

# REPORT COVID-19 (SETTIMANA 28 MARZO – 3 APRILE 2022)

## VIROLOGIA E DIAGNOSTICA

ESTENSORE : DOTT. FRANCESCO TACCARI

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
<p>Shoaib N et al. Mol Biol Rep. Factors associated with cycle threshold values (Ct-values) of SARS-CoV2-rRT-PCR. <a href="https://link.springer.com/content/pdf/10.1007/s11033-022-07360-x.pdf">https://link.springer.com/content/pdf/10.1007/s11033-022-07360-x.pdf</a></p>	<p>Abstract</p> <p>Background: Presented work studies the association of COVID-19 severity, patient demographics, and clinical history with cycle threshold (Ct) values of SARS CoV2-rRT-PCR. We studied the Ct values for Orf1ab, N, and RdRp genes in association with all the factors mentioned above.</p> <p>Methods and results: We examined the individuals (n = 6331) that consulted two private diagnostic centers for COVID-19 testing. SARS-CoV-2 was detected by RT-PCR assays using different commercial kits. Clinical and demographic information was collected by the attending health care professional. Ct values were not associated with the age, sex, or clinical history of the patient. Orf1ab and N genes Ct values were only weakly associated with symptoms at the time of the SARS-CoV-2 RT-PCR test. Also, the</p>	<p>In questo studio condotto su 6331 individui vengono posti in relazione severità dei sintomi, fattori demografici e storia clinica con i valori di cicli soglia di rRT-PCR (sia per gene Orf1ab, che per N e RdRp). Non è stata riscontrata correlazione fra valore di cicli soglia e età, sesso o storia clinica del paziente. E' stata riscontrata solo una debole correlazione fra valore di cicli soglia dei geni Orf1ab e N e la presenza di sintomi al momento del test molecolare, ma non è stata riscontrata una correlazione con la severità dei sintomi. Gli autori dello studio concludono che il valore di cicli soglia potrebbe essere poco utile nel predire la severità della COVID-19 e pertanto dovrebbe essere riportato con cautela nei referti.</p> <p>Mentre alcuni lavori sembrano suggerire come il valore di cicli soglia possa essere di una certa utilità a scopo diagnostico (ad esempio per differenziare una pregressa infezione da una infezione attiva), probabilmente, anche alla</p>

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	<p>distributions of Ct values in SARS-CoV-2 positive patients are very similar irrespective of symptomatology.</p> <p>Conclusion: We conclude that the Ct values may have limitations in reliably predicting COVID-19 severity and should be used or reported with caution.</p>	<p>luce di questo lavoro, è di scarsa utilità nella definizione prognostica della COVID-19.</p>
<p>Sheward DJ et al. Lancet Infect Dis. Neutralisation sensitivity of the SARS-CoV-2 omicron (B.1.1.529) variant: a cross-sectional study. <a href="https://reader.elsevier.com/reader/sd/pii/S1473309922001293?token=045A8DDD1975390F4756B9C37F35AD82438517884A3036DEB82E5326624F9E43A737A2C3C2FA357A7275844DA39C96A0&amp;originRegion=eu-west-1&amp;originCreation=20220325221634">https://reader.elsevier.com/reader/sd/pii/S1473309922001293?token=045A8DDD1975390F4756B9C37F35AD82438517884A3036DEB82E5326624F9E43A737A2C3C2FA357A7275844DA39C96A0&amp;originRegion=eu-west-1&amp;originCreation=20220325221634</a></p>	<p>Abstract</p> <p>Background: The SARS-CoV-2 omicron (B.1.1.529) variant, which was first identified in November, 2021, spread rapidly in many countries, with a spike protein highly diverged from previously known variants, and raised concerns that this variant might evade neutralising antibody responses. We therefore aimed to characterise the sensitivity of the omicron variant to neutralisation.</p> <p>Methods: For this cross-sectional study, we cloned the sequence encoding the omicron spike protein from a diagnostic sample to establish an omicron pseudotyped virus neutralisation assay. We quantified the neutralising antibody ID<sub>50</sub> (the reciprocal dilution that produces 50% inhibition) against the omicron spike protein, and the fold-change in ID<sub>50</sub> relative to the spike of wild-type SARS-CoV-2 (ie, the pandemic founder variant), for one convalescent reference plasma pool (WHO International Standard for anti-SARS-CoV-2 immunoglobulin [20/136]), three reference serum pools from vaccinated individuals, and two cohorts from Stockholm, Sweden: one comprising previously infected hospital workers (17 sampled in November, 2021, after vaccine rollout and nine in June or July, 2020, before vaccination) and one comprising serum from 40 randomly sampled blood donors donated during week 48 (Nov 29-Dec</p>	<p>Studio cross-sectional che mira a valutare la sensibilità della variante omicron al test di neutralizzazione. E' stato approntato uno specifico test di neutralizzazione del virus. Sono stati saggiati campioni di plasma convalescente, campioni di individui vaccinati, campioni di individui precedentemente infetti e campioni di donatori; è stata inoltre testata la capacità neutralizzante di cinque diversi anticorpi monoclonali di rilevanza clinica. E' stata riscontrata una ridotta potenza di neutralizzazione verso omicron, rispetto al ceppo wild type, nei campioni raccolti poco dopo l'infezione o la vaccinazione; i sieri di individui con pregressa infezione e poi vaccinati sembrano invece mantenere una quasi sovrapponibile potenza di neutralizzazione rispetto a omicron e wild type. L'unico anticorpo monoclonale con attività neutralizzante verso omicron sembrerebbe essere S309, parente del sotrovimab (anche se con potenza ridotta rispetto al wild type). Tale studio sembra confermare l'elevata capacità di omicron di evasione della risposta immunitaria; la combinazione più "immunogena" si conferma essere, come riportato anche in altri lavori di letteratura, anche nei confronti di omicron quella di pregressa infezione + successiva vaccinazione.</p>

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5) of 2021. Furthermore, we assessed the neutralisation of omicron by five clinically relevant monoclonal antibodies (mAbs).

Findings: Neutralising antibody responses in reference sample pools sampled shortly after infection or vaccination were substantially less potent against the omicron variant than against wild-type SARS-CoV-2 (seven-fold to 42-fold reduction in ID<sub>50</sub> titres). Similarly, for sera obtained before vaccination in 2020 from a cohort of convalescent hospital workers, neutralisation of the omicron variant was low to undetectable (all ID<sub>50</sub> titres <20). However, in serum samples obtained in 2021 from two cohorts in Stockholm, substantial cross-neutralisation of the omicron variant was observed. Sera from 17 hospital workers after infection and subsequent vaccination had a reduction in average potency of only five-fold relative to wild-type SARS-CoV-2 (geometric mean ID<sub>50</sub> titre 495 vs 105), and two donors had no reduction in potency. A similar pattern was observed in randomly sampled blood donors (n=40), who had an eight-fold reduction in average potency against the omicron variant compared with wild-type SARS-CoV-2 (geometric mean ID<sub>50</sub> titre 369 vs 45). We found that the omicron variant was resistant to neutralisation (50% inhibitory concentration [IC<sub>50</sub>] >10 µg/mL) by mAbs casirivimab (REGN-10933), imdevimab (REGN-10987), etesevimab (Ly-CoV016), and bamlanivimab (Ly-CoV555), which form part of antibody combinations used in the clinic to treat COVID-19. However, S309, the parent of sotrovimab, retained most of its activity, with only an approximately two-fold reduction in potency against the omicron variant compared with ancestral D614G

