REPORT COVID-19 (SETTIMANA 24-30 GENNAIO 2022)

VIROLOGIA E DIAGNOSTICA
ESTENSORE : DOTT. FRANCESCO TACCARI

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
Fajardo Á et al. Curr Opin Pharmacol. Molecular accuracy vs antigenic speed: SARS-CoV-2 testing strategies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8687762/pdf/main.pdf	Abstract The pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has hit every corner of the world faster than any infectious disease ever known. In this context, rapid and accurate testing of positive cases are essential to follow the test-trace-isolate strategy (TETRIS), which has proven to be a key approach to constrain viral spread. Here, we discuss how to interpret and combine molecular or/and antigen-based detection methods for SARS-CoV-2 as well as when they should be used. Their application can be cleverly designed as an algorithm to prevent viral dissemination according to distinct epidemiological contexts within surveillance programs.	In questo studio viene discusso come interpretare e combinare le diverse metodiche molecolari e antigentiche per la diagnosi di infezione da SARS-CoV-2. La RT-PCR, metodica molecolare, rimane al momento il gold standard diagnostico, grazie alle sua elevatissime sensibilità e specificità. Tuttavia, richiedere laboratori specializzati, personale formato, è una metodica costosa, necessita di tempi tecnici ed è, in alcuni casi, sensibile a tal punto da individuare frammenti genetici del virus in pazienti ormai non più contagiosi. Il test antigenico è molto più rapido del molecolare, meno costoso, non richiede personale specializzato, può essere effettuato « point-of-care » e ha una buona sensibilità nel paziente sintomatico, pur essendo meno sensibile dell'esame molecolare, specialmente nel paziente asintomatico. Gli autori suggeriscono infine un modello che combini test antigenico e molecolare in scenari differenti : un test antigenico positivo sarebbe sempre

		indicativo di infezione da SARS-CoV-2, mentre un test antigenico negativo dovrebbe essere confermato da un test molecolare nel caso di pazienti sintomatici o asintomatici contatti di casi sospetti o accertati ; un tampone antigenico negativo potrebbe invece essere sufficente per escludere l'infezione se effettuato come screening di popolazione. Lo studio riassume efficacemente pregi e difetti delle diverse metodiche diagnostiche : un approccio combinato delle due metodiche è il cardine della « test-trace-isolate strategy » (TETRIS) ed è di fondamentale importanza nell'ottica dell'ottimizzazione delle risorse.
Burki T. Lancet Infect Dis. The origin of SARS-CoV-2 variants of concern. https://www.thelancet.com/action/showPdf?pii=S1473-3099%2822%2900015-9	Abstract non disponibile	Articolo della sezione « newsdesk » della prestigiosa rivista Lancet Infectious Diseases nel quale vengono esposte le tre principali teorie dell'origine della variante omicron. La prima teoria sostiene che la variante omicron si sarebbe generata in una comunità chiusa, con scarsa possibilità di sequenziamento genico, poco plausibile, considerata la straordinaria trasmissibilità della variante e tenuto conto dell'interconnessione del mondo. Una seconda teoria prevede che una popolazione di animali sia stata infettata, il virus sia mutato e abbia di nuovo infettato l'uomo, tuttavia è estremamente difficile stabilire quanto comune sia la trasmissione animale-uomo, dato che molti animali sono stati infettati da SARS-CoV-2. La teoria più accreditata prevede un'infezione persistente in un paziente immunocompromesso : nell'ospite immunocompromesso il virus può infatti continuare a replicarsi e a mutare, sviluppando meccanismi per penetrare più efficacemente nella cellula e per evadere il sistema immunitario.

Møller IJB et al. Int J Infect Dis. Diagnostic performance, user acceptability, and safety of unsupervised SARS-CoV-2 rapid antigen detecting tests performed at home. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8759098/pdf/main.pdf	Abstract Background: One strategy for reducing spread of COVID-19 is to contain the infection with broad screening, isolate infected individuals, and trace contacts. This strategy requires widely available, reliable SARS-CoV-2 testing. To increase testing, rapid antigen detection tests (RADTs) were developed for self-sampling, self-testing, and self-interpretation. This study examined diagnostic performance, user acceptability, and safety of nasal self-RADTs, compared to PCR testing. Methods: Self-RADT kits were distributed at a public COVID-19 test center in Aarhus, Denmark or delivered to participants. Participants reported test results and test preferences. During enrollment, participants reported occurrence and duration of symptoms consistent with COVID-19. Sensitivity and specificity of self-RADT, relative to oropharyngeal PCR testing, were calculated. Results: Among 827 participants, 102 showed positive PCR test results. Sensitivities of the self-RADTs were 65.7% (95% CI: 49.2-79.2; DNA Diagnostic) and 62.1% (95% CI: 50.1-72.9; Hangzhou), and specificities were 100% (95% CI: 99.0-100; DNA Diagnostic) and 100% (95% CI: 98.9-100; Hangzhou). The sensitivities of both self-RADTs appeared higher in symptomatic participants than in asymptomatic participants. Two out of every three participants preferred self-RADT over PCR test. Conclusion: Self-performed RADTs were reliable, user acceptable, and safe among laypeople as supplement to	In questo studio danese su 827 partecipanti viene valutata la capacità diagnostica del tampone antigenico rapido effettuato a domicilio rispetto al tampone molecolare, standard diagnostico di riferimento. Ne emerge una discreta sensibilità (62-65%) e un'elevatissima specificità (100%) ; inoltre, la maggior parte dei pazienti sembra preferire il test antigenico a domicilio rispetto al test molecolare effettuato da personale specializzato. Identificare un valido test rapido, poco costoso e di facile esecuzione da poter effettuare a livello capillare rappresenta una sfida per la « test-trace-isolate strategy » (TETRIS). Il test rapido analizzato in questo studio, nonostante sia di facilissima esecuzione, interpretazione e abbia un costo contenuto, è gravato da una percentuale di falsi negativi troppo elevata.

