REPORT COVID-19 (SETTIMANA 7-13 FEBBRAIO 2022)

VIROLOGIA E DIAGNOSTICA

ESTENSORE : DOTT. FRANCESCO TACCARI

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
McCallum M et al. Science Structural basis of SARS-CoV-2 Omicron immune evasion and receptor engagement. https://www.science.org/doi/epdf/10.1126/science.abn8652	Abstract The SARS-CoV-2 Omicron variant of concern evades antibody-mediated immunity that comes from vaccination or infection with earlier variants due to accumulation of numerous spike mutations. To understand the Omicron antigenic shift, we determined cryo-electron microscopy and X-ray crystal structures of the spike protein and the receptor-binding domain bound to the broadly neutralizing sarbecovirus monoclonal antibody (mAb) S309 (the parent mAb of sotrovimab) and to the human ACE2 receptor. We provide a blueprint for understanding the marked reduction of binding of other therapeutic mAbs that leads to dampened neutralizing activity. Remodeling of interactions between the Omicron receptor-binding domain and human	Questo studio si focalizza sulla variante Omicron, determinandone la struttura cristallina della proteina spike e del "receptor-binding domain" che si lega all'anticorpo monoclonale S309 (simile al sotrovimab) che neutralizza i sarbecovirus e al recettore ACE2 umano. Tale lavoro fornisce le basi molecolari per comprendere più adeguatamente il motivo per cui la variante Omicron sia in grado di evadere estensivamente la risposta immunitaria. Permette inoltre di comprendere l'importanza di disegnare e modellare terapie e vaccini contro quegli epitopi del virus che tendono maggiormente a conservarsi: sarebbe di fondamentale importanza sviluppare delle strategie che possano non solo risolvere l'attuale pandemia, ma anche prepararci nei confronti di future pandemie da sarbecovirus.

	ACE2 likely explains the enhanced affinity for the host receptor relative to the ancestral virus.	
Stravalaci M et al. Nat Immunol. Recognition and inhibition of SARS-CoV-2 by humoral innate immunity pattern recognition molecules. https://www.nature.com/articles/s41590-021-01114-w.pdf	Abstract The humoral arm of innate immunity includes diverse molecules with antibody-like functions, some of which serve as disease severity biomarkers in coronavirus disease 2019 (COVID-19). The present study was designed to conduct a systematic investigation of the interaction of human humoral fluid-phase pattern recognition molecules (PRMs) with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Of 12 PRMs tested, the long pentraxin 3 (PTX3) and mannose-binding lectin (MBL) bound the viral nucleocapsid and spike proteins, respectively. MBL bound trimeric spike protein, including that of variants of concern (VoC), in a glycan-dependent manner and inhibited SARS-CoV-2 in three in vitro models. Moreover, after binding to spike protein, MBL activated the lectin pathway of complement activation. Based on retention of glycosylation sites and modeling, MBL was predicted to recognize the Omicron VoC. Genetic polymorphisms at the MBL2 locus were associated with disease severity. These results suggest that selected humoral fluid-phase PRMs can play an important role in resistance to, and pathogenesis of, COVID-19, a finding with translational implications.	Studio sulla risposta umorale dell'immunità innata, costituita da molecole che possono essere considerate veri e propri biomarker di severità della COVID-19. Vengono valutate sistemicamente le interazioni fra le « fluid-phase pattern recognition molecules" dell'immunità innata umorale e il virus SARS-CoV-2. Dall studio emerge che in particolare due molecole, la "long pentraxin 3" e la "mannose-binding lectin" (MBL), legano rispettivamente il nucleocapside la proteina spike del virus. Inoltre, dei polimorfismi genetici di alcuni loci della MBL2 sembrerebbero associati con la severità della malattia. Il riconoscimento del virus SARS-CoV-2 mediato dalla MBL sembrerebbe rivelarsi un'arma a doppio taglio: da un lato, nelle fasi iniziali della malattia, la MBL potrebbe essere implicata in un meccanismo di resistenza al virus, bloccandone l'ingresso nella cellula; dall'altro lato, nelle fasi avanzate della malattia, potrebbe contribuire all'attivazione del complemento e all'iper-attivazione della risposta immunitaria. I risultati di tale studio forniscono spunti per una valutazione comprensiva del rischio genetico di sviluppare una forma severa di malattia e spunti per implementare nuovi approcci terapeutici.
Fronza, F. et al. Viruses A Community Study of	Abstract Efficient, wide-scale testing for SARS-CoV-2 is crucial for monitoring the incidence of the infection in the community. The gold standard for COVID-19 diagnosis is the molecular	In questo studio viene valutato il potere diagnostico dell'esame molecolare su tampone salivare rispetto allo standard diagnostico (esame molecolare su tampone nasofaringeo). Sono stati inclusi 1003 campioni appaiati nasofaringei e salivari (questi ultimi raccolti