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	<p>SARS-CoV-2 (IC<sub>50</sub> 0.1-0.2 µg/mL).</p> <p>Interpretation: These data highlight the extensive, but incomplete, evasion of neutralising antibody responses by the omicron variant, and suggest that boosting with licensed vaccines might be sufficient to raise neutralising antibody titres to protective levels.</p>	
<p>Yen HL et al. Lancet.  Transmission of SARS-CoV-2 delta variant (AY.127) from pet hamsters to humans, leading to onward human-to-human transmission: a case study.  <a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8912929/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8912929/pdf/main.pdf</a></p>	<p>Abstract</p> <p>Background: Transmission of SARS-CoV-2 from humans to other mammals, including pet animals, has been reported. However, with the exception of farmed mink, there is no previous evidence that these infected animals can infect humans, resulting in sustained human-to-human transmission. Following a confirmed SARS-CoV-2 infection of a pet shop worker, animals in the shop and the warehouse supplying it were tested for evidence of SARS-CoV-2 infection.</p> <p>Methods: In this case study, viral swabs and blood samples were collected from animals in a pet shop and its corresponding warehouse in Hong Kong. Nasal swab or saliva samples from human COVID-19 patients epidemiologically linked to the pet shop and from subsequent local cases confirmed to be infected by SARS-CoV-2 delta variant were collected. Oral swabs were tested by quantitative RT-PCR (RT-qPCR) for SARS-CoV-2 and blood samples were serologically tested by a surrogate virus neutralisation test and plaque reduction neutralisation test. The SARS-CoV-2 RT-qPCR positive samples were sequenced</p>	<p>Studio che mira a dimostrare la possibile trasmissione del virus SARS-CoV-2 fra animali e uomo. Sono stati raccolti tamponi e campioni di sangue dagli animali di un negozio di animali e nel corrispondente magazzino di Hong Kong ; sno stati raccolti inoltre tampone nasofaringei o salivari di umani affetti da COVID-19 da virus delta legati epidemiologicamente al negozio di animali. La metà dei criceti siriani del negozio di animali e il 58% dei criceti siriani del rispettivo magazzino sono risultati positivi al virus. E' stata riscontrata una corrispondenza filogenetica fra il genoma di delta riscontrato nel criceto siriano e di quello riscontrato negli esseri umani epidemiologicamente legati criceti, con tuttavia alcuni gradi di eterogeneità. Da questo studio sembra confermarsi la capacità da parte del criceto siriano di infettarsi con il virus SARS-CoV-2, di poterlo trasmettere all'uomo e di generare quindi una trasmissione interumana.  Questo lavoro rappresenta un ulteriore esempio a sostegno della teoria dello spill-over del virus SARS-CoV-2 da diverse specie animali all'uomo.</p>

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by next generation viral full genome sequencing using the ISeq sequencing platform (Illumina), and the viral genomes were phylogenetically analysed.

Findings: Eight (50%) of 16 individually tested Syrian hamsters in the pet shop and seven (58%) of 12 Syrian hamsters in the corresponding warehouse were positive for SARS-CoV-2 infection in RT-qPCR or serological tests. None of the dwarf hamsters (n=75), rabbits (n=246), guinea pigs (n=66), chinchillas (n=116), and mice (n=2) were confirmed positive for SARS-CoV-2 in RT-qPCR tests. SARS-CoV-2 viral genomes deduced from human and hamster cases in this incident all belong to the delta variant of concern (AY.127) that had not been circulating locally before this outbreak. The viral genomes obtained from hamsters were phylogenetically related with some sequence heterogeneity. Phylogenetic dating suggests infection in these hamsters occurred around Oct 14, 2021 (95% CI Sept 15 to Nov 9, 2021). Multiple zoonotic transmission events to humans were detected, leading to onward human-to-human transmission.

Interpretation: Pet hamsters can be naturally infected with SARS-CoV-2. The virus can circulate among hamsters and lead to human infections. Both genetic and epidemiological results strongly suggest that there was more than one hamster-to-human transmission event in this study. This incident also led to onward human transmission. Importation of SARS-CoV-2-infected hamsters was a likely source of this outbreak.

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<p>Lai J et al. Microbiol Spectr. Comparison of Saliva and Midturbinate Swabs for Detection of SARS-CoV-2. <a href="https://journals.asm.org/doi/epub/10.1128/spectrum.00128-22">https://journals.asm.org/doi/epub/10.1128/spectrum.00128-22</a></p>	<p>Abstract</p> <p>Saliva is an attractive sample for detecting SARS-CoV-2. However, contradictory reports exist concerning the sensitivity of saliva versus nasal swabs. We followed close contacts of COVID-19 cases for up to 14 days from the last exposure and collected self-reported symptoms, midturbinate swabs (MTS), and saliva every 2 or 3 days. Ct values, viral load, and frequency of viral detection by MTS and saliva were compared. Fifty-eight contacts provided 200 saliva-MTS pairs, and 14 contacts (13 with symptoms) had one or more positive samples. Saliva and MTS had similar rates of viral detection (<math>P = 0.78</math>) and substantial agreement (<math>\kappa = 0.83</math>). However, sensitivity varied significantly with time since symptom onset. Early on (days -3 to 2), saliva had 12 times (95% CI: 1.2, 130) greater likelihood of viral detection and 3.2 times (95% CI: 2.8, 3.8) higher RNA copy numbers compared to MTS. After day 2 of symptoms, there was a nonsignificant trend toward greater sensitivity using MTS. Saliva and MTS demonstrated high agreement making saliva a suitable alternative to MTS for SARS-CoV-2 detection. Saliva was more sensitive early in the infection when the transmission was most likely to occur, suggesting that it may be a superior and cost-effective screening tool for COVID-19. <b>IMPORTANCE</b> The findings of this manuscript are increasingly important with new variants that appear to have shorter incubation periods emerging, which may be more prone to detection in saliva before detection in nasal swabs. Therefore, there is an urgent need to provide the science to support the use of a detection method that is highly sensitive and widely acceptable to the public to improve screening rates and early detection. The manuscript</p>	<p>Studio che compara il potere diagnostico del tampone molecolare su campioni di saliva con tampone molecolare su campione dei turbinati medi. Sono stati raccolti autonomamente dai partecipanti campioni appaiati di saliva e dei turbinati medi (200 campioni appaiati). Il tasso di detection virale è risultato simile per entrambi, con elevato agreement. E' stato tuttavia osservato che nella fase prodromica/sintomatica precoce (giorni da -3 a 2 rispetto allo sviluppo di sintomi) il campione salivare ha una capacità nettamente superiore di detection del virus e di riscontrare un numero più elevato di copie di RNA. Da questo studio sembrerebbe emergere un'ottima capacità diagnostica del tampone molecolare salivare che potrebbe rappresentare una valida alternativa, meno invasiva rispetto al tampone nasofaringeo, per lo screening di massa. La sua capacità diagnostica specialmente nelle fasi inicialissime dell'infezione virale, tenuto conto del rapidissimo tempo di incubazione delle nuove varianti virali, potrebbe fare del tampone salivare un prezioso strumento per la diagnosi precoce.</p>
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presents the first evidence that saliva-based RT-PCR is more sensitive than MTS-based RT-PCR in detecting SARS-CoV-2 during the presymptomatic period - the critical period for unwitting onward transmission. Considering other advantages of saliva samples, including the lower cost, greater acceptability within the general population, and less risk to health care workers, our findings further supported the use of saliva to identify presymptomatic infection and prevent transmission of the virus.

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### VACCINI

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

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
<p>Chandrashekar A. et al. Cell</p> <p>Journal pre-proof</p> <p>Vaccine Protection Against the SARS-CoV-2 Omicron Variant in Macaques</p> <p><a href="https://www.cell.com/cell/pdf/S0092-8674(22)00334-8.pdf?returnURL=https%3A%2F%2Flinkinghub.">https://www.cell.com/cell/pdf/S0092-8674(22)00334-8.pdf?returnURL=https%3A%2F%2Flinkinghub.</a></p>	<p>Background: The rapid spread of the SARS-CoV-2 Omicron (B.1.1.529) variant, including in highly vaccinated populations, has raised important questions about the efficacy of current vaccines. Immune correlates of vaccine protection against Omicron are not known. Methods: 30 cynomolgus macaques were immunized with homologous and heterologous prime-boost regimens with the mRNA-based BNT162b2 vaccine and the adenovirus vector-based Ad26.COVS vaccine. Following vaccination, animals were challenged with the SARS-CoV-2 Omicron variant by the intranasal and intratracheal routes. Results: Omicron neutralizing antibodies were observed following the boost immunization and were higher in animals that received BNT162b2, whereas Omicron CD8+ T cell responses were higher in animals that received Ad26.COVS. Following Omicron challenge, sham controls showed more prolonged virus in nasal swabs than in bronchoalveolar lavage. Vaccinated macaques demonstrated rapid control of</p>	<p><b>COMMENTO :</b> studio condotto su 30 macachi cynomolgus immunizzati contro SARS -CoV2 con vari regimi di BNT162b2 e Ad26.COVS o un finto vaccino su cui sono state valutate le risposte anticorpali al baseline e che alla settimana 19 sono stati esposti a 10<sup>6</sup> PFU SARS-CoV-2 della variante Omicron per via intranasale e intratracheale.</p> <p>Quasi tutti gli animali vaccinati hanno avuto segno di infezione breakthrough nel BAL, ma con cariche virali sostanzialmente inferiori nei vaccinati rispetto ai controlli al giorno 2, con risoluzione dell'infezione per il giorno 4.</p> <p>Per quanto riguarda la via intranasale, tutti gli animali vaccinati hanno avuto segni di infezioni breakthrough nel secreto nasale, ma con cariche virali irrisorie per la maggior parte dei soggetti al giorno 4, fatto salvo per 2 individui del gruppo BNTx3 e 2 del BNTx2/Ad26, che hanno mostrato alti livelli fino al giorno 7, in maniera simili ai controlli.</p> <p>4 animali vaccinati con titoli anticorpali neutralizzanti</p>