	professionally collected oropharyngeal PCR testing.	
Phetsouphanh C et al. Nat Immunol. Immunological dysfunction persists for 8 months following initial mild-to-moderate SARS-CoV-2 infection. https://www.nature.com/articles/s41590-021-01113-x.pdf	Abstract A proportion of patients surviving acute coronavirus disease 2019 (COVID-19) infection develop post-acute COVID syndrome (long COVID (LC)) lasting longer than 12 weeks. Here, we studied individuals with LC compared to age- and gender-matched recovered individuals without LC, unexposed donors and individuals infected with other coronaviruses. Patients with LC had highly activated innate immune cells, lacked naive T and B cells and showed elevated expression of type I IFN (IFN-β) and type III IFN (IFN-λ1) that remained persistently high at 8 months after infection. Using a log-linear classification model, we defined an optimal set of analytes that had the strongest association with LC among the 28 analytes measured. Combinations of the inflammatory mediators IFN-β, PTX3, IFN-γ, IFN-λ2/3 and IL-6 associated with LC with 78.5-81.6% accuracy. This work defines immunological parameters associated with LC and suggests future opportunities for prevention and treatment.	Studio che mira a valutare la funzionalità del sistema immunitario nel pazienti con sintomi fisici e neuropsichiatrici persistenti dopo l'infezione acuta da SARS-CoV-2 (il cosiddetto long COVID), nei pazienti senza sintomatologia compatbile con long COVID e nei pazienti con infezione da altri coronavirus. Rispetto alle altre categorie, i paziente affetti da long COVID hanno una persistente attivazione dell'immunità innata, un deficit della risposta T e B-mediata e un'elevata espressione di IFN-β e IFN-λ1. Da questo studio sembra emergere come questo virus abbia una peculiare capacità di modificare per lungo tempo la rispost immunitaria innata ed adattativa. Tale prolungata risposta infiammatoria potrebbe essere scatenata da antigeni persistenti, da una risposta autoimmune o da un lungo processo riparativo e sembrerebbe rappresentare il substrato scientifico del long COVID.

REPORT COVID-19 (SETTIMANA 24-30 GENNAIO 2022)

VACCINI

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

ARTICOLO	ABSTRACT	CONTENUTO E COMMENTO
Andrews N. et al. The NEJM Duration of Protection against Mild and Severe Disease by Covid-19 Vaccines https://www.nejm.org/doi/pdf/10.1056/NEJMoa2115481?articleTools=true	BACKGROUND Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19), have been used since December 2020 in the United Kingdom. Real-world data have shown the vaccines to be highly effective against Covid-19 and related severe disease and death. Vaccine effectiveness may wane over time since the receipt of the second dose of the ChAdOx1-S (ChAdOx1 nCoV-19) and BNT162b2 vaccines. METHODS We used a test-negative case–control design to estimate vaccine effectiveness against symptomatic Covid-19 and related hospitalization and death in England. Effectiveness of the ChAdOx1-S and BNT162b2 vaccines was assessed according to participant	COMMENTO: Studio caso-controllo (dicembre 2020-ottobre 2021, Regno Unito) finalizzato a stimare l'efficacia di due dosi dei vaccini per Sars-CoV-2 ChAdOx1-S, BNT162b2 e mRNA-1273 contro l'infezione sintomatica, l'ospedalizzazione entro 14 giorni da un test molecolare positivo e contro l'exitus a 28 giorni dal tampone nasofaringeo positivo. Per tutti gli outcomes sono stati confrontati i dati di pazienti vaccinati, sintomatici e con molecolare positivo per Sars-Cov-2 e di pazienti vaccinati con sintomi da COVID-19 ma con test molecolare negativi (n. tot=6,056,673). L'efficacia dei vaccini nei confronti della variante delta ha mostrato la massima efficacia nei confronti dell'infezione sintomatica nelle prime settimane dopo la

