RICERCA BIBLIOGRAFICA COVID 19 SETTIMANA 31.08-06.09.2020 FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE DOTT.SSA ELEONORA TADDEI			
AUTORE/RIVISTA	**TITOLO**	**OUTCOME PRINCIPALE**	**ABSTRACT**
Kelvin Kai-Wang To et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1275/5897019	COVID-19 re-infection by a phylogenetically distinct SARS-coronavirus-2 strain confirmed by whole genome sequencing	Dimostrazione di infezione e reinfezione da parte di due ceppi filogeneticamente distinti di SARS-CoV-2 nello stesso paziente immunocompetente a distanza di 142 giorni.	BACKGROUND: Waning immunity occurs in patients who have recovered from COVID-19. However, it remains unclear whether true re-infection occurs. METHODS: Whole genome sequencing was performed directly on respiratory specimens collected during two episodes of COVID-19 in a patient. Comparative genome analysis was conducted to differentiate re-infection from persistent viral shedding. Laboratory results, including RT-PCR Ct values and serum SARS-CoV-2 IgG, were analyzed. RESULTS: The second episode of asymptomatic infection occurred 142 days after the first symptomatic episode in an apparently immunocompetent patient. During the second episode, there was serological evidence of elevated C-reactive protein and SARS-CoV-2 IgG seroconversion. Viral genomes from first and second episodes belong to different clades/lineages. Compared to viral genomes in GISAID, the first virus genome has a stop codon at position 64 of orf8 leading to a truncation of 58 amino acids, and was phylogenetically closely

			related to strains collected in March/April 2020, while the second virus genome was closely related to strains collected in July/August 2020. Another 23 nucleotide and 13 amino acid differences located in 9 different proteins, including positions of B and T cell epitopes, were found between viruses from the first and second episodes. CONCLUSIONS: Epidemiological, clinical, serological and genomic analyses confirmed that the patient had re-infection instead of persistent viral shedding from first infection. Our results suggest SARS-CoV-2 may continue to circulate among the human populations despite herd immunity due to natural infection or vaccination. Further studies of patients with re-infection will shed light on protective correlates important for vaccine design.
Mi Seon Han et al JAMA Pediatrics https://jamanetwork.com/journals/jamapediatrics/fullarticle/2770150	Clinical Characteristics and Viral RNA Detection in Children With Coronavirus Disease 2019 in the Republic of Korea	L'infezione da SARS-CoV-2 è asintomatica in una parte rilevante della popolazione pediatrica studiata, mentre lo shedding virale è prolungato. Ciò potrebbe costituire una via di trasmissione silente di COVID-19.	Importance: There is limited information describing the full spectrum of coronavirus disease 2019 (COVID-19) and the duration of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA detection in children. Objective: To analyze the full clinical course and the duration of SARS-CoV-2 RNA detectability in children confirmed with COVID-19 in the Republic of Korea, where rigorous public health interventions have been implemented. Design, Setting, and Participants: This case series of children with COVID-19 was conducted in 20 hospitals and 2 nonhospital isolation facilities across the country from February 18, 2020, to March 31, 2020. Children younger than 19 years who had COVID-19 were included. Exposures: Confirmed COVID-19, detected via SARS-CoV-2 RNA in a combined nasopharyngeal and oropharyngeal swab or sputum by real-time reverse transcription-polymerase chain reaction. Main Outcomes and Measures: Clinical manifestations during the observation period, including the time and duration of symptom occurrence. The duration of SARS-CoV-2 RNA detection was also analyzed. Results: A total of 91 children with COVID-19 were

			included (median [range] age, 11 [0-18] years; 53 boys [58%]). Twenty children (22%) were asymptomatic during the entire observation period. Among 71 symptomatic cases, 47 children (66%) had unrecognized symptoms before diagnosis, 18 (25%) developed symptoms after diagnosis, and only 6 (9%) were diagnosed at the time of symptom onset. Twenty-two children (24%) had lower respiratory tract infections. The mean (SD) duration of the presence of SARS-CoV-2 RNA in upper respiratory samples was 17.6 (6.7) days. Virus RNA was detected for a mean (SD) of 14.1 (7.7) days in asymptomatic individuals. There was no difference in the duration of virus RNA detection between children with upper respiratory tract infections and lower respiratory tract infections (mean [SD], 18.7 [5.8] days vs 19.9 [5.6] days; P = .54). Fourteen children (15%) were treated with lopinavir-ritonavir and/or hydroxychloroquine. All recovered, without any fatal cases. Conclusions and Relevance: In this case series study, inapparent infections in children may have been associated with silent COVID-19 transmission in the community. Heightened surveillance using laboratory screening will allow detection in children with unrecognized SARS-CoV-2 infection.
Grasselli Giacomo et al The Lancet Respiratory Medicine https://www.sciencedirect.com/science/article/pii/S2213260020303702?via%3Dihub	Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study.	Confronto delle caratteristiche di danno polmonare tra pazienti con ARDS classica e COVID19-relata e correlazione con la mortalità a 28 giorni.	BACKGROUND: Patients with COVID-19 can develop acute respiratory distress syndrome (ARDS), which is associated with high mortality. The aim of this study was to examine the functional and morphological features of COVID-19-associated ARDS and to compare these with the characteristics of ARDS unrelated to COVID-19. METHODS: This prospective observational study was done at seven hospitals in Italy. We enrolled consecutive, mechanically ventilated patients with laboratory-confirmed COVID-19 and who met Berlin criteria for ARDS, who were admitted to the intensive care unit (ICU) between March 9 and March 22, 2020. All patients

			were sedated, paralysed, and ventilated in volume-control mode with standard ICU ventilators. Static respiratory system compliance, the ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air, ventilatory ratio (a surrogate of dead space), and D-dimer concentrations were measured within 24 h of ICU admission. Lung CT scans and CT angiograms were done when clinically indicated. A dataset for ARDS unrelated to COVID-19 was created from previous ARDS studies. Survival to day 28 was assessed. FINDINGS: Between March 9 and March 22, 2020, 301 patients with COVID-19 met the Berlin criteria for ARDS at participating hospitals. Median static compliance was 41 mL/cm H2O (33-52), which was 28% higher than in the cohort of patients with ARDS unrelated to COVID-19 (32 mL/cm H2O [25-43]; p<0.0001). 17 (6%) of 297 patients with COVID-19-associated ARDS had compliances greater than the 95th percentile of the classical ARDS cohort. Total lung weight did not differ between the two cohorts. CT pulmonary angiograms (obtained in 23 [8%] patients with COVID-19-related ARDS) showed that 15 (94%) of 16 patients with D-dimer concentrations greater than the median had bilateral areas of hypoperfusion, consistent with thromboembolic disease. Patients with D-dimer concentrations equal to or less than the median had ventilatory ratios lower than those of patients with D-dimer concentrations greater than the median (1.66 [1.32-1.95] vs 1.90 [1.50-2.33]; p=0.0001). Patients with static compliance equal to or less than the median and D-dimer concentrations greater than the median had markedly increased 28-day mortality compared with other patient subgroups (40 [56%] of 71 with high D-dimers and low compliance vs 18 [27%] of 67 with low D-dimers and high compliance, 13 [22%] of 60 with low D-dimers and low compliance, and 22 [35%] of 63 with high D-dimers and high compliance, all

			p=0.0001). INTERPRETATION: Patients with COVID-19-associated ARDS have a form of injury that, in many aspects, is similar to that of those with ARDS unrelated to COVID-19. Notably, patients with COVID-19-related ARDS who have a reduction in respiratory system compliance together with increased D-dimer concentrations have high mortality rates. FUNDING: None.
Baughn Linda B et al Mayo Clinic Proceedings https://www.mayoclinicproceedings.org/article/S0025-6196(20)30626-1/fulltext	Targeting TMPRSS2 in SARS-CoV-2 Infection.	I livelli di espressione di ACE2 e TMPRSS2 non sono significativamente differenti tra maschi e femmine e non sono sufficienti a spiegare la maggiore gravità di COVID19 nei maschi anziani. Le due proteine rimangono tuttavia interessanti bersagli terapeutici.	Severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) has rapidly caused a global pandemic associated with a novel respiratory infection: coronavirus disease-19 (COVID-19). Angiotensin-converting enzyme-2 (ACE2) is necessary to facilitate SARS-CoV-2 infection, but-owing to its essential metabolic roles-it may be difficult to target it in therapies. Transmembrane protease serine 2 (TMPRSS2), which interacts with ACE2, may be a better candidate for targeted therapies. Using publicly available expression data, we show that both ACE2 and TMPRSS2 are expressed in many host tissues, including lung. The highest expression of ACE2 is found in the testes, whereas the prostate displays the highest expression of TMPRSS2. Given the increased severity of disease among older men with SARS-CoV-2 infection, we address the potential roles of ACE2 and TMPRSS2 in their contribution to the sex differences in severity of disease. We show that expression levels of ACE2 and TMPRSS2 are overall comparable between men and women in multiple tissues, suggesting that differences in the expression levels of TMPRSS2 and ACE2 in the lung and other non-sex-specific tissues may not explain the gender disparities in severity of SARS CoV-2. However, given their instrumental roles for SARS-CoV-2 infection and their pleiotropic expression, targeting the activity and expression levels of TMPRSS2 is a rational approach to treat COVID-19.

Kucirka Lauren M et al American Journal of Reproductive Immunology https://onlinelibrary.wiley.com/doi/epdf/10.1111/aji.13332	Severity of COVID-19 In Pregnancy: A Review of Current Evidence.	Revisione delle conoscenze attuali riguardo la gravità di COVID19 nelle donne in gravidanza (apparentemente superiore rispetto a donne di pari età ma inferiore rispetto a SARS e MERS) con cenni di trattamento.	Coronavirus disease 19 (COVID-19), has recently emerged as a major threat to human health. Infections range from asymptomatic to severe (increased respiratory rate, hypoxia, significant lung involvement on imaging) or critical (multi-organ failure or dysfunction or respiratory failure requiring mechanical ventilation or high flow nasal canula). Current evidence suggests that pregnancy women are at increased risk of severe disease, specifically the need for hospitalization, ICU admission and mechanical ventilation, and the already complex management of infection with an emerging pathogen may be further complicated by pregnancy. The goal of this review is to provide an overview of what is known about the clinical course of COVID-19 in pregnancy, drawing on 1) experience with other coronaviruses such as SARS and MERS, 2) knowledge of immunologic and physiologic changes in pregnancy and how these might impact infection with SARS-CoV-2 and 3) the current literature reporting outcomes in pregnant women with SARS-CoV-2. We also briefly summarize considerations in management of severe COVID-19 in pregnancy.

Reiter Paul L et al Vaccine https://www.sciencedirect.com/science/article/pii/S0264410X20310847?via%3Dihub	Acceptability of a COVID-19 vaccine among adults in the United States: How many people would get vaccinated?	Sondaggio condotto online su 2006 adulti per indagare i fattori associati alla propensione ad accettare la vaccinazione contro SARS-CoV2. Il parere favorevole del Medico curante è fra i fattori più rilevanti nell'orientare la decisione.	BACKGROUND: Coronavirus disease 2019 (COVID-19) was declared a pandemic in March 2020. Several prophylactic vaccines against COVID-19 are currently in development, yet little is known about people's acceptability of a COVID-19 vaccine. METHODS: We conducted an online survey of adults ages 18 and older in the United States (n = 2,006) in May 2020. Multivariable relative risk regression identified correlates of participants' willingness to get a COVID-19 vaccine (i.e., vaccine acceptability). RESULTS: Overall, 69% of participants were willing to get a COVID-19 vaccine. Participants were more likely to be willing to get vaccinated if they thought their healthcare provider would recommend vaccination (RR = 1.73, 95% CI: 1.49-2.02) or if they were moderate (RR = 1.09, 95% CI: 1.02-1.16) or liberal (RR = 1.14, 95% CI: 1.07-1.22) in their political leaning. Participants were also more likely to be willing to get vaccinated if they reported higher levels of perceived likelihood getting a COVID-19 infection in the future (RR = 1.05, 95% CI: 1.01-1.09), perceived severity of COVID-19 infection (RR = 1.08, 95% CI: 1.04-1.11), or perceived effectiveness of a COVID-19 vaccine (RR = 1.46, 95% CI: 1.40-1.52). Participants were less likely to be willing to get vaccinated if they were non-Latinx black (RR = 0.81, 95% CI: 0.74-0.90) or reported a higher level of perceived potential vaccine harms (RR = 0.95, 95% CI: 0.92-0.98). CONCLUSIONS: Many adults are willing to get a COVID-19 vaccine, though acceptability should be monitored as vaccine development continues. Our findings can help guide future efforts to increase COVID-19 vaccine acceptability (and uptake if a vaccine becomes available).