SARS-CoV-2 Detection by RT-PCR in Saliva: A Reliable and Effective Method. https://www.mdpi.com/1999-4915/14/2/313/pdf	analysis of epithelial secretions from the upper respiratory system captured by nasopharyngeal (NP) or oropharyngeal swabs. Given the ease of collection, saliva has been proposed as a possible substitute to support testing at the population level. Here, we used a novel saliva collection device designed to favour the safe and correct acquisition of the sample, as well as the processivity of the downstream molecular analysis. We tested 1003 nasopharyngeal swabs and paired saliva samples self-collected by individuals recruited at a public drive-through testing facility. An overall moderate concordance (68%) between the two tests was found, with evidence that neither system can diagnose the infection in 100% of the cases. While the two methods performed equally well in symptomatic individuals, their discordance was mainly restricted to samples from convalescent subjects. The saliva test was at least as effective as NP swabs in asymptomatic individuals recruited for contact tracing. Our study describes a testing strategy of self-collected saliva samples, which is reliable for wide-scale COVID-19 screening in the community and is particularly effective for contact tracing.	autonomamente). Dallo studio emerge una non ottimale concordanza fra le due metodiche diagnostiche (68%) : mentre negli individui asintomatici si osserva il più basso tasso di concordanza fra le due tipologie di esame, negli individui sintomatici si apprezza un livello di concordanza più soddisfacente. Il test salivare, per la semplicità di esecuzione e la bassissima invasività della raccolta del campione, rappresenta chiaramente un'attraente metodica diagnostica da implementare su larga scala come test di screening e per supportare il contact tracing ; tuttavia, tenuto conto della bassa sensibilità dell'esame che emerge da questo lavoro, sono necessari ulteriori studi per validarlo.
Alqahtani M et al. Front Public Health Evaluation of Rapid Antigen Tests Using Nasal Samples to Diagnose SARS-CoV-2 in Symptomatic Patients.	Abstract Introduction: The best way to mitigate an outbreak besides mass vaccination is via early detection and isolation of infected cases. As such, a rapid, cost-effective test for the early detection of COVID-19 is required. Methods: The study included 4,183 mildly symptomatic patients. A nasal and nasopharyngeal sample obtained from each patient was analyzed to determine the diagnostic ability of the rapid antigen detection test (RADT, nasal swab) in comparison with the current gold-standard (RT-PCR,	In questo studio con elevatissima numerosità campionaria (4.183 soggetti inclusi) viene esplorata la capacità diagnostica del test antigenico nasofaringeo rispetto al test molecolare nasofaringeo in soggetti con sintomi lievi. Emerge un'elevata sensibilità del test (82.1%) e una elevatissima specificità (99.1%). La sensibilità del test sembretebbe essere maggiore nei soggetti con alte cariche virali (con valori di Ct inferiori a 24 all'esame molecolare). La rapidità di esecuzione, i costi contenuti, la possibilità di effettuarli in assenza di macchinari sofisticati, sono certamente i principali pregi dei test antigenici ; ulteriori

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8795669/pdf/fpubh-09-728969.pdf	nasopharyngeal swab). Results: The calculated sensitivity and specificity of the RADT was 82.1 and 99.1%, respectively. Kappa's coefficient of agreement between the RADT and RT-PCR was 0.859 (p < 0.001). Stratified analysis showed that the sensitivity of the RADT improved significantly when lowering the cut-off RT-PCR Ct value to 24. Conclusion: Our study's results support the potential use of nasal swab RADT as a screening tool in mildly symptomatic patients, especially in patients with higher viral loads.	sforzi dovrebbero essere volti a individuare e a perfezionare algoritmi diagnostici in cui test antigenici e test molecolari vengano combinati, al fine di massimizzare i punti di forza di entrambi.

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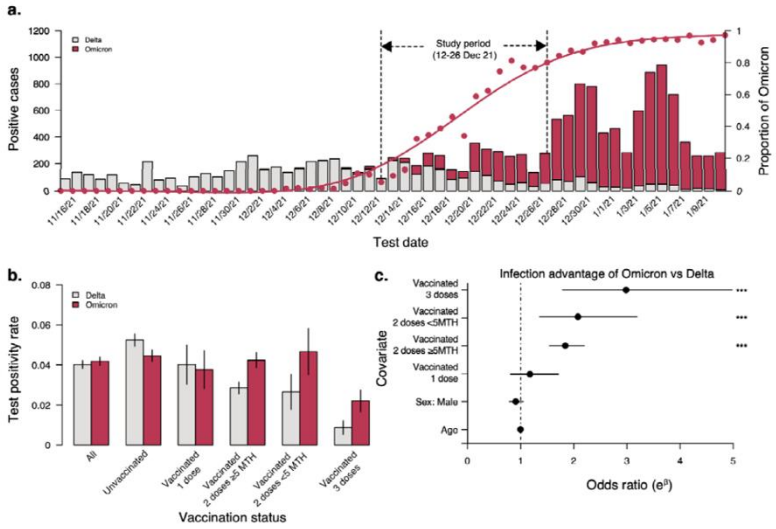
VACCINI

ESTENSORI : DOTT. PIERLUIGI DEL VECCHIO E DOTT.SSA GIULIA MICHELI

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
Chaguza C. et al. NOT PEER REVIEWED Rapid emergence of SARS-CoV-2 Omicron variant is associated with an infection advantage over Delta in vaccinated persons medRxiv preprint	The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants continues to shape the coronavirus disease 2019 (Covid-19) pandemic. The detection and rapid spread of the SARSCoV-2 'Omicron' variant (lineage B.1.1.529) in Botswana and South Africa became a global concern because it contained 15 mutations in the spike protein immunogenic receptor binding domain and was less neutralized by sera derived from vaccinees compared to the previously dominant Delta variant. To investigate if Omicron is more likely than Delta to cause infections in vaccinated persons, we analyzed 37,877 nasal swab PCR tests conducted from 12-26 December 2021 and calculated the test positivity rates for each variant by	CONTENUTO : Studio analitico condotto tramite un programma di sorveglianza nel sud del Connecticut (USA) per investigare l'emergenza di Omicron tramite una combinazione tra spike-gene target failure (SGTF) polymerase chain reaction (PCR) signatures (definito come gene target ORF1ab PCR cycle threshold (Ct) < 30 e gene target spike « non rilevato ») e sequenziamento. Il primo riscontro di Omicron (ceppo BA.1) si e' verificato in questa catchment area il 4 dicembre del 2021, fino a diventare la variante dominante della coorte il 20 dicembre: i casi Omicron sono raddoppiati ogni 3,2 giorni (95% confidence interval (CI): 3.0-3.5), tempo di raddoppiamento 3.7 volte piu' corto di quello di Delta nel periodo di emergenza di

