RICERCA BIBLIOGRAFICA COVID 19

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FONDAZIONE POLICLINICO UNIVERSITARIO A. GEMELLI IRCCS, UOC MALATTIE INFETTIVE

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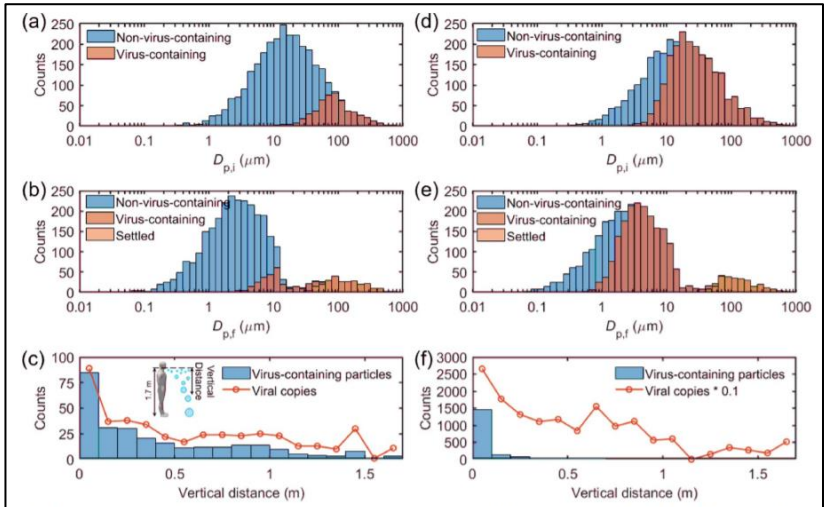
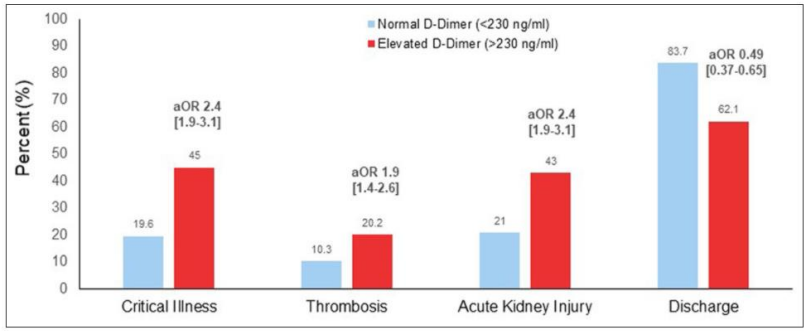
AUTORE/RIVISTA	TITOLO	OUTCOME PRINCIPALE	ABSTRACT
Wang Y et al PLoS One https://doi.org/10.1371/journal.pone.0241539	Modeling the load of SARS-CoV-2 virus in human expelled particles during coughing and speaking.	Simulazione della dinamica delle goccioline di saliva espulse con la tosse e predizione della carica virale così emessa da pazienti infetti : la convenzionale distinzione dimensionale fra « droplet » e « trasmissione aerea » viene messa in discussione in quanto non esiste un cut-off dimensionale in grado di prédire la distanza di precipitazione delle particelle.	Particle size is an essential factor when considering the fate and transport of virus-containing droplets expelled by human, because it determines the deposition pattern in the human respiratory system and the evolution of droplets by evaporation and gravitational settling. However, the evolution of virus-containing droplets and the size-dependent viral load have not been studied in detail. The lack of this information leads to uncertainties in understanding the airborne transmission of respiratory diseases, such as the COVID-19. In this study, through a set of differential equations describing the evolution of respiratory droplets and by using the SARS-CoV-2 virus as an example, we investigated the distribution of airborne virus in human expelled particles from coughing and speaking. More specifically, by calculating the vertical distances traveled by the respiratory droplets, we examined the number of viruses that can remain airborne and the size of particles carrying these airborne viruses after different elapsed times. From a single cough, a person

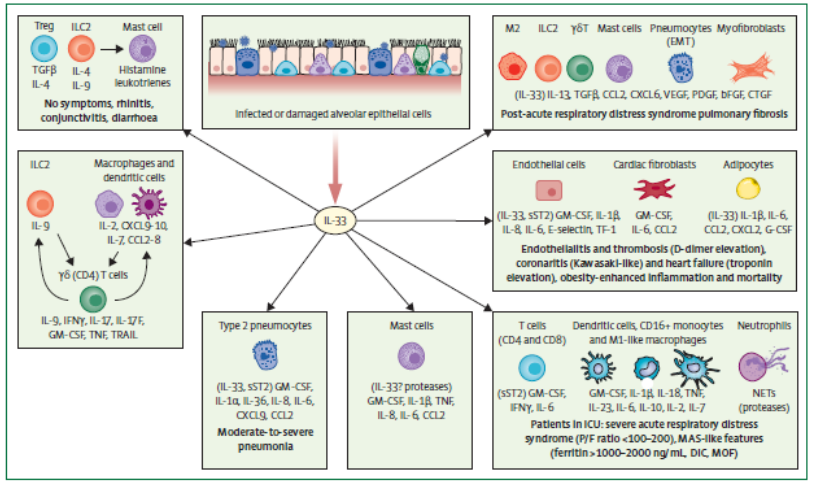
			with a high viral load in respiratory fluid (2.35 × 10^9 copies per ml) may generate as many as 1.23 × 10^5 copies of viruses that can remain airborne after 10 seconds, compared to 386 copies of a normal patient (7.00 × 10^6 copies per ml). Masking, however, can effectively block around 94% of the viruses that may otherwise remain airborne after 10 seconds. Our study found that no clear size boundary exists between particles that can settle and can remain airborne. The results from this study challenge the conventional understanding of disease transmission routes through airborne and droplet mechanisms. We suggest that a complete understanding of the respiratory droplet evolution is essential and needed to identify the transmission mechanisms of respiratory diseases.  **Fig 1.** Evolution of droplets emitted by a cough over an elapsed time of ten seconds at respiratory viral loads of (a–c) 7.00×10^6 and (d–f) 2.35×10^9 copies per ml. (a) and (d) Size distribution of droplets and virus-containing droplets at point of emission. (b) and (e) Size distribution of non-virus-containing (airborne), virus-containing (airborne), and settled particles at an elapsed time of ten seconds. (c) and (f) Distribution of vertical distances traveled by the virus-containing particles at an elapsed time of ten seconds. The inset figure in panel (c) shows a schematic of the modeled system.

Berger JS et al Circulation https://www.ahajournals.org/doi/10.1161/ATVBAHA.120.314872	Prevalence and Outcomes of D-Dimer Elevation in Hospitalized Patients With COVID-19	Descrizione dei livelli di D-dimero in 2377 persone ricoverate con COVID-19 a New York e osservazione della associazione di D-dimero elevato (>230 ng/mL) con infezione grave, trombosi, insufficienza rénale acuta e decesso.	OBJECTIVE:To determine the prevalence of D-dimer elevation in coronavirus disease 2019 (COVID-19) hospitalization, trajectory of D-dimer levels during hospitalization, and its association with clinical outcomes. APPROACH AND RESULTS:Consecutive adults admitted to a large New York City hospital system with a positive polymerase chain reaction test for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) between March 1, 2020 and April 8, 2020 were identified. Elevated D-dimer was defined by the laboratory-specific upper limit of normal (>230 ng/mL). Outcomes included critical illness (intensive care, mechanical ventilation, discharge to hospice, or death), thrombotic events, acute kidney injury, and death during admission. Among 2377 adults hospitalized with COVID-19 and ≥1 D-dimer measurement, 1823 (76%) had elevated D-dimer at presentation. Patients with elevated presenting baseline D-dimer were more likely than those with normal D-dimer to have critical illness (43.9% versus 18.5%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001), any thrombotic event (19.4% versus 10.2%; adjusted odds ratio, 1.9 [95% CI, 1.4–2.6]; P<0.001), acute kidney injury (42.4% versus 19.0%; adjusted odds ratio, 2.4 [95% CI, 1.9–3.1]; P<0.001), and death (29.9% versus 10.8%; adjusted odds ratio, 2.1 [95% CI, 1.6–2.9]; P<0.001). Rates of adverse events increased with the magnitude of D-dimer elevation; individuals with presenting D-dimer >2000 ng/mL had the highest risk of critical illness (66%), thrombotic event (37.8%), acute kidney injury (58.3%), and death (47%). CONCLUSIONS: Abnormal D-dimer was frequently observed at admission with COVID-19 and was associated with higher incidence of critical illness, thrombotic events, acute kidney injury, and death. The optimal management of patients with elevated D-dimer in COVID-19 requires further study.

			 Figure 1. **Baseline D-dimer measurements and adverse events.** aOR indicates adjusted odds ratio.
Castro VM et al JAMA https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2772376	Laboratory Findings Associated With Severe Illness and Mortality Among Hospitalized Individuals With Coronavirus Disease 2019 in Eastern Massachusetts	Studio di coorte retrospettivo su 2511 persone ricoverate con COVID-19 su cui si è cercato di sviluppare un modello predittivo di gravità del decorso (ricovero in terapia intensiva, ventilazione meccanica o decesso) in base a fattori sociodemografici, comorbidità e valori ematici al momento del ricovero.	IMPORTANCE The coronavirus disease 2019 (COVID-19) pandemic has placed unprecedented stress on health systems across the world, and reliable estimates of risk for adverse hospital outcomes are needed. OBJECTIVE To quantify admission laboratory and comorbidity features associated with critical illness and mortality risk across 6 Eastern Massachusetts hospitals. DESIGN, SETTING, AND PARTICIPANTS Retrospective cohort study of all individuals admitted to the hospital who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction across these 6 hospitals through June 5, 2020, using hospital course, prior diagnoses, and laboratory values in Emergency department and inpatient settings from 2 academic medical centers and 4 community hospitals. The data were extracted on June 11, 2020, and the analysis was conducted from June to July 2020. EXPOSURES SARS-CoV-2. MAIN OUTCOMES AND MEASURES Severe illness defined by admission to intensive care unit, mechanical ventilation, or death. RESULTS Of 2511 hospitalized individuals who tested positive for SARS-CoV-2 (of whom 50.9%were male, 53.9%White, and 27.0%Hispanic, with a mean [SD]age of 62.6 [19.0] years), 215 (8.6%)were admitted to the intensive

			care unit, 164 (6.5%) required mechanical ventilation, and 292 (11.6%) died. L1-regression models developed in 3 of these hospitals yielded an area under the receiver operating characteristic curve of 0.807 for severe illness and 0.847 for mortality in the 3 held-out hospitals. In total, 212 of 292 deaths (72.6%) occurred in the highest-risk mortality quintile. CONCLUSIONS AND RELEVANCE In this cohort, specific admission laboratory studies in concert with sociodemographic features and prior diagnosis facilitated risk Stratification among individuals hospitalized for COVID-19.
Gandhi RT NEJM https://www.nejm.org/doi/10.1056/NEJMcp2009249	Mild or Moderate Covid-19	Caso clinico e disamina delle evidenze su cui basare la più corretta gestione dell'infezione da SARS-CoV-2.	oronaviruses typically cause common cold symptoms, but two betacoronaviruses — SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) — can cause pneumonia, respiratory failure, and death. In late 2019, infection with a novel betacoronavirus, subsequently named SARS-CoV-2, was reported in people who had been exposed to a market in Wuhan, China, where live animals were sold. Since then, there has been rapid spread of the virus, leading to a global pandemic of Covid-19. Here, we discuss the presentation and management of Covid-19 in patients with mild or moderate illness, as well as prevention and control of the infection. Discussion of Covid-19 that occurs in children and during pregnancy and of severe disease is beyond the scope of this article.
Belhadjer Z et al Circulation https://doi.org/10.1161/CIRCULATIONAHA.120.050147	Addition of Corticosteroids to Immune Globulins is Associated with Recovery of Cardiac Function in Multi-inflammatory Syndrome in Children (MIS-C).	In questa lettera, 22 bambini con MIS (Multisystem Inflammatory State) associata a COVID-19 trattati con immunoglobuline endovena e steroidi vengono confrontati con 18 bambini	An entity related to SARS-CoV-2 infection associated with a multisystem inflammatory state in children (MIS-C) and acute heart failure has been described. Early treatment of MIS-C has mimicked that of Kawasaki disease with the use of intravenous immune globulin (IVIG) and other anti-inflammatory agents. This strategy seems to be effective as the outcomes are usually favorable with a very limited number of fatalities. Yet, there is no consensus nor evidence for the optimal treatment strategy in MIS-C, and the