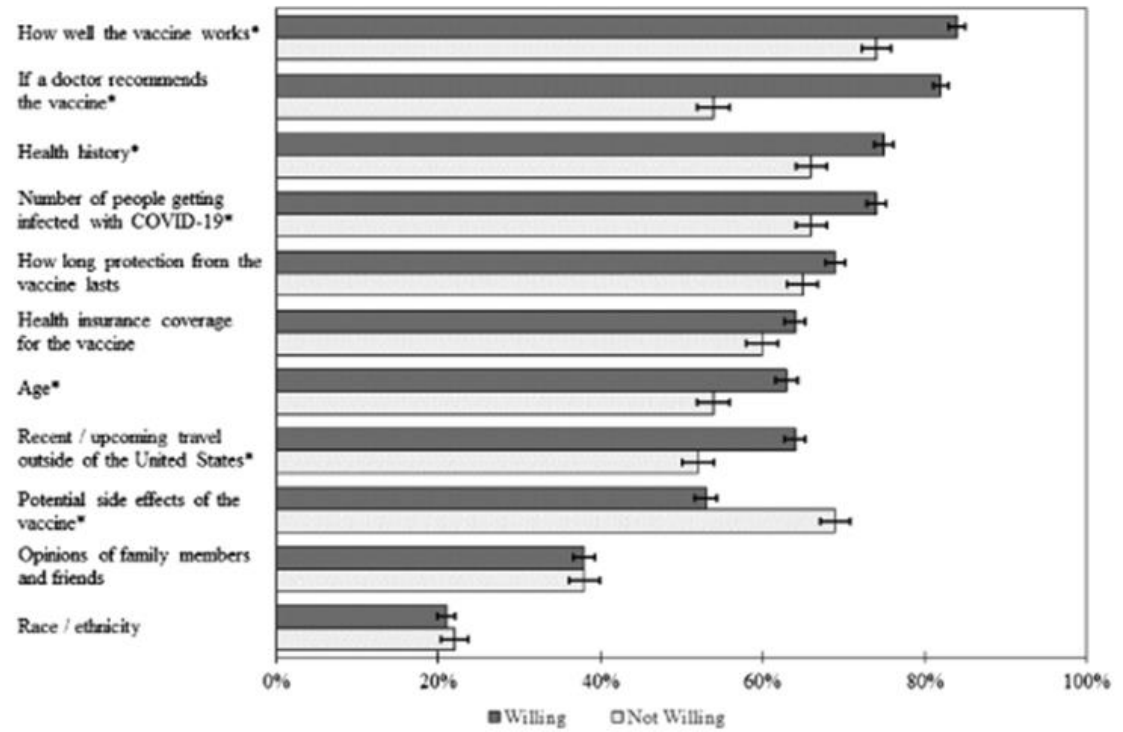
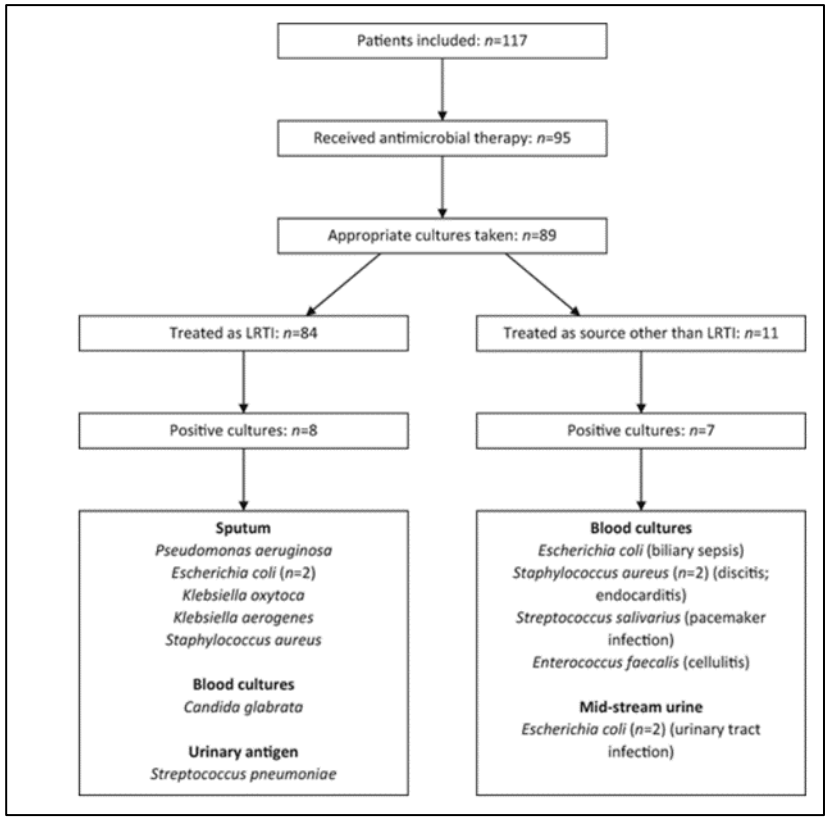


Fig. 1. Factors that would matter in participants' decisions about COVID-19 vaccination by vaccine willingness. Bars indicate standard errors. '*' indicates a comparison with $p < 0.05$, based on chi-square tests with the Bonferroni adjustment to account for multiple testing.

Townsend Liam et al JAC Antimicrobial Resistance https://academic.oup.com/jacamr/article/2/3/dlaa071/5897015	Bacterial pneumonia coinfection and antimicrobial therapy duration in SARS-CoV-2 (COVID-19) infection.	Valutazione dell'utilizzo di terapia antibiotica empirica, dell'esecuzione di esami microbiologici e dei germi eventualmente isolati in 117 pazienti con COVID19.	Background: Bacterial respiratory coinfection in the setting of SARS-CoV-2 infection remains poorly described. A description of coinfection and antimicrobial usage is needed to guide ongoing antimicrobial stewardship. Objectives: To assess the rate of empirical antimicrobial treatment in COVID-19 cases, assess the rate and methods of microbiological sampling, assess the rate of bacterial respiratory coinfections and evaluate the factors associated with antimicrobial therapy in this cohort. Methods: Inpatients with positive SARS-CoV-2 PCR were recruited. Antibiotic prescription, choice and duration were recorded. Taking of microbiological samples (sputum culture, blood culture, urinary antigens) and culture positivity rate was also recorded. Linear regression was performed to determine factors associated with prolonged antimicrobial administration. Results: A total of 117 patients were recruited; 84 (72%) were prescribed antimicrobial therapy for lower respiratory tract infections. Respiratory pathogens were identified in seven (6%) patients. The median duration of antimicrobial therapy was 7 days. C-reactive protein level, oxygen requirement and positive cultures were associated with prolonged duration of therapy. Conclusions: The rate of bacterial coinfection in SARS-CoV-2 is low. Despite this, prolonged courses of antimicrobial therapy were prescribed in our cohort. We recommend active antimicrobial stewardship in COVID-19 cases to ensure appropriate antimicrobial prescribing.


Patients included: n=117
Received antimicrobial therapy: n=95
Appropriate cultures taken: n=89
Treated as LRTI: n=84
Treated as source other than LRTI: n=11
Positive cultures: n=8
Positive cultures: n=7
Sputum
Pseudomonas aeruginosa
Escherichia coli (n=2)
Klebsiella oxytoca
Klebsiella aerogenes
Staphylococcus aureus
Blood cultures
Candida glabrata
Urinary antigen
Streptococcus pneumoniae
Blood cultures
Escherichia coli (biliary sepsis)
Staphylococcus aureus (n=2) (discitis; endocarditis)
Streptococcus salivarius (pacemaker infection)
Enterococcus faecalis (cellulitis)
Mid-stream urine
Escherichia coli (n=2) (urinary tract infection)

The WHO REACT Working Group JAMA https://jamanetwork.com/journals/jama/fullarticle/2770279?appid=scweb	Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19 A Meta-analysis	Metanalisi di 7 trial clinici che comparavano la terapia corticosteroidea allo standard of care/placebo nei pazienti con COVID19. Si rileva una minore mortalità a 28 giorni nei pazienti trattati con steroidi.	Importance : Effective therapies for patients with coronavirus disease 2019 (COVID-19) are needed, and clinical trial data have demonstrated that low-dose dexamethasone reduced mortality in hospitalized patients with COVID-19 who required respiratory support. Objective: To estimate the association between administration of corticosteroids compared with usual care or placebo and 28-day all-cause mortality. Design, Setting, and Participants : Prospective meta-analysis that pooled data from 7 randomized clinical trials that evaluated the efficacy of corticosteroids in 1703 critically ill patients with COVID-19. The trials were conducted in 12 countries from February 26, 2020, to June 9, 2020, and the date of final follow-up was July 6, 2020. Pooled data were aggregated from the individual trials, overall, and in predefined subgroups. Risk of bias was assessed using the Cochrane Risk of Bias Assessment Tool. Inconsistency among trial results was assessed using the I2 statistic. The primary analysis was an inverse variance–weighted fixed-effect meta-analysis of overall mortality, with the association between the intervention and mortality quantified using odds ratios (ORs). Random-effects meta-analyses also were conducted (with the Paule-Mandel estimate of heterogeneity and the Hartung-Knapp adjustment) and an inverse variance–weighted fixed-effect analysis using risk ratios. Exposures : Patients had been randomized to receive systemic dexamethasone, hydrocortisone, or methylprednisolone (678 patients) or to receive usual care or placebo (1025 patients). Main Outcomes and Measures : The primary outcome measure was all-cause mortality at 28 days after randomization. A secondary outcome was investigator-defined serious adverse events.

			Results : A total of 1703 patients (median age, 60 years [interquartile range, 52-68 years]; 488 [29%] women) were included in the analysis. Risk of bias was assessed as “low” for 6 of the 7 mortality results and as “some concerns” in 1 trial because of the randomization method. Five trials reported mortality at 28 days, 1 trial at 21 days, and 1 trial at 30 days. There were 222 deaths among the 678 patients randomized to corticosteroids and 425 deaths among the 1025 patients randomized to usual care or placebo (summary OR, 0.66 [95% CI, 0.53-0.82]; P < .001 based on a fixed-effect meta-analysis). There was little inconsistency between the trial results (I2 = 15.6%; P = .31 for heterogeneity) and the summary OR was 0.70 (95% CI, 0.48-1.01; P = .053) based on the random-effects meta-analysis. The fixed-effect summary OR for the association with mortality was 0.64 (95% CI, 0.50-0.82; P < .001) for dexamethasone compared with usual care or placebo (3 trials, 1282 patients, and 527 deaths), the OR was 0.69 (95% CI, 0.43-1.12; P = .13) for hydrocortisone (3 trials, 374 patients, and 94 deaths), and the OR was 0.91 (95% CI, 0.29-2.87; P = .87) for methylprednisolone (1 trial, 47 patients, and 26 deaths). Among the 6 trials that reported serious adverse events, 64 events occurred among 354 patients randomized to corticosteroids and 80 events occurred among 342 patients randomized to usual care or placebo. Conclusions and Relevance In this prospective meta-analysis of clinical trials of critically ill patients with COVID-19, administration of systemic corticosteroids, compared with usual care or placebo, was associated with lower 28-day all-cause mortality.