doi: https://doi.org/10.1101/2022.01.22.22269660 e commento su Nature How well can Omicron evade immunity from COVID vaccines? https://www.nature.com/articles/d41586-022-00283-4	vaccination status. We found that the positivity rate among unvaccinated persons was higher for Delta (5.2%) than Omicron (4.5%). We found similar results in persons who received a single vaccine dose. Conversely, our results show that Omicron had higher positivity rates than Delta among those who received two doses within five months (Omicron = 4.7% vs. Delta = 2.6%), two doses more than five months ago (4.2% vs. 2.9%), and three vaccine doses (2.2% vs. 0.9%). Our estimates of Omicron positivity rates in persons receiving one or two vaccine doses were not significantly lower than unvaccinated persons but were 49.7% lower after three doses. In comparison, the reduction in Delta positivity rates from unvaccinated to 2 vaccine doses was 45.6-49.6% and to 3 vaccine doses was 83.2%. Despite the higher positivity rates for Omicron in vaccinated persons, we still found that 91.2% of the Omicron infections in our study occurred in persons who were eligible for 1 or more vaccine doses at the time of PCR testing. In conclusion, escape from vaccine-induced immunity likely contributed to the rapid rise in Omicron infections.	quest'ultima variante (18 Aprile- 26 Maggio 2021 (11.9 giorni [95% CI: 10.7-13.3]). 34,980 unique persons that tested for SARS-CoV-2 (37,877 nasal swab eseguiti tra il 12-26 dicembre quando il numero di probabili infezioni Delta ed Omicron erano relativamente simili (Delta = 1463/2987, 49.0%; Omicron = 1524/2987, 51.0%). Il tasso di positivita' nelle persone non vaccinate della coorte era maggiore per Delta (5.2% [95% CI: 4.9-5.6%]) che per Omicron (4.5 [95% CI: 4.2-4.7%]). Omicron era responsabile di tassi di positivita' maggiori che Delta tra coloro che avevano ricevuto due dosi entro 5 mesi (Omicron = 4.7% [95% CI: 3.5-5.8%] vs. Delta = 2.6% [95% CI: 1.8-3.5%]), 2 dosi da piu' di 5 mesi (4.2% [95% CI: 3.9-4.6%] vs. 2.9% [95% CI:2.5-3.2%]), e 3 dosi di vaccino (2.2% [95% CI: 1.7-2.7%] vs. 0.9% [95% CI: 0.5-1.2%]). I tassi di positivita' per Omicron nei partecipanti con una o due dosi non erano significativamente piu' bassi nelle persone non vaccinate ma 49.7% piu' basse dopo 3 dosi. La riduzione dei tassi di positivita' per Delta tra non vaccinati e i partecipanti con 2 dosi era 45.6-49.6% e con 3 dosi di vaccino 83.2%. 91.2% (1401/1524) dei partecipanti con infezioni Omicron erano eleggibili per 1 o piu' dosi di vaccino al tempo del test PCR. Calcolando gli odds tra il rischio di test positivo per Omicron rispetto a Delta tramite modello logistico lineare generalizzato (GEE), per i pazienti vaccinati, si e' assistito a un maggior rischio di infezione con Omicron (vs Delta) e gli odds aumentavano con l'incrementare delle dosi di vaccino. I valori Ct erano simili tra le dosi di vaccino, ma piu' alti nelle infezioni Omicron che Delta, riflettenti

quindi una piu' bassa carica virale.



LIMITAZIONI : DATI NON PEER REVIEWED ; non sequenziati tutti i campioni ricavati tramite SGTF ; esclusi i partecipanti con informazione vaccinale incompleta ; non studiato impatto reinfezioni ; non analizzata indicazione per il test (motivi altri che malattia da COVID, non possibile quindi inferire sulla patogenicita' di Omicron nei vaccinati)

COMMENTO : Un'analisi retrospettiva che suggerisce che, data la scarsa diversita' genetica del virus circolante tra i vaccinati, i vaccini non promuovano nuove mutazioni. Nonostante l'escape immune della variante, i booster sono comunque efficaci nel ridurre il rischio di infezione Omicron del 50%. Rafforza inoltre l'idea dell'utilita' di un vaccino specifico per Omicron, anche se esiste sempre il rischio dell'emergenza di nuove varianti.

Alexander J. L. et al. The Lancet COVID-19 vaccine-induced antibody responses in immunosuppressed patients with inflammatory bowel disease (VIP): a multicentre, prospective, case-control study https://doi.org/10.1016/S2468-1253(22)00005-X	Background: The effects that therapies for inflammatory bowel disease (IBD) have on immune responses to SARS-CoV-2 vaccination are not yet fully known. Therefore, we sought to determine whether COVID-19 vaccine-induced antibody responses were altered in patients with IBD on commonly used immunosuppressive drugs. Methods: In this multicentre, prospective, case-control study (VIP), we recruited adults with IBD treated with one of six different immunosuppressive treatment regimens (thiopurines, infliximab, a thiopurine plus infliximab, ustekinumab, vedolizumab, or tofacitinib) and healthy control participants from nine centres in the UK. Eligible participants were aged 18 years or older and had received two doses of COVID-19 vaccines (either ChAdOx1 nCoV-19 [Oxford–AstraZeneca], BNT162b2 [Pfizer–BioNTech], or mRNA1273 [Moderna]) 6–12 weeks apart (according to scheduling adopted in the UK). We measured antibody responses 53–92 days after a second vaccine dose using the Roche Elecsys Anti-SARS-CoV-2 spike electrochemiluminescence immunoassay. The primary outcome was anti-SARS-CoV-2 spike protein antibody concentrations in participants without previous SARS-CoV-2 infection, adjusted by age and vaccine type, and was analysed by use of multivariable linear regression models. This study is registered in the ISRCTN Registry, ISRCTN13495664, and is ongoing. Findings: Between May 31 and Nov 24, 2021, we recruited	CONTENUTO : studio multicentrico, prospettico, caso controllo che indaga l'immunogenicita' dei vaccini per SARS-CoV2 nei pazienti con IBD trattati con 6 differenti regimi immunosoppressivi, che abbiano ricevuto due dosi di vaccino (ChAdOx1 nCoV-19, BNT162b2, o mRNA1273 [Moderna]) prima dell'arruolamento comparati con un controllo sano, arruolati tra il 31 maggio e il 24 novembre 2021, studio promosso da Pfizer. Per l'analisi primaria (concentrazioni di anticorpi contro RBD della proteina spike misurati a 53-92 giorni), sono stati inclusi 370 partecipanti senza evidenza di precedente infezione. La media geometrica delle concentrazioni di anticorpi contro la proteina spike erano significativamente piu' basse nei pazienti trattati con infliximab (156·8 U/mL [geometric SD 5·7]; p<0·0001), tiopurine piu' infliximab (111·1 U/mL [5·7]; p<0·0001), o tofacitinib (429·5 U/mL [3·1]; p=0·0012) rispetto ai controlli (1578·3 U/mL [3·7]). Non ci sono state differenze significative nelle concentrazioni di anticorpi contro la proteina spike nei pazienti trattati con monoterapia di tiopurine (1019·8 U/mL [4·3]; p=0·74), ustekinumab (582·4 U/mL [4·6]; p=0·11), or vedolizumab (954·0 U/mL [4·1]; p=0·50) e i controlli sani. Nel modello multivariato in cui si sono inclusi i 370 partecipanti con IBD senza evidenza di infezione previa, concentrazioni piu' basse di anticorpi contro la proteina spike erano independentemente associate a terapia con