		trattati con le sole immunoglobuline e dimostrano minore tempo di recupero della frazione di eiezione e minore incidenza di ricovero in rianimazione.	impact of treatment strategies on recovery of cardiac function has not been yet described.
Zizzo G et al The Lancet https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(20)30340-4/fulltext	Imperfect storm: is interleukin-33 the Achilles heel of COVID-19?	Ruolo di interleukina-33 nella fisiopatologia dell'infezione da SARS-CoV-2 : dalla deregolazione dell'infiammazione, alla trombosi, al possibile sviluppo di fibrosi polmonare.	The unique cytokine signature of COVID-19 might provide clues to disease mechanisms and possible future therapies. Here, we propose a pathogenic model in which the alarmin cytokine, interleukin (IL)-33, is a key player in driving all stages of COVID-19 disease (ie, asymptomatic, mild–moderate, severe–critical, and chronic–fibrotic). In susceptible individuals, IL-33 release by damaged lower respiratory cells might induce dysregulated GATA-binding factor 3-expressing regulatory T cells, thereby breaking immune tolerance and eliciting severe acute respiratory syndrome coronavirus 2-induced autoinflammatory lung disease. Such disease might be initially sustained by IL-33-differentiated type-2 innate lymphoid cells and locally expanded γδ T cells. In severe COVID-19 cases, the IL-33–ST2 axis might act to expand the number of pathogenic granulocyte–macrophage colony-stimulating factor-expressing T cells, dampen antiviral interferon responses, elicit hyperinflammation, and favour thromboses. In patients who survive severe COVID-19, IL-33 might drive pulmonary fibrosis by inducing myofibroblasts and epithelial–mesenchymal transition. We discuss the therapeutic implications of these hypothetical pathways, including use of therapies that target IL-33 (eg, anti-ST2), T helper 17-like γδ T cells, immune cell homing, and cytokine balance.

			 *Figure 2:* IL-33 might orchestrate all pathogenic phases of COVID-19
Ng OT et al The Lancet https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30833-1/fulltext	SARS-CoV-2 seroprevalence and transmission risk factors among high-risk close contacts: a retrospective cohort study	Studio di coorte retrospettivo sulla sieroprevalenza in 7517 contatti di 1114 casi di infezione da SARS-CoV-2 : i contatti casuali, indiretti, la condivisione di un pasto o del bagno non sono associati alla trasmissione del virus, mentre lo sono la condivisione della stanza da letto o dell'auto e conversazioni più lunghe di 30 minuti.	Background : The proportion of asymptomatic carriers and transmission risk factors of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among household and non-household contacts remains unclear. In Singapore, extensive contact tracing by the Ministry of Health for every diagnosed COVID-19 case, and legally enforced quarantine and intensive health surveillance of close contacts provided a rare opportunity to determine asymptomatic attack rates and SARS-CoV-2 transmission risk factors among community close contacts of patients with COVID-19. Methods : This retrospective cohort study involved all close contacts of confirmed COVID-19 cases in Singapore, identified between Jan 23 and April 3, 2020. Household contacts were defined as individuals who shared a residence with the index COVID-19 case. Non-household close contacts were defined as those who had contact for at least 30 min within 2 m of the index case. All patients with COVID-19 in Singapore received inpatient treatment, with access restricted to health-care staff. All close contacts were

			quarantined for 14 days with thrice-daily symptom monitoring via telephone. Symptomatic contacts underwent PCR testing for SARS-CoV-2. Secondary clinical attack rates were derived from the prevalence of PCR-confirmed SARS-CoV-2 among close contacts. Consenting contacts underwent serology testing and detailed exposure risk assessment. Bayesian modelling was used to estimate the prevalence of missed diagnoses and asymptomatic SARS-CoV-2-positive cases. Univariable and multivariable logistic regression models were used to determine SARS-CoV-2 transmission risk factors. Findings : Between Jan 23 and April 3, 2020, 7770 close contacts (1863 household contacts, 2319 work contacts, and 3588 social contacts) linked to 1114 PCR-confirmed index cases were identified. Symptom-based PCR testing detected 188 COVID-19 cases, and 7582 close contacts completed quarantine without a positive SARS-CoV-2 PCR test. Among 7518 (96·8%) of the 7770 close contacts with complete data, the secondary clinical attack rate was 5·9% (95% CI 4·9–7·1) for 1779 household contacts, 1·3% (0·9–1·9) for 2231 work contacts, and 1·3% (1·0–1·7) for 3508 social contacts. Bayesian analysis of serology and symptom data obtained from 1150 close contacts (524 household contacts, 207 work contacts, and 419 social contacts) estimated that a symptom-based PCR-testing strategy missed 62% (95% credible interval 55–69) of COVID-19 diagnoses, and 36% (27–45) of individuals with SARS-CoV-2 infection were asymptomatic. Sharing a bedroom (multivariable odds ratio [OR] 5·38 [95% CI 1·82–15·84]; p=0·0023) and being spoken to by an index case for 30 min or longer (7·86 [3·86–16·02]; p<0·0001) were associated with SARS-CoV-2 transmission among household contacts. Among non-household contacts, exposure to more than one case (multivariable OR 3·92 [95% CI 2·07–7·40],

			p<0·0001), being spoken to by an index case for 30 min or longer (2·67 [1·21–5·88]; p=0·015), and sharing a vehicle with an index case (3·07 [1·55–6·08]; p=0·0013) were associated with SARS-CoV-2 transmission. Among both household and non-household contacts, indirect contact, meal sharing, and lavatory co-usage were not independently associated with SARS-CoV-2 transmission. Interpretation : Targeted community measures should include physical distancing and minimising verbal interactions. Testing of all household contacts, including asymptomatic individuals, is warranted.

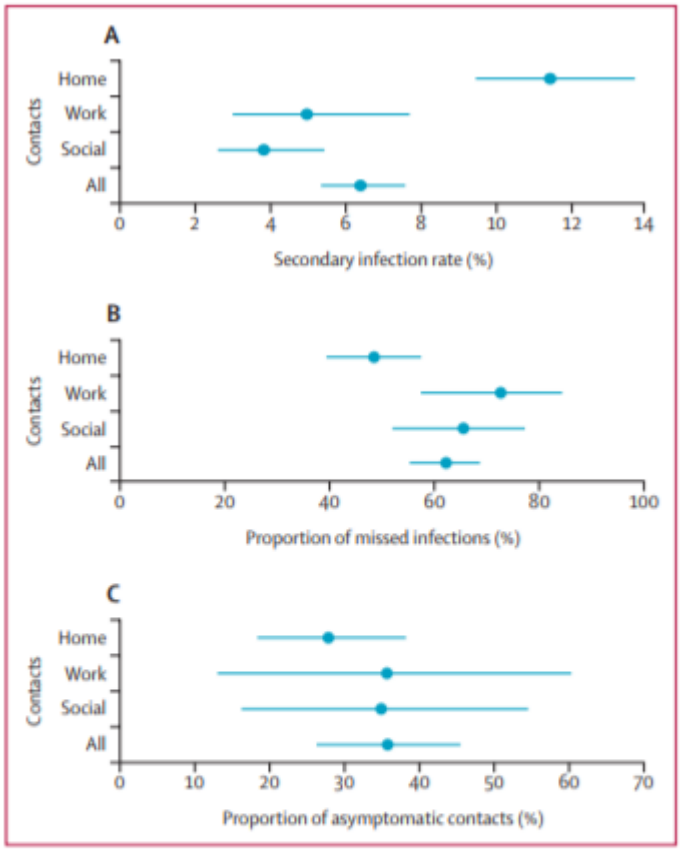
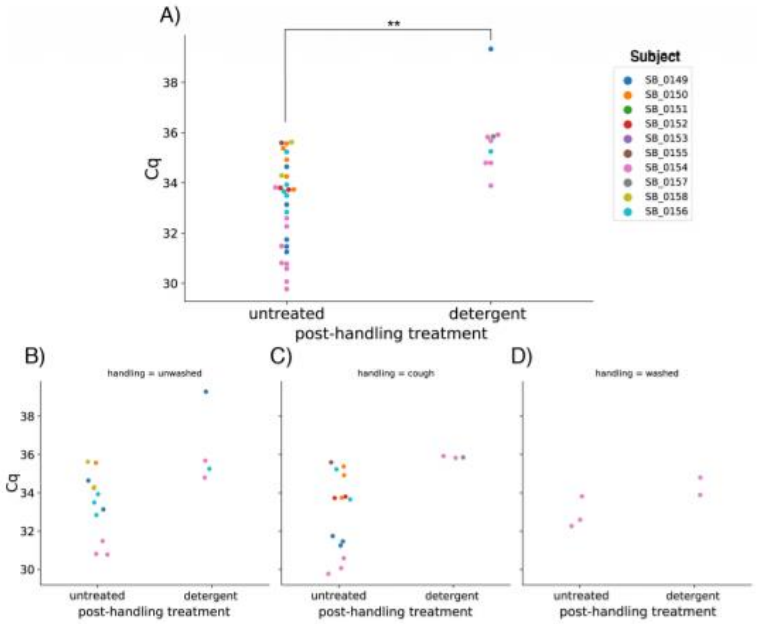


Figure 2: **Bayesian modelling estimates of secondary infection rates, proportion of missed infections, and proportion of asymptomatic contacts, among all contacts**

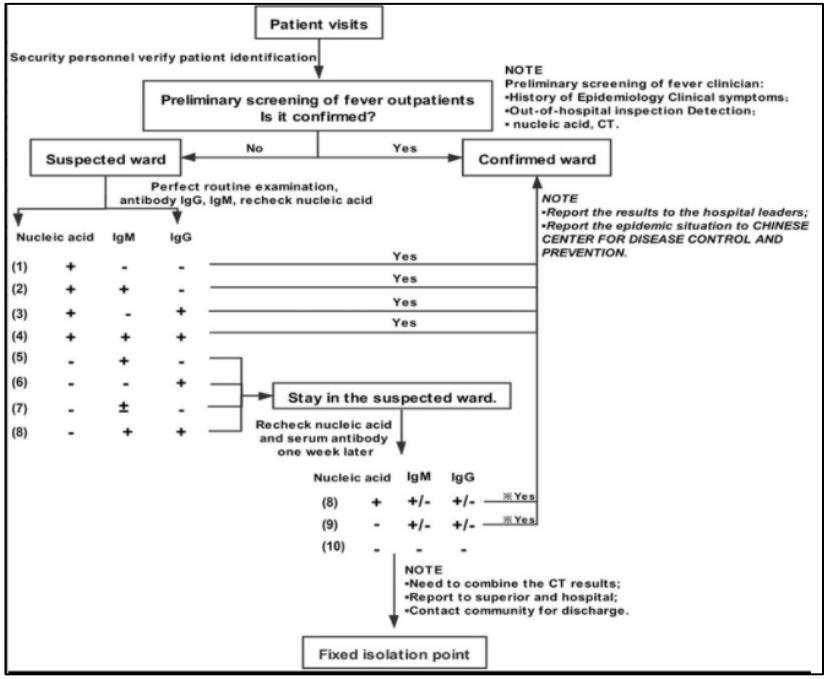
(A) Overall secondary infection rate among 1779 home, 2231 work, and 3508 social contacts. (B) Proportion of infections missed by symptom-based PCR among estimated infected contacts. (C) Proportion of infected contacts estimated to be asymptomatic, among home, work, or social contacts of a case, or among all contacts. Dots are posterior means and lines are 95% credible intervals.