	age and status with regard to coexisting conditions and over time since receipt of the second vaccine dose to investigate waning of effectiveness separately for the B.1.1.7 (alpha) and B.1.617.2 (delta) variants. RESULTS Vaccine effectiveness against symptomatic Covid-19 with the delta variant peaked in the early weeks after receipt of the second dose and then decreased by 20 weeks to 44.3% (95% confidence interval [CI], 43.2 to 45.4) with the ChAdOx1-S vaccine and to 66.3% (95% CI, 65.7 to 66.9) with the BNT162b2 vaccine. Waning of vaccine effectiveness was greater in persons 65 years of age or older than in those 40 to 64 years of age. At 20 weeks or more after vaccination, vaccine effectiveness decreased less against both hospitalization, to 80.0% (95% CI, 76.8 to 82.7) with the ChAdOx1-S vaccine and 91.7% (95% CI, 90.2 to 93.0) with the BNT162b2 vaccine, and death, to 84.8% (95% CI, 76.2 to 90.3) and 91.9% (95% CI, 88.5 to 94.3), re- spectively. Greater waning in vaccine effectiveness against hospitalization was observed in persons 65 years of age or older in a clinically extremely vulnerable group and in persons 40 to 64 years of age with underlying medical conditions than in healthy adults. CONCLUSIONS We observed limited waning in vaccine effectiveness against Covid-19–related hospitalization and death at 20 weeks or more after vaccination with two doses of the ChAdOx1-S or BNT162b2 vaccine. Waning was greater in older adults and in those in a clinical risk group.	seconda dose con una riduzione a 5 mesi fino al 44.3% con ChAdOx-1-S ed al 66.3% con BNT162b2. A 5 mesi dalla seconda dose vaccinale si è invece osservato un tasso minore di riduzione di efficacia nei confronti dell'ospedalizzazione (80%. ChAdOx-1-se. 91.7% BNT162b2) e dei decessi da Sars-CoV-2 (84.8% vs 91.9%). Lo studio fornisce dati importanti sul timing della terza dose di vaccino, alla luce dell'elevata protezione nei confronti dell'ospedalizzazione e del decesso a 5 mesi dalla seconda somministrazione. Le limitazioni dello studio sono in primis legate allo stesso disegno test-negative case-control, uno studio osservazionale soggetto a bias potenziali.

Haas J.W. et al. JAMA Frequency of Adverse Events in the Placebo Arms of COVID-19 Vaccine Trials A Systematic Review and Meta-analysis https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2788172	IMPORTANCE Adverse events (AEs) after placebo treatment are common in randomized clinical drug trials. Systematic evidence regarding these nocebo responses in vaccine trials is important for COVID-19 vaccination worldwide especially because concern about AEs is reported to be a reason for vaccination hesitancy. OBJECTIVE To compare the frequencies of AEs reported in the placebo groups of COVID-19 vaccine trials with those reported in the vaccine groups. DATA SOURCES For this systematic review and meta-analysis, the Medline (PubMed) and Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched systematically using medical subheading terms and free-text keywords for trials of COVID-19 vaccines published up to July 14, 2021. STUDY SELECTION Randomized clinical trials of COVID-19 vaccines that investigated adults aged 16 years or olderwere selected if they assessed solicited AEs within 7 days of injection, included an inert placebo arm, and provided AE reports for both the vaccine and placebo groups separately. Full texts were reviewed for eligibility by 2 independent reviewers. DATA EXTRACTION AND SYNTHESIS Data extraction and quality assessment were performed independently by 2 reviewers, adhering to the Preferred	COMMENTO : Review sistematica e metanalisi eseguita con lo scopo di comparare la frequenza di reazioni avverse nei gruppi riceventi placebo dei trials vaccinali con quelle dei gruppi riceventi il vaccino per Sars-Cov2. Per la selezione degli studi sono stati considerati trial clinici randomizzati che comprendevano persone di età > di 16 anni e ovviamente con un gruppo ricevente placebo, con la registrazione degli eventi avversi per entrambi i gruppi separatamente. L'outcome primario rigurdava le proporzioni delle segnalazioni di reazioni avverse, sia locali che sistemiche, nel gruppo placebo così come i log odds ratios per valutare la differenza trai gruppi. 12 trials per un totale di 45.380 partecipanti venivano analizzati. I dati dimostrano che già dopo la prima dose un 35% dei riceventi placebo segnalava reazioni avverse sistemiche (cefalea ed astenia tra le più frequenti) mentre dopo la seconda dose un 31.8%. Il rapporto tra il braccio placebo e quello del vaccino mostra che le reazioni avverse nel primo (nocebo) rappresentano il 76% delle segnalazioni dopo la prima dose e il 51.8% dopo la seconda. In totale un numero maggiore di partecipanti sottoposti alla somministrazione vaccinale segnalava reazioni avverse, ma il rapporto delle reazioni avverse riportate nel gruppo placebo restava importante e da considerare nell'ambito delle campagne vaccinali, essendo

	Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guideline and using the Cochrane risk-of-bias tool. Meta-analyses were based on random-effects models. MAIN OUTCOMES AND MEASURES The primary outcomes were the proportions of placebo recipients reporting overall, systemic, and local (injection-site) AEs as well as logarithmic odds ratios. (ORs) to evaluate group differences. Outcomes were tested for significance using z tests with 95%CIs. RESULTS Twelve articles with AE reports for 45 380 participants (22 578 placebo recipients and 22 802 vaccine recipients) were analyzed. After the first dose, 35.2%(95%CI, 26.7%-43.7%) of placebo recipients experienced systemic AEs, with headache (19.3%; 95%CI, 13.6%-25.1%) and fatigue (16.7%; 95%CI, 9.8%-23.6%) being most common. After the second dose, 31.8%(95%CI, 28.7%-35.0%) of placebo recipients reported systemic AEs. The ratio between placebo and vaccine arms showed that nocebo responses accounted for 76.0% of systemic AEs after the first COVID-19 vaccine dose and for 51.8%after the second dose. Significantly more vaccine recipients reported AEs, but the group difference for systemic AEswas small after the first dose (OR, −0.47; 95%CI, −0.54 to −0.40; P < .001; standardized mean difference, −0.26; 95%CI, −0.30 to −0.22) and large after the second dose (OR, −1.36; 95%CI, −1.86 to −0.86; P < .001; standardized mean difference, −0.75; 95% CI, −1.03 to −0.47).CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis, significantly more AEs were reported in vaccine groups compared with placebo	proprio la preoccupazione per le reazioni avverse uno dei maggiori fattori di esitazione nella popolazione a sottoporsi al vaccino. Tra le limitazioni maggiori dello studio si riportano un relativo basso numero di trials analizzati e la loro elevata eterogeneità.

	groups, but the rates of reported AEs in the placebo armswere still substantial. Public vaccination programs should consider these high rates of AEs in placebo arms.	
Roos S.G. Sablerolles et al The NEJM Immunogenicity and Reactogenicity of Vaccine Boosters after Ad26.COV2.S Priming https://www.nejm.org/doi/full/10.1056/NEJMoa2116747	BACKGROUND: The Ad26.COV2.S vaccine, which was approved as a single-shot immunization regimen, has been shown to be effective against severe coronavirus disease 2019. However, this vaccine induces lower severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike protein (S)–specific antibody levels than those induced by messenger RNA (mRNA)–based vaccines. The immunogenicity and reactogenicity of a homologous or heterologous booster in persons who have received an Ad26.COV2.S priming dose are unclear. METHODS: In this single-blind, multicenter, randomized, controlled trial involving health care workers who had received a priming dose of Ad26.COV2.S vaccine, we assessed immunogenicity and reactogenicity 28 days after a homologous or heterologous booster vaccination. The participants were assigned to receive no booster, an Ad26.COV2.S booster, an mRNA-1273 booster, or a BNT162b2 booster. The primary end point was the level of S-specific binding antibodies, and the secondary end points were the levels of neutralizing antibodies, S-specific T-cell responses, and reactogenicity. A post hoc analysis was performed to compare mRNA-1273 boosting with BNT162b2 boosting.	Trial clinico randomizzato controllato multicentrico in singolo cieco in operatori sanitari (HCW) nei Paesi Bassi : sono stati selezionati HCW tra i 18 e 65, senza fattori coesistenti/comorbidita' gravi, nessuna storia di infezione da SARS CoV-2, vaccinati con Ad26.COV2.S 3 mesi prima dell'arruolamento e assegnati in maniera casuale (ratio 1:1:1:1) a booster con Ad26.COV2.S, mRNA-1273, BNT162b2 o nessun booster (n=434 partecipanti). L'endpoint primario, ossia il livello di anticorpi IgG contro la subunita' S1 della proteina spike dopo booster, e' stato significamente superiore nei pazienti che hanno ricevuto booster rispetto a chi non lo ha ricevuto e questo maggiormente dopo booster con mRNA 1273 (beta coefficient, 0.21; 98.3% CI, 0.13 to 0.37). La vaccinazione eterologa con booster a mRNA hanno avuto livelli di anticorpi leganti superiori alla vaccinazione omologa, con una maggiore quota di anticorpi neutralizzanti. Per quanto riguarda le risposte cellulari T-mediate, queste sono state maggiori nel gruppo che ha ricevuto il booster a mRNA: risposta al 91.7% con il booster mRNA-1273 e 91.5% con il booster BNT162b2; entrambi con migliori performance del booster omologo (risposta 72.7%).