	483 participants, including patients with IBD being treated with thiopurines (n=78), infliximab (n=63), a thiopurine plus infliximab (n=72), ustekinumab (n=57), vedolizumab (n=62), or tofacitinib (n=30), and 121 healthy controls. We included 370 participants without evidence of previous infection in our primary analysis. Geometric mean anti-SARS-CoV-2 spike protein antibody concentrations were significantly lower in patients treated with infliximab (156·8 U/mL [geometric SD 5·7]; p<0·0001), infliximab plus thiopurine (111·1 U/mL [5·7]; p<0·0001), or tofacitinib (429·5 U/mL [3·1]; p=0·0012) compared with controls (1578·3 U/mL [3·7]). There were no significant differences in antibody concentrations between patients treated with thiopurine monotherapy (1019·8 U/mL [4·3]; p=0·74), ustekinumab (582·4 U/mL [4·6]; p=0·11), or vedolizumab (954·0 U/mL [4·1]; p=0·50) and healthy controls. In multivariable modelling, lower anti-SARS-CoV-2 spike protein antibody concentrations were independently associated with infliximab (geometric mean ratio 0·12, 95% CI 0·08–0·17; p<0·0001) and tofacitinib (0·43, 0·23–0·81; p=0·0095), but not with ustekinumab (0·69, 0·41–1·19; p=0·18), thiopurines (0·89, 0·64–1·24; p=0·50), or vedolizumab (1·16, 0·74–1·83; p=0·51). mRNA vaccines (3·68, 2·80–4·84; p<0·0001; vs adenovirus vector vaccines) were independently associated with higher antibody concentrations and older age per decade (0·79, 0·72–0·87; p<0·0001) with lower antibody concentrations. Interpretation: For patients with IBD, the immunogenicity of	infliximab (GMR 0·12 [95% CI 0·08–0·17]) e tofacitinib (GMR 0·43 [0·23–0·81]), ma non con ustekinumab (GMR 0·69 [0·41–1·19]), tiopurine (GMR 0·89 [0·64–1·24]), o vedolizumab (GMR 1·16 [0·74–1·83]), maggiore eta' per decade (GMR 0·79 [0·72–0·87]) (vs i controlli). I vaccini a mRNA (GMR 3·68 [95% CI 2·80–4·84]; vs i vaccini a vettore adenovirus) erano indipendemente associati a piu' alte concentrazioni di anticorpi. Di rilievo notare come l'importanza della riduzione della risposta anticorpale nei pazienti trattati con inflixiamb (riduzione di 10 volte rispetto ai controlli). Il 10% e il 13% dei pazienti rispettivamente in terapia con Infliximab e quelli con infliximab+tiopurine non hanno montato risposte anticorpali significative dopo la vaccinazione. Il sottotipo IBD, l'etnia, il tabagismo non erano associati ad impatti sulla concentrazioni degli anticorpi. In analisi post-hoc escludenti i partecipanti in terapia cortisonica al momento della vaccinazione, le associazioni sono rimaste significative, mentre in analisi post-hoc di sensibilita' includenti l'uso di corticosteroidi, BMI e genere, queste ultime variabili non sono state associate a variazioni delle concentrazioni di anticorpi. I partecipanti con IBD e i controlli sani con evidenza di pregressa infezione hanno avuto una risposta anticorpale maggiore alla vaccinazione, come atteso. In linea con quanto gia' noto del waning anticorpale in popolazioni sane, desta preoccupazione la durabilita' della protezione anticorpale nei pazienti trattati

	COVID-19 vaccines varies according to immunosuppressive drug exposure, and is attenuated in recipients of infliximab, infliximab plus thiopurines, and tofacitinib. Scheduling of third primary, or booster, doses could be personalised on the basis of an individual's treatment, and patients taking anti-tumour necrosis factor and tofacitinib should be prioritised.	con tofacitinib, la cui risposta post vaccinazione era significativamente diminuita rispetto ai controlli sani (concentrazione geometrica media 430 U/mL vs 1578 U/mL). LIMITAZIONI : misurazione della risposta umorale come singolo timepoint ; non dati disponibili sulla dose booster; numerosi fattori confondenti ; il piccolo numero di pazienti trattati con corticosteroidi non permette conclusioni forti sul sull'effetto dei corticosteroidi sulla vaccinazione; grandezza del sottogruppo trattato con tofacitinib piu' piccola dei restanti gruppi ; aggiustamento per comparazioni multiple non effettuata nell'analisi primaria ; dati prima dell'emergenza di omicron ; studio senza la potenza necessaria per determinare modeste riduzioni della risposta anticorpale.
Corrao G. et al. The Lancet Persistence of protection against SARS-CoV-2 clinical outcomes up to 9 months since vaccine completion: a retrospective observational analysis	Background: Scarce information is available on the duration of the protective effect of COVID-19 vaccination against the risk of SARS-CoV-2 infection and its severe clinical consequences. We investigated the effect of time since vaccine completion on the SARS-CoV-2 infection and its severe forms. Methods: In this retrospective observational analysis using the vaccination campaign integrated platform of the Italian region of Lombardy, 5 351 085 individuals aged 12 years or older who received complete vaccination from Jan 17 to July 31, 2021, were followed up from 14 days after vaccine completion until Oct 20, 2021. Changes over time in	COMMENTO: Studio osservazionel retrospettivo, finalizzato a valutare la persistenza della protezione nei confronti degli otucomes clinici (infezione e malattia severa) del Sars-Cov2, a nove mesi dal completamento del ciclo vaccinale. In questo studio, 5.351.085 individui sono stati seguiti a 14 giorni dal completamento del ciclo vaccinale tra il gennaio ed il giugno 2021 e poi fino all' ottobre dello stesso anno. In tale lasso di tempo sono stati valutati i cambiamenti nel tempo degli outcomes considerati, come l'infezione e la gravità della stessa nella popolazione vaccinata ed il trend dell'efficacia dei vaccini. In totale sono state osservate 14.140 infezioni e 2450 malattie severe (1.2 casi/10000 persone). Dal primo mese di follow-up fino al mese di