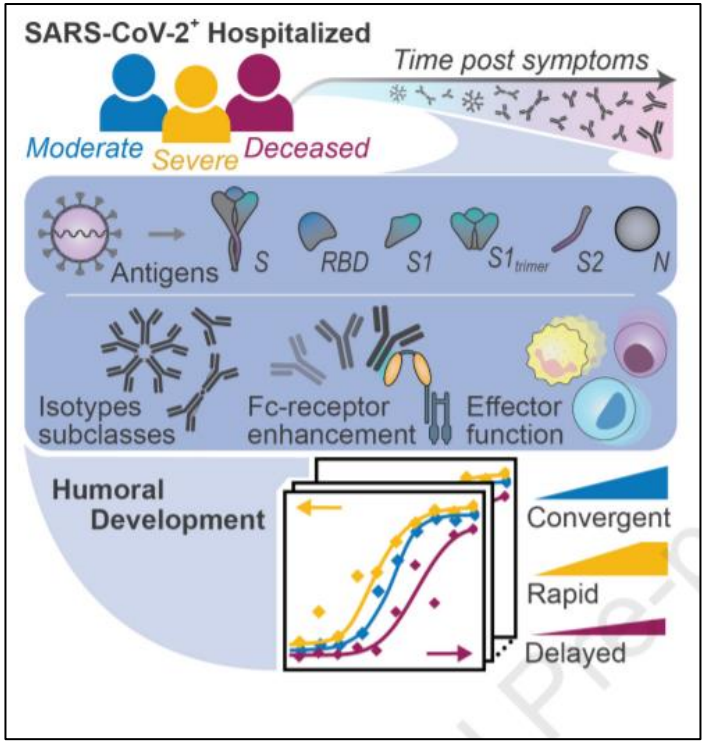
Salido R et al mSystems https://msystems.asm.org/content/5/6/e01074-20	Handwashing and Detergent Treatment Greatly Reduce SARS-CoV-2 Viral Load on Halloween Candy Handled by COVID-19 Patients.	La trasmissione di SARS-CoV-2 tramite fomiti è plausibile ma difficile da dimostrare ; in questo studio, si dimostra che il lavaggio delle mani e la pulizia delle superfici (nello specifico dolcetti di Halloween) con detergenti domestici convenzionali abbattono significativamente la carica virale.	Due to the COVID-19 pandemic and potential public health implications, we are publishing this peer-reviewed manuscript in its accepted form. The final, copyedited version of the paper will be available at a later date. Although SARS-CoV-2 is primarily transmitted by respiratory droplets and aerosols, transmission by fomites remains plausible. During Halloween, a major event for children in numerous countries, SARS-CoV-2 transmission risk via candy fomites worries many parents. To address this concern, we enrolled 10 recently diagnosed asymptomatic or mildly/moderately symptomatic COVID-19 patients to handle typical Halloween candy (pieces individually wrapped) under three conditions: normal handling with unwashed hands, deliberate coughing and extensive touching, and normal handling following handwashing. We then used a factorial design to subject the candies to two post-handling treatments: no washing (untreated) and household dishwashing detergent. We measured SARS-CoV-2 load by RT-qPCR and LAMP. From the candies not washed post-handling, we detected SARS-CoV-2 on 60% of candies that were deliberately coughed on, 60% of candies normally handled with unwashed hands, but only 10% of candies handled after hand washing. We found that treating candy with dishwashing detergent reduced SARS-CoV-2 load by 62.1% in comparison to untreated candy. Taken together, these results suggest that although the risk of transmission of SARS-CoV-2 by fomites is low even from known COVID-19 patients, viral RNA load can be reduced to near zero by the combination of handwashing by the infected patient and >/=1 minute detergent treatment after collection. We also found that the inexpensive and fast LAMP protocol was more than 80% concordant with RT-qPCR.IMPORTANCE The COVID-19 pandemic is leading to important tradeoffs between risk of SARS-CoV-2 transmission and mental

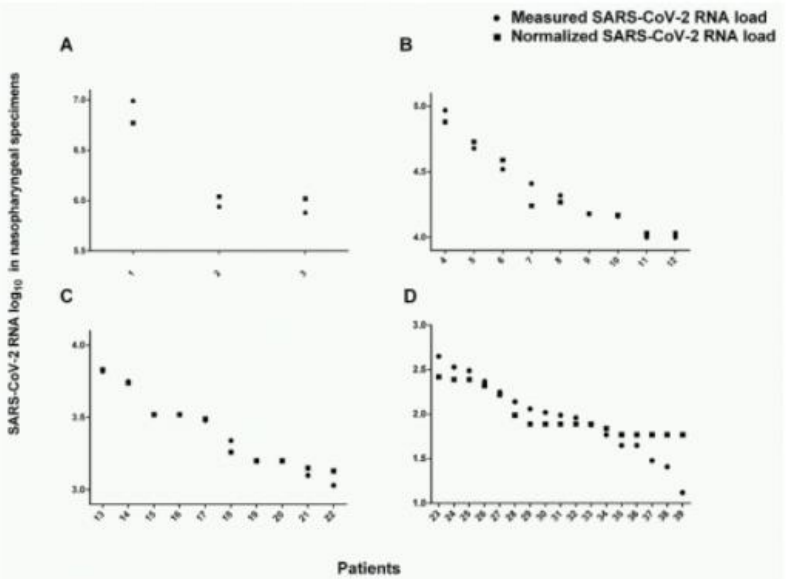
			health due to deprivation from normal activities, with these impacts being especially profound in children. Due to the ongoing pandemic, Halloween activities will be curtailed as a result of the concern that candy from strangers might act as fomites. Here we demonstrate that these risks can be mitigated by ensuring that prior to handling candy, the candy giver washes their hands, and by washing collected candy with household dishwashing detergent. Even in the most extreme case, with candy deliberately coughed on by known COVID-19 patients, viral load was reduced dramatically after washing with household detergent. We conclude that with reasonable precautions, even if followed only by either the candy giver or the candy recipient, the risk of viral transmission by this route is very low.

			 **FIG 2 A) Swarmplot of Cq values for detected viral genes across all candy grouped into post-handling treatments. The distribution of Cq values for the untreated candy was significantly different than that of detergent(** p<0.001). (B-D) Swarmplots of Cq values for detected viral genes divided by handling conditions and grouped into post-handling treatments. Both the extensively handled and coughed candy (B) and the candy that was normally handled with unwashed hands (C) had detectable viral genes with comparable Cq values ranging from 29.77 - 39.28. Treating with detergent reduced the viral load on candies, measured as an increase in Cq, or resulted in undetectable viral load. Washing hands before handling candy (D) markedly decreased viral gene detection rate and decreased viral load on positive candies.**
Henss L et al The Journal of Infectious Diseases	Analysis of humoral immune responses in SARS-CoV-2 infected patients.	Studio di coorte su 143 pazienti con storia di infezione da SARS-CoV-2 in cui si dimostra una associazione fra gravità di malattia e livelli di IgG e IgA specifiche e loro attività	BACKGROUND: The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection has caused a pandemic with tens of millions of cases and hundreds of thousands of deaths. The infection causes COVID-19, a disease of the respiratory system of divergent severity. Here, the humoral immune response of a cohort of 143 COVID-19 patients from the University Hospital

https://doi.org/10.1093/infdis/jiaa680		neutralizzante. Inoltre, la risposta contro la proteina S di superficie è più duratura di quella contro la nucleoproteina di SARS-CoV-2.	Frankfurt/Main, Germany was characterized. METHODS: SARS-CoV-2-specific antibodies were detected by enzyme-linked immunosorbent assay (ELISA). SARS-CoV-2 and hCoV NL63 neutralization activity was analyzed with pseudotyped lentiviral vectors. RESULTS: COVID-19 severity increased with age and male patients encountered more serious symptoms than females. Disease severity correlated with the amount of SARS-CoV-2 specific IgG and IgA and the neutralization activity of the antibodies. The amount of SARS-CoV-2 specific IgG antibodies decreased with time after PCR conformation of the infection and antibodies directed against the nucleoprotein waned faster than spike directed antibodies. In contrast, for the common flu coronavirus NL63, COVID19 disease severity seemed to correlate with low NL63-neutralizing activities, suggesting the possibility of cross-reactive protection. CONCLUSION: The results describe the humoral immune responses against SARS-CoV-2 and might aid the identification of correlates of protection needed for vaccine development.
Kuang M et al Medicine https://doi.org/10.1097/MD.0000000000022720	Management of a "suspected ward" in a COVID-19 designated hospital in Wuhan.	Descrizione dell'organizzazione di un reparto medico per pazienti sospetti per infezione da SARS-CoV-2 a Wuhan, Cina.	During December 2019, an outbreak of unexplained pneumonia occurred in Wuhan, Hubei Province. The disease was subsequently named coronavirus disease 2019 (COVID-19) and the causative virus as severe acute respiratory syndrome conronavirus-2 (SARS-CoV-2). Based on experience, it is vital to exclude or diagnose suspected patients as soon as possible to prevent disease spread. Our hospital is a COVID-19 designated hospital in Wuhan. During the epidemic period, there was a reconstruction of the medical facilities to accommodate patients with different disease status. We document the development of "suspected ward," a ward that cared for patients with suspected COVID-19, in a large designated hospital during the COVID-19 outbreak in Wuhan City, China, and explain the suspected ward spatial layout, organization structure, diagnosis,

			and treatment flow chart of suspected cases. The key characteristics of our "suspected ward" is isolation, triage, fast diagnosis, and rapid referral. Our description of this suspected ward provides a reference for further improvements in the care of patients with suspected disease in emergency medical institutions. 
Zohar T et al Cell https://www.cell.com/cell/fulltext/S0092-8674(20)31459-	Compromised humoral functional evolution tracks with SARS-CoV-2 mortality	In cosa differisce la risposta immunitaria di pazienti gravi/deceduti per COVID-19 e pazienti con infezione più lieve ? Questo studio retrospettivo su 193 casi evidenzia un deficit di sviluppo della risposta IgG-	The urgent need for an effective SARS-CoV-2 vaccine has forced development to progress in the absence of well-defined correlates of immunity. While neutralization has been linked to protection against other pathogens, whether neutralization alone will be sufficient to drive protection against SARS-CoV-2 in the broader population remains unclear. Therefore, to fully define protective humoral immunity we dissected the early evolution of the humoral

8?utm_medium=homepage		mediata nei pazienti con evoluzione infausta.	response in 193 hospitalized individuals ranging from moderate-to severe. Although robust IgM and IgA responses evolved in both survivors and non-survivors with severe disease, non-survivors showed attenuated IgG responses, accompanied by compromised Fcɣ-receptor binding and Fc-effector activity, pointing to deficient humoral development rather than disease-enhancing humoral immunity. In contrast, individuals with moderate disease exhibited delayed responses that ultimately matured. These data highlight distinct humoral trajectories associated with resolution of SARS-CoV-2 infection and the need for early functional humoral immunity. 

