative period suggests that sternal wound infections can be prevented. We propose that the now widespread COVID-19 guidelines to reduce transmission risk be adapted to help reduce the incidence of sternal wound infections.
Kuhen BM et al JAMA https://doi.org/10.1001/jama.2020.22227	Hand Hygiene Gaps Identified	Esito di due survey condotte dai CDC americani sui fattori associati a minore aderenza alle pratiche di igiene delle mani : gli uomini giovani sono meno inclini ad osservare le raccomandazioni.	Hand washing or using an alcohol-based hand sanitizer after touching shopping carts, gas pumps, automated teller machines, and other frequently touched surfaces is a key strategy the CDC recommends to curb the spread of coronavirus disease 2019 (COVID-19). Yet a pair of surveys in the CDC's Morbidity and Mortality Weekly Report found serious gaps in hand hygiene practices by race, age, and sex.
Van Dorp L et al Nature Communications https://doi.org/10.1038/s41467-020-19818-2	No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2	Le mutazioni di SARS-CoV-2 emerse nel corso della recente storia di questo virus non sembrano associate a un aumento della trasmissibilità nell'uomo, secondo i risultati di questo studio filogenetico.	COVID-19 is caused by the coronavirus SARS-CoV-2, which jumped into the human population in late 2019 from a currently uncharacterised animal reservoir. Due to this recent association with humans, SARS-CoV-2 may not yet be fully adapted to its human host. This has led to speculations that SARS-CoV-2 may be evolving towards higher transmissibility. The most plausible mutations under putative natural selection are those which have emerged repeatedly and independently (homoplasies). Here, we formally test whether any homoplasies observed in SARS-CoV-2 to date are significantly associated with increased viral transmission. To do so, we develop a phylogenetic index to quantify the relative number of descendants

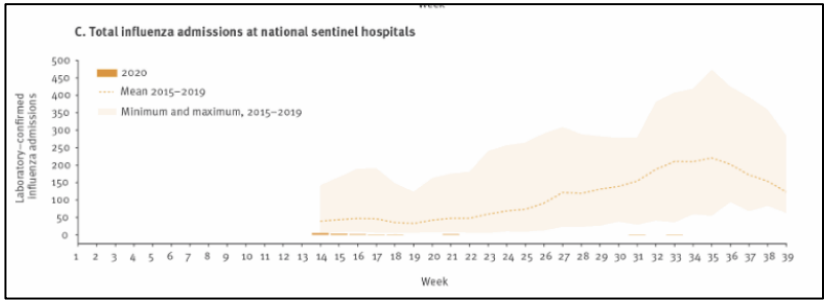
			in sister clades with and without a specific allele. We apply this index to a curated set of recurrent mutations identified within a dataset of 46,723 SARS-CoV-2 genomes isolated from patients worldwide. We do not identify a single recurrent mutation in this set convincingly associated with increased viral transmission. Instead, recurrent mutations currently in circulation appear to be evolutionary neutral and primarily induced by the human immune system via RNA editing, rather than being signatures of adaptation. At this stage we find no evidence for significantly more transmissible lineages of SARS-CoV-2 due to recurrent mutations.  **Fig. 1 Overview of the global genomic diversity across 46,723 SARS-CoV-2 assemblies (sourced 30 July 2020) coloured as per continental regions.** **a** Maximum likelihood phylogeny for complete SARS-CoV-2 genomes. Tips are coloured by the continental region of sampling. D614G haplotype status is annotated by the presence/absence coloured columns (positions 241, 3037, 14,408 and 23,403, respectively). **b** Viral assemblies available from 99 countries displayed on a world map. **c** Within-continent pairwise genetic distance on a random subsample of 300 assemblies from each continental region. Colours in all three panels represent continents where isolates were collected. Magenta: Africa; Turquoise: Asia; Blue: Europe; Purple: North America; Yellow: Oceania; Dark Orange: South America according to metadata annotations available on GISAID (https://www.gisaid.org) and provided in Supplementary Data 1. The map in Fig. 1b was created using the R package rworldmap using the public domain Natural Earth data set.
Rasmussen SA et al NEJM	Delaying Pregnancy during a Public Health Crisis — Examining Public Health Recommendations for Covid-19 and Beyond	In che misura è etico che le autorità sanitarie raccomandino alle donne di non intraprendere una gravidanza durante la pandemia da COVID-19 ?	During previous public health emergencies, the issue of whether public health agencies should recommend that women avoid becoming pregnant because of potential risks to themselves and their newborns has been controversial. The ongoing Covid-19 pandemic has again led to questions regarding whether women