	RESULTS: Homologous or heterologous booster vaccination in 434 participants resulted in higher levels of S-specific binding antibodies, neutralizing antibodies, and T-cell responses than a single Ad26.COV2.S vaccination. The increase in binding antibodies was significantly larger with heterologous regimens that included mRNA-based vaccines than with the homologous booster. The mRNA-1273 booster was most immunogenic and was associated with higher reactogenicity than the BNT162b2 and Ad26.COV2.S boosters. Local and systemic reactions were generally mild to moderate in the first 2 days after booster administration. CONCLUSIONS: The Ad26.COV2.S and mRNA boosters had an acceptable safety profile and were immunogenic in health care workers who had received a priming dose of Ad26.COV2.S vaccine. The strongest responses occurred after boosting with mRNA-based vaccines. Boosting with any available vaccine was better than not boosting. (Funded by the Netherlands Organization for Health Research and Development ZonMw; SWITCH ClinicalTrials.gov number, NCT04927936. opens in new tab.)	Sul versante reattogenicita', il booster mRNA1273 e' stato associato a una piu' grande percezione di severita' e durata delle reazioni locali e sistemiche (comunque lievi-moderate senza necessita' di ospedalizzazione, risoltesi nelle 48 ore). Limiti: popolazione piu' giovane degli studi di vaccinazione omologa, neutralizzazione misurata sulla variante su cui questi vaccini sono stati sviluppati (e non le nuove varianti di interesse), durata ottimale per booster non nota, ruolo dei anticorpi non neutralizzanti nella protezione contro il COVID19 grave, longevita' della risposta non analizzata (follow-up a 28 giorni), risposta cellulo-mediata non ancora ben studiata.
Gruell H. et al. mRNA booster immunization elicits potent neutralizing serum activity against the SARS-CoV-2	The Omicron variant of SARS-CoV-2 is causing a rapid increase in infections across the globe. This new variant of concern carries an unusually high number of mutations in key epitopes of neutralizing antibodies on the viral spike glycoprotein, suggesting potential immune evasion. Here we assessed serum neutralizing capacity in longitudinal cohorts	Studio in vitro sull'attivita' neutralizzante indotta da vaccino sul siero di una coorte di 30 individui senza evidenza di pregressa infezione, vaccinato con 2 dosi di BNT162b2, sul siero di 30 individui convalescent che hanno poi ricevuto una dose di BNT162b2, studiati mediante un pseudovirus assay basato su lentivirus. I sieri sono stati quindi testati sull'espressione sugli pseudovirus delle protein spike dei

Omicron variant https://www.nature.com/articles/s41591-021-01676-0.pdf	of vaccinated and convalescent individuals, as well as monoclonal antibody activity against Omicron using pseudovirus neutralization assays. We report a near-complete lack of neutralizing activity against Omicron in polyclonal sera from individuals vaccinated with two doses of the BNT162b2 COVID-19 vaccine and from convalescent individuals, as well as resistance to different monoclonal antibodies in clinical use. However, mRNA booster immunizations in vaccinated and convalescent individuals resulted in a significant increase of serum neutralizing activity against Omicron. This study demonstrates that booster immunizations can critically improve the humoral immune response against the Omicron variant.	ceppi Wu01, Alpha (B.1.1.7), Delta (B.1.617.2), Beta (B.1.351) e Omicron. Tutti i campioni dei vaccinati hanno mostrato attivita' neutralizzante contro il ceppo Wu01 con una media geometrica al 50% di diluzione inibitoria sierica (GeoMean ID50) di 546. L'attivita' neutralizzante sierica per le varianti Alpha, Delta, and Beta e' stata minore (GeoMean ID50s di 331, 172 e 40, rispettivamente). Solo 9 sieri sui 30 dei vaccinati (30%) aveva attivita' neutralizzante sierica contro Omicron, con una GeoMean ID50 di 8, significativamente minore che con la variante Beta ($P < 0.0001$), una delle varianti note per la sua maggiore evasione immune. Dopo il completamento del ciclo vaccinale con due dosi di vaccino BNT162b2 vaccine, l'attivita' neutralizzante sierica contro il ceppo Wu01 e' diminuita di 4 volte lungo un periodo di 5 mesi (GeoMean ID50 da 546 a 139), ma e' incrementata in maniera robusta dopo il booster (GeoMean ID50 6,241). Dopo il completamento del ciclo vaccinale (due dosi di vaccino BNT162b2), solo il 30–37% dei campioni aveva attivita' neutralizzante determinabile contro la variante Omicron (GeoMean ID50s di 8 e 9 in tempo precoce e tardivo): quest'ultima e' aumentata di 100 volte dopo la somministrazione di dose booster con BNT162b2 (GeoMean ID50 di 1,195 in tutti I 30 partecipanti)

		Analizzando la risposta neutralizzante sierica contro omicron in una coorte longitudinale di 30 individui non vaccinati con pregressa infezione, successivamente vaccinati con una singola dose di BNT162b2, si e' osservato invece che, nell'immediato periodo post infezione (1 mese e mezzo dopo), l'attivita' neutralizzante verso il ceppo Wu01 era variabile (ID50s 37 - 11,008, GeoMean ID50 494, con decremento fino a 93 dopo 12 mesi). Dopo una singola dose di BNT162b2, si e' documentato un forte incremento dell'attivita' neutralizzante sierica (GeoMean ID50 7,997 contro il ceppo Wu01). Contro la variante Omicron, nell'immediato period post infezione e tardive (12 mesi dopo), si e' mostrata scarsa attivita' neutralizzante sierica, con un modesto incremento nel periodo tardivo per alcuni soggetti (possibile indice di una maturazione dell'affinita' anticorpale in atto). Dopo una singola dose di vaccino BNT162b2, si e' osservato un forte aumento dell'attivita' neutralizzante sierica nei precedentemente infetti (GeoMean ID50 1,549 1 mese dopo la vaccinazione) L'attivita' neutralizzante contro omicron e' stata inoltre studiata sugli anticorpi monoclonali maggiormente usati (bamlanvimab, etesevimab, REGN10933 (casirivimab), REGN10987 (imdevimab), S309 (sotrovimab)), un anticorpo attualmente studiato (DZIF-10c)) si e' assistito ad una marcata riduzione dell'attivita' in 7 anticorpi su 9 (conservata per sotrovimab e DZIF-10c).