Eliseo A et al Journal of Medical Virology https://doi.org/10.1002/jmv.26644	Assessing the potential association between SARS-CoV-2 RNA load in the respiratory tract and COVID-19 mortality.	Ancora una riflessione sul valore prognostico della carica virale per i pazienti con COVID-19 : la carica rilevata andrebbe normalizzata per la cellularità del campione nasofaringeo, stimata tramite un PCR parallela su un gene cellulare come la beta-glucuronidasi utilizzata in questo studio, prima di eseguire analisi di associazione con l'outcome dell'infezione.	The magnitude of nasopharyngeal (NP) SARS-CoV-2 load either at hospital admission or during the course of hospitalization has been directly associated with mortality of COVID-19 patients. Figure 1. Raw and normalized SARS-CoV-2 RNA loads in 39 hospitalized COVID-19 patients with detectable levels of SARS-CoV-2 RNA and β-glucuronidase mRNA in nasopharyngeal specimens. Raw SARS-CoV-2 RNA load $>10^5$ $\log_{10}$ copies/mL (A), load $>10^4$ $\log_{10}$ copies/mL (B), load $>10^3$ $\log_{10}$ copies/mL (C) and $< 10^3$ $\log_{10}$ copies/mL (D). Amplification of β-glucuronidase mRNA gene was not possible in nasopharyngeal exudate from one patient. 
Gulholm T et al Pathology	Laboratory diagnosis of severe acute respiratory syndrome coronavirus 2.	Una disamina delle metodiche di laboratorio per la diagnosi di infezione da SARS-CoV-2, con un preliminare ripasso di tassonomia virale: ordine	The first laboratory confirmed case of Coronavirus disease 2019 (COVID-19) in Australia was in Victoria on 25 January 2020 in a man returning from Wuhan city, Hubei province, the People's Republic of China. This was followed by three cases in New South Wales the following day. The Australian Government activated the Australian

https://doi.org/10.1016/j.pathol.2020.09.011		*Nidovirales*, famiglia *Coronaviridae*, sottofamiglia *Coronavirinae*, genere *Betacoronavirus*, sottogenere *Sarbecovirus* (lo stesso di SARS -CoV).	Health Sector Emergency Response Plan for Novel Coronavirus on 27 February 2020 in anticipation of a pandemic. Subsequently, the World Health Organization declared COVID-19 to be a Public Health Emergency of International Concern followed by a pandemic on 30 January 2020 and 11 March 2020, respectively. Laboratory testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for COVID-19, is key in identifying infected persons to guide timely public health actions of contact tracing and patient isolation to limit transmission of infection. This article aims to provide a comprehensive overview of current laboratory diagnostic methods for SARS-CoV-2, including nucleic acid testing, serology, rapid antigen detection and antibody tests, virus isolation and whole genome sequencing. The relative advantages and disadvantages of the different diagnostic tests are presented, as well as their value in different clinical, infection control and public health contexts. We also describe the challenges in the provision of SARS-CoV-2 diagnostics in Australia, a country with a relatively low COVID-19 incidence in the first pandemic wave but in which prevalence could rapidly change.

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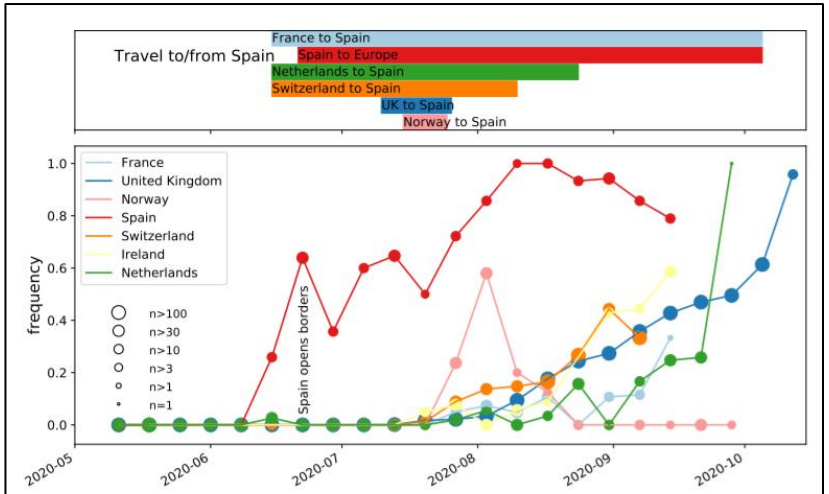
Table 1 Summary of SARS-CoV-2 diagnostics available in Australia for routine and reference use
<table>
<tr><th>Methods</th><th>Sample type</th><th>Comments</th><th>Advantages</th><th>Disadvantages</th><th>TAT/approximate reagent cost[a]</th><th>Availability in Australia</th></tr>
<tr><td>Nucleic acid testing (NAT) or nucleic acid amplification test (NAAT)</td><td>Upper and Lower respiratory tract samples</td><td>In-house initially; available commercially since February 2020</td><td>Acute diagnosis</td><td>Low viral titres can mean lack of reproducibility
Reduced predictive values in low incidence settings
False positives, contamination</td><td>1–6 hours (once sample in lab)
~AU$10–50</td><td>Widespread in both public and private laboratories across Australia
Assays in use include:
In-house tests targeting various combinations of (E, M, N, ORF1a/b, ORF1b, RdRp and S)
Commercial assays (see Table 2)</td></tr>
<tr><td>Serology</td><td>Serum</td><td>In-house/ commercial
POCT
IgM, IgA, IgG
MN
IFA
ELISA</td><td>Useful for diagnosis of past cases (i.e. follow up of suspected cases who either did not undergo NAT during the acute illness or were NAT negative)
Broad-based population serological surveillance, vaccine efficacy and research activities</td><td>Not useful for acute diagnosis.
Not clear if development of neutralising antibodies is indicative of immunity
Not all PCR-positive cases have positive serology
Falling titres over time (2–3 months)</td><td>Usually <12 hours
~AU$10</td><td>Limited availability, generally state public health reference laboratories
Commercial kits (see Table 3)</td></tr>
<tr><td>Virus culture</td><td>Upper and lower respiratory tract samples</td><td></td><td>Infectivity demonstrated</td><td>Need PC3 laboratory.
Need equipment and skilled scientist</td><td>4–7 days
~AU$100</td><td>PC3 laboratory facilities
State public health reference laboratories</td></tr>
<tr><td>Sequencing</td><td>RNA extracts</td><td>Generally needs higher viral loads, represented by a Ct value of <30 on most commercial assays</td><td>Linking transmission
Cluster analysis
Mutation development informing diagnostic targets, later vaccine studies</td><td>Needs to be PCR positive with high enough viral load/ low Ct to produce adequate sequencing results</td><td>1–7 days
~AU$100
Usually batched which increases TAT
High costs compared with RT-PCR</td><td>State public health reference laboratories
Research institutes</td></tr>
<tr><td>Electron microscopy (EM)</td><td>EM specific preparation of respiratory tract samples</td><td>Requires highly trained staff; available in few centres</td><td>Virus agnostic (that is not dependent upon genomic sequence)</td><td>Labour intensive</td><td>Several days</td><td>State public health reference laboratories, some only</td></tr>
</table>
ELISA, enzyme linked immunosorbent assay; IFA, immunofluorescent assay; MN, microneutralisation; NAT, nucleic acid test; PC3, Physical Containment level 3; POCT, point of care test; TAT, turnaround time.
[a] Cost is very approximate in Australian dollars for reagents and does not include labour costs.
</td>
</tr>
<tr>
<td>O’Driscoll M et al

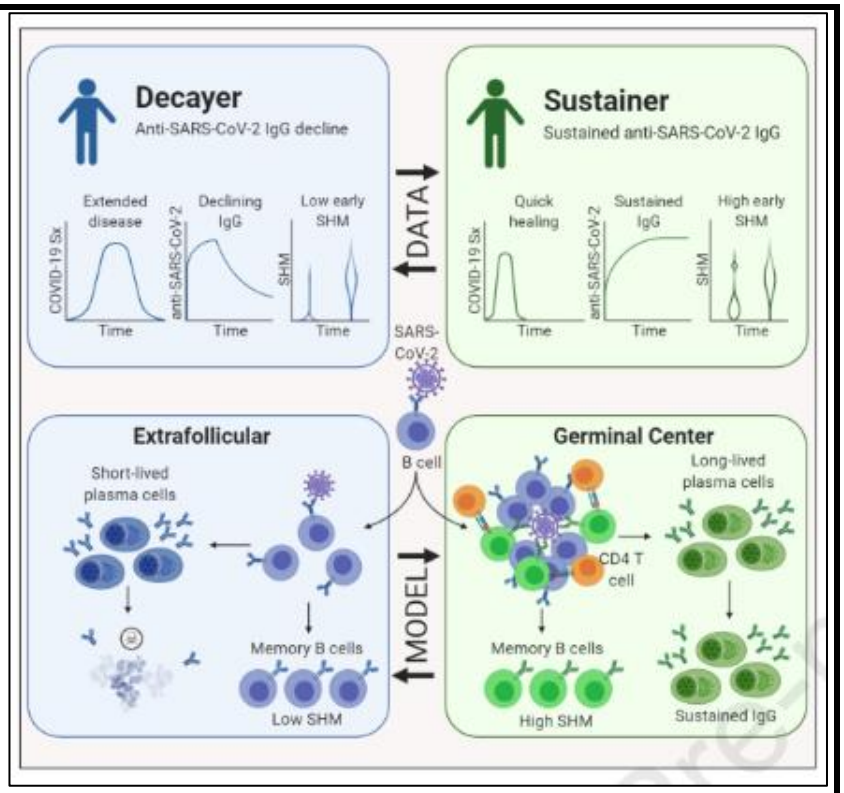
Nature

https://doi.org/10.1038/s41586-020-2918-0</td>
<td>Age-specific mortality and immunity patterns of SARS-CoV-2.</td>
<td>Analisi retrospettiva della mortalità da COVID-19 in 45 Paesi, considerando quanto sono rappresentate le diverse fasce di età della popolazione : grande eterogeneità per quanto riguarda la fascia d’età superiore a 65 anni.</td>
<td>Estimating the size and infection severity of the SARS-CoV-2 epidemic is made challenging by inconsistencies in available data. The number of COVID-19 deaths is often used as a key indicator for the epidemic size, but observed deaths represent only a minority of all infections. Additionally, the heterogeneous burden in nursing homes and variable reporting of deaths in elderly individuals can hamper direct comparisons across countries of the underlying level of transmission and mortality rates. Here we use age-specific COVID-19 death data from 45 countries and the results of 22 seroprevalence studies to investigate the consistency of infection and fatality patterns across multiple countries. We find that the age distribution of deaths in younger age groups (<65 years) is very</td>
</tr>
</table>

			consistent across different settings and demonstrate how this data can provide robust estimates of the share of the population that has been infected. We estimate that the infection-to-fatality ratio (IFR) is lowest among 5-9 years old, with a log-linear increase by age among individuals older than 30 years. Population age-structures and heterogeneous burdens in nursing homes explain some but not all of the heterogeneity between countries in infection-fatality ratios. Among the 45 countries included in our analysis, we estimate approximately 5% of these populations had been infected by the 1st of September 2020, with much higher transmission likely to have occurred in a number of Latin American countries. This simple modelling framework can help countries assess the progression of the pandemic and can be applied wherever reliable age-specific death data exists.
Fontana I et al Trends in Neurosciences https://doi.org/10.1016/j.tins.2020.10.010	PET Imaging as a Tool for Assessing COVID-19 Brain Changes.	Suggerimenti per l'utilizzo della tomografia a emissione di positroni (PET) per l'approfondimento delle alterazioni neurologiche osservate in corso di infezione da SARS-CoV-2.	A substantial fraction of coronavirus disease 2019 (COVID-19) patients experience neurological manifestations. Nevertheless, brain changes caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain largely unknown. Here, we provide a brief overview of positron emission tomography (PET) applications that could advance current understanding of CNS pathophysiological alterations associated with SARS-CoV-2 infection.
Hodcroft EB et al medRXiv https://www.medrxiv.org/content/10.1101/2020.10.25.20219063v1	Emergence and spread of a SARS-CoV-2 variant through Europe in the summer of 2020	La variante 20A.EU1 di SARS-CoV2 (portatrice fra le altre della mutazione A222V a carico della proteina S) si è diffusa in Europa a partire dalla Spagna ove è emersa in giugno 2020. Si ipotizza	A variant of SARS-CoV-2 emerged in early summer 2020, presumably in Spain, and has since spread to multiple European countries. The variant was first observed in Spain in June and has been at frequencies above 40% since July. Outside of Spain, the frequency of this variant has increased from very low values prior to 15th July to 40-70% in Switzerland, Ireland, and the United Kingdom in September. It is also prevalent in Norway, Latvia, the

		un vantaggio di trasmissione, oppure un effetto degli spostamenti umani, mentre non è evidente una maggiore virulenza.	Netherlands, and France. Little can be said about other European countries because few recent sequences are available. Sequences in this cluster (20A.EU1) differ from ancestral sequences at 6 or more positions, including the mutation A222V in the spike protein and A220V in the nucleoprotein. We show that this variant was exported from Spain to other European countries multiple times and that much of the diversity of this cluster in Spain is observed across Europe. It is currently unclear whether this variant is spreading because of a transmission advantage of the virus or whether high incidence in Spain followed by dissemination through tourists is sufficient to explain the rapid rise in multiple countries.  FIG. 2 **Frequency of submitted samples that fall within the cluster, with quarantine-free travel dates shown above.** We include the seven countries which have at least 20 sequences from the considered cluster. The symbol size indicates the number of available sequence by country and time point in a non-linear manner. Travel restrictions are shown to/from Spain, as this is the possible origin of the cluster. Most European countries allowed quarantine-free travel to other (non-Spanish) countries in Europe for a longer period.