Figure 2. Association Between Corticosteroids and 28-Day All-Cause Mortality in Each Trial, Overall, and According to Corticosteroid Drug

Drug and trial	ClinicalTrials.gov identifier	Initial dose and administration	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Dexamethasone						
DEXA-COVID 19	NCT04325061	High: 20 mg/d intravenously	2/7	2/12	2.00 (0.21-18.69)	0.92
CoDEX	NCT04327401	High: 20 mg/d intravenously	69/128	76/128	0.80 (0.49-1.31)	18.69
RECOVERY	NCT04381936	Low: 6 mg/d orally or intravenously	95/324	283/683	0.59 (0.44-0.78)	57.00
Subgroup fixed effect			166/459	361/823	0.64 (0.50-0.82)	76.60
Hydrocortisone						
CAPE COVID	NCT02517489	Low: 200 mg/d intravenously	11/75	20/73	0.46 (0.20-1.04)	6.80
COVID STEROID	NCT04348305	Low: 200 mg/d intravenously	6/15	2/14	4.00 (0.65-24.66)	1.39
REMAP-CAP	NCT02735707	Low: 50 mg every 6 h intravenously	26/105	29/92	0.71 (0.38-1.33)	11.75
Subgroup fixed effect			43/195	51/179	0.69 (0.43-1.12)	19.94
Methylprednisolone						
Steroids-SARI	NCT04244591	High: 40 mg every 12 h intravenously	13/24	13/23	0.91 (0.29-2.87)	3.46
Overall (fixed effect) $P = .31$ for heterogeneity; $I^2 = 15.6\%$			222/678	425/1025	0.66 (0.53-0.82)	100.0
Overall (random effects[a])			222/678	425/1025	0.70 (0.48-1.01)	

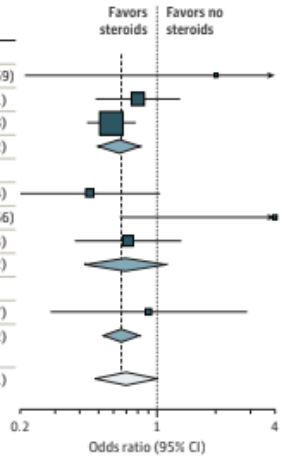
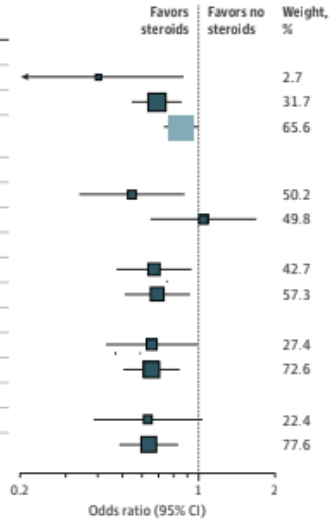


Figure 3. Association Between Corticosteroids and 28-Day All-Cause Mortality Within Subgroups Defined by Patient Characteristics at the Time of Randomization

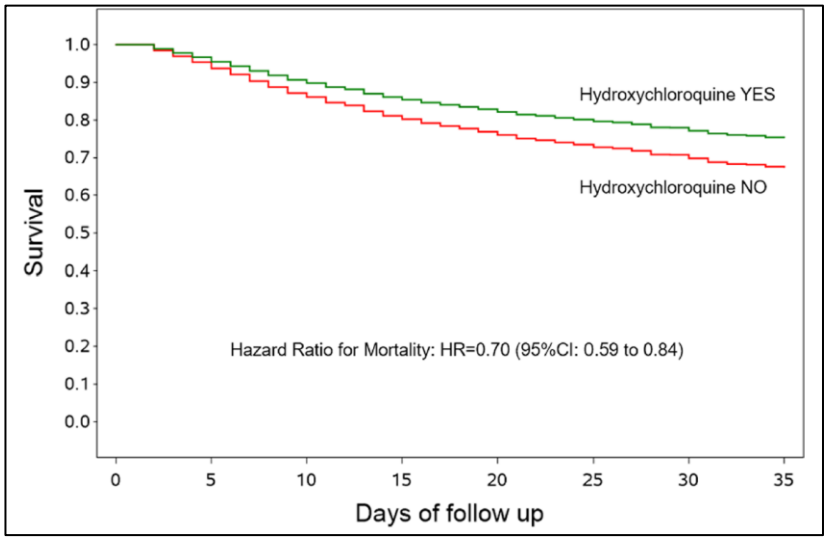
Subgroup	No. of deaths/total No. of patients: Steroids	No. of deaths/total No. of patients: No steroids	Odds ratio (95% CI)	Weight, %
Invasive mechanical ventilation (IMV)				
No ($I^2 = 0\%$)	14/70	28/74	0.41 (0.19-0.88)	2.7
Yes ($I^2 = 44.1\%$)	208/608	397/951	0.69 (0.55-0.86)	31.7
Oxygen treatment without IMV (RECOVERY)	298/1279	682/2604	0.86 (0.73-1.00)	65.6
Taking vasoactive medication				
No ($I^2 = 0\%$)	51/184	68/184	0.55 (0.34-0.88)	50.2
Yes ($I^2 = 0\%$)	76/169	74/158	1.05 (0.65-1.69)	49.8
Age, y				
≤60 ($I^2 = 0\%$)	72/338	141/483	0.67 (0.48-0.94)	42.7
>60 ($I^2 = 49.7\%$)	150/339	284/541	0.69 (0.51-0.93)	57.3
Sex				
Female ($I^2 = 0\%$)	60/202	106/286	0.66 (0.43-0.99)	27.4
Male ($I^2 = 14.7\%$)	162/476	319/739	0.66 (0.51-0.84)	72.6
Symptomatic, d				
≤7 ($I^2 = 69.1\%$)	51/130	99/211	0.63 (0.39-1.04)	22.4
>7 ($I^2 = 0\%$)	139/418	293/693	0.64 (0.49-0.83)	77.6



The COVID-19 RISK and Treatments (CORIST) Collaboration members European Journal of Internal Medicine https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7446618/pdf/main.pdf	Use of hydroxychloroquine in hospitalised COVID-19 patients is associated with reduced mortality: Findings from the observational multicentre Italian CORIST study	Studio retrospettivo osservazionale multicentrico italiano su 3451 pazienti ricoverati per COVID19 che mostra una riduzione del rischio di mortalità intraospedaliera del 30% (95%CI: 16% - 41%) nei pazienti trattati rispetto ai non trattati con idrossiclorochina.	Background: Hydroxychloroquine (HCQ) was proposed as potential treatment for COVID-19. Objective: We set-up a multicenter Italian collaboration to investigate the relationship between HCQ therapy and COVID-19 in-hospital mortality. Methods: In a retrospective observational study, 3,451 unselected patients hospitalized in 33 clinical centers in Italy, from February 19, 2020 to May 23, 2020, with laboratory-confirmed SARS-CoV-2 infection, were analyzed. The primary end-point in a time-to event analysis was in-hospital death, comparing patients who received HCQ with patients who did not. We used multivariable Cox proportional-hazards regression models with inverse probability for treatment weighting by propensity scores, with the addition of subgroup analyses. Results: Out of 3,451 COVID-19 patients, 76.3% received HCQ. Death rates (per 1,000 person-days) for patients receiving or not HCQ were 8.9 and 15.7, respectively. After adjustment for propensity scores, we found 30% lower risk of death in patients receiving HCQ (HR=0.70; 95%CI: 0.59 to 0.84; E-value=1.67). Secondary analyses yielded similar results. The inverse association of HCQ with inpatient mortality was particularly evident in patients having elevated C-reactive protein at entry. Conclusions: HCQ use was associated with a 30% lower risk of death in COVID-19 hospitalized patients. Within the limits of an observational study and awaiting results from randomized controlled trials, these data do not discourage the use of HCQ in inpatients with COVID-19.

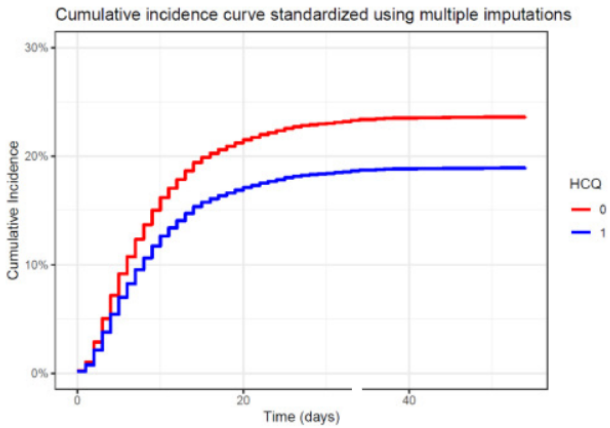
Hazard ratios for mortality according to hydroxychloroquine use in different subgroups

	Hydroxychloroquine NO (N = 817)	Hydroxychloroquine YES (N = 2,634)	
Subgroups	**No. death/patient at risk**	**No. death/patient at risk**	**HR (95% CI)***
Women	80/361	116/940	0.63 (0.46 to 0.86)
Men	110/456	270/1,694	0.74 (0.60 to 0.93)
Age <70 years	22/357	93/1,542	0.76 (0.50 to 1.16)
Age ≥70 years	168/460	293/1,092	0.68 (0.56 to 0.83)
Highest degree of COVID-19 severity experienced at hospital			
Mild pneumonia or less	28/424	40/1,358	0.70 (0.41 to 1.18)
Severe pneumonia	80/253	172/764	0.76 (0.58 to 0.99)
Acute respiratory distress syndrome	82/140	174/512	0.68 (0.52 to 0.90)
Use of other COVID-19 treatments^			
No	101/439	64/570	0.63 (0.45 to 0.88)
Yes	89/378	322/2,064	0.77 (0.61 to 0.99)
C-Reactive Protein at basal**			
<10 mg/L	56/412	125/1,138	1.23 (0.86 to 1.77)
≥10 mg/L	123/361	241/1,362	0.59 (0.47 to 0.73)



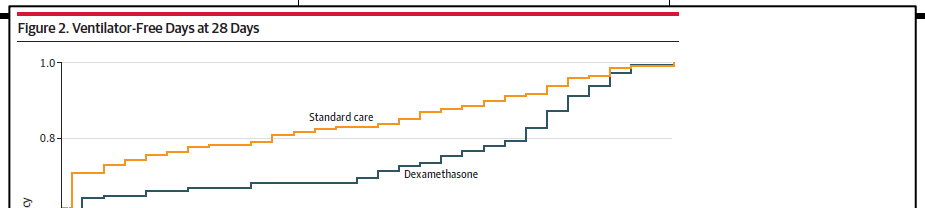
Catteau Lucy et al International Journal of Antimicrobial Agents https://www.sciencedirect.com/science/article/pii/S0924857920303423?via%3Dihub	Low-dose Hydroxychloroquine Therapy and Mortality in Hospitalized Patients with COVID-19: A Nationwide Observational Study of 8075 Participants.	Studio retrospettivo osservazionale multicentrico belga su 8075 pazienti ricoverati per COVID19 che mostra una riduzione del rischio di mortalità intraospedaliera nei pazienti trattati rispetto ai non trattati con idrossiclorochina (hazard ratio 0.684, IC 95% 0.617–0.758), indipendentemente dalla latenza dall'esordio dei sintomi.	BACKGROUND: Hydroxychloroquine (HCQ) has been largely used and investigated as therapy of COVID-19 across various settings, at total dose usually ranging from 2400 mg to 9600 mg. In Belgium, off-label use of low-dose HCQ (2400 mg in total over five days) was recommended for hospitalized patients with COVID-19. METHODS: We conducted a retrospective analysis of in-hospital mortality in the Belgian national COVID-19 hospital surveillance data. Patients treated either with HCQ alone and supportive care (HCQ group) were compared to patients treated with supportive care only (no-HCQ group) using a competing risks proportional hazards regression with discharge alive as competing risk, adjusted for demographic and clinical features with robust standard errors. RESULTS: Of 8075

			patients with complete discharge data on 24(th) of May and diagnosed before the 1(st) of May, 4542 received HCQ in monotherapy and 3533 were in the no-HCQ group. Death was reported in 804/4542 (17.7%) and 957/3533 (27.1%), respectively. In the multivariable analysis, the mortality was lower in the HCQ group compared to the no-HCQ group (adjusted hazard ratio [HR] 0.684, 95% confidence interval [CI] 0.617-0.758). Compared to the no-HCQ group, mortality in the HCQ group was reduced both in patients diagnosed </= 5 days (n=3975) and > 5 days (n=3487) after symptom onset (adjusted HR 0.701, 95% CI 0.617-0.796 and adjusted HR 0.647, 95% CI 0.525-0.797, respectively). CONCLUSIONS: Compared to supportive care only, low-dose HCQ monotherapy was independently associated with lower mortality in hospitalized patients with COVID-19 diagnosed and treated early or

			later after symptom onset.  Figure 3. Cumulative incidence of in-hospital mortality. Inverse propensity weighted standardized cumulative incidence of in-hospital death according to treatment received. Hydroxychloroquine (HCQ) (blue line) vs no-HCQ (red line).
Yan Chen et al Frontiers in Pharmacology https://www.frontiersin.org/articles/10.3389/fphar.2020.01167/full	Research Progress of Chloroquine and Hydroxychloroquine on the COVID-19 and Their Potential Risks in Clinic Use	Revisione dei più recenti trial clinici sull'utilizzo di clorochina e idrossiclorochina contro COVID19 in Cina.	In December 2019, a severe outbreak of a novel coronavirus (COVID-19) occurred in the whole world, posing a great threat to people's health. With the outbreak and development of the epidemic, how to improve the cure rate, find effective drugs against this virus, has been the most urgent problem. Chloroquine (CQ) was verified effective against COVID-19 in vitro. As CQ's analogue, hydroxychloroquine (HCQ) was also reminded as a potential candidate for treating COVID-19. This review summarizes the latest clinical trials of CQ and HCQ against COVID-19 and its therapeutic regimen in China aiming to share their current usage to the whole world and provide insight into its appropriate future use in the treatment of COVID-19. Through searching the CNKI and Wangfang databases in Chinese language and PubMed, EMBASE, and Ovid