in Lombardy, Italy https://doi.org/10.1016/S1473-3099(21)00813-6	outcome rates (ie, SARS-CoV-2 infection and severe illness among vaccinated individuals) were analysed with age-period-cohort models. Trends in vaccine effectiveness (ie, outcomes comparison in vaccinated and unvaccinated individuals) were also measured. Findings: Overall, 14 140 infections and 2450 severe illnesses were documented, corresponding to incidence rates of 6·7 (95% CI 6·6–6·8) and 1·2 (1·1–1·2) cases per 10 000 person-months, respectively. From the first to the ninth month since vaccine completion, rates increased from 4·6 to 10·2 infections, and from 1·0 to 1·7 severe illnesses every 10 000 person-months. These figures correspond to relative reduction of vaccine effectiveness of 54·9% (95% CI 48·3–60·6) for infection and of 40·0% (16·2–57·0) for severe illness. The increasing infection rate was greater for individuals aged 60 years or older who received adenovirus-vectored vaccines (from 4·0 to 23·5 cases every 10 000 person-months). The increasing severe illness rates were similar for individuals receiving mRNA-based vaccines (from 1·1 to 1·5 every 10 000 person-months) and adenovirus-vectored vaccines (from 0·5 to 0·9 every 10 000 person-months). Interpretation: Although the risk of infection after vaccination, and even more of severe illness, remains low, the gradual increase in clinical outcomes related to SARS-CoV-2 infection suggests that the booster campaign should be accelerated and that social and individual protection	ottobre si è osservato un aumento di questo tasso fino al 6.7/10000. Le infezioni più severe sono state riscontrate nella popolazione over60, senza una particolare variazione nella popolazione ricevente un vaccino a mRNA o con vettore virale. Ovviamente tale dato è direttamente proporzionale alla riduzione dell'efficacia della protezione vaccinale nel tempo, ponendo l'attenzione sull'importanza della necessità di una dose booster, con tempistiche non eccessivamente prolungate.

	measures against COVID-19 spread should not be abandoned	
Shuo Feng et al. Nature Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection https://doi.org/10.1038/s41591-021-01540-1	The global supply of COVID-19 vaccines remains limited. An understanding of the immune response that is predictive of protection could facilitate rapid licensure of new vaccines. Data from a randomized efficacy trial of the ChAdOx1 nCoV-19 (AZD1222) vaccine in the United Kingdom was analyzed to determine the antibody levels associated with protection against SARS-CoV-2. Binding and neutralizing antibodies at 28 days after the second dose were measured in infected and noninfected vaccine recipients. Higher levels of all immune markers were correlated with a reduced risk of symptomatic infection. A vaccine efficacy of 80% against symptomatic infection with majority Alpha (B.1.1.7) variant of SARS-CoV-2 was achieved with 264 (95% CI: 108, 806) binding antibody units (BAU)/ml: and 506 (95% CI: 135, not computed (beyond data range) (NC)) BAU/ml for anti-spike and anti-RBD antibodies, and 26 (95% CI: NC, NC) international unit (IU)/ml and 247 (95% CI: 101, NC) normalized neutralization titers (NF50) for pseudovirus and live-virus neutralization, respectively. Immune markers were not correlated with asymptomatic infections at the 5% significance level. These data can be used to bridge to new populations using validated assays, and allow extrapolation of efficacy estimates to new COVID-19 vaccines.	COMMENTO : Trial randomizzato di efficacia, condotto nel Regno Unito, per determinare i livelli anticorpali in pazienti vaccinati con ChAdOx1 nCoV19 (vettore virale), a 28 giorni dalla seconda dose in pazienti infetti (171 pazienti) e non infetti (1404) da Sars-Cov2. Il proposito di tale studio era appunto valutare la correlazione della protezione anticorpale in pazienti vaccinati, infetti, con infezione sintomatica e non. Elevati livelli anticorpali sono stati correlati ad una riduzione del rischio di infezioni sintomatiche, con una protezione dell'89% nei confronti della stessa a 28 giorni dalla seconda dose. La limitazione principale dello studio riguarda la popolazione presa in considerazione e l'intervallo di tempo considerato, predominante la variante Beta nei pazienti considerati.

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FISIOPATOLOGIA CLINICA E TERAPIA DI COVID-19

ESTENSORI : DOTT.SSA FRANCESCA GIOVANNENZE, DOTT.SSA FRANCESCA RAFFAELLI, DOTT.SSA ELEONORA TADDEI

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
Bhattacharyya RP et al NEJM Challenges in Inferring Intrinsic Severity of the SARS-CoV-2 Omicron Variant https://www.nejm.org/doi/full/10.1056/NEJMp2119682	Omicron's growth advantage over the delta variant has now been documented in multiple locations. Omicron's rapid spread throughout South Africa has resulted in fewer hospitalizations and deaths per documented case than were seen during previous Covid-19 waves, an observation that some members of a weary public are understandably eager to ascribe to an intrinsic tendency of this variant to cause less severe illness. Even more than for previous variants, however, caution is warranted when it comes to making inferences about omicron's intrinsic traits, particularly its severity, on the basis of population-level observations.	L'apparente minore gravità e letalità della variante omicron di SARS-CoV-2 potrebbero dipendere dalle caratteristiche della popolazione (sudafricana) da cui derivano i primi dati, una popolazione giovane e priva di comorbidità, e dal maggior numero di soggetti testati rispetto alle scorse « ondate ».