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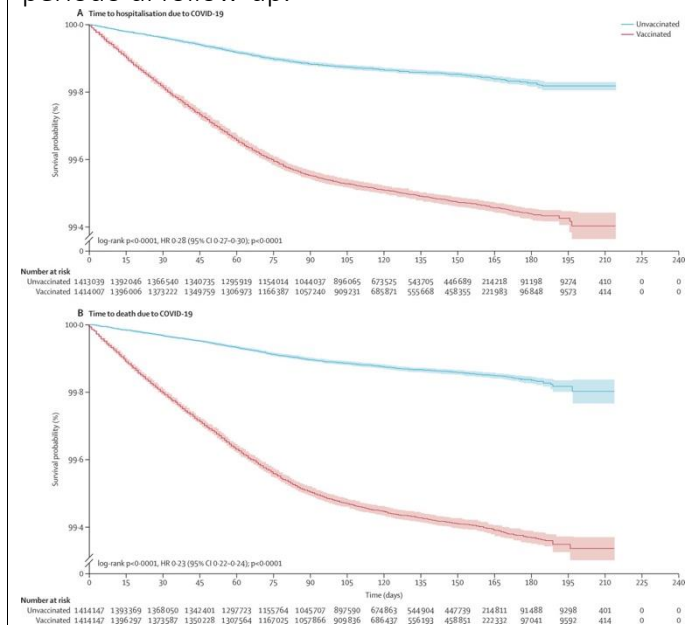
<p><a href="https://www.euro.who.int/en/health-topics/communicable-diseases/news/news/2022/03/omicron-specific-immune-responses">elsevier.com%2Fretrieve%2Fpii%2FS0092867422003348%3Fshowall%3Dtrue</a></p>	<p>virus in bronchoalveolar lavage, and most vaccinated animals also controlled virus in nasal swabs, showing that current vaccines provide substantial protection against Omicron in this model. However, vaccinated animals that had moderate levels of Omicron neutralizing antibodies but negligible Omicron CD8+ T cell responses failed to control virus in the upper respiratory tract. Virologic control correlated with both antibody and T cell responses. Conclusions: BNT162b2 and Ad26.COVS provided robust protection against high-dose challenge with the SARS-CoV-2 Omicron variant in macaques. Protection against this highly mutated SARS-CoV-2 variant correlated with both humoral and cellular immune responses.</p>	<p>omicron-specifici moderati ma con risposta cellulare T CD8+ hanno fallito il controllo virale nel secreto nasale per il giorno 7. Questi dati suggeriscono l'importanza della risposta T CD8+ indotta dal vaccino, gettando luce sulla possibile differenza tra i correlati di protezione contro la patologia severa e quelli contro l'infezione. la potenziale importanza delle risposte T indotte da vaccino potrebbe essere maggiore di quanto pensato nelle varianti come omicron che evadono la risposta umorale.</p> <p>In questo contesto, considerando quindi anche la prolungata durata dello shedding virale nell'alto tratto respiratorio dimostrata in questo studio, insieme come l'evasione dagli anticorpi neutralizzanti, potrebbe contribuire all'alto grado di trasmissibilita' della variante omicron.</p>
<p>Arregocés-Castillo L. et al. The Lancet</p> <p>Effectiveness of COVID-19 vaccines in older adults in Colombia: a retrospective, population-based study of the ESPERANZA cohort</p> <p><a href="https://www.thelancet.com/action/showPdf?pii=S2666-7568%2822%2900035-6">https://www.thelancet.com/action/showPdf?pii=S2666-7568%2822%2900035-6</a></p>	<p>Background: Although clinical trials showed that vaccines have high efficacy and safety, differences in study designs and populations do not allow for comparison between vaccines and age groups. The objective of this study was to evaluate the effectiveness of vaccines against COVID-19 in real-world conditions in adults aged 60 years and older in Colombia.</p> <p>Methods: In this retrospective, population-based, matched cohort study, we evaluated the effectiveness of vaccines against COVID-19-related hospitalisation and death in people aged 60 years and older. The full cohort consisted of every person who was eligible to receive a COVID-19 vaccine in Colombia (the ESPERANZA cohort). The exposed cohort consisted of older adults who were fully vaccinated with Ad26.COVS, BNT162b2, ChAdOx1 nCoV-19, or CoronaVac, and who did not have a history of confirmed SARS-CoV-2 infection. The unexposed cohort were people aged 60 years</p>	<p><b>CONTENUTO:</b> Studio di coorte retrospettivo, population-based, matchato per valutare l'efficacia dei vaccini nei pazienti over 60 nel prevenire le ospedalizzazioni COVID-relate e morte in Colombia, includendo soggetti con schedula vaccinale completa tra 11 marzo 2021 e 26 ottobre 2021, quando la variante mu era prevalente nel paese. Si e' dimostrata un'alta efficacia, con un'efficacia totale per tutti i vaccini del 61,6% nel prevenire l'ospedalizzazione, del 79,8% nel prevenire la morte dopo l'ospedalizzazione e 72,8% nel prevenire la mortalita' prima dell'ospedalizzazione.</p> <p>In questo studio, l'efficacia e' stata negativamente correlata all'eta', qualunque il vaccino sia stato impiegato : nelle eta' avanzate, i vaccini piu' efficaci sono stati quelli a vettore virale e mRNA rispetto ai vaccini a virus inattivato. Nelle fasce di eta' piu' anziane, come quelle dagli 80 anni in su, l'efficacia nel prevenire la mortalita' post ospedalizzazione si e' ridotta del 22,6% e 26,4% nella prevenzione della morte prima dell'ospedalizzazione.</p>

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and older who had not received any dose of a COVID-19 vaccine during the study period. Participant follow-up was done between March 11, 2021, and Oct 26, 2021. Vaccine effectiveness was estimated as 1-hazard ratio from cause-specific proportional hazards models in the presence of competing risks. We estimated the overall effectiveness of being fully vaccinated, as well as effectiveness for each vaccine, adjusting by main potential confounders. The effectiveness of each vaccine was also assessed by age groups (ages 60–69 years, 70–79 years, and ≥80 years). Findings: 2 828 294 participants were assessed between March 11 and Oct 26, 2021. For all ages, the overall effectiveness across all assessed COVID-19 vaccines at preventing hospitalisation without subsequent death was 61·6% (95% CI 58·0–65·0,  $p < 0·0001$ ), 79·8% (78·5–81·1,  $p < 0·0001$ ) for preventing death after hospitalisation with COVID-19, and 72·8% (70·1–75·3,  $p < 0·0001$ ) for preventing death without previous COVID-19 hospitalisation. The effectiveness of all vaccines analysed at preventing death after hospitalisation for COVID-19 was 22·6% lower in adults who were aged 80 and older (68·4% [65·7–70·9],  $p < 0·0001$ ) compared with adults aged between 60 and 69 years (91·0% [89·0–92·6],  $p < 0·0001$ ).

Interpretation: All vaccines analysed in this study were effective at preventing hospitalisation and death from COVID-19 in fully vaccinated older adults, which is a promising result for the national vaccination programme against COVID-19 in Colombia and in countries where these biologics have been applied. Efforts should be improved to increase coverage

LIMITI: sola variante mu circolante nel periodo studiato, vaccino CoronaVac favorito in questa fascia di eta' per maggiore diffusione e quantita' sul territorio, possibile autoselezione di gravita' dei pazienti non vaccinati (bias comportamentali), confondenti non noti, possibili ritardi nel registro vaccinazioni da cui gli studiosi hanno attinto e conseguente rischio di misclassificazione, dati incompleti sulla prima vaccinazione per una buona parte del campione, corto periodo di follow-up.