https://doi.org/10.1056/NEJMp2027940		Problema già emerso durante altri periodi, come all'inizio della diffusione di HIV, che si presta a molte considerazioni e presenta lacune conoscitive da colmare.	should consider postponing pregnancy because of potential virus-related risks. Such discussions involve important ethical considerations.
Alexandersen S et al Nature Communications https://doi.org/10.1038/s41467-020-19883-7	SARS-CoV-2 genomic and subgenomic RNAs in diagnostic samples are not an indicator of active replication.	La positività a lungo termine dei test diagnostici in persone non più contagiose per SARS-CoV-2 può essere spiegata con la persistenza di frammenti di RNA virale resistenti alle nucleasi.	Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first detected in late December 2019 and has spread worldwide. Coronaviruses are enveloped, positive sense, single-stranded RNA viruses and employ a complicated pattern of virus genome length RNA replication as well as transcription of genome length and leader containing subgenomic RNAs. Although not fully understood, both replication and transcription are thought to take place in so-called double-membrane vesicles in the cytoplasm of infected cells. Here we show detection of SARS-CoV-2 subgenomic RNAs in diagnostic samples up to 17 days after initial detection of infection and provide evidence for their nuclease resistance and protection by cellular membranes suggesting that detection of subgenomic RNAs in such samples may not be a suitable indicator of active coronavirus replication/infection.  **Fig. 2 Read count per 5 million (5 M) showing reads mapped to either the first 21,500 nucleotides (nt) of the virus genome, to the subgenomic region from nucleotide 21,500 onward, to subgenomic RNA containing the leader sequence, to the included cellular control mRNA amplicons and reads not mapped to any of these.** *n* = 15 data points from 13 biological samples from nine individuals run once.

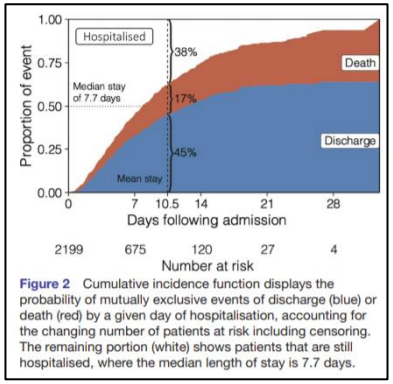
Walsh MG et al One Health https://www.sciencedirect.com/science/article/pii/S2352771420302780	Whence the next pandemic? The intersecting global geography of the animal-human interface, poor health systems and air transit centrality reveals conduits for high-impact spillover	L'emergere di una nuova pandemia, tipicamente zoonosi, è da collegare da un lato all'aumentato sfruttamento del mondo animale che favorisce la promiscuità fra specie e dall'altro alla globalizzazione che facilita la diffusione: i luoghi in cui questi fenomeni sono più evidenti saranno prevedibilmente il punto di partenza di future infezioni.	The health and economic impacts of infectious disease pandemics are catastrophic as most recently manifested by coronavirus disease 2019 (COVID-19). The emerging infections that lead to substantive epidemics or pandemics are typically zoonoses that cross species boundaries at vulnerable points of animal-human interface. The sharing of space between wildlife and humans, and their domesticated animals, has dramatically increased in recent decades and is a key driver of pathogen spillover. Increasing animal-human interface has also occurred in concert with both increasing globalisation and failing health systems, resulting in a trifecta with dire implications for human and animal health. Nevertheless, to date we lack a geographical description of this trifecta that can be applied strategically to pandemic prevention. This investigation provides the first geographical quantification of the intersection of animal-human interfaces, poor human health system performance and global connectivity via the network of air travel. In so doing, this work provides a systematic, data-driven approach to classifying spillover hazard based on the distribution of animal-human interfaces while simultaneously identifying globally connected cities that are adjacent to these interfaces and which may facilitate global pathogen dissemination. We present this geography of high-impact spillover as a tool for developing targeted surveillance systems and improved health infrastructure in vulnerable areas that may present conduits for future pandemics.