The Severe Covid-19 GWAS Group NEJM Genomewide Association Study of Severe Covid-19 with Respiratory Failure https://www.nejm.org/doi/full/10.1056/NEJMoa2020283	BACKGROUND There is considerable variation in disease behavior among patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19). Genomewide association analysis may allow for the identification of potential genetic factors involved in the development of Covid-19. METHODS We conducted a genomewide association study involving 1980 patients with Covid-19 and severe disease (defined as respiratory failure) at seven hospitals in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe. After quality control and the exclusion of population outliers, 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain were included in the final analysis. In total, we analyzed 8,582,968 single-nucleotide polymorphisms and conducted a meta-analysis of the two case–control panels. RESULTS We detected cross-replicating associations with rs11385942 at locus 3p21.31 and with rs657152 at locus 9q34.2, which were significant at the genomewide level ($P<5\times10-8$) in the meta-analysis of the two case–control panels (odds ratio, 1.77; 95% confidence interval [CI], 1.48 to 2.11; $P=1.15\times10-10$; and odds ratio, 1.32; 95% CI, 1.20 to 1.47;	Studio genome-wide (GWAS) su 1980 pazienti con COVID-19, in cui si osserva che un cluster di geni del locus 3p21.31 fra cui quelli determinanti il gruppo sanguigno A sono associati a maggiore gravità di malattia.

	P=4.95×10−8, respectively). At locus 3p21.31, the association signal spanned the genes SLC6A20, LZTFL1, CCR9, FYCO1, CXCR6 and XCR1. The association signal at locus 9q34.2 coincided with the ABO blood group locus; in this cohort, a blood-group–specific analysis showed a higher risk in blood group A than in other blood groups (odds ratio, 1.45; 95% CI, 1.20 to 1.75; P=1.48×10−4) and a protective effect in blood group O as compared with other blood groups (odds ratio, 0.65; 95% CI, 0.53 to 0.79; P=1.06×10−5). CONCLUSIONS We identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with Covid-19 with respiratory failure and confirmed a potential involvement of the ABO blood-group system.s	
Mastboim NS et al MedRXiv An immune-protein signature combining TRAIL, IP-10 and CRP for accurate prediction of severe COVID-19 outcome https://www.semanticscholar.org/paper/An-	BACKGROUND Accurately identifying COVID-19 patients at-risk to deteriorate remains challenging. Tools integrating host-protein expression have proven useful in determining infection etiology and hold potential for prognosticating disease severity. METHODS Adults with COVID-19 were recruited at medical centers in Israel, Germany, and the United States. Severe outcome was defined as intensive care unit admission, noninvasive or invasive ventilation, or death. Tumor necrosis factor related apoptosis inducing ligand (TRAIL) and interferon gamma inducible protein-10 (IP-10; also known as CXCL10) and C-reactive protein (CRP) were measured using an analyzer providing values within 15 minutes. A signature indicating the likelihood of severe outcome was derived generating a score (0-100). Patients were assigned to 4 score	Creazione di uno score predittivo di outcome avverso (ricovero in Rianimazione, ventilazione meccanica o decesso) per pazienti con COVID-19, a partire dai dati di 394 adulti ricoverati in diversi centri in Israele, Germania e Stati Uniti.

immune-protein-signature-combining-TRAIL%2C-IP-10-Mastboim-Angel/f5d96efc49e00537794f9e729c8b6f683df4d86b	bins. RESULTS Between March and November 2020, 518 COVID-19 patients were enrolled, of whom 394 were eligible, 29% meeting a severe outcome. The signature's area under the receiver operating characteristic curve (AUC) was 0.86 (95% confidence interval: 0.81-0.91). Performance was not confounded by age, sex, or comorbidities and superior to IL-6 (AUC 0.77; p = 0.033) and CRP (AUC 0.78; p < 0.001). Likelihood of severe outcome increased significantly (p < 0.001) with higher scores. The signature differentiated patients who further deteriorated after meeting a severe outcome from those who improved (p = 0.004) and projected 14-day survival probabilities (p < 0.001). CONCLUSION The derived immune-protein signature combined with a rapid measurement platform is an accurate predictive tool for early detection of COVID-19 patients at-risk for severe outcome, facilitating timely care escalation and de-escalation and appropriate resource allocation.	
Wadman M et al Science A rampage through the body https://www.science.org/content/article/how-does-coronavirus-kill-clinicians-trace-	This map of the devastation that COVID-19 can inflict on the body is still just a sketch. It will take years of painstaking research to sharpen the picture of its reach, and the cascade of cardiovascular and immune effects it might set in motion. As science races ahead, from probing tissues under microscopes to testing drugs on patients, the hope is for treatments more wily than the virus that has stopped the world in its tracks.	Una narrazione del « percorso » di SARS-CoV-2 nell'organismo umano e dei danni provocati nei principali distretti corporei.