Chen Y et al Cell https://www.cell.com/cell/pdf/S0092-8674(20)31458-6.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2FS0092867420314586%3Fshowall%3Dtrue	Quick COVID-19 Healers Sustain Anti-SARS-CoV-2 Antibody Production	In questo studio su 76 soggetti con storia di COVID-19 seguiti per circa 100 giorni si dimostra che, mentre all'esordio di malattia i livelli di IgG e IgM sieriche anti-SARS-CoV-2 sono uniformemente elevati, una quota di pazienti (« sustainers ») li mantiene a lungo mentre la maggior parte (« decayers ») mostra un rapido decadimento. I primi hanno un recupero clinico più rapido e precoci fenomeni di ipermutazione somatica nelle cellule B della memoria, che conferirebbero un vantaggio nella risposta durevole al virus.	Antibodies are key immune effectors that confer protection against pathogenic threats. The nature and longevity of the antibody response to SARS-CoV-2 infection is not well defined. We charted longitudinal antibody responses to SARS-CoV-2 in 92 subjects after symptomatic COVID-19. Antibody responses to SARS-CoV-2 are unimodally distributed over a broad range, with symptom severity correlating directly with virus-specific antibody magnitude. Seventy-six subjects followed longitudinally to ~100 days demonstrated marked heterogeneity in antibody duration dynamics. Virus-specific IgG decayed substantially in most individuals, whereas a distinct subset had stable or increasing antibody levels in the same timeframe despite similar initial antibody magnitudes. These individuals with increasing responses recovered rapidly from symptomatic COVID-19 disease, harbored increased somatic mutations in virus-specific memory B cell antibody genes, and had persistent higher frequencies of previously activated CD4+ T cells. These findings illuminate an efficient immune phenotype that connects rapid symptom clearance to differential antibody durability dynamics.

			
Blot M et al Critical Care https://ccforum.biomedcentral.com/articles/10.1186/s13054-020-03328-0	CXCL10 could drive longer duration of mechanical ventilation during COVID-19 ARDS.	In questo studio si confrontano clinica e profili di risposta infiammatoria sierica e su BAL di 14 pazienti con ARDS COVID-19 relata, 7 pazienti con ARDS da altra causa e 7 controlli : elevati livelli sierici e su BAL della chemochina CXCL10 sono associati a maggiore durata della ventilazione	BACKGROUND: COVID-19-related ARDS has unique features when compared with ARDS from other origins, suggesting a distinctive inflammatory pathogenesis. Data regarding the host response within the lung are sparse. The objective is to compare alveolar and systemic inflammation response patterns, mitochondrial alarmin release, and outcomes according to ARDS etiology (i.e., COVID-19 vs. non-COVID-19). METHODS: Bronchoalveolar lavage fluid and plasma were obtained from 7 control, 7 non-COVID-19 ARDS, and 14 COVID-19 ARDS patients. Clinical data, plasma, and epithelial lining fluid (ELF) concentrations of 45 inflammatory mediators and cell-free mitochondrial DNA were measured and compared.

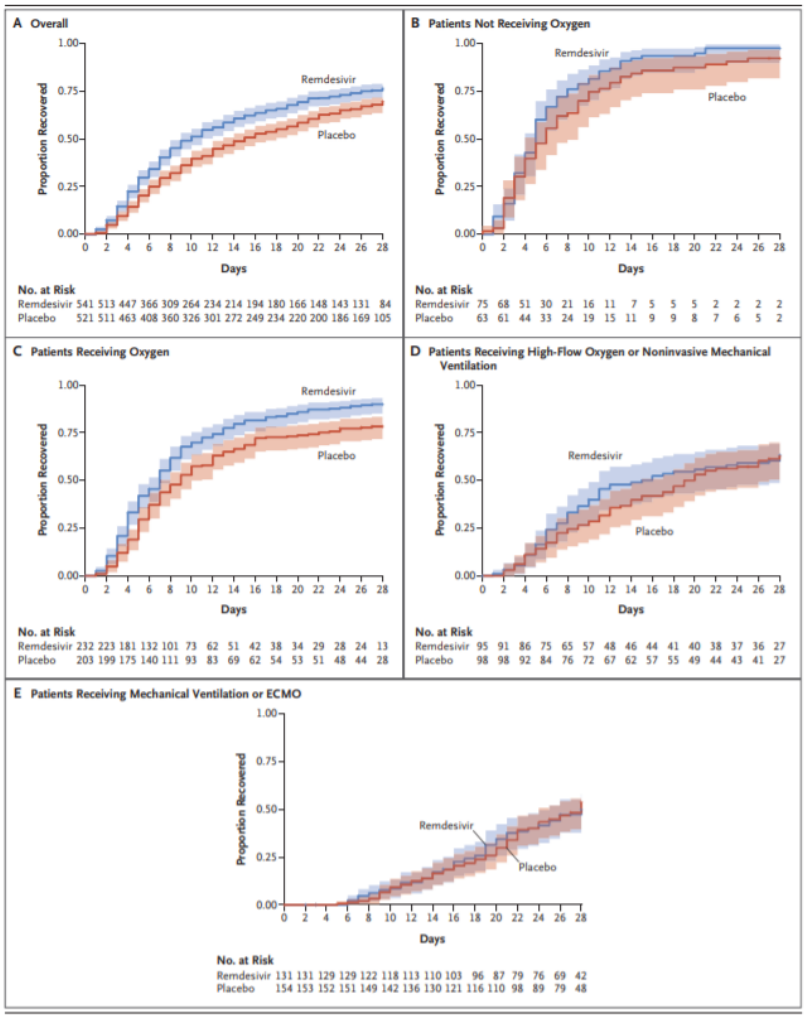
		meccanica nei soggetti con COVID-19.	RESULTS: COVID-19 ARDS patients required mechanical ventilation (MV) for significantly longer, even after adjustment for potential confounders. There was a trend toward higher concentrations of plasma CCL5, CXCL2, CXCL10, CD40 ligand, IL-10, and GM-CSF, and ELF concentrations of CXCL1, CXCL10, granzyme B, TRAIL, and EGF in the COVID-19 ARDS group compared with the non-COVID-19 ARDS group. Plasma and ELF CXCL10 concentrations were independently associated with the number of ventilator-free days, without correlation between ELF CXCL-10 and viral load. Mitochondrial DNA plasma and ELF concentrations were elevated in all ARDS patients, with no differences between the two groups. ELF concentrations of mitochondrial DNA were correlated with alveolar cell counts, as well as IL-8 and IL-1beta concentrations. CONCLUSION: CXCL10 could be one key mediator involved in the dysregulated immune response. It should be evaluated as a candidate biomarker that may predict the duration of MV in COVID-19 ARDS patients. Targeting the CXCL10-CXCR3 axis could also be considered as a new therapeutic approach.
Chen J et al Virulence https://doi.org/10.1080/21505594.2020.1840122	Clinical characteristics of asymptomatic carriers of novel coronavirus disease 2019: A multi-center study in Jiangsu Province.	Caratteristiche cliniche ed ematobiochimiche di 648 soggetti con infezione da SARS-CoV-2 fra cui 50 asintomatici messi a confronto con infezione di gravità crescente.	Asymptomatic SARS-CoV-2-infected individuals are thought to play major roles in virus transmission. This study aimed to analyze the characteristics of asymptomatic carriers with COVID-19 to control the spread of the virus. We retrospectively investigated the clinical characteristics of 648 consecutive subjects who were enrolled in the study and were divided into asymptomatic carriers, mild cases, ordinary cases, severe or critical cases, and evaluated their impact on disease severity by means of Spearman correlation and multiple regression analyses. Receiver operating characteristic curve analysis was conducted to determine the optimum cutoff levels of laboratory findings for diagnostic predictors of asymptomatic carriers of COVID-19. In our study, a total of 648 subjects on

			admission with a mean age of 45.61 y including 345 males and 303 females were enrolled in our study. The leukocyte, lymphocyte, eosinophil, platelet, C-reactive protein, interleukin-6, CD3+, CD4+, and CD8 + T lymphocyte levels, and the erythrocyte sedimentation rate differed significantly among the groups (all p </= 0.05). Disease severity was negatively associated with the CD3+ (r = -0.340; p < 0.001), CD4+ (r = -0.290; p = 0.001) and CD8+ (r = -0.322; p < 0.001) T lymphocyte levels. The significant diagnostic predictors of asymptomatic carriers of COVID-19 included the blood cell, cytokine, and T lymphocyte subset levels. Inflammation and immune response may play important roles in disease progression. Hence, the laboratory parameters identified should be considered in clinical practice, which provide new insights into the identification of asymptomatic individuals and the prevention of virus transmission.
Wong F et al Proceedings of the National Academy of Science USA https://www.pnas.org/content/early/2020/10/30/2018490117	Evidence that coronavirus superspreading is fat-tailed.	I fenomeni di « superspreading » sono la coda destra della distribuzione dei casi secondari di infezione a partire dal caso indice. Rivedendo tutti i lavori su SARS-CoV-2 e SARS-CoV in cui sono riportati >6 casi secondari, in questo studio si dimostra che gli eventi di superspreading sono più consistenti di quanto atteso e meritano attenzione a fini di contenimento.	Superspreaders, infected individuals who result in an outsized number of secondary cases, are believed to underlie a significant fraction of total SARS-CoV-2 transmission. Here, we combine empirical observations of SARS-CoV and SARS-CoV-2 transmission and extreme value statistics to show that the distribution of secondary cases is consistent with being fat-tailed, implying that large superspreading events are extremal, yet probable, occurrences. We integrate these results with interaction-based network models of disease transmission and show that superspreading, when it is fat-tailed, leads to pronounced transmission by increasing dispersion. Our findings indicate that large superspreading events should be the targets of interventions that minimize tail exposure.