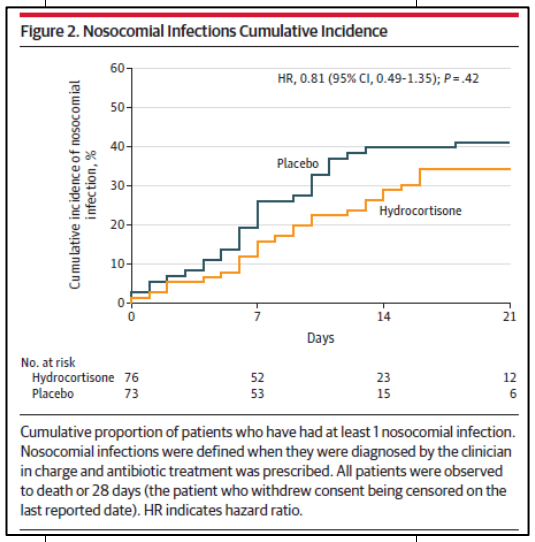
			databases in English language to identify published reports with the keywords including “coronavirus/COVID, chloroquine, hyroxychloroquine” in alone or combined, we found out the potential preclinical or clinical evidence for using CQ and HCQ against COVID-19. Consequently, we also searched the website of Chinese Clinical Trial Registry (http://www.chictr.org.cn/) till the day on 27th, June, 2020. This review found that there are 23 programs aimed to treat the different phases under COVID-19 pipeline in clinic with CQ and HCQ, totally. The inclusion criteria, exclusion criteria and therapeutic regimen were all shared to consult. Among them, seven have been canceled due to lack of patients or other objective factors. There are two trials have completed, which the potential relationship between usage and adverse reactions was discussed emphatically. Through literature research, we suggested that paid close attention to retinal toxicity and ophthalmologic adverse symptom of CQ and HCQ. And the outcome of HCQ in clinic shows better than CQ especially in protective effect with low dosage.
Tomazini Bruno M et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2770277?resultClick=1	Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 The CoDEX Randomized Clinical Trial	Trial randomizzato multicentrico open-label brasiliano su 299 pazienti COVID19 ricoverati in rianimazione con ARDS moderata/grave, trattati con desametasone EV contro standard of care. Si dimostra un maggior numero di giorni liberi da ventilazione meccanica (VFD) nei primi 28 giorni nei pazienti randomizzati a desametasone.	IMPORTANCE Acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19) is associated with substantial mortality and use of health care resources. Dexamethasone use might attenuate lung injury in these patients. OBJECTIVE To determine whether intravenous dexamethasone increases the number of ventilator-free days among patients with COVID-19–associated ARDS. DESIGN, SETTING, AND PARTICIPANTS Multicenter, randomized, open-label, clinical trial conducted in 41 intensive care units (ICUs) in Brazil. Patients with COVID-19 and moderate to severe ARDS, according to the Berlin definition, were enrolled from April 17 to June 23, 2020. Final follow-up was completed on July 21, 2020. The

		Trial interrotto prematuramente dopo la comunicazione dei risultati del RECOVERY trial.	trial was stopped early following publication of a related study before reaching the planned sample size of 350 patients. INTERVENTIONS Twenty mg of dexamethasone intravenously daily for 5 days, 10mg of dexamethasone daily for 5 days or until ICU discharge, plus standard care (n =151) or standard care alone (n = 148). MAIN OUTCOMES AND MEASURES The primary outcome was ventilator-free days during the first 28 days, defined as being alive and free from mechanical ventilation. Secondary outcomes were all-cause mortality at 28 days, clinical status of patients at day 15 using a 6-point ordinal scale (ranging from 1, not hospitalized to 6, death), ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, and Sequential Organ Failure Assessment (SOFA) scores (range, 0-24, with higher scores indicating greater organ dysfunction) at 48 hours, 72 hours, and 7 days. RESULTS A total of 299 patients (mean [SD] age, 61 [14] years; 37%women) were enrolled and all completed follow-up. Patients randomized to the dexamethasone group had a mean 6.6 ventilator-free days (95%CI, 5.0-8.2) during the first 28 days vs 4.0 ventilator-free days (95%CI, 2.9-5.4) in the standard care group (difference, 2.26; 95%CI, 0.2-4.38; P = .04). At 7 days, patients in the dexamethasone group had a mean SOFA score of 6.1 (95%CI, 5.5-6.7) vs 7.5 (95%CI, 6.9-8.1) in the standard care group (difference, −1.16; 95%CI, −1.94 to −0.38; P = .004). There was no significant difference in the prespecified secondary outcomes of all-cause mortality at 28 days, ICU-free days during the first 28 days, mechanical ventilation duration at 28 days, or the 6-point ordinal scale at 15 days. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections, 47 (31.1%) vs 42 (28.3%) needed



			insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events. CONCLUSIONS AND RELEVANCE Among patients with COVID-19 and moderate or severe ARDS, use of intravenous dexamethasone plus standard care compared with standard care alone resulted in a statistically significant increase in the number of ventilator-free days (days alive and free of mechanical ventilation) over 28 days. TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT04327401
Dequin Pierre-François et al JAMA https://jamanetwork.com/journals/jama/fullarticle/2770276?resultClick=1	Effect of Hydrocortisone on 21-Day Mortality or Respiratory Support Among Critically Ill Patients With COVID-19 A Randomized Clinical Trial	Trial clinico randomizzato su 149 pazienti ricoverati in rianimazione in Francia. Non si dimostra una differenza significativa nel rischio di outcome sfavorevole (morte o persistente necessità di ventilazione meccanica/cannule nasali ad alto flusso) al giorno 21 fra pazienti trattati con idrocortisone a basse dosi contro placebo. Non si osserva maggiore incidenza di infezioni nosocomiali nei trattati con idrocortisone. Trial interrotto prematuramente dopo la	Importance: Coronavirus disease 2019 (COVID-19) is associated with severe lung damage. Corticosteroids are a possible therapeutic option. Objective: To determine the effect of hydrocortisone on treatment failure on day 21 in critically ill patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and acute respiratory failure. Design, Setting, and Participants: Multicenter randomized double-blind sequential trial conducted in France, with interim analyses planned every 50 patients. Patients admitted to the intensive care unit (ICU) for COVID-19–related acute respiratory failure were enrolled from March 7 to June 1, 2020, with last follow-up on June 29, 2020. The study intended to enroll 290 patients but was stopped early following the recommendation of the data and safety monitoring board.

		comunicazione dei risultati del RECOVERY trial.	Interventions: Patients were randomized to receive low-dose hydrocortisone (n = 76) or placebo (n = 73). Main Outcomes and Measures: The primary outcome, treatment failure on day 21, was defined as death or persistent dependency on mechanical ventilation or high-flow oxygen therapy. Prespecified secondary outcomes included the need for tracheal intubation (among patients not intubated at baseline); cumulative incidences (until day 21) of prone position sessions, extracorporeal membrane oxygenation, and inhaled nitric oxide; Pao2:Fio2 ratio measured daily from day 1 to day 7, then on days 14 and 21; and the proportion of patients with secondary infections during their ICU stay. Results: The study was stopped after 149 patients (mean age, 62.2 years; 30.2% women; 81.2% mechanically ventilated) were enrolled. One hundred forty-eight patients (99.3%) completed the study, and there were 69 treatment failure events, including 11 deaths in the hydrocortisone group and 20 deaths in the placebo group. The primary outcome, treatment failure on day 21, occurred in 32 of 76 patients (42.1%) in the hydrocortisone group compared with 37 of 73 (50.7%) in the placebo group (difference of proportions, –8.6% [95.48% CI, –24.9% to 7.7%]; P = .29). Of the 4 prespecified secondary outcomes, none showed a significant difference. No serious adverse events were related to the study treatment. Conclusions and Relevance: In this study of critically ill patients with COVID-19 and acute respiratory failure, low-dose hydrocortisone, compared with placebo, did not significantly reduce treatment failure (defined as death or persistent respiratory support) at day 21. However, the study was stopped early and likely was underpowered to find a statistically and clinically important difference in the primary outcome.



			Trial Registration: ClinicalTrials.gov Identifier: NCT02517489

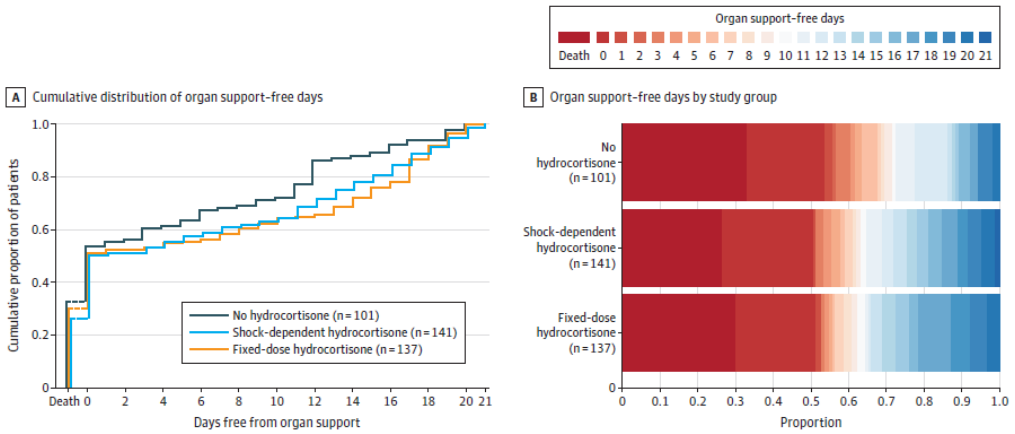
TheWriting Committee for the REMAP-CAP Investigators JAMA https://jamanetwork.com/journals/jama/fullarticle/2770278?resultClick=1	Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19. The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial	Trial clinico randomizzato multicentrico, corrispondente a un *dominio* del più ampio REMAP-CAP trial. Su 403 pazienti ricoverati in rianimazione e trattati con idrocortisone in due differenti schemi contro no idrocortisone, l'ipotesi che idrocortisone conferisca un beneficio in termini di outcome composito (organ support free days) rispetto al placebo non è dimostrata in quanto il trial è stato prematuramente terminato alla pubblicazione dei risultati di RECOVERY. Si dimostra tuttavia una probabilità di beneficio, a supporto della terapia steroidea contro COVID19.	IMPORTANCE: Evidence regarding corticosteroid use for severe coronavirus disease 2019 (COVID-19) is limited. OBJECTIVE: To determine whether hydrocortisone improves outcome for patients with severe COVID-19. DESIGN, SETTING, AND PARTICIPANTS: An ongoing adaptive platform trial testing multiple interventions within multiple therapeutic domains, for example, antiviral agents, corticosteroids, or immunoglobulin. Between March 9 and June 17, 2020, 614 adult patients with suspected or confirmed COVID-19 were enrolled and randomized within at least 1 domain following admission to an intensive care unit (ICU) for respiratory or cardiovascular organ support at 121 sites in 8 countries. Of these, 403 were randomized to open-label interventions within the corticosteroid domain. The domain was halted after results from another trial were released. Follow-up ended August 12, 2020. INTERVENTIONS The corticosteroid domain randomized participants to a fixed 7-day course of intravenous hydrocortisone (50mg or 100mg every 6 hours) (n = 143), a shock-dependent course (50mg every 6 hours when shock was clinically evident) (n = 152), or no hydrocortisone (n = 108). MAIN OUTCOMES AND MEASURES The primary end pointwas organ support–free days (days alive and free of ICU-based respiratory or cardiovascular support) within 21 days, where patients who died were assigned –1 day. The primary analysis was a bayesian cumulative logistic model that included all patients enrolled with severe COVID-19, adjusting for age, sex, site, region, time, assignment to interventions within other domains, and domain and intervention eligibility. Superiority was defined as the posterior probability of an odds ratio greater than 1 (threshold for trial conclusion of superiority >99%).

RESULTS After excluding 19 participants who withdrew consent, therewere 384 patients (mean age, 60years;29%female) randomized to the fixed-dose (n = 137), shock-dependent (n = 146), and no (n = 101) hydrocortisone groups; 379 (99%) completed the study andwere included in the analysis. The mean age for the 3 groups ranged between 59.5 and 60.4 years; most patients were male (range, 70.6%-71.5%); mean body mass index ranged between 29.7 and 30.9; and patients receiving mechanical ventilation ranged between 50.0%and 63.5%. For the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively, the median organ support–free days were0(IQR, –1 to 15),0(IQR, –1 to 13), and0(–1 to 11) days (composed of 30%, 26%, and 33%mortality rates and 11.5, 9.5, and 6 median organ support–free days among survivors). The median adjusted odds ratio and bayesian probability of superioritywere 1.43 (95% credible interval, 0.91-2.27) and 93%for fixed-dose hydrocortisone, respectively, andwere 1.22 (95% credible interval,0.76-1.94) and80%for shock-dependent hydrocortisone compared with no hydrocortisone. Serious adverse eventswere reported in 4 (3%), 5 (3%), and 1 (1%) patients in the fixed-dose, shock-dependent, and no hydrocortisone groups, respectively.