ferocious-rampage-through-body-brain-toes		
Garcia-Flores V et al Nature Communications Maternal-fetal immune responses in pregnant women infected with SARS-CoV-2. https://www.nature.com/articles/s41467-021-27745-z.pdf	Pregnant women are a high-risk population for severe/critical COVID-19 and mortality. However, the maternal-fetal immune responses initiated by SARS-CoV-2 infection, and whether this virus is detectable in the placenta, are still under investigation. Herein, we report that SARS-CoV-2 infection during pregnancy primarily induced specific maternal inflammatory responses in the circulation and at the maternal-fetal interface, the latter being governed by T cells and macrophages. SARS-CoV-2 infection during pregnancy was also associated with a cytokine response in the fetal circulation (i.e. umbilical cord blood) without compromising the cellular immune repertoire. Moreover, SARS-CoV-2 infection neither altered fetal cellular immune responses in the placenta nor induced elevated cord blood levels of IgM. Importantly, SARS-CoV-2 was not detected in the placental tissues, nor was the sterility of the placenta compromised by maternal viral infection. This study provides insight into the maternal-fetal immune responses triggered by SARS-CoV-2 and further emphasizes the rarity of placental infection.	Studio osservazionale su 15 donne in gravidanza con infezione da SARS-CoV-2, nelle quali si osserva come il virus induca una risposta immunitaria prevalentemente cellulo-mediata nella madre, in assenza di elevati titoli anticorpali nel sangue cordonale. Il virus non è stato rinvenuto in nessun caso nella placenta, confermando il dato che l'infezione transplacentare non sia una evenienza significativa.
Behr CR et al JAMA	Monoclonal antibodies (mAbs) are highly effective in treating mild to moderate COVID-19 among nonhospitalized patients.1 Given limited supply, federal guidelines prioritize patients at higher risk of progression to hospitalization or	Studio della allocazione delle terapia con anticorpi monoclonali contro SARS-CoV-2 in quasi 2 milioni di adulti con COVID-19 negli USA. Si osserva che per lo più le terapie erano destinate a pazienti a minor rischio, possibilmente a causa della difficoltà per i pazienti a rischio maggiore di

Anti–SARS-CoV-2 Monoclonal Antibody Distribution to High-risk Medicare Beneficiaries, 2020-2021 https://jamanetwork.com/journals/jama/fullarticle/2788904?widget=personalizedcontent&previousarticle=2788849	mortality from COVID-19, with risk factors including age and comorbid conditions.2,3 Antibodies were initially allocated to states by the federal government,4 then distributed through suppliers in 2021.5 We assessed how the limited supply of mAb therapy was allocated to patients at highest risk of severe disease.	malattia grave di ricevere diagnosi e prescrizione nei tempi adeguati.

REPORT COVID-19 (SETTIMANA 7-13 FEBBRAIO 2022)

SANITA' PUBBLICA, EPIDEMIOLOGIA, EPIDEMIOLOGIA BIOMOLECOLARE ESTENSORI : DOTT. SSA PAOLA DEL GIACOMO- DOTT. FRANCESCO V. SEGALA		
ARTICOLO	ABSTRACT	CONTENUTO
Glocker, M.O.; et al. Compared with SARS-CoV2 wild type´s spike protein, the SARS-CoV2 omicron´s receptor binding motif (RBM) has adopted a more SARS-CoV1 and/or bat/civet-like structure. file:///C:/Users/00122705/Dow	Our study focuses on free energy calculations of SARS -CoV2 spike protein receptor binding motives (RBMs) from wild type and variants-of-concern with particul ar emphasis on currently emerging SARSCoV2 omicro n variants of concern (VOC). Our computational free energy analysis underlines the occurrence of positive selection processes that specify omicron host adaptio n and bring changes on the molecular level into cont ext with clinically relevant observations. Our free ene rgy calculations studies regarding the interaction of	Lavoro non ancora peer-reviewed che sottolinea come il legame più debole della proteina spike di SARS- CoV-2 variante omicron al suo recettore sembrerebbe rallentare l'assorbimento del virus nelle cellule e, quindi, ritardare la risposta immunitaria innata. Ciò potrebbe essere responsabile di una maggiore carica virale nel tratto respiratorio superiore. L'assunto che ci sia un legame recettoriale più debole di omicron rispetto a quelli di virus wild type, alfa o delta corrobora le osservazioni cliniche di esiti di malattie meno gravi dell'infezione da omicron rispetto alle infezioni con altri SARS-CoV-2. Gli autori inoltre ipotizzano che la somministrazione del vaccino

nloads/Glocker.pdf	omicron´s RBM with human ACE2 shows weaker binding to ACE2 than alpha´s, delta´s, or wild type´s RBM. Thus, less virus is predicted to be generated in time per infected cell. Our mutant analyses predict with focus on omicron variants a reduced spike-protein binding to ACE2-receptor protein possibly enhancing viral fitness / transmissibility and resulting in a delayed induction of danger signals as trade-off. Finally, more virus is produced but less per cell accompanied with delayed Covid-19 immunogenicity and pathogenicity. Regarding the latter, more virus is assumed to be required to initiate inflammatory immune responses.	nei soggetti infettati con SARS-CoV-2 omicron potrebbe indurre un'immunità più generale e di lunga durata estendendo i repertori di anticorpi protettivi e migliorando contemporaneamente l'immunità mediata dai linfociti T, in definitiva preparando, in tal modo, un individuo a sconfiggere più varianti di virus patogeni in futuro.
ECDC Guidance on ending the isolation period for people with COVID 19 third update. 28 January 2022. file:///C:/Users/00122705/Downloads/Guidance-for-discharge-and-ending-of-isolation-of-people-with-COVID-19-third-update.pdf	Not available	Aggiornamento degli ECDC sulle indicazioni sul periodo di isolamento ottimale per la prevenzione della trasmissione, nonché opzioni per ridurre il periodo di isolamento per i casi di COVID-19 quando i paesi affrontano una pressione elevata o estrema sul loro sistema sanitario e sulle società a causa di aumenti significativi dei casi di COVID-19.