			
Ranran J et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1325/6007043?searchresult=1	How Could In Vitro Antiviral Activity Be Applied to Optimize the Dosing Regimens of Candidates for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)?	Applicazione di modelli adeguati di farmacocinetica per la stima della dose appropriata di farmaci contro SARS-COV-2.	TO THE EDITOR—Recently, Yao et al reported an optimized dosing regimen design of hydroxychloroquine (HCQ) for the treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) based on model and simulation (M&S). The authors integrated the in vitro antiviral activity and the target tissue (lung) concentration of HCQ using physiologically based pharmacokinetic (PBPK) model. This study provided a novel strategy for optimization of HCQ dose regimen and potentially could be applied for other antivirus drug candidates. However, the recommended dosing regimen proposed by Yao et al cannot reach the effective antiviral concentration in vivo, even assuming HCQ is an effective candidate for anti-SARS-CoV-2, because the target tissue (lung) concentration was overestimated and then mismatched the in vitro experiment result. We think that the application of PBPK modeling and simulation to optimize clinical study must rely on rigorous pharmacokinetic mechanism and reasonable assumption.
Li K et al Nature	Dynamic changes in anti-SARS-CoV-2 antibodies during SARS-CoV-2 infection and recovery from COVID-19.	Studio della dinamica degli anticorpi anti-SARS-CoV-2 (totali, diretti contro la proteina spike S, contro il receptor binding domain	Deciphering the dynamic changes in antibodies against SARS-CoV-2 is essential for understanding the immune response in COVID-19 patients. Here we analyze the laboratory findings of 1,850 patients to describe the dynamic changes of the total antibody, spike protein (S)-, receptor-binding domain (RBD)-, and nucleoprotein (N)-specific

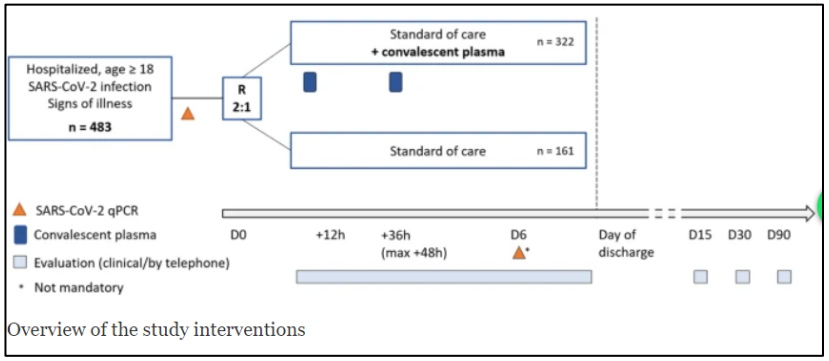
https://doi.org/10.1038/s41467-020-19943-y		della proteina spike e contro la nucleoproteina N) in 1850 pazienti guariti da COVID-19 di diversa gravità.	immunoglobulin M (IgM) and G (IgG) levels during SARS-CoV-2 infection and recovery. The generation of S-, RBD-, and N-specific IgG occurs one week later in patients with severe/critical COVID-19 compared to patients with mild/moderate disease, while S- and RBD-specific IgG levels are 1.5-fold higher in severe/critical patients during hospitalization. The RBD-specific IgG levels are 4-fold higher in older patients than in younger patients during hospitalization. In addition, the S- and RBD-specific IgG levels are 2-fold higher in the recovered patients who are SARS-CoV-2 RNA negative than those who are RNA positive. Lower S-, RBD-, and N-specific IgG levels are associated with a lower lymphocyte percentage, higher neutrophil percentage, and a longer duration of viral shedding. Patients with low antibody levels on discharge might thereby have a high chance of being tested positive for SARS-CoV-2 RNA after recovery. Our study provides important information for COVID-19 diagnosis, treatment, and vaccine development. 
Sullivan AG et al Eurosurveillance https://www.eurosurveillance.org/content/10.2807/1560-	Where has all the influenza gone? The impact of COVID-19 on the circulation of influenza and other respiratory viruses, Australia, March to September 2020	In Australia, la temuta sovrapposizione fra COVID-19 e influenza non si è verificata, presumibilmente per effetto delle misure di distanziamento sociale.	The World Health Organization (WHO) declared a coronavirus disease (COVID-19) pandemic on 11 March 2020, as southern hemisphere countries prepared for their usual winter respiratory pathogen epidemics. The announcement prompted concern that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), influenza and other respiratory viruses might co-circulate, straining and possibly overwhelming healthcare systems. In Australia, these