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	<p>among older adults. In addition, given that we observed that the effectiveness of vaccines declined with increasing age, a booster dose is also justified, which should be prioritised for older adults.</p>	
<p>Infantino M. et al. CCLM The role of neutralizing antibodies by sVNT after two doses of BNT162b2 mRNA vaccine in a cohort of Italian healthcare workers <a href="https://www.degruyter.com/document/doi/10.1515/cclm-2022-0170/html?lang=en">https://www.degruyter.com/document/doi/10.1515/cclm-2022-0170/html?lang=en</a></p>	<p>Objectives: Evaluating anti-SARS-CoV-2 antibody levels is a current priority to drive immunization, as well as to predict when a vaccine booster dose may be required and for which priority groups. The aim of our study was to investigate the kinetics of anti-SARS-CoV-2 Spike S1 protein IgG (anti-S1 IgG) antibodies and neutralizing antibodies (NAbs) in an Italian cohort of healthcare workers (HCWs), following the Pfizer/BNT162b2 mRNA vaccine, over a period of up to six months after the second dose.</p> <p>Methods: We enrolled 57 HCWs, without clinical history of COVID-19 infection. Fluoroenzyme-immunoassay was used for the quantitative anti-S1 IgG antibodies at different time points T1 (one month), T3 (three months) and T6 (six months) following the second vaccine shot. Simultaneously, a commercial surrogate virus neutralization test (sVNT) was used for the determination of NAbs, expressed as inhibition percentage (% IH).</p> <p>Results: Median values of anti-S1 IgG antibodies decreased from T1 (1,452 BAU/mL) to T6 (104 BAU/mL) with a percent variation of 92.8% while the sVNT showed a percent variation of 34.3% for the same time frame. The decline in anti-S1 IgG antibodies from T1 to T6 was not accompanied by a loss of</p>	<p><b>COMMENTO:</b> Studio in vitro condotto con lo scopo di valutare la cinetica delle IgG contro la proteina spike S1 del Sars-Cov2 e gli anticorpi neutralizzanti in una popolazione di healthcare workers, a sei mesi dalla seconda dose di vaccino a mRNA BNT162b2. Sono stati arruolati 57 operatori sanitari (66% di sesso femminile), senza storia clinica pregressa di COVID-19, di cui sono stati valutate le IgG anti S1 a un mese, tre mesi e sei mesi dopo la seconda dose. Contestualmente sono stati condotti virus neutralization test per la determinazione degli anticorpi neutralizzanti. I risultati riscontrati hanno mostrato un netto decremento della mediana del valore di anti-S1 IgG dal T1 (1.452 BAU/mL) al T6 (104 BAU/mL), e in maniera analoga si è assistito ad una riduzione, seppur molto minore in percentuale, degli anticorpi neutralizzanti, passando da un 98.6% al T1 contro un 64.8% al T6. Proprio tale riscontro porta ad affermare gli autori dello studio che il dosaggio delle sole IgG anti-spike non offre una valutazione esaustiva dell'efficacia vaccinale, con la necessità di un dosaggio degli anticorpi neutralizzanti. Come evidenziato infatti elevati livelli di anti-S1 si correlano sempre ad alti livelli di anticorpi neutralizzanti, ma livelli medio-bassi di IgG anti-S1 possono correlarsi a livelli variabili di anticorpi neutralizzanti. Sicuramente una limitazione dello studio è legata alla scarsa numerosità del campione e alla non inclusione di pazienti con storia di pregresso COVID-19.</p>

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	<p>the neutralizing capacity of antibodies. In fact at T6 a neutralization percentage &lt;20% IH was observed only in 3.51% of HCWs.</p> <p>Conclusions: Our findings reveal that the decrease of anti-S1 IgG levels do not correspond in parallel to a decrease of NABs over time, which highlights the necessity of using both assays to assess vaccination effectiveness</p>	
<p>Moreira E.D. et al. The NEJM Safety and Efficacy of a Third Dose of BNT162b2 Covid-19 Vaccine <a href="https://www.nejm.org/doi/pdf/10.1056/NEJMoa2200674?articleTools=true">https://www.nejm.org/doi/pdf/10.1056/NEJMoa2200674?articleTools=true</a></p>	<p>BACKGROUND Active immunization with the BNT162b2 vaccine (Pfizer–BioNTech) has been a critical mitigation tool against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection during the coronavirus disease 2019 (Covid-19) pandemic. In light of reports of waning protection occurring 6 months after the primary twodose vaccine series, data are needed on the safety and efficacy of offering a third (booster) dose in persons 16 years of age or older. METHODS In this ongoing, placebo-controlled, randomized, phase 3 trial, we assigned participants who had received two 30-µg doses of the BNT162b2 vaccine at least 6 months earlier to be injected with a third dose of the BNT162b2 vaccine or with placebo. We assessed vaccine safety and efficacy against Covid-19 starting 7 days after the third dose. RESULTS A total of 5081 participants received a third BNT162b2 dose and 5044 received placebo. The median interval between dose 2 and dose 3 was 10.8 months in the vaccine group and 10.7 months in the placebo group; the median follow-up was 2.5</p>	<p><b>COMMENTO:</b> Trial clinico controllato randomizzato di fase 3 (giugno-agosto 2021), finalizzato a valutare l'efficacia e la sicurezza di una terza dose booster di vaccino per Sars-CoV2 BNT162b2. In particolare, 5081 partecipanti allo studio hanno ricevuto una terza dose di vaccino e 5044 invece il placebo, almeno a 6 mesi dalle precedenti due dosi di vaccino Pfizer. Per quanto riguarda il profilo di sicurezza nel corso del follow-up (mediana di 2.5 mesi) non sono state riscontrate segnalazioni di nuove reazioni avverse, con la maggior parte delle reazioni di grado lieve e moderato, perlopiù correlate al sito di iniezione. Le reazioni avverse severe sono state riscontrate con maggiore frequenza nel gruppo dei vaccinati rispetto al placebo (0.5% vs 0.3%) Nessun caso di miocardite o pericardite è stato riportato. Per quanto riguarda l'efficacia della dose booster, nel gruppo ricevente il vaccino, solo 6 pazienti sono risultati positivi ad almeno una settimana dalla somministrazione. Viceversa, nel gruppo ricevente il placebo, sono stati 123 i casi di infezione da Sars-CoV2 segnalati. I dati finora acquisiti in fase 2-3 di questo trial mostrano una efficacia complessiva della dose booster del 90%, da 7 giorni fino a 6 mesi dalla somministrazione con una efficacia del</p>

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months. Local and systemic reactogenicity events from the third dose were generally of low grade. No new safety signals were identified, and no cases of myocarditis or pericarditis were reported. Among the participants without evidence of previous SARS-CoV-2 infection who could be evaluated, Covid-19 with onset at least 7 days after dose 3 was observed in 6 participants in the vaccine group and in 123 participants in the placebo group, which corresponded to a relative vaccine efficacy of 95.3% (95% confidence interval, 89.5 to 98.3). CONCLUSIONS A third dose of the BNT162b2 vaccine administered a median of 10.8 months after the second dose provided 95.3% efficacy against Covid-19 as compared with two doses of the BNT162b2 vaccine during a median follow-up of 2.5 months

95.3% ad una mediana di 2.5 mesi di follow-up in pazienti senza storia di pregressa infezione. Non sono stati osservati casi di COVID-19 severo nel gruppo di pazienti vaccinati. Sicuramente i risultati preliminari dimostrano l'importanza e l'efficacia di una terza dose booster di vaccino, seppur in tal caso i dati riguardano un periodo storico in cui la variante predominante era la Delta, con limitazioni legate inoltre ai differenti tempi di ricezione della dose booster nella popolazione di studio e alla perdita di partecipanti nel gruppo placebo per permettere la ricezione della terza dose in casi specifici.