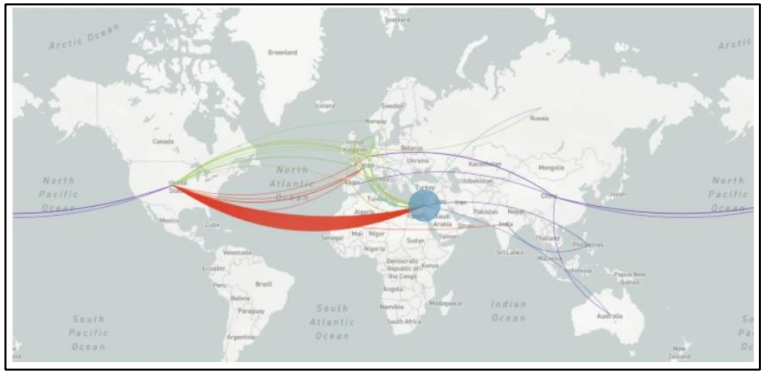
Di Castelnuovo et al medRXiv https://www.medrxiv.org/content/10.1101/2020.11.01.20223958v1	Low dose hydroxychloroquine is associated with lower mortality in COVID-19: a meta-analysis of 26 studies and 44,521 patients	Risultati di due metanalisi che valutano la associazione fra terapia con idrossiclorochina (HCQ), oppure idrossiclorochina e azitromicina, sulla mortalità da COVID-19 : sulla base dei soli dati provenienti da 4 trial clinici, nessuna influenza di HCQ sulla mortalità. Se si includono anche gli studi osservazionali esiste una riduzione variabile di mortalità dall'8 al 31%, che scompare per dosaggi superiori a 400 mg/die. Non emergono significativi effetti avversi.	Background: Hydroxychloroquine (HCQ) was proposed as potential treatment for COVID-19, but its association with mortality is not well characterized. We conducted two meta-analyses to evaluate the association between HCQ (with or without azithromycin (AZM)) and total mortality in COVID-19 patients. Methods: Articles were retrieved until October 20th, 2020 by searching in seven databases. Data were combined using the general variance-based method on relative risk estimates. Results: A total of 26 articles were found (N=44,521 COVID-19 patients, including N=7,324 from 4 randomized clinical trials (RCTs)); 10 studies were valuable for analysing the association of HCQ+AZM. Overall, the use of HCQ was associated with 21% lower mortality risk (pooled risk ratio: 0.79, 95%CI: 0.67 to 0.93; high level of heterogeneity: I2=82%, random effects). This association vanished (1.10, 95%CI: 0.99 to 1.23 and 1.10, 95%CI: 0.99 to 1.23) when daily dose >400 mg or total dose >4,400 mg were used, respectively). HCQ+AZM was also associated with 25% lower mortality risk, but uncertainty was large (95%CI: 0.50 to 1.13; P=0.17). No association was apparent when only pooling the 4 RCTs (13.8% of the overall weight; pooled risk ratio: 1.11, 95%CI: 0.99 to 1.24). Conclusions: HCQ use was not associated with either increased or decreased mortality in COVID-19 patients when 4 RCTs only were evaluated, while a 7% to 33% reduced mortality was observed when observational studies were also included. The association was mainly apparent when pooling studies using lower doses of HCQ. These findings can help disentangling the debate on HCQ use in COVID-19.
Baillargeon J et al Psychiatric Services	The Impact of Substance Use Disorder on COVID-19 Outcomes.	La farmacodipendenza è correlata a ospedalizzazione, ventilazione meccanica e	OBJECTIVE: The goal of this study was to examine the impact of substance use disorder on the risk of hospitalization, complications, and mortality among adult patients diagnosed as having COVID-19. METHODS: The authors conducted a propensity score (PS)-matched

https://doi.org/10.1176/appi.ps.202000534		morte nei soggetti con COVID-19 in base a questo studio retrospettivo su 11124 adulti. Probabile contributo di patologie polmonari e cardiache associate.	double-cohort study (N=5,562 in each cohort) with data from the TriNetX Research Network database to identify 54,529 adult patients (>/=18 years) diagnosed as having COVID-19 between February 20 and June 30, 2020. RESULTS: Primary analysis (PS matched on demographic characteristics and presence of diabetes and obesity) showed that substance use disorder was associated with an increased risk of hospitalization (odds ratio [OR]=1.84, 95% confidence interval [CI]=1.69-2.01), ventilator use (OR=1.45, 95% CI=1.22-1.72), and mortality (OR=1.30, 95% CI=1.08-1.56). CONCLUSIONS: The findings suggest that COVID-19 patients with substance use disorders are at increased risk for adverse outcomes. The attenuation of ORs in the model that matched for chronic respiratory and cardiovascular diseases associated with substance abuse suggests that the observed risks may be partially mediated by these conditions.
Beigel JH et al NEJM https://www.nejm.org/doi/pdf/10.1056/NEJMoa2007764?articleTools=true	Remdesivir for the Treatment of Covid-19 — Final Report	Risultato finali del trial di Beigel et al su remdesivir EV per 10 giorni vs placebo in pazienti con polmonite COVID-19 relata, outcome principale tempo di guarigione. Il remdesivir è superiore al placebo, in particolare nei pazienti trattati con ossigenoterapia, ma non con alti flussi, ventilazione non invasiva o ventilazione meccanica.	BACKGROUND : Although several therapeutic agents have been evaluated for the treatment of coronavirus disease 2019 (Covid-19), no antiviral agents have yet been shown to be efficacious. METHODS : We conducted a double-blind, randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. Patients were randomly assigned to receive either remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) or placebo for up to 10 days. The primary outcome was the time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. RESULTS : A total of 1062 patients underwent randomization (with 541 assigned to remdesivir and 521 to placebo). Those who received remdesivir had a median recovery time of 10 days (95%

			confidence interval [CI], 9 to 11), as compared with 15 days (95% CI, 13 to 18) among those who received placebo (rate ratio for recovery, 1.29; 95% CI, 1.12 to 1.49; P<0.001, by a log-rank test). In an analysis that used a proportional-odds model with an eight-category ordinal scale, the patients who received remdesivir were found to be more likely than those who received placebo to have clinical improvement at day 15 (odds ratio, 1.5; 95% CI, 1.2 to 1.9, after adjustment for actual disease severity). The Kaplan–Meier estimates of mortality were 6.7% with remdesivir and 11.9% with placebo by day 15 and 11.4% with remdesivir and 15.2% with placebo by day 29 (hazard ratio, 0.73; 95% CI, 0.52 to 1.03). Serious adverse events were reported in 131 of the 532 patients who received remdesivir (24.6%) and in 163 of the 516 patients who received placebo (31.6%). CONCLUSIONS : Our data show that remdesivir was superior to placebo in shortening the time to recovery in adults who were hospitalized with Covid-19 and had evidence of lower respiratory tract infection. (Funded by the National Institute of Allergy and Infectious Diseases and others; ACTT-1 ClinicalTrials.gov number, NCT04280705.)

			
Tsai A et al Scientific Reports	Impact of tocilizumab administration on mortality in severe COVID-19	Studio di coorte monocentrico su 132 pazienti ospedalizzati per COVID-19 e trattati con tocilizumab EV contro standard of care, in cui non	The novel coronavirus disease 2019 (COVID-19) worldwide pandemic has placed a significant burden on hospitals and healthcare providers. The immune response to this disease is thought to lead to an aberrant inflammatory response or cytokine storm, which contributes to the severity of illness. There is an

https://www.nature.com/articles/s41598-020-76187-y		si dimostra un vantaggio in sopravvivenza con l'uso del tocilizumab.	urgent need to confirm whether the use of tocilizumab provides a benefit in individuals with COVID-19. A single-center propensity-score matched cohort study, including all consecutive COVID-19 patients, admitted to the medical center who were either discharged from the medical center or expired between March 1, 2020, and May 5, 2020, was performed. Patients were stratified according to the receipt of tocilizumab for cytokine storm and matched to controls using propensity scores. The primary outcome was in-hospital mortality. A total of 274 patients meeting inclusion and exclusion criteria were identified and 132 patients were included in the matched dataset (tocilizumab = 66; no tocilizumab = 66). Approximately 73% of the patients were male. Hypertension (55%), diabetes mellitus (31%), and chronic pulmonary disease (15%) were the most common comorbidities present. There were 18 deaths (27.3%) in the tocilizumab group and 18 deaths (27.3%) in the no tocilizumab group (odds ratio, 1.0; 95% confidence interval, 0.465 – 2.151; p = 1.00). Advanced age, history of myocardial infarction, dementia, chronic pulmonary disease, heart failure, and malignancy were significantly more common in patients who died. The current analysis does not support the use of tocilizumab for the management of cytokine storm in patients with COVID-19. Use of this therapeutic agent should be limited to the context of a clinical trial until more evidence is available.
Lundholm MD et al Journal of the Endocrine Society	SARS-CoV-2 (COVID-19) and the Endocrine System.	Revisione degli effetti noti di SARS-CoV-2 sul sistema endocrino e sul metabolismo umano.	As SARS-CoV-2 (COVID-19) overtakes the world, causing moderate to severe disease in about 15% of infected patients, COVID-19 is also found to have widespread effects throughout the body with a myriad of clinical manifestations including the endocrine system. This manuscript reviews what is known about the impact of COVID-19 on the pathophysiology and management of diabetes (both outpatient and inpatient) as well as pituitary, adrenal, thyroid,

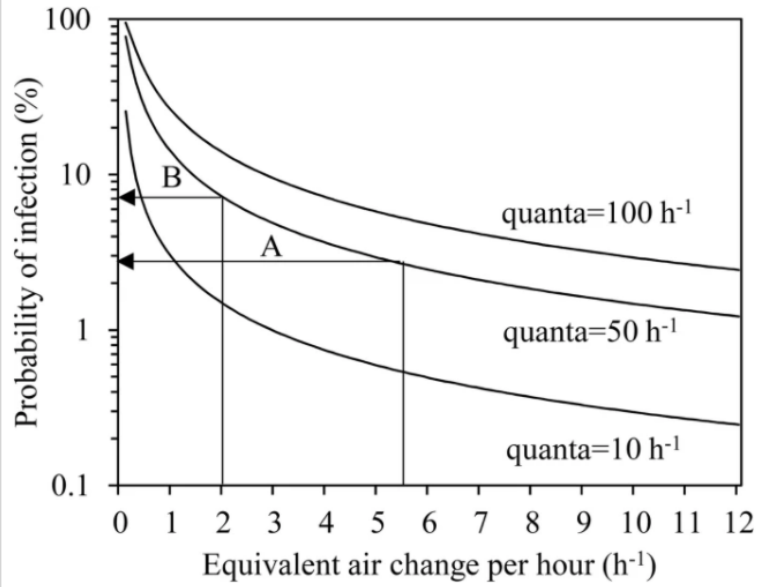
https://academic.oup.com/jes/article/4/11/bvaa144/5916481			bone, and gonadal function. Findings in this area are evolving, and long-term effects of infection remain an active area of further research.
Miller D et al Nature Communications https://www.nature.com/articles/s41467-020-19248-0	Full genome viral sequences inform patterns of SARS-CoV-2 spread into and within Israel.	Studio dei ceppi di SARS-CoV-2 diffusi nello Stato di Israele, dell'efficacia delle misure di contenimento e degli effetti di eventi di superspreading nel Paese.	Full genome sequences are increasingly used to track the geographic spread and transmission dynamics of viral pathogens. Here, with a focus on Israel, we sequence 212 SARS-CoV-2 sequences and use them to perform a comprehensive analysis to trace the origins and spread of the virus. We find that travelers returning from the United States of America significantly contributed to viral spread in Israel, more than their proportion in incoming infected travelers. Using phylodynamic analysis, we estimate that the basic reproduction number of the virus was initially around 2.5, dropping by more than two-thirds following the implementation of social distancing measures. We further report high levels of transmission heterogeneity in SARS-CoV-2 spread, with between 2-10% of infected individuals resulting in 80% of secondary infections. Overall, our findings demonstrate the effectiveness of social distancing measures for reducing viral spread. 

Azuma K et al Environmental Health and Preventive Medicine https://environhealthprevmed.biomedcentral.com/articles/10.1186/s12199-020-00904-2	Environmental factors involved in SARS-CoV-2 transmission: effect and role of indoor environmental quality in the strategy for COVID-19 infection control.	La chiave per prevenire la trasmissione di SARS-CoV-2 negli ambienti chiusi sembra essere la adeguata ventilazione come concluso da questo panel di esperti in Giappone.	The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new zoonotic agent that emerged in December 2019, causes coronavirus disease 2019 (COVID-19). This infection can be spread by asymptomatic, presymptomatic, and symptomatic carriers. SARS-CoV-2 spreads primarily via respiratory droplets during close person-to-person contact in a closed space, especially a building. This article summarizes the environmental factors involved in SARS-CoV-2 transmission, including a strategy to prevent SARS-CoV-2 transmission in a building environment. SARS-CoV-2 can persist on surfaces of fomites for at least 3 days depending on the conditions. If SARS-CoV-2 is aerosolized intentionally, it is stable for at least several hours. SARS-CoV-2 is inactivated rapidly on surfaces with sunlight. Close-contact aerosol transmission through smaller aerosolized particles is likely to be combined with respiratory droplets and contact transmission in a confined, crowded, and poorly ventilated indoor environment, as suggested by some cluster cases. Although evidence of the effect of aerosol transmission is limited and uncertainty remains, adequate preventive measures to control indoor environmental quality are required, based on a precautionary approach, because COVID-19 has caused serious global damages to public health, community, and the social economy. The expert panel for COVID-19 in Japan has focused on the "3 Cs," namely, "closed spaces with poor ventilation," "crowded spaces with many people," and "close contact." In addition, the Ministry of Health, Labour and Welfare of Japan has been recommending adequate ventilation in all closed spaces in accordance with the existing standards of the Law for Maintenance of Sanitation in Buildings as one of the initial political actions to prevent the spread of COVID-19. However, specific standards for indoor environmental quality control have not been recommended

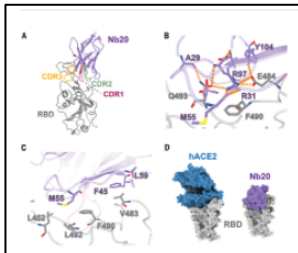
and many scientific uncertainties remain regarding the infection dynamics and mode of SARS-CoV-2 transmission in closed indoor spaces. Further research and evaluation are required regarding the effect and role of indoor environmental quality control, especially ventilation.