7917.ES.2020.25.47.2001847			fears were not realised and—in contrast to expectations—influenza activity was at an all-time low during the southern hemisphere's 2020 winter. Here, we describe the decreased activity of influenza and other respiratory pathogens in Australia and the measures that have likely contributed to their decline. 
Van Halem K et al BMC Infectious Diseases https://doi.org/10.1186/s12879-020-05605-3	Risk factors for mortality in hospitalized patients with COVID-19 at the start of the pandemic in Belgium: a retrospective cohort study.	Caratteristiche cliniche e outcome di 319 pazienti ricoverati per COVID-19 in Belgio all'inizio della pandemia nel 2020. I fattori più fortemente associati alla mortalità sono età avanzata, insufficienza renale, livelli di LDH e trombocitopenia. La mortalità è stata più alta nei pazienti ricoverati nelle prime settimane (entro il 30.03), come probabile effetto dell'inesperienza della comunità medica.	BACKGROUND: Belgium was among the first countries in Europe with confirmed coronavirus disease 2019 (COVID-19) cases. Since the first diagnosis on February 3rd, the epidemic has quickly evolved, with Belgium at the crossroads of Europe, being one of the hardest hit countries. Although risk factors for severe disease in COVID-19 patients have been described in Chinese and United States (US) cohorts, good quality studies reporting on clinical characteristics, risk factors and outcome of European COVID-19 patients are still scarce. METHODS: This study describes the clinical characteristics, complications and outcomes of 319 hospitalized COVID-19 patients, admitted to a tertiary care center at the start of the pandemic in Belgium, and aims to identify the main risk factors for in-hospital mortality in a European context using univariate and multivariate logistic regression analysis. RESULTS: Most patients were male (60%), the median age was 74 (IQR 61-83) and 20% of patients were admitted to the intensive care unit, of whom 63% needed invasive mechanical ventilation. The overall case fatality rate was 25%. The best predictors of in-hospital mortality in

			multivariate analysis were older age, and renal insufficiency, higher lactate dehydrogenase and thrombocytopenia. Patients admitted early in the epidemic had a higher mortality compared to patients admitted later in the epidemic. In univariate analysis, patients with obesity did have an overall increased risk of death, while overweight on the other hand showed a trend towards lower mortality. CONCLUSIONS: Most patients hospitalized with COVID-19 during the first weeks of the epidemic in Belgium were admitted with severe disease and the overall case fatality rate was high. The identified risk factors for mortality are not easily amenable at short term, underscoring the lasting need of effective therapeutic and preventative measures. **Table 4** Admission early in the epidemic versus later in the epidemic | | Early [a] (*n* = 206) | Late [b] (*n* = 113) | p-value | | --- | --- | --- | --- | | Age — median (IQR) | 74 (62–83) | 73 (59–83) | 0.3138 | | Hypertension — no. (%) | 116 (56.31) | 46 (40.71) | 0.008 | | Diabetes — no. (%) | 45 (21.84) | 20 (17.70) | 0.3754 | | Coronary heart disease — no. (%) | 45 (21.84) | 27 (23.89) | 0.677 | | Chronic renal disease — no. (%) | 42 (20.49) | 20 (17.70) | 0.5457 | | Number of days ill before admission – days (IQR) | 6.5 (2–10) | 7.8 (4–10) | 0.0384 | | - Not measured | 8 | 22 | | | Admission to ICU — no. (%) | 44 (21.36) | 19 (16.81) | 0.3248 | | Death — no. (%) | 62 (30.10) | 19 (16.81) | 0008 | [a]Patients admitted between March 11 and March 30 [b]Patients admitted between March 31 and April 15
Paranjpe I et al BMJ Open https://doi.org/10.1136/bmjopen-2020-040736	Retrospective cohort study of clinical characteristics of 2199 hospitalised patients with COVID-19 in New York City.	Confronto fra deceduti e sopravvissuti in un campione di 2199 adulti ricoverate per COVID-19 a New York nel periodo 27 febbraio – 2 aprile 2020 : l'analisi retrospettiva mostra maggiore prevalenza di comorbidità preesistenti, linfopenia al momento del	OBJECTIVE: The COVID-19 pandemic is a global public health crisis, with over 33 million cases and 999 000 deaths worldwide. Data are needed regarding the clinical course of hospitalised patients, particularly in the USA. We aimed to compare clinical characteristic of patients with COVID-19 who had in-hospital mortality with those who were discharged alive. DESIGN: Demographic, clinical and outcomes data for patients admitted to five Mount Sinai Health System hospitals with confirmed COVID-19 between 27 February and 2 April 2020 were identified through institutional electronic health records. We performed a retrospective comparative analysis of patients who had in-hospital mortality or were discharged alive.