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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
<p>Tommy Nyberg et al.</p> <p>Comparative analysis of the risks of hospitalisation and death associated with SARS-CoV-2 omicron (B.1.1.529) and delta (B.1.617.2) variants in England: a cohort study</p> <p>The Lancet</p> <p><a href="https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2900462-7">https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2900462-7</a></p>	<p><b>Background</b> The omicron variant (B.1.1.529) of SARS-CoV-2 has demonstrated partial vaccine escape and high transmissibility, with early studies indicating lower severity of infection than that of the delta variant (B.1.617.2). We aimed to better characterise omicron severity relative to delta by assessing the relative risk of hospital attendance, hospital admission, or death in a large national cohort.</p> <p><b>Methods</b> Individual-level data on laboratory-confirmed COVID-19 cases resident in England between Nov 29, 2021, and Jan 9, 2022, were linked to routine datasets on vaccination status, hospital attendance and admission, and mortality. The relative risk of hospital attendance or admission within 14 days, or death within 28 days after confirmed infection, was estimated using proportional hazards regression. Analyses were stratified by test date, 10-year age band, ethnicity, residential region, and vaccination</p>	<p>Studio condotto in Inghilterra che quantifica il rischio di ospedalizzazione e morte a causa dell'infezione da Sars-CoV-2 da variante Omicron rispetto alla Delta sulla base di dati di circa 1.5 milioni di casi COVID-19, di cui circa 1 milione infettati con la variante Omicron. Il rischio complessivo di esiti gravi per l'infezione da Omicron è sostanzialmente inferiore rispetto alla variante Delta. Tuttavia, la riduzione del rischio di ospedalizzazione non è stata osservata tra i bambini di età inferiore ai 10 anni con Omicron rispetto a Delta. La riduzione del rischio di ospedalizzazione osservata a livello generale riflette una riduzione della gravità intrinseca della patologia.</p> <p>La precedente infezione documentata da SARS-CoV-2 offriva una protezione contro il ricovero in ospedale ma soprattutto contro la morte in individui non vaccinati. La vaccinazione di richiamo con i vaccini a mRNA mantiene oltre il 70% di protezione contro l'ospedalizzazione e la morte nelle infezioni da Omicron.</p>

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status, and were further adjusted for sex, index of multiple deprivation decile, evidence of a previous infection, and year of age within each age band. A secondary analysis estimated variant-specific and vaccine-specific vaccine effectiveness and the intrinsic relative severity of omicron infection compared with delta (ie, the relative risk in unvaccinated cases).

**Findings** The adjusted hazard ratio (HR) of hospital attendance (not necessarily resulting in admission) with omicron compared with delta was 0.56 (95% CI 0.54–0.58); for hospital admission and death, HR estimates were 0.41 (0.39–0.43) and 0.31 (0.26–0.37), respectively. Omicron versus delta HR estimates varied with age for all endpoints examined. The adjusted HR for hospital admission was 1.10 (0.85–1.42) in those younger than 10 years, decreasing to 0.25 (0.21–0.30) in 60–69-year-olds, and then increasing to 0.47 (0.40–0.56) in those aged at least 80 years. For both variants, past infection gave some protection against death both in vaccinated (HR 0.47 [0.32–0.68]) and unvaccinated (0.18 [0.06–0.57]) cases. In vaccinated cases, past infection offered no additional protection against hospital admission beyond that provided by vaccination (HR 0.96 [0.88–1.04]); however, for unvaccinated cases, past infection gave moderate protection (HR 0.55 [0.48–0.63]). Omicron versus delta HR estimates were lower for hospital admission (0.30 [0.28–0.32]) in unvaccinated cases than the corresponding HR estimated for all cases in the primary analysis. Booster

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	<p>vaccination with an mRNA vaccine was highly protective against hospitalisation and death in omicron cases (HR for hospital admission 8–11 weeks post-booster vs unvaccinated: 0.22 [0.20–0.24]), with the protection afforded after a booster not being affected by the vaccine used for doses 1 and 2.</p> <p>Interpretation The risk of severe outcomes following SARS-CoV-2 infection is substantially lower for omicron than for delta, with higher reductions for more severe endpoints and significant variation with age. Underlying the observed risks is a larger reduction in intrinsic severity (in unvaccinated individuals) counterbalanced by a reduction in vaccine effectiveness. Documented previous SARS-CoV-2 infection offered some protection against hospitalisation and high protection against death in unvaccinated individuals, but only offered additional protection in vaccinated individuals for the death endpoint. Booster vaccination with mRNA vaccines maintains over 70% protection against hospitalisation and death in breakthrough confirmed omicron infections.</p>	
<p>Yan Xie et al.</p> <p>Risks and burdens of incident diabetes in long COVID: a cohort study</p>	<p>Background</p> <p>There is growing evidence suggesting that beyond the acute phase of SARS-CoV-2 infection, people with COVID-19 could experience a wide range of post-acute sequelae, including diabetes. However, the risks and burdens of diabetes in the post-acute phase of the disease have not yet been comprehensively characterised. To address this knowledge</p>	<p>Studio di coorte condotto negli USA su 181.280 pazienti guariti dal COVID-19 e circa 8 milioni di controlli, con l'obiettivo di esaminare il rischio post-acuto di insorgenza di diabete nei primi 30 giorni dopo la guarigione dall'infezione da SARS-CoV-2.</p> <p>I risultati suggeriscono che vi è un maggior rischio di diabete incidente e di utilizzo di farmaci ipoglicemizzanti. Pertanto il diabete dovrebbe essere considerato come un aspetto della</p>



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The Lancet

<https://www.thelancet.com/action/showPdf?pii=S2213-8587%2822%2900044-4>

gap, we aimed to examine the post-acute risk and burden of incident diabetes in people who survived the first 30 days of SARS-CoV-2 infection.

### Methods

In this cohort study, we used the national databases of the US Department of Veterans Affairs to build a cohort of 181280 participants who had a positive COVID-19 test between March 1, 2020, and Sept 30, 2021, and survived the first 30 days of COVID-19; a contemporary control (n=4118441) that enrolled participants between March 1, 2020, and Sept 30, 2021; and a historical control (n=4286911) that enrolled participants between March 1, 2018, and Sept 30, 2019. Both control groups had no evidence of SARS-CoV-2 infection. Participants in all three comparison groups were free of diabetes before cohort entry and were followed up for a median of 352 days (IQR 245–406). We used inverse probability weighted survival analyses, including predefined and algorithmically selected high dimensional variables, to estimate post-acute COVID-19 risks of incident diabetes, antihyperglycaemic use, and a composite of the two outcomes. We reported two measures of risk: hazard ratio (HR) and burden per 1000 people at 12 months.

### Findings

In the post-acute phase of the disease, compared with the contemporary control group, people with COVID-19 exhibited an increased risk (HR 1·40, 95% CI 1·36–1·44) and excess burden (13·46, 95% CI 12·11–14·84, per 1000 people

sindrome Long COVID. Le strategie di cura dei pazienti post-COVID dovrebbero integrare lo screening e la gestione del diabete.

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	<p>at 12 months) of incident diabetes; and an increased risk (1.85, 1.78–1.92) and excess burden (12.35, 11.36–13.38) of incident antihyperglycaemic use. Additionally, analyses to estimate the risk of a composite endpoint of incident diabetes or antihyperglycaemic use yielded a HR of 1.46 (95% CI 1.43–1.50) and an excess burden of 18.03 (95% CI 16.59–19.51) per 1000 people at 12 months. Risks and burdens of post-acute outcomes increased in a graded fashion according to the severity of the acute phase of COVID-19 (whether patients were non-hospitalised, hospitalised, or admitted to intensive care). All the results were consistent in analyses using the historical control as the reference category.</p> <p>Interpretation</p> <p>In the post-acute phase, we report increased risks and 12-month burdens of incident diabetes and antihyperglycaemic use in people with COVID-19 compared with a contemporary control group of people who were enrolled during the same period and had not contracted SARS-CoV-2, and a historical control group from a pre-pandemic era. Post-acute COVID-19 care should involve identification and management of diabetes.</p>	
<p>Franck Touret et al.</p> <p>In vitro evaluation of therapeutic antibodies against a SARS-CoV-2</p>	<p>Abstract</p> <p>The emergence and rapid spread of the Omicron variant of SARS-CoV-2, which has more than 30 substitutions in the spike glycoprotein, compromises the efficacy of currently available vaccines and therapeutic antibodies. Using a clinical strain of the Omicron variant, we analyzed the</p>	<p>In questo studio è stato analizzato il potere neutralizzante di otto anticorpi monoclonali attualmente utilizzati contro la variante Omicron. È stato osservato che sei di questi anticorpi hanno perso la loro capacità di neutralizzazione. Degli anticorpi che mantengono attività neutralizzante, Sotrovimab/Vir-7831 mostra una lieve riduzione, Cilgavimab/AZD1061 da solo mostra una notevole riduzione</p>