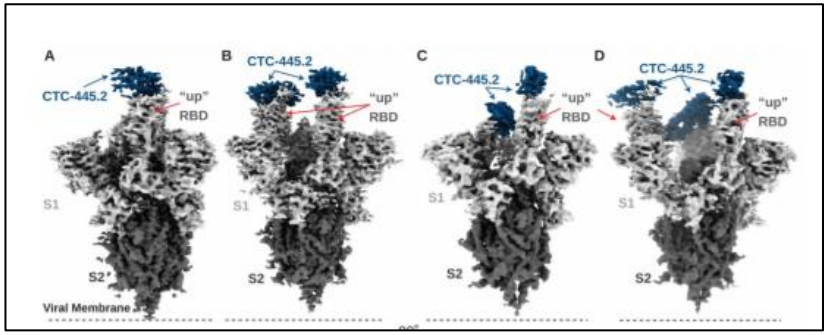
Figure 2 shows the probability of infection plotted against the equivalent air change rate (hourly rate of room ventilation with clean air) based on Eq. (1). The prediction conditions are shown as I = 1 person, p = 0.48 m^3/(hour·person), t = 8 h, room floor area = 500 m^2, ceiling height = 2.6 m. The higher the equivalent air change rate (the room ventilation rate with clean air/room volume), the lower the probability of infection. Furthermore, the CS shows a lower probability of infections than the IS because of the larger amount of clean air.

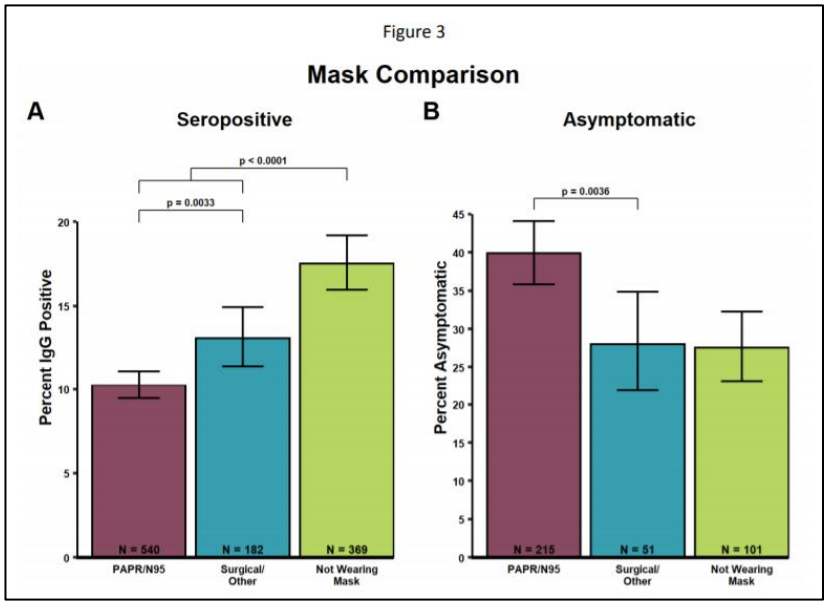
Fig. 2



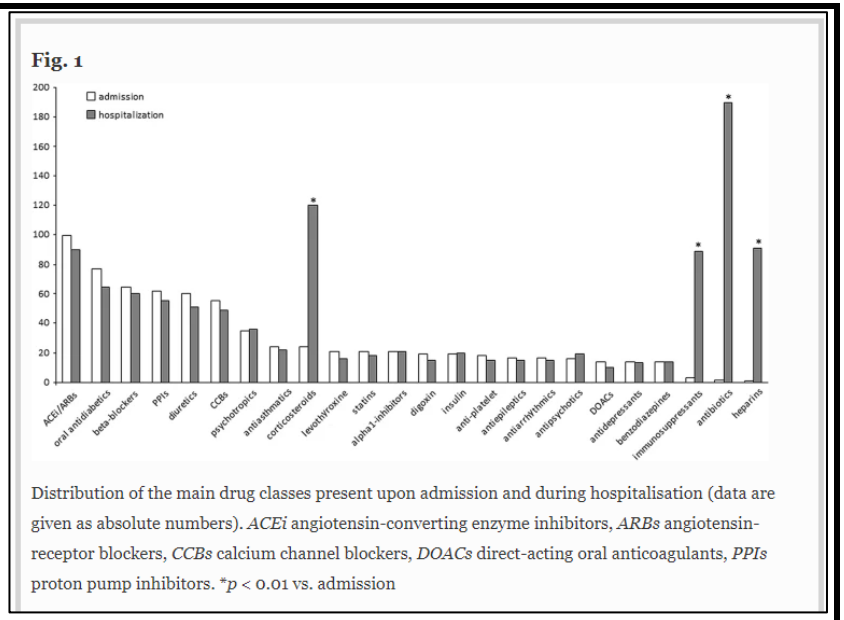
Probability of infection plotted against the equivalent air changes per hour. Conditions: I = 1 person; p = 0.48 m^3/h; t = 8 h; floor area = 500 m^2; room volume = 1300 m^3

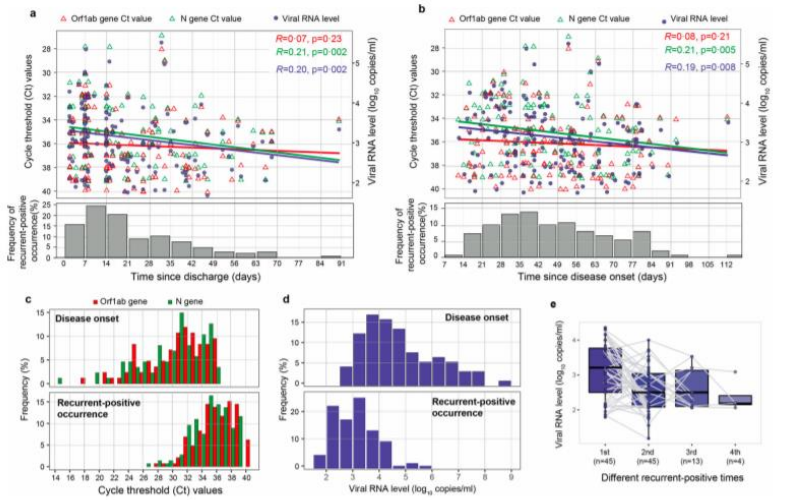
Yifei X et al Nature https://science.sciencemag.org/content/early/2020/11/04/science.abe4747	Versatile and multivalent nanobodies efficiently neutralize SARS-CoV-2	Grazie a studi di proteomica, questo gruppo ha disegnato e sintetizzato un gran numero di « nanobodies », una versione monomerica degli anticorpi monoclonali, altamente stabile, utilizzabile ad esempio per aerosol e sintetizzabile su più larga scala, in grado di neutralizzare la proteina S di SARS-CoV-2 impedendone il legame con il recettore ACE-2 con elevatissima affinità.	Cost-effective, efficacious therapeutics are urgently needed against the COVID-19 pandemic. Here, we used camelid immunization and proteomics to identify a large repertoire of highly potent neutralizing nanobodies (Nbs) to the SARS-CoV-2 spike (S) protein receptor-binding domain (RBD). We discovered Nbs with picomolar to femtomolar affinities that inhibit viral infection at sub-ng/ml concentration and determined a structure of one of the most potent in complex with RBD. Structural proteomics and integrative modeling revealed multiple distinct and non-overlapping epitopes and indicated an array of potential neutralization mechanisms. We constructed multivalent Nb constructs that achieved ultrahigh neutralization potency (IC50s as low as 0.058 ng/ml) and may prevent mutational escape. These thermostable Nbs can be rapidly produced in bulk from microbes and resist lyophilization, and aerosolization.  **Fig. 3 Crystal structure analysis of an ultrahigh affinity Nb in complex with the RBD.** (**A**) Cartoon presentation of Nb20 in complex with the RBD. CDR1, 2, and 3 are in red, green, and orange, respectively. (**B**) Zoomed-in view of an extensive polar interaction network that centers on R35 of Nb20. (**C**) Zoomed-in view of hydrophobic interactions. (**D**) Surface presentation of the Nb20-RBD and hACE2-RBD complex (PDB: 6M0J).
Linsky TW et al Nature https://science.sciencemag.org/content/early/2020/11/04/science.abe0075	De novo design of potent and resilient hACE2 decoys to neutralize SARS-CoV-2	Messa a punto di « trappole » molecolari per il dominio della proteina S di SARS-CoV-2 che lega il recettore cellulare per il virus. Una di queste, CTC-445.2d (in figura), somministrata per via intranasale a topi di	We developed a de novo protein design strategy to swiftly engineer decoys for neutralizing pathogens that exploit extracellular host proteins to infect the cell. Our pipeline allowed the design, validation, and optimization of de novo hACE2 decoys to neutralize SARS-CoV-2. The best decoy, CTC-445.2, binds with low nanomolar affinity and high specificity to the RBD of the spike protein. Cryo-EM shows that the design is accurate and can simultaneously bind to all

		laboratorio in seguito infettati con SARS-CoV-2, determina l'assenza di segni di infezione respiratoria rispetto ai controlli. Tecnologia costosa, forse non ancora applicabile su larga scala, ma interessante proof of concept.	three RBDs of a single spike protein. Because the decoy replicates the spike protein target interface in hACE2, it is intrinsically resilient to viral mutational escape. A bivalent decoy, CTC-445.2d, shows ~10-fold improvement in binding. CTC-445.2d potently neutralizes SARS-CoV-2 infection of cells in vitro and a single intranasal prophylactic dose of decoy protected Syrian hamsters from a subsequent lethal SARS-CoV-2 challenge. 
Sims MD et al Clinical Infectious Diseases https://doi.org/10.1093/cid/ciaa1684	COVID-19 seropositivity and asymptomatic rates in healthcare workers are associated with job function and masking.	Studio su 20614 operatori sanitari impiegati nell'area di Detroit, Michigan, dei quali l'8.8% è risultato sieropositivo contro SARS-CoV-2 e di questi il 44% ha dichiarato di essere asintomatico dal mese precedente l'esame sierologico. Le categorie più rappresentate tra i positivi sono state infermieri, fra cui in particolare flebotomisti, operatori di fisioterapia respiratoria e	BACKGROUND: Although the risk of exposure to SARS-CoV-2 is higher for frontline healthcare workers, not all personnel have similar risks. Determining infection rate is difficult due to the limits on testing and the high rate of asymptomatic individuals. Detection of antibodies against SARS-CoV-2 may be useful for determining prior exposure to the virus and assessing mitigation strategies, such as isolation, masks, and other protective equipment. METHODS: An online assessment that included demographic, clinical, and exposure information and a blood sample was collected from 20,614 participants out of ~43,000 total employees at Beaumont Health, which includes eight hospitals distributed across the Detroit metropolitan area in southeast Michigan. The presence of anti-SARS-CoV-2 IgG was determined using the EUROIMMUN assay. RESULTS: A total of 1,818 (8.8%) participants were seropositive