CONCLUSIONS AND RELEVANCE Among patients with severe COVID-19, treatment with a 7-day fixed-dose course of hydrocortisone or shock-dependent dosing of hydrocortisone, compared with no hydrocortisone, resulted in 93%and 80% probabilities of superiority with regard to the odds of improvement in organ support–free days within 21 days. However, the trial was stopped early and no treatment strategymet prespecified criteria for statistical superiority, precluding definitive conclusions.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02735707

Figure 2. Organ Support-Free Days



A, Distributions of organ support-free days (see the Methods section for definition) by study group as the cumulative proportion (y-axis) for each study group by day (x-axis), with death listed first. Curves that rise more slowly are more favorable. B, Organ support-free days as horizontally stacked proportions by study group. Red represents worse values and blue represents better values. The median adjusted odds ratios from the primary analysis, using a bayesian cumulative logistic model, were 1.43 (95% credible interval, 0.91-2.27) and 1.22 (95% credible interval, 0.76-1.94) for the fixed-dose and shock-dependent hydrocortisone groups compared with the no hydrocortisone group, yielding 93% and 80% probabilities of superiority over the no hydrocortisone group, respectively.

Keech Cheryl et al NEJM https://www.nejm.org/doi/full/10.1056/NEJMoa2026920?query=featured_home	Phase 1–2 Trial of a SARS-CoV-2 Recombinant Spike Protein Nanoparticle Vaccine	Analisi al giorno 35 della fase 1 di un trial randomizzato controllato di fase 1-2 per dimostrare sicurezza e immunogenicitià di un candidato vaccino contro SARS-CoV-2.	BACKGROUND: NVX-CoV2373 is a recombinant severe acute respiratory syndrome coronavirus 2 (rSARS-CoV-2) nanoparticle vaccine composed of trimeric full-length SARS-CoV-2 spike glycoproteins and Matrix-M1 adjuvant. METHODS: We initiated a randomized, placebo-controlled, phase 1–2 trial to evaluate the safety and immunogenicity of the rSARS-CoV-2 vaccine (in 5-µg and 25-µg doses, with or without Matrix-M1 adjuvant, and with observers unaware of trial-group assignments) in 131 healthy adults. In phase 1, vaccination comprised two intramuscular injections, 21 days apart. The primary outcomes were reactogenicity; laboratory values (serum chemistry and hematology), according to Food and Drug Administration toxicity scoring, to assess safety; and IgG anti–spike protein response (in enzyme-linked immunosorbent assay [ELISA] units). Secondary outcomes included unsolicited adverse events, wild-type virus neutralization (microneutralization assay), and T-cell responses (cytokine staining). IgG and microneutralization assay results were compared with 32 (IgG) and 29 (neutralization) convalescent serum samples from patients with Covid-19, most of whom were symptomatic. We performed a primary analysis at day 35. RESULTS: After randomization, 83 participants were assigned to receive the vaccine with adjuvant and 25 without adjuvant, and 23 participants were assigned to receive placebo. No serious adverse events were noted. Reactogenicity was absent or mild in the majority of participants, more common with adjuvant, and of short duration (mean, ≤2 days). One participant had mild fever that lasted 1 day. Unsolicited adverse events were mild in most participants; there were no severe adverse events. The addition of adjuvant resulted in enhanced immune responses, was antigen dose–sparing, and induced a T helper 1 (Th1) response. The two-dose 5-µg adjuvanted regimen induced geometric mean anti-spike IgG (63,160

			ELISA units) and neutralization (3906) responses that exceeded geometric mean responses in convalescent serum from mostly symptomatic Covid-19 patients (8344 and 983, respectively). CONCLUSIONS: At 35 days, NVX-CoV2373 appeared to be safe, and it elicited immune responses that exceeded levels in Covid-19 convalescent serum. The Matrix-M1 adjuvant induced CD4+ T-cell responses that were biased toward a Th1 phenotype.
Burke Rachel M et al PloS One https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0238342&type=printable	Enhanced contact investigations for nine early travel-related cases of SARS-CoV-2 in the United States.	Esiti del tracciamento dei contatti di 9 pazienti COVID19 originari degli USA con storia di viaggi all'estero. Sono state monitorate in totale 404 persone fra conviventi, operatori sanitari e altri contatti comunitari, raccogliendo dettagli sul tipo di esposizione. Si sono riscontrati 2 casi secondari, entrambi coniugi di un caso indice (secondary attack rate 13% per i conviventi e 25% per i coniugi). Nessun caso fra gli operatori sanitari.	Coronavirus disease 2019 (COVID-19), the respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first identified in Wuhan, China and has since become pandemic. In response to the first cases identified in the United States, close contacts of confirmed COVID-19 cases were investigated to enable early identification and isolation of additional cases and to learn more about risk factors for transmission. Close contacts of nine early travel-related cases in the United States were identified and monitored daily for development of symptoms (active monitoring). Selected close contacts (including those with exposures categorized as higher risk) were targeted for collection of additional exposure information and respiratory samples. Respiratory samples were tested for SARS-CoV-2 by real-time reverse transcription polymerase chain reaction at the Centers for Disease Control and Prevention. Four hundred four close contacts were actively monitored in the jurisdictions that managed the travel-related cases. Three hundred thirty-eight of the 404 close contacts provided at least basic exposure information, of whom 159 close contacts had >/=1 set of respiratory samples collected and tested. Across all actively monitored close contacts, two additional symptomatic COVID-19 cases (i.e., secondary cases) were identified; both secondary cases were in spouses of travel-associated case patients. When considering only household members, all of whom

			had >/=1 respiratory sample tested for SARS-CoV-2, the secondary attack rate (i.e., the number of secondary cases as a proportion of total close contacts) was 13% (95% CI: 4-38%). The results from these contact tracing investigations suggest that household members, especially significant others, of COVID-19 cases are at highest risk of becoming infected. The importance of personal protective equipment for healthcare workers is also underlined. Isolation of persons with COVID-19, in combination with quarantine of exposed close contacts and practice of everyday preventive behaviors, is important to mitigate spread of COVID-19.
Ferguson John et al Journal of Clinical Pharmacology https://accp1.onlinelibrary.wiley.com/doi/epdf/10.1002/jcph.1749	Empiric therapeutic anticoagulation and mortality in critically ill patients with respiratory failure from SARS-CoV-2: A retrospective cohort study	Studio di coorte retrospettivo su 141 pazienti sottoposti a ventilazione meccanica e trattati con eparina a dosaggio profilattico o terapeutico iniziate prima dell'intubazione. Non si dimostra una differenza significativa di mortalità a 28 giorni fra i due gruppi. Da notare che i due gruppi differivano significativamente per la terapia concomitante somministrata.	The pathophysiology of respiratory failure associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains under investigation. One hypothesis is that progressive endothelial damage from the virus leads to microvascular thrombosis. It is uncertain if empiric therapeutic anticoagulation provides benefit over standard deep vein thrombosis (DVT) prophylaxis in critically ill patients with SARS-CoV-2. A retrospective cohort study was performed to evaluate adult patients admitted to the intensive care unit at three hospitals with PCR-confirmed SARS-CoV-2 associated respiratory failure requiring invasive mechanical ventilation. A Kaplan-Meier survival analysis was used to compare patients who were initiated on therapeutic anticoagulation prior to the time of intubation, and those receiving standard DVT prophylaxis doses. The primary outcome was the difference in the 28-day mortality of patients between the two groups. 28-day mortality was not different between groups, occurring in 26.1% in patients who received therapeutic anticoagulation and 29.5% in those who received a prophylaxis dose only (hazard ratio 0.52, p = 0.055). There was no difference in 28-day mortality between groups in patients who were admitted with a serum D-dimer greater than or equal to 2 mcg/mL (hazard ratio 0.67, p = 0.41). Empiric therapeutic

			anticoagulation in patients who require invasive mechanical ventilation for confirmed SARS-CoV-2 infection does not improve 28-day mortality when compared to standard DVT prophylaxis, even among those with elevated D-dimer levels. This article is protected by copyright. All rights reserved.
Logunov Denis Y et al The Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31866-3/fulltext	Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomised phase 1/2 studies from Russia	Risultati di due studi di fase 1/2 condotti in Russia su due forme (congelata e liofilizzata) di un candidato vaccino bicomponente basato su un vettore adenovirale e contenente il gene della glicoproteina spike di SARS-CoV-2. Entrambe le formulazioni inducono elevati livelli di immunità umorale e cellulare e hanno un buon profilo di tollerabilità.	Background: We developed a heterologous COVID-19 vaccine consisting of two components, a recombinant adenovirus type 26 (rAd26) vector and a recombinant adenovirus type 5 (rAd5) vector, both carrying the gene for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike glycoprotein (rAd26-S and rAd5-S). We aimed to assess the safety and immunogenicity of two formulations (frozen and lyophilised) of this vaccine. Methods: We did two open, non-randomised phase 1/2 studies at two hospitals in Russia. We enrolled healthy adult volunteers (men and women) aged 18–60 years to both studies. In phase 1 of each study, we administered intramuscularly on day 0 either one dose of rAd26-S or one dose of rAd5-S and assessed the safety of the two components for 28 days. In phase 2 of the study, which began no earlier than 5 days after phase 1 vaccination, we administered intramuscularly a prime-boost vaccination, with rAd26-S given on day 0 and rAd5-S on day 21. Primary outcome measures were antigen-specific humoral immunity (SARS-CoV-2-specific antibodies measured by ELISA on days 0, 14, 21, 28, and 42) and safety (number of participants with adverse events monitored throughout the study). Secondary outcome measures were antigen-specific cellular immunity (T-cell responses and interferon-γ concentration) and change in neutralising antibodies (detected with a SARS-CoV-2 neutralisation assay). These trials are registered with ClinicalTrials.gov, NCT04436471 and NCT04437875. Findings: Between June 18 and Aug 3, 2020, we enrolled 76 participants to the two studies (38 in each study). In each study,

			nine volunteers received rAd26-S in phase 1, nine received rAd5-S in phase 1, and 20 received rAd26-S and rAd5-S in phase 2. Both vaccine formulations were safe and well tolerated. The most common adverse events were pain at injection site (44 [58%]), hyperthermia (38 [50%]), headache (32 [42%]), asthenia (21 [28%]), and muscle and joint pain (18 [24%]). Most adverse events were mild and no serious adverse events were detected. All participants produced antibodies to SARS-CoV-2 glycoprotein. At day 42, receptor binding domain-specific IgG titres were 14 703 with the frozen formulation and 11 143 with the lyophilised formulation, and neutralising antibodies were 49·25 with the frozen formulation and 45·95 with the lyophilised formulation, with a seroconversion rate of 100%. Cell-mediated responses were detected in all participants at day 28, with median cell proliferation of 2·5% CD4+ and 1·3% CD8+ with the frozen formulation, and a median cell proliferation of 1·3% CD4+ and 1·1% CD8+ with the lyophilised formulation. Interpretation The heterologous rAd26 and rAd5 vector-based COVID-19 vaccine has a good safety profile and induced strong humoral and cellular immune responses in participants. Further investigation is needed of the effectiveness of this vaccine for prevention of COVID-19.
Schultz Marcus J et al JAMA https://jamanetwork.com/journals/jamaotolaryngology/fullarticle/2770091	Timing of Tracheostomy for Patients With COVID-19 in the ICU—Setting Precedent in Unprecedented Times	Discussione sulla tempistica ottimale di confezionamento di tracheostomia in pazienti ventilati con COVID19 e critica di alcune diffuse convinzioni al riguardo non basate su evidenza.	Navigating the uncharted has been a pervasive theme during the coronavirus disease 2019 (COVID-19) pandemic, and lack of data to guide decisions has been the most evident regarding the timing of tracheostomy. Tracheostomy, an aerosol-generating procedure with risk of infectious transmission for health care workers, also has important implications for patient care and stewardship of critical resources. Emerging data concerning infectivity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the course of