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<p>Omicron B.1.1.529 isolate</p> <p>Nature</p> <p><a href="https://www.nature.com/articles/s41598-022-08559-5.pdf">https://www.nature.com/articles/s41598-022-08559-5.pdf</a></p>	<p>neutralizing power of eight currently used monoclonal antibodies compared to the ancestral B.1 BavPat1 D614G strain. We observed that six of these antibodies have lost their ability to neutralize the Omicron variant. Of the antibodies still having neutralizing activity, Sotrovimab/Vir-7831 shows the smallest reduction in activity, with a factor change of 3.1. Cilgavimab/AZD1061 alone shows a reduction in efficacy of 15.8, resulting in a significant loss of activity for the Evusheld cocktail (42.6-fold reduction) in which the other antibody, Tixagevimab, does not retain significant activity against Omicron. Our results suggest that the clinical efficacy of the initially proposed doses should be rapidly evaluated and the possible need to modify doses or propose combination therapies should be considered.</p>	<p>nell'efficacia, con conseguente perdita significativa di attività di Evusheld (Tixagevimab-Cilgavimab ) in cui Tixagevimab non conserva attività significativa contro Omicron.</p>
<p>Victoria Male et al.</p> <p>SARS- CoV-2 infection and COVID-19 vaccination in pregnancy</p> <p>Nature Reviews Immunology</p> <p><a href="https://www.nature.com/articles/s41577-022-00703-6.pdf">https://www.nature.com/articles/s41577-022-00703-6.pdf</a></p>	<p>SARS-CoV-2 infection poses increased risks of poor outcomes during pregnancy, including preterm birth and stillbirth. There is also developing concern over the effects of SARS-CoV-2 infection on the placenta, and these effects seem to vary between different viral variants. Despite these risks, many pregnant individuals have been reluctant to be vaccinated against the virus owing to safety concerns. We now have extensive data confirming the safety and effectiveness of COVID-19 vaccination during pregnancy, although it will also be necessary to determine the effectiveness of these vaccines specifically against newly emerging viral variants, including Omicron. In this Progress article, I cover recent developments in our understanding of the risks of SARS-CoV-2 infection in pregnancy, and how</p>	<p>In questa review vengono illustrati i recenti sviluppi scientifici nella comprensione dei rischi dell'infezione da SARS-CoV-2 specifici della gravidanza per la donna e per il feto, e come la vaccinazione può ridurli in modo sicuro.</p>

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	<p>vaccination can reduce these.</p>	
<p>Ferrara A et al.</p> <p><b>Perinatal Complications in Individuals in California With or Without SARS-CoV-2 Infection During Pregnancy</b></p> <p><i>JAMA Intern Med</i></p> <p><a href="https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2790318">https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2790318</a></p>	<p><b>Importance</b> Additional research from population-based studies is needed to inform the treatment of SARS-CoV-2 infection during pregnancy and to provide health risk information to pregnant individuals.</p> <p><b>Objective</b> To assess the risk of perinatal complications associated with SARS-CoV-2 infection and to describe factors associated with hospitalizations.</p> <p><b>Design, Setting, and Participants</b> This population-based cohort study included 43 886 pregnant individuals with longitudinal electronic health record data from preconception to delivery who delivered at Kaiser Permanente Northern California between March 1, 2020, and March 16, 2021. Individuals with diagnostic codes for COVID-19 that did not have a confirmatory polymerase chain reaction test for SARS-CoV-2 were excluded.</p> <p><b>Exposures</b> SARS-CoV-2 infection detected by polymerase chain reaction test (from 30 days before conception to 7 days after delivery) as a time varying exposure.</p> <p><b>Main Outcomes and Measures</b> Severe maternal morbidity including 21 conditions (eg, acute myocardial infarction, acute renal failure, acute respiratory distress syndrome, and sepsis) that occurred at any time during pregnancy or delivery; preterm birth; pregnancy hypertensive disorders; gestational diabetes; venous thromboembolism (VTE);</p>	<p>Studio retrospettivo di popolazione condotto in California su una coorte di 43886 donne in gravidanza, di cui 1332 (3%) con tampone molecolare positivo per SARS-CoV-2. In questo studio viene dimostrato che l'infezione da SARS-CoV-2 in gravidanza è associata ad un aumentato rischio di patologie gestazionali gravi (tra cui infarto del miocardio, insufficienza renale acuta e sepsi), parto pretermine e tromboembolismo venoso. Oltre a fornire informazioni sul rischio di complicanze perinatali associate all'infezione da SARS-CoV-2 durante la gravidanza, lo studio supporta la vaccinazione delle donne in gravidanza e in coloro che programmano una gravidanza.</p>

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stillbirth; cesarean delivery; and newborn birth weight and respiratory conditions. Standardized mean differences between individuals with and without SARS-CoV-2 were calculated. Cox proportional hazards regression was used to estimate the hazard ratios (HRs) and 95% CIs for the association between SARS-CoV-2 infection and perinatal complications and hospitalization and to consider the timing of SARS-CoV-2 infection relative to outcomes.

**Results** In this study of 43 886 pregnant individuals (mean [SD] age, 30.7 [5.2] years), individuals with a SARS-CoV-2 infection (1332 [3.0%]) were more likely to be younger, Hispanic, multiparous individuals with a higher neighborhood deprivation index and obesity or chronic hypertension. After adjusting for demographic characteristics, comorbidities, and smoking status, individuals with SARS-CoV-2 infection had higher risk for severe maternal morbidity (HR, 2.45; 95% CI, 1.91-3.13), preterm birth (<37 weeks; HR, 2.08; 95% CI, 1.75-2.47), and VTE (HR, 3.08; 95% CI, 1.09-8.74) than individuals without SARS-CoV-2. SARS-CoV-2 infection was also associated with increased risk of medically indicated preterm birth (HR, 2.56; 95% CI, 2.06-3.19); spontaneous preterm birth (HR, 1.61; 95% CI, 1.22-2.13); and early (HR, 2.52; 95% CI, 1.49-4.24), moderate (HR, 2.18; 95% CI, 1.25-3.80), and late (HR, 1.95; 95% CI, 1.61-2.37) preterm birth. Among individuals with SARS-CoV-2 infection, 76 (5.7%) had a hospitalization; pregestational diabetes (HR, 7.03; 95% CI, 2.22-22.2) and Asian or Pacific Islander (HR, 2.33; 95% CI, 1.06-5.11) and

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	<p>Black (HR, 3.14; 95% CI, 1.24-7.93) race and ethnicity were associated with an increased risk of hospitalization.</p> <p><b>Conclusions and Relevance</b> In this cohort study, SARS-CoV-2 infection was associated with increased risk of severe maternal morbidity, preterm birth, and VTE. The study findings inform clinicians and patients about the risk of perinatal complications associated with SARS-CoV-2 infection in pregnancy and support vaccination of pregnant individuals and those planning conception.</p>	
<p><a href="#">Tangye</a> SG et al</p> <p>Getting to the (germinal) center of humoral immune responses to SARS-CoV-2 <i>Cell</i></p> <p><a href="https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8928419/pdf/main.pdf">https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8928419/pdf/main.pdf</a></p>	<p>Long-term protection against SARS-CoV-2 requires effective and durable immunity. In this issue of <i>Cell</i>, two papers closely examine germinal centers, the physiological birthplace of adaptive immunity, to quantify the specificity, breadth, magnitude, and persistence of systemic and local humoral immune responses following natural infection with, or vaccination against, SARS-CoV-2.</p>	<p>La protezione a lungo termine contro SARS-CoV-2 richiede una risposta immunitaria efficace e duratura. In questo numero di <i>Cell</i> due articoli esaminano i centri germinativi linfonodali (luogo di nascita e sviluppo dell'immunità adattativa) per quantificare la specificità, l'intensità e la persistenza delle risposte immunitarie umorali locali e sistemiche indotte dall'infezione o dalla vaccinazione contro SARS-CoV-2. Entrambi gli studi ipotizzano che la vaccinazione, rispetto all'infezione naturale, produca una risposta umorale superiore, dovuta alla formazione di centri germinativi spike-specifici.</p>
<p>Peghin M et al</p> <p>Post-COVID-19 syndrome and humoral response association after one year in vaccinated and unvaccinated patients</p>	<p><b>Objectives</b></p> <p>To describe the impact of vaccination and the role of humoral responses on post-coronavirus disease 2019 (COVID-19) syndrome one year after the onset of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).</p> <p><b>Methods</b></p> <p>A prospective study. Interviews investigated post-COVID-19 syndrome 6 and 12 months after the disease onset of all</p>	<p>Studio prospettico su 479 individui con infezione da SARS-CoV-2 sia ospedalizzati che non, intervistati a 6 e 12 mesi dopo l'infezione acuta, con l'obiettivo di valutare l'impatto della vaccinazione e il ruolo della risposta umorale sulla sindrome post-COVID-19.</p> <p>Gli autori dimostrano che la vaccinazione da SARS-CoV-2 non è associata ad un aumento dei sintomi post-COVID-19 a un anno dall'infezione acuta, mentre la persistenza di alti titoli di anticorpi indotti dall'infezione naturale (non-RBD-SARS-</p>

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Clinical Microbiology  
and Infection

[https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X\(22\)00155-0/fulltext](https://www.clinicalmicrobiologyandinfection.com/article/S1198-743X(22)00155-0/fulltext)

adult in- and outpatients with COVID-19 attending Udine Hospital (March–May 2020). Vaccination status and two different serological assays to distinguish between response to vaccination (receptor-binding domain –RBD SARS-CoV-2 IgG) and/or natural infection (non-RBD- SARS-CoV-2 IgG) were also assessed.