REPORT COVID-19 (SETTIMANA 24-30 GENNAIO 2022)

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
Wolter N et al Early assessment of the clinical severity of the SARS-CoV-2 omicron variant in South Africa: a data linkage study The Lancet https://www.thelancet.com/action/showPdf?pii=S0140-6736%2822%2900017-4	Background The SARS-CoV-2 omicron variant of concern was identified in South Africa in November, 2021, and was associated with an increase in COVID-19 cases. We aimed to assess the clinical severity of infections with the omicron variant using S gene target failure (SGTF) on the Thermo Fisher Scientific TaqPath COVID-19 PCR test as a proxy. Methods We did data linkages for national, South African COVID-19 case data, SARS-CoV-2 laboratory test data, SARS-CoV-2 genome data, and COVID-19 hospital admissions data. For individuals diagnosed with COVID-19 via TaqPath PCR tests, infections were designated as either SGTF or non-SGTF. The delta variant was identified by genome sequencing. Using multivariable logistic regression models, we assessed disease severity and hospitalisations by	Studio retrospettivo nazionale di data linkages condotto in Sud-Africa con l'obiettivo di valutare la gravità clinica delle infezioni da variante omicron a confronto con infezioni da variante delta, utilizzando la perdita del gene S al test PCR per COVID-19 (SGTF) come proxy di variante omicron. I risultati dell'analisi suggeriscono che pazienti con SGTF hanno un ridotto rischio di ospedalizzazione e di malattia severa, probabilmente come risultato di una precedente immunità.

	comparing individuals with SGTF versus non-SGTF infections diagnosed between Oct 1 and Nov 30, 2021, and we further assessed disease severity by comparing SGTF-infected individuals diagnosed between Oct 1 and Nov 30, 2021, with delta variant-infected individuals diagnosed between April 1 and Nov 9, 2021. Findings From Oct 1 (week 39), 2021, to Dec 6 (week 49), 2021, 161 328 cases of COVID-19 were reported in South Africa. 38 282 people were diagnosed via TaqPath PCR tests and 29 721 SGTF infections and 1412 non-SGTF infections were identified. The proportion of SGTF infections increased from two (3·2%) of 63 in week 39 to 21 978 (97·9%) of 22 455 in week 48. After controlling for factors associated with hospitalisation, individuals with SGTF infections had significantly lower odds of admission than did those with non-SGTF infections (256 [2·4%] of 10 547 *vs* 121 [12·8%] of 948; adjusted odds ratio [aOR] 0·2, 95% CI 0·1–0·3). After controlling for factors associated with disease severity, the odds of severe disease were similar between hospitalised individuals with SGTF versus non-SGTF infections (42 [21%] of 204 *vs*45 [40%] of 113; aOR 0·7, 95% CI 0·3–1·4). Compared with individuals with earlier delta variant infections, SGTF-infected individuals had a significantly lower odds of severe disease (496 [62·5%] of 793 *vs* 57 [23·4%] of 244; aOR 0·3, 95% CI 0·2–0·5), after controlling for factors associated with disease severity. Interpretation Our early analyses suggest a significantly	

	reduced odds of hospitalisation among individuals with SGTF versus non-SGTF infections diagnosed during the same time period. SGTF-infected individuals had a significantly reduced odds of severe disease compared with individuals infected earlier with the delta variant. Some of this reduced severity is probably a result of previous immunity.	
Berger JS et al Effect of P2Y12 Inhibitors on Survival Free of Organ Support Among Non–Critically Ill Hospitalized Patients With COVID-19 A Randomized Clinical Trial JAMA https://jamanetwork.com/journals/jama/fullarticle/2788141	Importance Platelets represent a potential therapeutic target for improved clinical outcomes in patients with COVID-19. Objective To evaluate the benefits and risks of adding a P2Y12 inhibitor to anticoagulant therapy among non–critically ill patients hospitalized for COVID-19. Design, Setting, and Participants An open-label, bayesian, adaptive randomized clinical trial including 562 non–critically ill patients hospitalized for COVID-19 was conducted between February 2021 and June 2021 at 60 hospitals in Brazil, Italy, Spain, and the US. The date of final 90-day follow-up was September 15, 2021. Interventions Patients were randomized to a therapeutic dose of heparin plus a P2Y12 inhibitor (n=293) or a therapeutic dose of heparin only (usual care) (n=269) in a 1:1 ratio for 14 days or until hospital discharge, whichever was sooner. Ticagrelor was the preferred P2Y12 inhibitor. Main Outcomes and Measures The composite primary outcome was organ support–free days evaluated on an ordinal scale that combined in-hospital death (assigned a value of −1) and, for those who survived to hospital	Trial clinico randomizzato adattativo multicentrico condotto in Brasile, Italia, Spagna e USA con l'obiettivo di valutare benefici e rischi dati dall'aggiunta di un inibitore di P2Y12, principalmente ticagrelor, alla terapia anticoagulante in pazienti ospedalizzati per COVID-19 non critici. Lo studio è stato interrotto precocemente per futility, poichè l'aggiunta di un inibitore di P2Y12 alla terapia standard con eparina a dosaggio terapeutico non ha mostrato benefici in termini di giorni liberi da necessità di supporto d'organo durante l'ospedalizzazione.