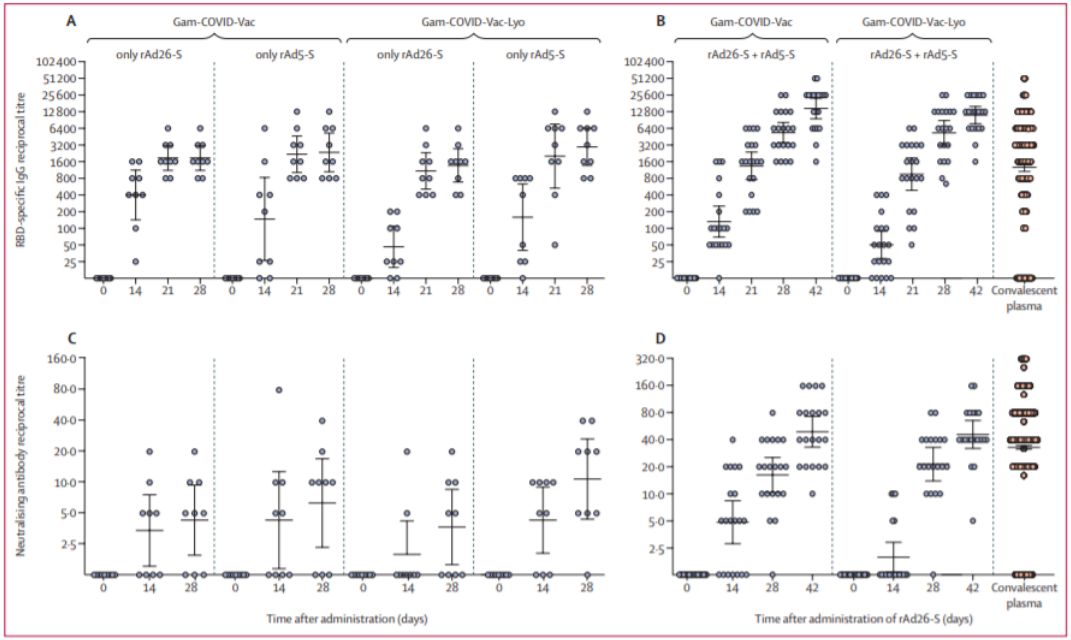


Figure 2: **Humoral immune response**
Data are geometric mean titres and 95% CIs. (A) RBD-specific antibodies on days 0, 14, 21, and 28, as measured by ELISA, in participants vaccinated with rAd26-S or rAd5-S only. (B) RBD-specific antibodies on days 0, 14, 21, 28, and 42, as measured by ELISA, in participants vaccinated with rAd26-S on day 0 and rAd5-S on day 21. (C) Neutralising antibodies on days 0, 14, and 28, as measured by neutralisation assay with 100 TCID50, in participants vaccinated with rAd26-S or rAd5-S only. (D) Neutralising antibodies on days 0, 14, 28, and 42, as measured by microneutralisation assay with 100 TCID50, in participants vaccinated with rAd26-S on day 0 and rAd5-S on day 21. RBD-specific IgGs and neutralising antibodies of in convalescent plasma are also shown in (B) and (D). Gam-COVID-Vac=frozen vaccine formulation. Gam-COVID-Vac-Lyo=lyophilised vaccine formulation. rAd26-S=recombinant adenovirus type 26 carrying the gene for SARS-CoV-2 full-length glycoprotein S. rAd5-S=recombinant adenovirus type 5 carrying the gene for SARS-CoV-2 full-length glycoprotein S. SARS-CoV-2=severe acute respiratory syndrome coronavirus 2. RBD=receptor-binding domain. TCID50=50% tissue culture infective dose.

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<td>patients with COVID-19, and clinical experience may alter practice, even preempting publication. For example, Chao et al4 originally recommended deferring tracheostomy beyond 21 days of intubation and recommended open surgical tracheostomy over percutaneous dilatational tracheostomy; however, updated practices at the authors' institution reflect outcomes of tracheostomy performed at 10 to 14 days after intubation, with percutaneous technique performed regularly. Similarly, shortly after the New York Head and Neck Society advocated a 14-day standard,5 the New York University thoracic group published a series of 98 COVID-19 tracheostomy procedures, with surgical procedures at a mean (SD) of 10.6. (5) days of intubation,6 indicating that many patients underwent tracheostomy well before day 10 of intubation. When COVID-19 overwhelms capacity in intensive care units (ICUs), early timing of tracheostomy may accelerate ventilator weaning and free up critical equipment, staff, and units. Guidelines now recommend that timing of tracheostomy consider scarcity of ventilators and other ICU resources.</td>
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<td>Papadopoulos Nikolaos et al

Annals of Gastroenterology

http://www.annalsgastro.gr/files/journals/1/earlyview/2020/ev-07-2020-22-AG_5214-0522.pdf</td>
<td>COVID-19 and liver injury: where do we stand?</td>
<td>Disamina delle conoscenze attuali sull'epatopatia associata a COVID19, di frequente riscontro nella pratica clinica.</td>
<td>The coronavirus SARS-CoV-2 was identified as the cause of COVID-19, a severe acute respiratory syndrome. Several clinical studies refer to liver injury as the most frequent clinical extrapulmonary manifestation. In this review, we summarize the available clinical data concerning liver injury during COVID-19. Although the underlying mechanism of liver impairment is somewhat unclear, transaminases and bilirubin levels are elevated in a substantial proportion of patients. Moreover, more severe alterations in liver enzymes may correlate with a worse clinical course of COVID-19. However, several other cofactors, such as drug-induced liver injury, hyper-inflammatory response to infection, hypoxic hepatitis or preexisting underlying liver disease, cannot be excluded.</td>
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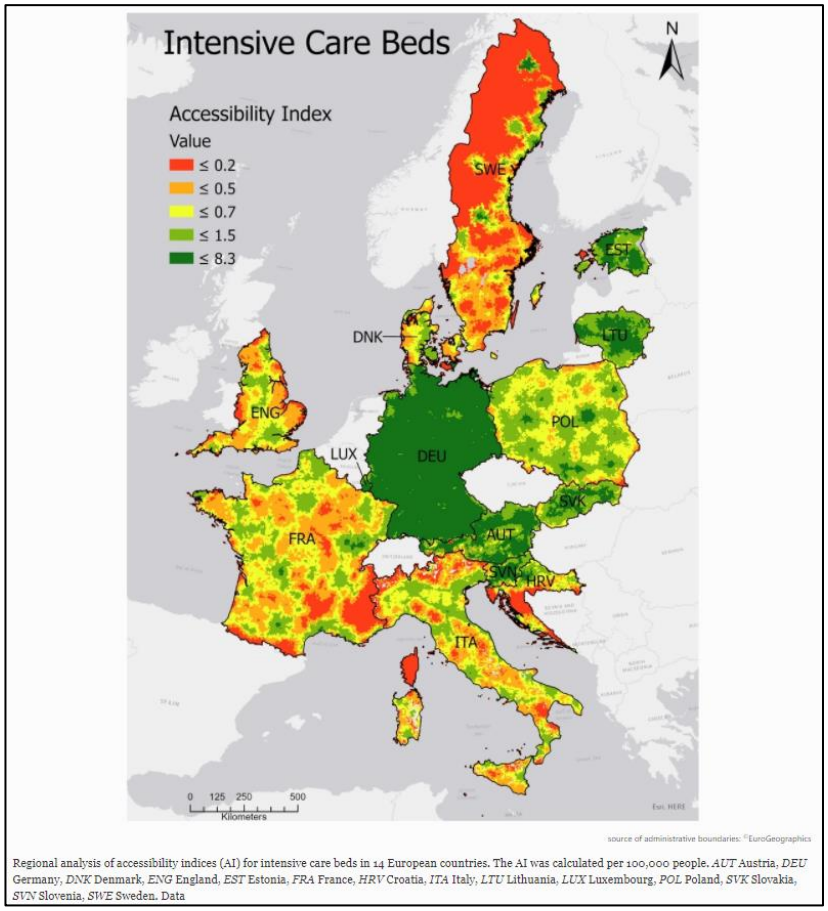
Table. Misconceptions That Predispose to Uncontrolled Variation in Tracheostomy Among Patients With COVID-19

Table. Misconceptions That Predispose to Uncontrolled Variation in Tracheostomy Among Patients With COVID-19

Misconception	Available evidence	Translation to practice
Safety of the clinicians		
Performing tracheostomy earlier than 21 d is associated with increased risk to health care workers and offers no benefit	• RT-PCR may amplify dead or inert virus • No evidence of increased transmission of COVID-19 when performing tracheostomy at 10 d vs >21 d • Tracheostomy may reduce ICU/hospital days and risk of pneumonia	• Otolaryngologists are encouraged to work with multidisciplinary teams to identify the optimal, patient-centered timing of tracheostomy
Because patients with COVID-19 receiving ventilator assistance may not tolerate apnea or loss of PEEP during tracheostomy, there is elevated risk of exposure to SARS-CoV-2 aerosols	• Owing to favorable pulmonary compliance characteristic of patients with COVID-19, high PEEP is seldom needed • Most patients have sufficient reserve to allow an apneic procedure to be performed, although this finding may differ from patient to patient	• Before surgery, pulmonary reserve and need for PEEP can be assessed with an apnea trial • Dissection to tracheal wall minimizes apnea • In percutaneous technique, placing bronchoscope alongside endotracheal tube reduces aerosols
Benefit to the patient		
Risk of subglottic stenosis and laryngeal complications account for nearly all of the morbidity from prolonged intubation	• Prolonged sedation/intubation for patients with COVID-19 delays rehabilitation, can exacerbate resource scarcity, and may increase risk for thrombotic sequelae (CVA, VTE) or other complications	• Well-established, evidence-based critical care standards should be followed • Prospective trials randomizing to early and late tracheostomy among patients with COVID-19 are needed but may never occur
COVID-19 ARDS requires a fundamentally new care paradigm	• COVID-19 induces severe pulmonary injury, including diffuse alveolar damage, pulmonary microthrombosis, and clinical characteristics that largely mirror classic ARDS	• Proven standards for ARDS are indicated during the pandemic; tracheostomy is not recommended when prone positioning is needed to improve oxygenation
Critically ill patients with COVID-19 "declare themselves" by 21 d after intubation	• While many ICU patients either recover or worsen during this period, roughly 10% of patients require prolonged ventilation, occasionally for many weeks	• Global, multidisciplinary guidance on tracheostomy for patients with COVID-19 suggests 10-21 d as recommended window for tracheostomy[2]

Abbreviations: ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; CVA, cerebrovascular accident; ICU, intensive care unit; PEEP, positive end-expiratory pressure; RT-PCR, reverse transcription polymerase chain reaction; SARS-CoV-2, serious acute respiratory syndrome coronavirus 2; VTE, venous thromboembolism.

Bauer Jan et al Intensive Care Medicine https://link.springer.com/article/10.1007/s00134-020-06229-6	Access to intensive care in 14 European countries: a spatial analysis of intensive care need and capacity in the light of COVID-19	Studio dell'accessibilità delle terape intensive, in termini di letti/100.000 abitanti (AI) e distanze da percorrere, in 14 Paesi europei, con dimostrazione di ampia disomogeneità fra essi. Prevedibilmente, l'accessibilità è negativamente associata con la mortalità per COVID19.	Purpose: The coronavirus disease 2019 (COVID-19) poses major challenges to health-care systems worldwide. This pandemic demonstrates the importance of timely access to intensive care and, therefore, this study aims to explore the accessibility of intensive care beds in 14 European countries and its impact on the COVID-19 case fatality ratio (CFR). Methods: We examined access to intensive care beds by deriving (1) a regional ratio of intensive care beds to 100,000 population capita (accessibility index, AI) and (2) the distance to the closest intensive care unit. The cross-sectional analysis was performed at a 5-by-5 km spatial resolution and results were summarized nationally for 14 European countries. The relationship between AI and CFR was analyzed at the regional level. Results: We found national-level differences in the levels of access to intensive care beds. The AI was highest in Germany (AI = 35.3), followed by Estonia (AI = 33.5) and Austria (AI = 26.4), and lowest in Sweden (AI = 5) and Denmark (AI = 6.4). The average travel distance to the closest hospital was highest in Croatia (25.3 min by car) and lowest in Luxembourg (9.1 min). Subnational results illustrate that capacity was associated with population density and national-level inventories. The correlation analysis revealed a negative correlation of ICU accessibility and COVID-19 CFR ($r = -0.57$; $p < 0.001$). Conclusion: Geographical access to intensive care beds varies significantly across European countries and low ICU accessibility was associated with a higher proportion of COVID-19 deaths to cases (CFR). Important differences in access are due to the sizes of national resource inventories and the distribution of health-care facilities relative to the human population. Our findings provide a resource for officials planning public health responses beyond the current COVID-19 pandemic, such as identifying potential locations

			suitable for temporary facilities or establishing logistical plans for moving severely ill patients to facilities with available beds.  Regional analysis of accessibility indices (AI) for intensive care beds in 14 European countries. The AI was calculated per 100,000 people. *AUT* Austria, *DEU* Germany, *DNK* Denmark, *ENG* England, *EST* Estonia, *FRA* France, *HRV* Croatia, *ITA* Italy, *LTU* Lithuania, *LUX* Luxembourg, *POL* Poland, *SVK* Slovakia, *SVN* Slovenia, *SWE* Sweden. Data