Klompas, M.; Karan, A. JAMA Preventing SARS-CoV-2 Transmission in Health Care Settings in the Context of the Omicron Variant. file:///C:/Users/00122705/Downloads/jama_klompas_2022_vp_220006_1643401941.87023.pdf	No abstract available	Il lavoro analizza separatamente tre misure fondamentali per ridurre la diffusione della variante Omicron all'interno degli ospedali, evento che purtroppo pone a rischio le strutture di focolai all'interno dei reparti nonchè di numerose e improvvise assenze da parte del personale sanitario. Le misure analizzate sono : - il booster negli operatori ; - lo screening frequente degli asintomatici (Il rischio stimato di infezione per un paziente ricoverato in una stanza condivisa con un vettore SARS-CoV-2 positivo occulto va dal 30% al 40%). - Le mascherine N95 (l'equivalente certificazione americana della mascherina FFP2 europea).
Dheda, K.; et al. Afr J Thorac Crit Care Med A position statement and practical guide to the use of particulate filtering facepiece respirators (N95, FFP2, or equivalent) for South African health workers exposed to respiratory pathogens including Mycobacterium tuberculosis and SARS-CoV-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8545268/pdf/AJTCCM-27-4-173.pdf	Summary: Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is transmitted mainly by aerosol in particles <10 µm that can remain suspended for hours before being inhaled. Because particulate filtering facepiece respirators ('respirators'; e.g. N95 masks) are more effective than surgical masks against bio-aerosols, many international organisations now recommend that health workers (HWs) wear a respirator when caring for individuals who may have COVID-19. In South Africa (SA), however, surgical masks are still recommended for the routine care of individuals with possible or confirmed COVID-19, with respirators reserved for so-called aerosol-generating procedures. In contrast, SA guidelines do recommend respirators for routine care of individuals with possible or confirmed tuberculosis (TB), which is also	Linea guida Sudafricana sull'uso delle FFP2 nei contesti ad elevata trasmissione di SARS-CoV-2 e *M. tuberculosis*. Contiene una sintesi sulle raccomandazioni sudafricane e internazionali per l'uso di maschere e respiratori da parte degli operatori sanitari. SARS-CoV-2 è trasmesso anche per via aerosolica. I respiratori FFP offrono prestazioni migliori in termini di protezione dagli aerosol infettivi rispetto alle mascherine chirurgiche, e dunque sono consigliati per l'uso da parte di tutti gli operatori sanitari in contesti con tassi elevati di TB e COVID-19.

	transmitted via aerosol. In health facilities in SA, distinguishing between TB and COVID-19 is challenging without examination and investigation, both of which may expose HWs to potentially infectious individuals. Symptom-based triage has limited utility in defining risk. Indeed, significant proportions of individuals with COVID-19 and/or pulmonary TB may not have symptoms and/or test negative. The prevalence of undiagnosed respiratory disease is therefore likely significant in many general clinical areas (e.g. waiting areas). Moreover, a proportion of HWs are HIV-positive and are at increased risk of severe COVID-19 and death. Recommendations: Sustained improvements in infection prevention and control (IPC) require reorganisation of systems to prioritise HW and patient safety. While this will take time, it is unacceptable to leave HWs exposed until such changes are made. We propose that the SA health system adopts a target of 'zero harm', aiming to eliminate transmission of respiratory pathogens to all individuals in every healthcare setting. Accordingly, we recommend: the use of respirators by all staff (clinical and non-clinical) during activities that involve contact or sharing air in indoor spaces with individuals who: (i) have not yet been clinically evaluated; or (ii) are thought or known to have TB and/or COVID-19 or other potentially harmful	

	respiratory infections;the use of respirators that meet national and international manufacturing standards;evaluation of all respirators, at the least, by qualitative fit testing; andthe use of respirators as part of a 'package of care' in line with international IPC recommendations. We recognise that this will be challenging, not least due to global and national shortages of personal protective equipment (PPE). SA national policy around respiratory protective equipment enables a robust framework for manufacture and quality control and has been supported by local manufacturers and the Department of Trade, Industry and Competition. Respirator manufacturers should explore adaptations to improve comfort and reduce barriers to communication. Structural changes are needed urgently to improve the safety of health facilities: persistent advocacy and research around potential systems change remain essential.	
Ma, Q.; et al. JAMA Global Percentage of Asymptomatic SARS-CoV-2 Infections Among the Tested Population and Individuals With Confirmed COVID-19 Diagnosis A Systematic Review and Meta-analysis.	IMPORTANCE Asymptomatic infections are potential sources of transmission for COVID-19. OBJECTIVE To evaluate the percentage of asymptomatic infections among individuals undergoing testing (tested population) and those with confirmed COVID-19 (confirmed population). DATA SOURCES PubMed, EMBASE, and ScienceDirect were searched on February 4, 2021. STUDY SELECTION Cross-sectional studies, cohort	In questa revisione sistematica e meta-analisi di 95 studi unici con 29.776.306 individui sottoposti a test (soltanto però fino a febbraio 2021), la percentuale aggregata di infezioni asintomatiche era dello 0,25% tra la popolazione testata e del 40,5% tra la popolazione con COVID-19 confermato. L'elevata percentuale di infezioni asintomatiche in questo studio evidenzia il potenziale rischio di trasmissione del virus nella comunità.

file:///C:/Users/00122705/Downloads/ma_2021_oi_211054_1638886091.86274.pdf	studies, case series studies, and case series on transmission reporting the number of asymptomatic infections among the tested and confirmed COVID-19 populations that were published in Chinese or English were included. DATA EXTRACTION AND SYNTHESIS This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline. Random-effects models were used to estimate the pooled percentage and its 95% CI. Three researchers performed the data extraction independently. MAIN OUTCOMES AND MEASURES The percentage of asymptomatic infections among the tested and confirmed populations. RESULTS Ninety-five unique eligible studies were included, covering 29 776 306 individuals undergoing testing. The pooled percentage of asymptomatic infections among the tested population was 0.25% (95% CI, 0.23%-0.27%), which was higher in nursing home residents or staff (4.52% [95% CI, 4.15%-4.89%]), air or cruise travelers (2.02% [95% CI, 1.66%-2.38%]), and pregnant women (2.34% [95% CI, 1.89%-2.78%]). The pooled percentage of asymptomatic infections among the confirmed population was 40.50% (95% CI, 33.50%-47.50%), which was higher in pregnant women (54.11% [95% CI, 39.16%-69.05%]), air or	

	cruise travelers (52.91% [95% CI, 36.08%-69.73%]), and nursing home residents or staff (47.53% [95% CI, 36.36%-58.70%]). CONCLUSIONS AND RELEVANCE In this meta-analysis of the percentage of asymptomatic SARSCoV-2 infections among populations tested for and with confirmed COVID-19, the pooled percentage of asymptomatic infections was 0.25% among the tested population and 40.50% among the confirmed population. The high percentage of asymptomatic infections highlights the potential transmission risk of asymptomatic infections in communities	