### Results

479 individuals (52.6% female, mean age 53 years) were interviewed 13.5 months (0.6 SD) after acute infection. Post-COVID-19 syndrome was observed in 47.2% (226/479) of patients after one year. There were no significant differences in the worsening of post-COVID 19 symptoms (22.7% vs 15.8%,  $p = 0.209$ ) among vaccinated ( $n=132$ ) and unvaccinated ( $n=347$ ) patients. The presence of non-RBD SARS-CoV-2 IgG induced by natural infection showed a significant association with post-COVID-19 syndrome (OR 1.35, 95% CI 1.11–1.64,  $p = 0.003$ ), and median non-RBD SARS-CoV-2 IgG titres were significantly higher in long-haulers than in patients without symptoms 22 (IQR 9.7–37.2) vs 14.1 (IQR 5.4–31.3) kAU/L,  $p = 0.009$ ) after one year. In contrast, the presence of RBD SARS-CoV-2 IgG was not associated with the occurrence of post-COVID-19 syndrome ( $>2500$  U/mL vs 0.9–2500 U/mL, OR 1.36, 95% CI 0.62–3.00,  $p = 0.441$ ) and RBD SARS-CoV-2 IgG titres were similar in long-haulers than in patients without symptoms (50% values  $> 2500$  U/mL vs 55.6% values  $> 2500$  U/mL,  $p = 0.451$ )

### Conclusions

The SARS-CoV-2 vaccination is not associated with the

CoV-2 IgG) potrebbe giocare un ruolo nel long-COVID-19.

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	<p>emergence of post-COVID-19 symptoms over one year after acute infection. The persistence of high serological titres response induced by natural infection but not by vaccination, may play a role in long-COVID-19.</p>	
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SANITA' PUBBLICA, EPIDEMIOLOGIA, EPIDEMIOLOGIA BIOMOLECOLARE  
ESTENSORI : DOTT. SSA PAOLA DEL GIACOMO- DOTT. FRANCESCO V. SEGALA

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
<p>Koelle, K.; et al. Science The changing epidemiology of SARS-CoV-2. <a href="https://www.science.org/doi/epdf/10.1126/science.abm4915">https://www.science.org/doi/epdf/10.1126/science.abm4915</a></p>	<p>We have come a long way since the start of the COVID-19 pandemic—from hoarding toilet paper and wiping down groceries to sending our children back to school and vaccinating billions. Over this period, the global community of epidemiologists and evolutionary biologists has also come a long way in understanding the complex and changing dynamics of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes COVID-19. In this Review, we retrace our steps through the questions that this community faced as the pandemic unfolded. We focus on the key roles that mathematical modeling and quantitative analyses of empirical data have played in allowing us to address these questions and</p>	<p>Questa review sull'evoluzione dell'epidemiologia della pandemia di COVID-19 e sulle sfide da essa poste si concentra sui ruoli chiave che i modelli matematici e le analisi quantitative dei dati empirici hanno giocato nel permetterci di affrontare i vari interrogativi che via via ci siamo posti e nel provare a controllare la pandemia. Questi interrogativi, succedutisi nel corso di questi due anni vengono messi in correlazione, in questo lavoro, con le fasi della pandemia, ad esempio all'inizio del 2020 ci siamo chiesti se SARS-CoV-2 avesse il potenziale di causare una pandemia, oggi invece ci stiamo chiedendo: SARS-CoV-2 continuerà ancora ad evolversi per sfuggire all'immunità ?? Le domande sul vaccino si sono invece allargate a quelle riguardanti la misura in cui la vaccinazione potrebbe ridurre</p>

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	<p>ultimately to better understand and control the pandemic.</p>	<p>la trasmissione.</p> <p>Altre questioni analizzate sono le proporzioni delle diffusionsi delle diverse varianti di SARS-CoV-2, o il rischio di reinfezione.</p>
<p>ECDC Technical Report</p> <p>Considerations for the use of face masks in the community in the context of the SARS-CoV-2 Omicron variant of concern.</p> <p><a href="https://www.ecdc.europa.eu/sites/default/files/documents/Considerations-for-use-of-face-masks-in-the-community-in-the-context-of-the-SARS-CoV-2-Omicron-variant-of-concern.pdf">https://www.ecdc.europa.eu/sites/default/files/documents/Considerations-for-use-of-face-masks-in-the-community-in-the-context-of-the-SARS-CoV-2-Omicron-variant-of-concern.pdf</a></p>	<p>A public health policy for wearing a face mask in public spaces should be considered in areas with community transmission when the public health objective is to limit community transmission. An additional option is to focus on the use of face masks in specific settings to protect people vulnerable to severe COVID-19, such as the elderly and people with underlying medical conditions.</p> <ul style="list-style-type: none"> <li>• The appropriate use of face masks is important. The face mask should completely cover the face from the bridge of the nose down to the chin. The mask should be correctly adjusted on the bridge of the nose and to the face to minimise open space between the face and the mask.</li> <li>• When community face coverings are used, it is advisable to choose coverings that comply with available standards for filtration efficacy and breathability, e.g. CEN CWA 17553.</li> <li>• Respirators are expected to be more effective than medical masks, while community face coverings not manufactured according to the specifications in available guidelines for filtration efficacy and breathability are expected to be less effective than medical face masks. Selecting the type of face mask should take into account</li> </ul>	<p>Report aggiornato dell'ECDC sull'uso delle mascherine in comunità nel contesto epidemiologico attuale e dunque durante la diffusione della variante Omicron.</p> <p>Nelle aree in cui l'obiettivo di salute pubblica è quello di ridurre la trasmissione comunitaria del COVID-19, indossare una maschera facciale dovrebbe essere considerata come una delle possibili misure di prevenzione in spazi pubblici ristretti, come negozi, supermercati, snodi di trasporto (es. porti, aeroporti, stazioni di treni/autobus) e quando si usano i trasporti pubblici.</p> <p>Indossare una maschera facciale dovrebbe essere considerato in ambienti esterni affollati dove non è possibile il distanziamento fisico quando l'obiettivo di salute pubblica è quello di limitare la trasmissione comunitaria.</p> <p>Sulla base di dati sperimentali sull'efficacia delle maschere filtranti (FFP), è stato stimato che quando sia la fonte che la persona esposta indossano un respiratore ben aderente, il tempo per raggiungere la dose infettante aumenta da 15' (quando nè la fonte, nè l'esposto indossano una maschera facciale) a 25 ore. Tuttavia, sebbene le maschere filtranti sembrino più efficaci delle mascherine chirurgiche in ambito di studi sperimentali, le evidenze di real life sull'efficacia dei</p>

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	<p>access, availability and tolerability, in addition to effectiveness.</p>	<p>filtranti facciali rispetto alle mascherine chirurgiche in termini di riduzione della trasmissione di SARS-CoV-2 in contesti comunitari rimane molto limitata e inconcludente.</p>
<p>Cohen. C.; et al.  SARS-CoV-2 incidence, transmission, and reinfection in a rural and an urban setting: results of the PHIRST-C cohort study, South Africa, 2020–21.  Lancet Infect Dis  <a href="https://www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900069-X">https://www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900069-X</a></p>	<p><b>Background:</b> By August, 2021, South Africa had been affected by three waves of SARS-CoV-2; the second associated with the beta variant and the third with the delta variant. Data on SARS-CoV-2 burden, transmission, and asymptomatic infections from Africa are scarce. We aimed to evaluate SARS-CoV-2 burden and transmission in one rural and one urban community in South Africa.</p> <p><b>Methods:</b> We conducted a prospective cohort study of households in Agincourt, Mpumalanga province (rural site) and Klerksdorp, North West province (urban site) from July, 2020 to August, 2021. We randomly selected households for the rural site from a health and sociodemographic surveillance system and for the urban site using GPS coordinates. Households with more than two members and where at least 75% of members consented to participate were eligible. Midturbinate nasal swabs were collected twice a week from household members irrespective of symptoms and tested for SARS-CoV-2 using real-time RT-PCR (RT-rtPCR). Serum was collected every 2 months and tested for anti-SARS-CoV-2 antibodies. Main outcomes were the cumulative incidence of SARS-CoV-2 infection, frequency of reinfection, symptomatic fraction (percent of infected individuals with <math>\geq 1</math> symptom), the duration of viral RNA shedding (number of days of SARS-CoV-2 RT-rtPCR</p>	<p>Studio prospettico condotto in Sud Africa per studiare la trasmissione intra-familiare di SARS-CoV-2.</p> <p>Lo studio conclude che questo fenomeno è stato centrale nelle tre ondate di COVID nel paese.</p> <p>Nonostante oltre l'85% dei casi sia rimasto asintomatico durante tutta l'infezione (che durava in media circa 11 giorni), questo non ha influenzato l'HCIR, ovvero rapporto tra il numero di contatti familiari contagiati e il numero di membri familiari suscettibili.</p> <p>Inoltre viene sottolineato un aspetto interessante: i soggetti HIV+ non virologicamente soppressi hanno un maggior rischio di avere una infezione sintomatica e di rilasciare il virus più a lungo rispetto alla controparte sieronegativa.</p> <p>Lo studio ha evidenziato i limiti del fare affidamento esclusivamente su interventi non farmacologici. La vaccinazione rimane uno degli strumenti più importanti nella prevenzione della trasmissione.</p>

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positivity), and the household cumulative infection risk (HCIR; number of infected household contacts divided by the number of susceptible household members).