	discharge, the number of days free of respiratory or cardiovascular organ support up to day 21 of the index hospitalization (range, −1 to 21 days; higher scores indicate less organ support and better outcomes). The primary safety outcome was major bleeding by 28 days as defined by the International Society on Thrombosis and Hemostasis. Results Enrollment of non–critically ill patients was discontinued when the prespecified criterion for futility was met. All 562 patients who were randomized (mean age, 52.7 [SD, 13.5] years; 41.5% women) completed the trial and 87% received a therapeutic dose of heparin by the end of study day 1. In the P2Y12 inhibitor group, ticagrelor was used in 63% of patients and clopidogrel in 37%. The median number of organ support–free days was 21 days (IQR, 20-21 days) among patients in the P2Y12 inhibitor group and was 21 days (IQR, 21-21 days) in the usual care group (adjusted odds ratio, 0.83 [95% credible interval, 0.55-1.25]; posterior probability of futility [defined as an odds ratio <1.2], 96%). Major bleeding occurred in 6 patients (2.0%) in the P2Y12 inhibitor group and in 2 patients (0.7%) in the usual care group (adjusted odds ratio, 3.31 [95% CI, 0.64-17.2]; *P*=.15). Conclusions and Relevance Among non–critically ill patients hospitalized for COVID-19, the use of a P2Y12 inhibitor in addition to a therapeutic dose of heparin, compared with a therapeutic dose of heparin only, did not result in an increased odds of improvement in organ support–free days within 21 days during hospitalization.	

O'Brien MP et al Effect of Subcutaneous Casirivimab and Imdevimab Antibody Combination vs Placebo on Development of Symptomatic COVID-19 in Early Asymptomatic SARS-CoV-2 Infection A Randomized Clinical Trial JAMA https://jamanetwork.com/journals/jama/fullarticle/2788256	Importance Easy-to-administer anti–SARS-CoV-2 treatments may be used to prevent progression from asymptomatic infection to symptomatic disease and to reduce viral carriage. Objective To evaluate the effect of combination subcutaneous casirivimab and imdevimab on progression from early asymptomatic SARS-CoV-2 infection to symptomatic COVID-19. Design, Setting, and Participants Randomized, double-blind, placebo-controlled, phase 3 trial of close household contacts of a SARS-CoV-2–infected index case at 112 sites in the US, Romania, and Moldova enrolled July 13, 2020–January 28, 2021; follow-up ended March 11, 2021. Asymptomatic individuals (aged ≥12 years) were eligible if identified within 96 hours of index case positive test collection. Results from 314 individuals positive on SARS-CoV-2 reverse transcriptase–quantitative polymerase chain reaction (RT-qPCR) testing are reported. Interventions Individuals were randomized 1:1 to receive 1 dose of subcutaneous casirivimab and imdevimab, 1200 mg (600 mg of each; n=158), or placebo (n=156). Main Outcomes and Measures The primary end point was the proportion of seronegative participants who developed symptomatic COVID-19 during the 28-day efficacy assessment period. The key secondary efficacy end points were the number of weeks of symptomatic SARS-CoV-2 infection and the number of weeks of high viral load (>4 $\log_{10}$ copies/mL).	Trial clinico randomizzato controllato in doppio-cieco di fase 3 con l'biettivo di valutare l'effetto della somministrazione sottocutanea della combinazione di anticorpi monoclonali casirivimab e imdevimab nel prevenire la progressione dell'infezione da SARS-CoV-2 dalla forma asintomatica alla malattia sintomatica. Studio condotto in USA, Romania e Moldavia tra luglio 2020 e marzo 2021. Lo studio dimostra che la somministrazione sottocutanea di casirivimab e imdevimab nei pazienti asintomatici con infezione da SARS-CoV-2 riduce significativamente il rischio di sviluppare malattia sintomatica e la durata dei sintomi sviluppati. Questo studio ha il vantaggio di indagare la somministrazione di anticorpi monoclonali per via sottocutanea, di più facile applicabilità rispetto all'infusione endovenosa, facilità che ne consentirebbe una maggiore diffusione anche a livello territoriale. D'altro canto lo studio è stato condotto in un arco temporale in cui non era ancora diffusa la variante omicron, contro cui casirivimab e imdevimab sembrano aver perso potere neutralizzante ed efficacia, come emerso da recenti studi di laboratorio.