		ricovero, elevati D-dimeri e PCR nei deceduti.	SETTING: All patients were admitted to the Mount Sinai Health System, a large quaternary care urban hospital system. PARTICIPANTS: Participants over the age of 18 years were included. PRIMARY OUTCOMES: We investigated in-hospital mortality during the study period. RESULTS: A total of 2199 patients with COVID-19 were hospitalised during the study period. As of 2 April, 1121 (51%) patients remained hospitalised, and 1078 (49%) completed their hospital course. Of the latter, the overall mortality was 29%, and 36% required intensive care. The median age was 65 years overall and 75 years in those who died. Pre-existing conditions were present in 65% of those who died and 46% of those discharged. In those who died, the admission median lymphocyte percentage was 11.7%, D-dimer was 2.4 mug/mL, C reactive protein was 162 mg/L and procalcitonin was 0.44 ng/mL. In those discharged, the admission median lymphocyte percentage was 16.6%, D-dimer was 0.93 mug/mL, C reactive protein was 79 mg/L and procalcitonin was 0.09 ng/mL. CONCLUSIONS: In our cohort of hospitalised patients, requirement of intensive care and mortality were high. Patients who died typically had more pre-existing conditions and greater perturbations in inflammatory markers as compared with those who were discharged.  **Figure 2** Cumulative incidence function displays the probability of mutually exclusive events of discharge (blue) or death (red) by a given day of hospitalisation, accounting for the changing number of patients at risk including censoring. The remaining portion (white) shows patients that are still hospitalised, where the median length of stay is 7.7 days.

Devos T et al Trials https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-020-04876-0	A randomized, multicentre, open-label phase II proof-of-concept trial investigating the clinical efficacy and safety of the addition of convalescent plasma to the standard of care in patients hospitalized with COVID-19: the Donated Antibodies Working against nCoV (DAWn-Plasma) trial.	Protocollo di un trial clinico di fase II che indagherà efficacia e sicurezza dell'utilizzo di plasma di soggetti guariti, in aggiunta alla terapia standard, per 483 pazienti ospedalizzati con COVID-19 in Belgio. Da notare l'eleggibilità di pazienti con quadro radiologico di polmonite interstiziale senza altra causa. Completamento atteso per luglio 2021.	BACKGROUND: The COVID-19 pandemic has imposed an enormous burden on health care systems around the world. In the past, the administration of convalescent plasma of patients having recovered from SARS and severe influenza to patients actively having the disease showed promising effects on mortality and appeared safe. Whether or not this also holds true for the novel SARS-CoV-2 virus is currently unknown. METHODS: DAWn-Plasma is a multicentre nation-wide, randomized, open-label, phase II proof-of-concept clinical trial, evaluating the clinical efficacy and safety of the addition of convalescent plasma to the standard of care in patients hospitalized with COVID-19 in Belgium. Patients hospitalized with a confirmed diagnosis of COVID-19 are eligible when they are symptomatic (i.e. clinical or radiological signs) and have been diagnosed with COVID-19 in the 72 h before study inclusion through a PCR (nasal/nasopharyngeal swab or bronchoalveolar lavage) or a chest-CT scan showing features compatible with COVID-19 in the absence of an alternative diagnosis. Patients are randomized in a 2:1 ratio to either standard of care and convalescent plasma (active treatment group) or standard of care only. The active treatment group receives 2 units of 200 to 250 mL of convalescent plasma within 12 h after randomization, with a second administration of 2 units 24 to 36 h after ending the first administration. The trial aims to include 483 patients and will recruit from 25 centres across Belgium. The primary endpoint is the proportion of patients that require mechanical ventilation or have died at day 15. The main secondary endpoints are clinical status on day 15 and day 30 after randomization, as defined by the WHO Progression 10-point ordinal scale, and safety of the administration of convalescent plasma. DISCUSSION: This trial will either provide support or discourage the

			use of convalescent plasma as an early intervention for the treatment of hospitalized patients with COVID-19 infection.  Overview of the study interventions
Wadman M et al Science https://science.sciencemag.org/content/370/6520/1022	Public needs to prep for vaccine side effects	Preparare il pubblico agli effetti avversi dei vaccini contro COVID-19, prevedibili come per qualunque farmaco, appare una strategia fondamentale per stabilire una corretta informazione.	This summer, computational biologist Luke Hutchison volunteered for a trial of Moderna's COVID-19 vaccine. But after the second injection, his arm swelled up to the size of a “goose egg,” Hutchison says. He can't be sure he got the vaccine and not a placebo, but within a few hours, Hutchison, who was healthy and 43, was beset by bone and muscle aches and a 38.9°C fever. “I started shaking. I had cold and hot rushes,” he says. “I was sitting by the phone all night long thinking: ‘Should I call 911?’”