**Findings:** 222 households (114 at the rural site and 108 at the urban site), and 1200 household members (643 at the rural site and 557 at the urban site) were included in the analysis. For 115759 nasal specimens from 1200 household members (follow-up 92.5%), 1976 (1.7%) were SARS-CoV-2-positive on RT-rtPCR. By RT-rtPCR and serology combined, 749 of 1200 individuals (62.4% [95% CI 58.1–66.4]) had at least one SARS-CoV-2 infection episode, and 87 of 749 (11.6% [9.4–14.2]) were reinfected. The mean infection episode duration was 11.6 days (SD 9.0; range 4–137). Of 662 RT-rtPCR-confirmed episodes (>14 days after the start of follow-up) with available data, 97 (14.7% [11.9–17.9]) were symptomatic with at least one symptom (in individuals aged <19 years, 28 [7.5%] of 373 episodes symptomatic; in individuals aged ≥19 years, 69 [23.9%] of 289 episodes symptomatic). Among 222 households, 200 (90.1% [85.3–93.7]) had at least one SARS-CoV-2-positive individual on RT-rtPCR or serology. HCIR overall was 23.9% (195 of 817 susceptible household members infected [95% CI 19.8–28.4]). HCIR was 23.3% (20 of 86) for symptomatic index cases and 23.9% (175 of 731) for asymptomatic index cases (univariate odds ratio [OR] 1.0 [95% CI 0.5–2.0]). On multivariable analysis, accounting for age and sex, low minimum cycle threshold value (≤30 vs >30) of the index

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	<p>case (OR 5.3 [2.3–12.4]) and beta and delta variant infection (vs Wuhan-Hu-1, OR 3.3 [1.4–8.2] and 10.4 [4.1–26.7], respectively) were associated with increased HCIR. People living with HIV who were not virally suppressed (<math>\geq 400</math> viral load copies per mL) were more likely to develop symptomatic illness when infected with SARS-CoV-2 (OR 3.3 [1.3–8.4]), and shed SARS-CoV-2 for longer (hazard ratio 0.4 [95% CI 0.3–0.6]) compared with HIV-uninfected individuals.</p> <p><b>Interpretation:</b> In this study, 565 (85.3%) SARS-CoV-2 infections were asymptomatic and index case symptom status did not affect HCIR, suggesting a limited role for control measures targeting symptomatic individuals. Increased household transmission of beta and delta variants was likely to have contributed to successive waves of SARS-CoV-2 infection, with more than 60% of individuals infected by the end of follow-up.</p>	
<p>COVID-19 Excess Mortality Collaborators The Lancet Estimating excess mortality due to the COVID-19 pandemic: a systematic analysis of COVID-19-related mortality, 2020–21.</p>	<p><b>Background:</b> Mortality statistics are fundamental to public health decision making. Mortality varies by time and location, and its measurement is affected by well known biases that have been exacerbated during the COVID-19 pandemic. This paper aims to estimate excess mortality from the COVID-19 pandemic in 191 countries and territories, and 252 subnational units for selected countries, from Jan 1, 2020, to Dec 31, 2021.</p> <p><b>Methods:</b> All-cause mortality reports were collected for 74 countries and territories and 266 subnational locations (including 31 locations in low-income and middle-income</p>	<p>Questo lavoro, finanziato tra gli altri dalla Bill &amp; Melinda Gates Foundation ha lo scopo di valutare le morti in eccesso – ovvero la differenza tra il numero di decessi registrati per tutte le cause e il numero previsto in base alle tendenze passate – per avere una misura del vero bilancio delle vittime della pandemia.</p> <p>Le prime stime globali peer-reviewed delle morti in eccesso indicano che, al 31.12.2021, 18,2 milioni di persone potrebbero essere decedute a causa della pandemia di COVID-19, contro i 5,9 dichiarati.</p>

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<https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902796-3>

countries) that had reported either weekly or monthly deaths from all causes during the pandemic in 2020 and 2021, and for up to 11 year previously. In addition, we obtained excess mortality data for 12 states in India. Excess mortality over time was calculated as observed mortality, after excluding data from periods affected by late registration and anomalies such as heat waves, minus expected mortality. Six models were used to estimate expected mortality; final estimates of expected mortality were based on an ensemble of these models. Ensemble weights were based on root mean squared errors derived from an out-of-sample predictive validity test. As mortality records are incomplete worldwide, we built a statistical model that predicted the excess mortality rate for locations and periods where all-cause mortality data were not available. We used least absolute shrinkage and selection operator (LASSO) regression as a variable selection mechanism and selected 15 covariates, including both covariates pertaining to the COVID-19 pandemic, such as seroprevalence, and to background population health metrics, such as the Healthcare Access and Quality Index, with direction of effects on excess mortality concordant with a meta-analysis by the US Centers for Disease Control and Prevention. With the selected best model, we ran a prediction process using 100 draws for each covariate and 100 draws of estimated coefficients and residuals, estimated from the regressions run at the draw level using draw-level input data on both excess mortality and covariates. Mean

Con 5,3 milioni di decessi in eccesso, l'Asia meridionale ha registrato il numero più alto di morti in eccesso stimate per COVID-19, seguita dal Nord Africa e dal Medio Oriente (1,7 milioni) e dall'Europa orientale (1,4 milioni).

Sono necessari ulteriori studi per comprendere la percentuale di decessi in eccesso dovuti direttamente al COVID-19 e gli effetti indiretti della pandemia, quali l'impatto sui servizi sanitari, i decessi per altre malattie e gli impatti economici più ampi.

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values and 95% uncertainty intervals were then generated at national, regional, and global levels. Out-of-sample predictive validity testing was done on the basis of our final model specification.

**Findings:** Although reported COVID-19 deaths between Jan 1, 2020, and Dec 31, 2021, totalled 5.94 million worldwide, we estimate that 18.2 million (95% uncertainty interval 17.1–19.6) people died worldwide because of the COVID-19 pandemic (as measured by excess mortality) over that period. The global all-age rate of excess mortality due to the COVID-19 pandemic was 120.3 deaths (113.1–129.3) per 100000 of the population, and excess mortality rate exceeded 300 deaths per 100 000 of the population in 21 countries. The number of excess deaths due to COVID-19 was largest in the regions of south Asia, north Africa and the Middle East, and eastern Europe. At the country level, the highest numbers of cumulative excess deaths due to COVID-19 were estimated in India (4.07 million [3.71–4.36]), the USA (1.13 million [1.08–1.18]), Russia (1.07 million [1.06–1.08]), Mexico (798 000 [741000–867000]), Brazil (792 000 [730 000–847000]), Indonesia (736 000 [594000–955000]), and Pakistan (664 000 [498 000–847000]). Among these countries, the excess mortality rate was highest in Russia (374.6 deaths [369.7–378.4] per 100 000) and Mexico (325.1 [301.6–353.3] per 100000), and was similar in Brazil (186.9 [172.2–199.8] per 100000) and the USA (179.3 [170.7–187.5] per 100 000).

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	<p><b>Interpretation:</b> The full impact of the pandemic has been much greater than what is indicated by reported deaths due to COVID-19 alone. Strengthening death registration systems around the world, long understood to be crucial to global public health strategy, is necessary for improved monitoring of this pandemic and future pandemics. In addition, further research is warranted to help distinguish the proportion of excess mortality that was directly caused by SARS-CoV-2 infection and the changes in causes of death as an indirect consequence of the pandemic.</p>	
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