Furtado Remo HM et al Lancet https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)31862-6/fulltext	Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial.	Trial randomizzato multicentrico condotto in Brasile allo scopo di valutare il beneficio dell'aggiunta di azitromicina allo standard of care (contenente idrossiclorochina) in 447 pazienti ospedalizzati e in ossigenoterapia con almeno 4 lpm. Nessun vantaggio in termini di miglioramento clinico e mortalità.	Background: The efficacy and safety of azithromycin in the treatment of COVID-19 remain uncertain. We assessed whether adding azithromycin to standard of care, which included hydroxychloroquine, would improve clinical outcomes of patients admitted to the hospital with severe COVID-19. Methods We did an open-label, randomised clinical trial at 57 centres in Brazil. We enrolled patients admitted to hospital with suspected or confirmed COVID-19 and at least one additional severity criteria as follows: use of oxygen supplementation of more than 4 L/min flow; use of high-flow nasal cannula; use of non-invasive mechanical ventilation; or use of invasive mechanical ventilation. Patients were randomly assigned (1:1) to azithromycin (500 mg via oral, nasogastric, or intravenous administration once daily for 10 days) plus standard of care or to standard of care without macrolides. All patients received hydroxychloroquine (400 mg twice daily for 10 days) because that was part of standard of care treatment in Brazil for patients with severe COVID-19. The primary outcome, assessed by an independent adjudication committee masked to treatment allocation, was clinical status at day 15 after randomisation, assessed by a six-point ordinal scale, with levels ranging from 1 to 6 and higher scores indicating a worse condition (with odds ratio [OR] greater than 1·00 favouring the control group). The primary outcome was assessed in all patients in the intention-to-treat (ITT) population who had severe acute respiratory syndrome coronavirus 2 infection confirmed by molecular or serological testing before randomisation (ie, modified ITT [mITT] population). Safety was assessed in all patients according to which treatment they received, regardless of original group assignment. This trial was registered at ClinicalTrials.gov, NCT04321278.

			Findings: 447 patients were enrolled from March 28 to May 19, 2020. COVID-19 was confirmed in 397 patients who constituted the mITT population, of whom 214 were assigned to the azithromycin group and 183 to the control group. In the mITT population, the primary endpoint was not significantly different between the azithromycin and control groups (OR 1·36 [95% CI 0·94–1·97], p=0·11). Rates of adverse events, including clinically relevant ventricular arrhythmias, resuscitated cardiac arrest, acute kidney failure, and corrected QT interval prolongation, were not significantly different between groups. Interpretation: In patients with severe COVID-19, adding azithromycin to standard of care treatment (which included hydroxychloroquine) did not improve clinical outcomes. Our findings do not support the routine use of azithromycin in combination with hydroxychloroquine in patients with severe COVID-19.

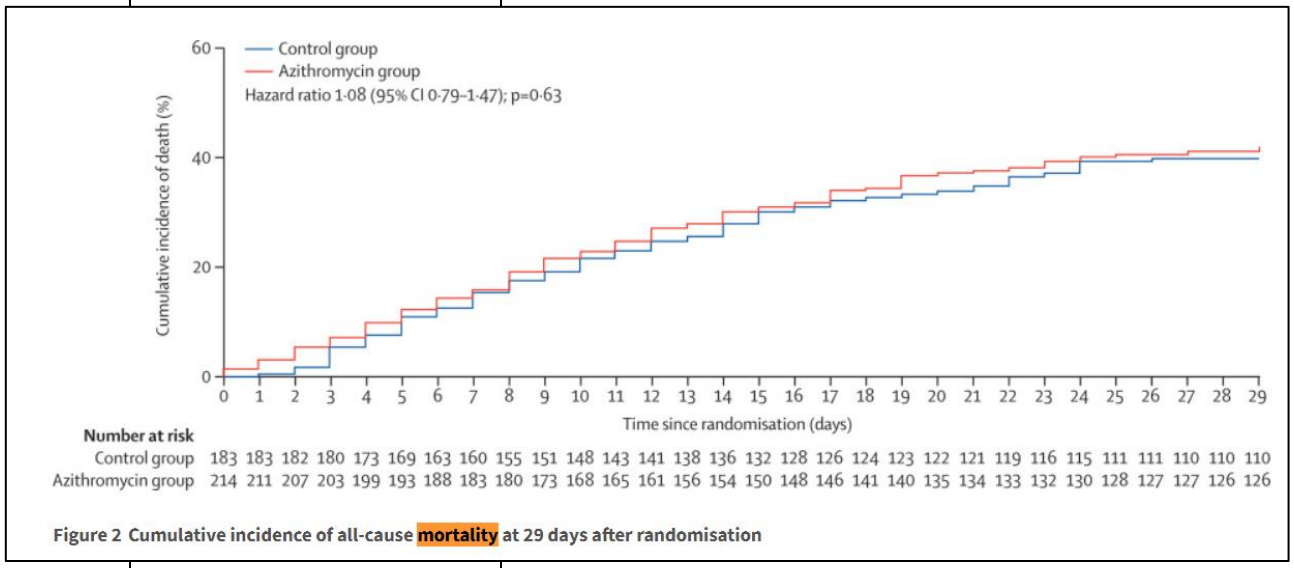
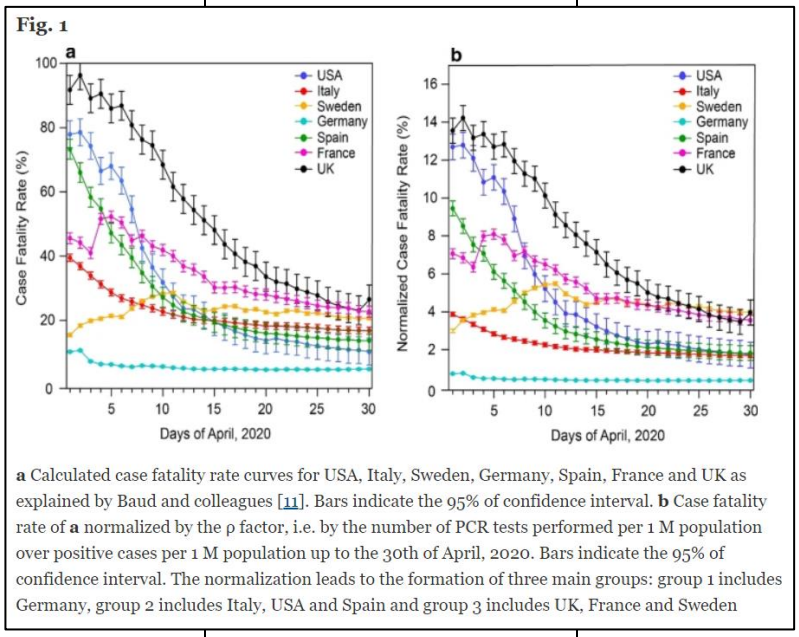
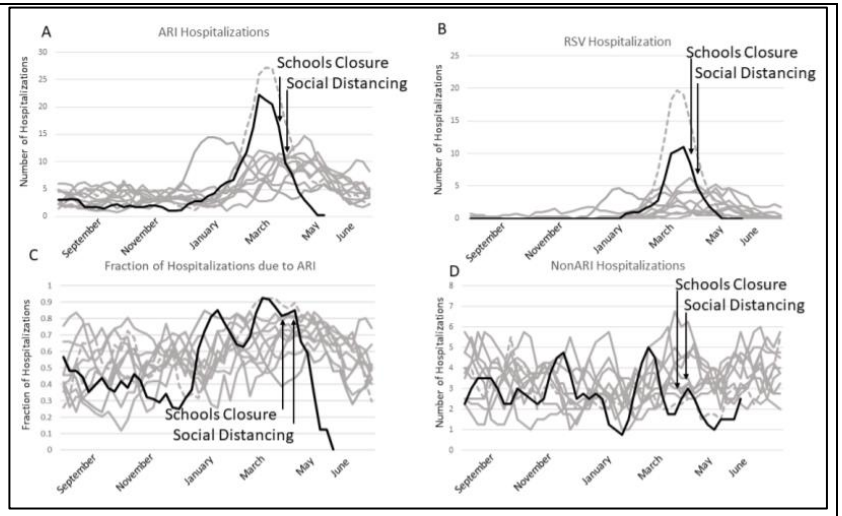


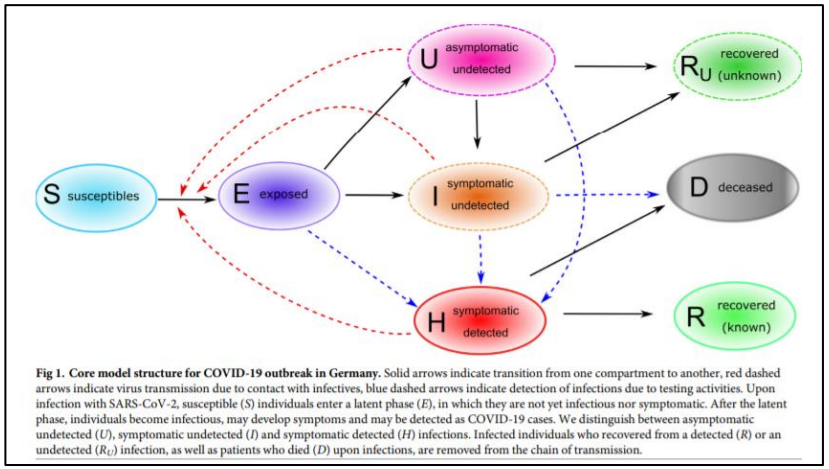
Figure 2 Cumulative incidence of all-cause mortality at 29 days after randomisation

Pachetti Maria et al Journal of Translational Medicine https://translational-medicine.biomedcentral.com/articles/10.1186/s12967-020-02501-x	Impact of lockdown on Covid-19 case fatality rate and viral mutations spread in 7 countries in Europe and North America.	Impatto sulla mortalità da COVID19 delle misure di lockdown e della capacità di eseguire test diagnostici in 6 Paesi europei più gli USA. Studio delle mutazioni virali rilevate su un campione di isolati nello stesso periodo, la cui distribuzione sembra risentire delle misurerestrittive. Non si può stabilire una sicura relazione fra mutazioni circolanti e riduzione della mortalità da COVID19.	Background: Severe acute respiratory syndrome CoV-2 (SARS-CoV-2) caused the first coronavirus disease 2019 (COVID-19) outbreak in China and has become a public health emergency of international concern. SARS-CoV-2 outbreak has been declared a pandemic by WHO on March 11th, 2020 and the same month several Countries put in place different lockdown restrictions and testing strategies in order to contain the spread of the virus. Methods: The calculation of the Case Fatality Rate of SARS-CoV-2 in the Countries selected was made by using the data available at https://github.com/owid/covi-19-data/tree/master/public/data. Case fatality rate was calculated as the ratio between the death cases due to COVID-19, over the total number of SARS-CoV-2 reported cases 14 days before. Standard Case Fatality Rate values were normalized by the Country-specific ρ factor, i.e. the number of PCR tests/1 million inhabitants over the number of reported cases/1 million inhabitants. Case-fatality rates between Countries were compared using proportion test. Post-hoc analysis in the case of more than two groups was performed using pairwise comparison of proportions and p value was adjusted using Holm method. We also analyzed 487 genomic sequences from the GISAID database derived from patients infected by SARS-CoV-2 from January 2020 to April 2020 in Italy, Spain, Germany, France, Sweden, UK and USA. SARS-CoV-2 reference genome was obtained from the GenBank database (NC_045512.2). Genomes alignment was performed using Muscle and Jalview software. We, then, calculated the Case Fatality Rate of SARS-CoV-2 in the Countries selected. Results: In this study we analyse how different lockdown strategies and PCR testing capability adopted by Italy, France, Germany, Spain, Sweden, UK and USA have influenced the Case Fatality Rate and the