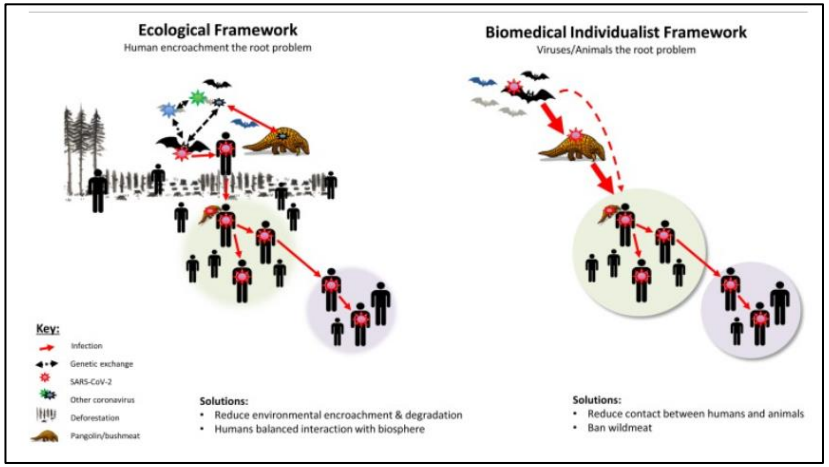
		« assistenti infermieri » (i nostri OSS, Operatori Socio-Sanitari). L'utilizzo di maschere FFP2 è negativamente associato con la positività.	between April 13 and May 28, 2020. Among the seropositive individuals, 44% reported that they were asymptomatic during the month prior to blood collection. Healthcare roles such as phlebotomy, respiratory therapy, and nursing/nursing support exhibited significantly higher seropositivity. Among participants reporting direct exposure to a COVID-19 positive individual, those wearing an N95/PAPR mask had a significantly lower seropositivity rate (10.2%) compared to surgical/other masks (13.1%) or no mask (17.5%). CONCLUSIONS: Direct contact with COVID-19 patients increased the likelihood of seropositivity among employees but study participants who wore a mask during COVID-19 exposures were less likely to be seropositive. Additionally, a large proportion of seropositive employees self-reported as asymptomatic. 

Cattaneo D et al Drugs and Aging https://doi.org/10.1007/s40266-020-00812-8	Drug-Drug Interactions and Prescription Appropriateness in Patients with COVID-19: A Retrospective Analysis from a Reference Hospital in Northern Italy.	Studio delle interazioni farmacologiche in 502 pazienti (età media 61 anni) ricoverati con COVID-19 : una gran parte di esse era attribuibile a idrossiclorochina e lopinavir/ritonavir, ormai in disuso, mentre non si osserverebbero rischi di interazione con remdesivir.	BACKGROUND: Patients hospitalised with severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2; coronavirus 2019 disease (COVID-19)] infection are frequently older with co-morbidities and receiving polypharmacy, all of which are known risk factors for drug-drug interactions (DDIs). The pharmacological burden may be further aggravated by the addition of treatments for COVID-19. OBJECTIVE: The aim of this study was to assess the risk of potential DDIs upon admission and during hospitalisation in patients with COVID-19 treated at our hospital. METHODS: We retrospectively analysed 502 patients with COVID-19 (mean age 61 +/- 16 years, range 15-99) treated at our hospital with a proven diagnosis of SARS-CoV-2 infection hospitalised between 21 February and 30 April 2020 and treated with at least two drugs. RESULTS: Overall, 68% of our patients with COVID-19 were exposed to at least one potential DDI, and 55% were exposed to at least one potentially severe DDI. The proportion of patients experiencing potentially severe DDIs increased from 22% upon admission to 80% during hospitalisation. Furosemide, amiodarone and quetiapine were the main drivers of potentially severe DDIs upon admission, and hydroxychloroquine and particularly lopinavir/ritonavir were the main drivers during hospitalisation. The majority of potentially severe DDIs carried an increased risk of cardiotoxicity. No potentially severe DDIs were identified in relation to tocilizumab and remdesivir. CONCLUSIONS: Among hospitalised patients with COVID-19, concomitant treatment with lopinavir/ritonavir and hydroxychloroquine led to a dramatic increase in the number of potentially severe DDIs. Given the high risk of cardiotoxicity and the scant and conflicting data concerning their efficacy in treating SARS-CoV-2 infection, the use of lopinavir/ritonavir and hydroxychloroquine in patients with COVID-19 with polypharmacy needs to be carefully considered.

			 Distribution of the main drug classes present upon admission and during hospitalisation (data are given as absolute numbers). *ACEi* angiotensin-converting enzyme inhibitors, *ARBs* angiotensin-receptor blockers, *CCBs* calcium channel blockers, *DOACs* direct-acting oral anticoagulants, *PPIs* proton pump inhibitors. *$p < 0.01$ vs. admission
Yang C et al Emerging Microbes and Infections https://doi.org/10.1080/22221751.2020.1837018	Viral RNA level, serum antibody responses, and transmission risk in recovered COVID-19 patients with recurrent positive SARS-CoV-2 RNA test results: a population-based observational cohort study.	Studio osservazionale su 479 pazienti guariti da COVID-19 in Cina e dimessi dall'ospedale sulla base di doppio tampone negativo per ricerca molecolare di SARS-CoV-2. Di questi, 93 (19%) sono andati incontro a ricorrenza di positività del tampone dopo una mediana di 8 giorni dalla dimissione. Tuttavia, nei 6 casi in cui è stato eseguito un sequenziamento dell'RNA virale da tampone sono stati rilevati solo frammenti	Managing recovered COVID-19 patients with recurrent-positive SARS-CoV-2 RNA test results is challenging. We performed a population-based observational study to characterize the viral RNA level and serum antibody responses in recurrent-positive patients and evaluate their viral transmission risk. Of 479 recovered COVID-19 patients, 93 (19%) recurrent-positive patients were identified, characterized by younger age, with a median discharge-to-recurrent-positive length of 8 days. After readmission, recurrent-positive patients exhibited mild (28%) or absent (72%) symptoms, with no disease progression. The viral RNA level in recurrent-positive patients ranged from 1.8 to 5.7 log10 copies/mL (median: 3.2), which was significantly lower than the corresponding values at disease onset. There are generally no significant differences in antibody levels between recurrent-positive and non-recurrent-positive patients, or in recurrent-positive patients over time

		genetici ; inoltre, il virus non è stato isolato in coltura in nessuno dei 9 tentativi eseguiti ; infine, tutti i 1296 tamponi eseguiti su contatti stretti – sempre asintomatici - sono risultati negativi.	(before, during, or after recurrent-positive detection). Virus isolation of nine representative specimens returned negative results. Whole genome sequencing of six specimens yielded only genomic fragments. 96 close contacts and 1,200 candidate contacts of 23 recurrent-positive patients showed no clinical symptoms; their viral RNA (1,296/1,296) and antibody (20/20) tests were negative. After full recovery (no longer/never recurrent-positive), 60% (98/162) patients had neutralizing antibody titers of >/=1:32. Our findings suggested that an intermittent, non-stable excretion of low-level viral RNA may result in recurrent-positive occurrence, rather than re-infection. Recurrent-positive patients pose a low transmission risk, a relatively relaxed management of recovered COVID-19 patients is recommended.  **Figure 3.** RT-qPCR cycle threshold (Ct) values and viral RNA levels in recurrent-positive patients. (a, b) Temporal distribution of Ct values (red and green triangles indicate the Orf1ab and N genes, respectively) and viral RNA levels (blue points) since discharge (a) or disease onset (b). The frequency of recurrent-positive occurrence is shown by grey bars. (c) Ct values of recurrent-positive patients at the time of disease onset (top) or recurrent-positive occurrence (bottom); colours indicate different target SARS-CoV-2 genes. (d) Estimated viral RNA level based on the correlation between viral RNA level and Ct value at the time of disease onset (top) or recurrent-positive occurrence (bottom). (e) Viral RNA level dynamics in multiple-recurrent-positive patients. Specimens from individual patients are linked by grey lines.

Mascolo S et al Journal of Medical Virology https://doi.org/10.1002/jmv.26651	SARS-CoV-2 and inflammatory responses: from mechanisms to the potential therapeutic use of intravenous immunoglobulin.	Revisione dell'esperienza sull'uso di immunoglobuline EV per COVID-19.	A novel coronavirus (SARS-CoV-2) is responsible for severe acute respiratory syndrome, called Coronavirus disease 2019 (COVID-19). It is originated in Wuhan, China, in December 2019. Due to its extreme transmissibility with droplets and human contacts, in a few months, it has become pandemic. Nowadays, no effective therapy is available, and the scientific community is moving to find a therapeutic choice to fight this silent enemy. Studies are ongoing on several therapeutic options, including antiviral agents, immunomodulant drugs, immunotherapy. Due to viral features, including the ability to start an inflammatory response that seems to be the fulcrum of COVID-19 pathogenic action, immunotherapy could represent a promising alternative waiting for the vaccine. High dose intravenous immunoglobulin (IVIg), already used in other infectious diseases could represent an effective help. The aim of this narrative review is to reassemble the clinical experiences on the use of IVIg in COVID-19 and the rationale of its use.
Kenyon C Epidemics https://doi.org/10.1016/j.epidem.2020.100410	Emergence of zoonoses such as COVID-19 reveals the need for health sciences to embrace an explicit eco-social conceptual framework of health and disease.	L'ecologia dovrebbe tornare a interessare chi si occupa di scienze della salute, secondo l'autore di questa review, in quanto l'emergere di zoonosi come SARS-CoV-2 potrebbe essere meglio compreso in un'ottica « eco-sociale », come egli la definisce.	An accurate understanding of why zoonoses such as SARS-CoV-2 are emerging at an increased rate, is vital to prevent future pandemics from the approximately 700,000 viruses with zoonotic potential. Certain authors have argued that the consumption of wildlife, or human contact with bats was responsible for the emergence of SARS-CoV-2. Others argue that a range of anthropogenic environmental degradations have played a vital role in the emergence of SARS-CoV-2 and other zoonoses. In this opinion piece, I argue that these divergent viewpoints stem, in part, from different foundational conceptual frameworks - biomedical individualist and eco-social frameworks, respectively. Based on the fact that the eco-social framework provides a more complete account of the different types of causal factors underpinning the emergence of zoonoses, I propose that the COVID-19 pandemic provides an additional reason

			for the health sciences to ground its theory of health and disease in an eco-social conceptual framework. 
Donno F et al Journal of Preventive Medicine and Hygiene https://doi.org/10.15167/2421-4248/jpmh2020.61.3.1597	An original logigramme to make safe discharge and community reintegration for COVID-19 patients.	L'algoritmo della Regione Puglia per la dimissione dei pazienti con COVID-19, che differisce ad esempio da quello in uso nella Regione Lazio, mette in luce la necessità di uniformare a le indicazioni date ai cittadini.	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is the microorganism responsible for the aggressive Coronavirus Disease (COVID-19) pandemic. During the such pandemic, discharge and community reintegration of patients are critical phases in guaranteeing public health. A review of the international and Italian experiences that represent the best available evidence was carried out, mainly focusing on the precise allocation of tasks and related responsibilities. The report provides a proposal for a systematic management pathway dedicated to COVID-19 patients. The original result is a logigramme to guide health practitioners on discharge and community reintegration of COVID-19 patients. To standardize clinical attitudes helps in ensuring quality of care and patient safety, should be a core element even during a public health emergency. The logigramme suggests, after discharge, 14 days of further isolation with regular health monitoring and, finally, the execution of a nasopharyngeal swab for identification of SARS-CoV-2 viral

			RNA. Home-cared patients should be placed on 7 days of further isolation after at least 2 negative RT-PCR tests for respiratory tract samples (nasopharyngeal swab). The logigramme is already used in the Department of Prevention - Local Health Agency of Lecce (Apulia) but it will be updated according to the latest research findings.