 **Fig. 1** **a** Calculated case fatality rate curves for USA, Italy, Sweden, Germany, Spain, France and UK as explained by Baud and colleagues [11]. Bars indicate the 95% of confidence interval. **b** Case fatality rate of **a** normalized by the ρ factor, i.e. by the number of PCR tests performed per 1 M population over positive cases per 1 M population up to the 30th of April, 2020. Bars indicate the 95% of confidence interval. The normalization leads to the formation of three main groups: group 1 includes Germany, group 2 includes Italy, USA and Spain and group 3 includes UK, France and Sweden			viral mutations spread. We calculated case fatality rates by dividing the death number of a specific day by the number of patients with confirmed COVID-19 infection observed 14 days before and normalized by a ρ factor which takes into account the diagnostic PCR testing capability of each Country and the number of positive cases detected. We notice the stabilization of a clear pattern of mutations at sites nt241, nt3037, nt14408 and nt23403. A novel nonsynonymous SARS-CoV-2 mutation in the spike protein (nt24368) has been found in genomes sequenced in Sweden, which enacted a soft lockdown strategy. Conclusions: Strict lockdown strategies together with a wide diagnostic PCR testing of the population were correlated with a relevant decline of the case fatality rate in different Countries. The emergence of specific patterns of mutations concomitant with the decline in case fatality rate needs further confirmation and their biological significance remains unclear.
Ting-Chun Yeh et al Geriatrics Gerontology International https://pubmed.ncbi.nlm.nih.gov/32886842/	Family members' concerns about relatives in long-term care facilities: Acceptance of visiting restriction policy amid the COVID-19 pandemic	Una finestra, tramite un questionario condotto su 156 persone, sulla percezione e l'accettazione da parte dei familiari delle misure di isolamento dei pazienti ricoverati in lungodegenza in Cina.	Aim: The policy enforcing visiting restriction during the COVID-19 pandemic may cause feelings of social isolation among residents in long-term care facilities. This study aimed to explore family members' concerns for their relatives during the lockdown period, assess their level of acceptance of the visiting restriction policy and determine the associated factors. Methods: From the 156 family members interviewed, demographic data, satisfaction with overall care quality, worry and concerns for their relatives, acceptance of the visiting restriction and arrangement for the residents if cluster infections occur in the facility were recorded. Results: Among the members interviewed, 83 (53.2%) were men; mean age of members was 56.3 ± 9.8; most were offspring of residents in the facility (n = 121, 77.6%), most visited the residents at least once a week (n = 113, 72.4%) before the lockdown. The

			most common concerns of the family members for their relatives were psychological stress (38.5%), followed by nursing care (26.9%) and daily activity (21.1%). Nearly 84.6% of those interviewed accepted the visiting restriction policy, and a higher satisfaction rating independently associated with acceptance of the visiting restriction policy (odds ratio 2.15). Conclusions: During the lockdown period, staff members should provide more psychological information about residents to their family members. Higher satisfaction rating was found to be independent of the acceptance of the visiting restriction policy. Therefore, good quality of care of the facility wins the trust of family members, and this might mitigate the tension between the family members and staff during a major crisis.
Leisha D Nolen et al Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1328/5901658	Impact of Social Distancing and Travel Restrictions on non-COVID-19 Respiratory Hospital Admissions in Young Children in Rural Alaska	Studio retrospettivo condotto in Alaska – regione ad alta incidenza di affezioni respiratorie - riguardo il numero di ospedalizzazioni pediatriche per infezioni respiratorie in generale e da Virus Respiratorio Sinciziale in particolare. Dopo l'introduzione delle misure di contenimento della pandemia da SARS-CoV-2 i ricoveri per queste patologie sono diminuiti drasticamente rispetto ai dati storici degli anni passati.	Hospitalizations due to non-COVID-19 respiratory illnesses decreased dramatically after social distancing was implemented in a high-risk population in rural Alaska. Our data from the past ten respiratory seasons show that this decline is unprecedented. This demonstrates the potential secondary benefits of implementing social distancing and travel restrictions on respiratory illnesses.

			
Barbarossa MV et al PLoS One https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0238559	Modeling the spread of COVID-19 in Germany: Early assessment and possible scenarios.	Modellizzazione della diffusione di SARS-CoV-2 in Germania nei primi mesi della pandemia e tentativo di predire l'effetto di differenti misure di contenimento in futuro. In particolare, un potenziamento della capacità diagnostica e un efficace contact-tracing potrebbero consentire di ridurre le misure di distanziamento.	The novel coronavirus (SARS-CoV-2), identified in China at the end of December 2019 and causing the disease COVID-19, has meanwhile led to outbreaks all over the globe with about 2.2 million confirmed cases and more than 150,000 deaths as of April 17, 2020. In this work, mathematical models are used to reproduce data of the early evolution of the COVID-19 outbreak in Germany, taking into account the effect of actual and hypothetical non-pharmaceutical interventions. Systems of differential equations of SEIR type are extended to account for undetected infections, stages of infection, and age groups. The models are calibrated on data until April 5. Data from April 6 to 14 are used for model validation. We simulate different possible strategies for the mitigation of the current outbreak, slowing down the spread of the virus and thus reducing the peak in daily diagnosed cases, the demand for hospitalization or intensive care units admissions, and eventually the number of fatalities. Our results suggest that a partial (and gradual) lifting of introduced control measures could soon be

			possible if accompanied by further increased testing activity, strict isolation of detected cases, and reduced contact to risk groups.  **Fig 1. Core model structure for COVID-19 outbreak in Germany.** Solid arrows indicate transition from one compartment to another, red dashed arrows indicate virus transmission due to contact with infectives, blue dashed arrows indicate detection of infections due to testing activities. Upon infection with SARS-CoV-2, susceptible (*S*) individuals enter a latent phase (*E*), in which they are not yet infectious nor symptomatic. After the latent phase, individuals become infectious, may develop symptoms and may be detected as COVID-19 cases. We distinguish between asymptomatic undetected (*U*), symptomatic undetected (*I*) and symptomatic detected (*H*) infections. Infected individuals who recovered from a detected (*R*) or an undetected (R_U) infection, as well as patients who died (*D*) upon infections, are removed from the chain of transmission.
Kox Matthijs et al JAMA https://jamanetwork.com/journals/jama/article-abstract/2770484	Cytokine Levels in Critically Ill Patients With COVID-19 and Other Conditions	I livelli di citochine infiammatorie non sono significativamente più elevati in pazienti con COVID19 ricoverati in rianimazone rispetto a pazienti con altre affezioni acute (shock settico, arresto cardiaco extraospedaliero, politrauma) il che metterebbe in discussione il concetto di “tempesta citochinica” associato a COVID19.	An abnormally strong proinflammatory response known as “cytokine storm” may play an important role in the pathophysiology of coronavirus disease 2019 (COVID-19), although cytokine storm remains ill defined. Sinha and colleagues reported that although IL-6 levels are elevated in severe COVID-19, they are lower than levels usually observed in (non–COVID-19) acute respiratory distress syndrome (ARDS). However, this comparison is limited by the use of different assays, which are not well standardized. We compared cytokine levels in critically ill patients with COVID-19 vs levels in patients with other critical illnesses.
Singh, Praveen Kumar et al Journal of Laboratory Physicians	Mutations in SARS-CoV-2 Leading to Antigenic Variations in Spike Protein: A Challenge in Vaccine Development.	Studio del genoma di SARS-CoV-2 per predire le mutazioni a carico della proteina spike (S) e viceversa individuarne le	Objectives The spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) virus has been unprecedentedly fast, spreading to more than 180 countries within 3 months with variable severity. One of the major reasons attributed to this variation is

https://www.thieme-connect.de/products/ejournals/pdf/10.1055/s-0040-1715790.pdf		regioni conservate, al fine di guidare la ricerca di regioni bersaglio per vaccini e terapia contro SARS-CoV-2. La proteina S è sede di un gran numero di mutazioni.	genetic mutation. Therefore, we aimed to predict the mutations in the spike protein (S) of the SARS-CoV-2 genomes available worldwide and analyze its impact on the antigenicity. Materials and Methods Several research groups have generated whole genome sequencing data which are available in the public repositories. A total of 1,604 spike proteins were extracted from 1,325 complete genome and 279 partial spike coding sequences of SARS-CoV-2 available in NCBI till May 1, 2020 and subjected to multiple sequence alignment to find the mutations corresponding to the reported single nucleotide polymorphisms (SNPs) in the genomic study. Further, the antigenicity of the predicted mutations inferred, and the epitopes were superimposed on the structure of the spike protein. Results The sequence analysis resulted in high SNPs frequency. The significant variations in the predicted epitopes showing high antigenicity were A348V, V367F and A419S in receptor binding domain (RBD). Other mutations observed within RBD exhibiting low antigenicity were T323I, A344S, R408I, G476S, V483A, H519Q, A520S, A522S and K529E. The RBD T323I, A344S, V367F, A419S, A522S and K529E are novel mutations reported first time in this study. Moreover, A930V and D936Y mutations were observed in the heptad repeat domain and one mutation D1168H was noted in heptad repeat domain 2. Conclusion S protein is the major target for vaccine development, but several mutations were predicted in the antigenic epitopes of S protein across all genomes available globally. The emergence of various mutations within a short period might result in the conformational changes of the protein structure, which suggests that developing a universal vaccine may be a challenging task.

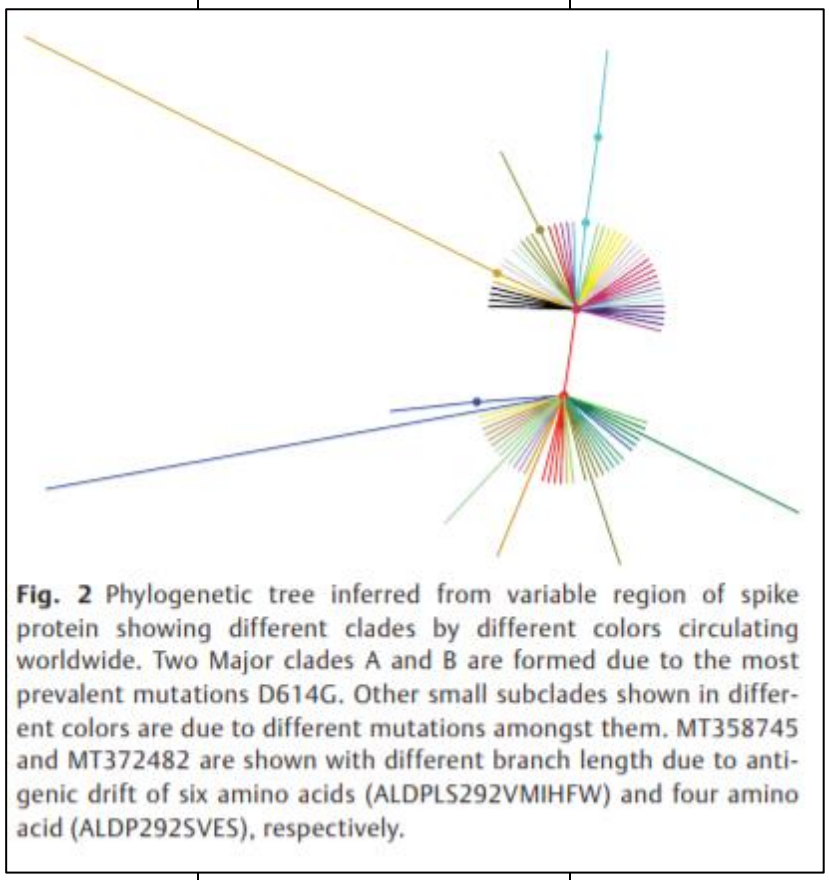


Fig. 2 Phylogenetic tree inferred from variable region of spike protein showing different clades by different colors circulating worldwide. Two Major clades A and B are formed due to the most prevalent mutations D614G. Other small subclades shown in different colors are due to different mutations amongst them. MT358745 and MT372482 are shown with different branch length due to antigenic drift of six amino acids (ALDPLS292VMIHFW) and four amino acid (ALDP292SVES), respectively.

Van Elslande J Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1330/5901661	Symptomatic SARS-CoV-2 reinfection by a phylogenetically distinct strain.	Un altro caso di reinfezione -sintomatica- da ceppo diverso di SARS-CoV-2 nella medesima paziente a distanza di circa 3 mesi dal primo episodio. Gli Autori commentano che le reinfezioni da Coronavirus non-SARS, tipicamente più lievi negli episodi successivi, sono un fenomeno ben conosciuto.	To et al. reported the first documented case of a asymptomatic reinfection with SARSCoV-2 after 4.5 months. As the patient experienced only mild symptoms during the first episode, the question remains whether a weak immune response after the first episode might explain the reinfection. It has been suggested that patients with an asymptomatic or mild SARS-CoV-2 infection have a weaker immune response since their antibody titers are significantly lower than in patients with pneumonia. An estimated 20% do not seroconvert. It also remains unclear whether patients can have a symptomatic reinfection. A recent Italian study reported no clinical reinfections within 3 months after hospital discharge. We here report a symptomatic reinfection 93 days after a moderate SARS-CoV-2 infection.