	Results Among 314 randomized participants (mean age, 41.0 years; 51.6% women), 310 (99.7%) completed the efficacy assessment period; 204 were asymptomatic and seronegative at baseline and included in the primary efficacy analysis. Subcutaneous casirivimab and imdevimab, 1200 mg, significantly prevented progression to symptomatic disease (29/100 [29.0%] vs 44/104 [42.3%] with placebo; odds ratio, 0.54 [95% CI, 0.30-0.97]; *P*=.04; absolute risk difference, −13.3% [95% CI, −26.3% to −0.3%]). Casirivimab and imdevimab reduced the number of symptomatic weeks per 1000 participants (895.7 weeks vs 1637.4 weeks with placebo; *P*=.03), an approximately 5.6-day reduction in symptom duration per symptomatic participant. Treatment with casirivimab and imdevimab also reduced the number of high viral load weeks per 1000 participants (489.8 weeks vs 811.9 weeks with placebo; *P*=.001). The proportion of participants receiving casirivimab and imdevimab who had 1 or more treatment-emergent adverse event was 33.5% vs 48.1% for placebo, including events related (25.8% vs 39.7%) or not related (11.0% vs 16.0%) to COVID-19. Conclusions and Relevance Among asymptomatic SARS-CoV-2 RT-qPCR–positive individuals living with an infected household contact, treatment with subcutaneous casirivimab and imdevimab antibody combination vs placebo significantly reduced the incidence of symptomatic COVID-19 over 28 days.	

Zhang L et al Engineered ACE2 decoy mitigates lung injury and death induced by SARS-CoV-2 variants Nature Chemical Biology https://www.nature.com/articles/s41589-021-00965-6.pdf	Vaccine hesitancy and emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) variants of concern (VOCs) escaping vaccine-induced immune responses highlight the urgency for new COVID-19 therapeutics. Engineered angiotensin-converting enzyme 2 (ACE2) proteins with augmented binding affinities for SARS-CoV-2 spike (S) protein may prove to be especially efficacious against multiple variants. Using molecular dynamics simulations and functional assays, we show that three amino acid substitutions in an engineered soluble ACE2 protein markedly augmented the affinity for the S protein of the SARS-CoV-2 WA-1/2020 isolate and multiple VOCs: B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma) and B.1.617.2 (Delta). In humanized K18-hACE2 mice infected with the SARS-CoV-2 WA-1/2020 or P.1 variant, prophylactic and therapeutic injections of soluble $ACE2_2$.v2.4-IgG1 prevented lung vascular injury and edema formation, essential features of CoV-2-induced SARS, and above all improved survival. These studies demonstrate broad efficacy in vivo of an engineered ACE2 decoy against SARS-CoV-2 variants in mice and point to its therapeutic potential.	Studio su animali in vivo (topo) che dimostra l'efficacia di proteine ACE2 ingegnerizzate con aumentata affinità per la proteina Spike (S) di SARS-CoV-2 nel prevenire il danno vascolare polmonare e la formazione di edema, e di conseguenza nel migliorare la sopravvivenza.
Krasemann S et al The blood-brain barrier is dysregulated in COVID-19 and serves as a CNS entry route for SARS-CoV-2	Neurological complications are common in COVID-19. Although SARS-CoV-2 has been detected in patients' brain tissues, its entry routes and resulting consequences are not well understood. Here, we show a pronounced upregulation of interferon signaling pathways of the neurovascular unit in fatal COVID-19. By investigating the susceptibility of human induced pluripotent stem cell (hiPSC)-derived brain capillary	Studio in vitro su cellule simil-endoteliali di capillari cerebrali derivate da cellule staminali pluripotenti umane, in cui viene dimostrata la replicazione attiva di SARS-CoV-2 e la sua capacità di trasporto transcellulare attraverso la barriera emato-encefalica. Il passaggio di SARS-CoV-2 attraverso la barriera emato-encefalica può essere ridotto dalla presenza di anticorpi anti-Spike, anti-ACE2 e anti-neuropilina-1. Questi dati sono a supporto della capacità di SARS-CoV-2 di

Stem Cell Reports https://www.cell.com/stem-cell-reports/fulltext/S2213-6711(21)00650-0	endothelial-like cells (BCECs) to SARS-CoV-2 infection, we found that BCECs were infected and recapitulated transcriptional changes detected *in vivo*. While BCECs were not compromised in their paracellular tightness, we found SARS-CoV-2 in the basolateral compartment in transwell assays after apical infection, suggesting active replication and transcellular transport of virus across the blood-brain barrier (BBB) *in vitro*. Moreover, entry of SARS-CoV-2 into BCECs could be reduced by anti-spike-, anti-angiotensin-converting enzyme 2 (ACE2)-, and anti-neuropilin-1 (NRP1)-specific antibodies or the transmembrane protease serine subtype 2 (TMPRSS2) inhibitor nafamostat. Together, our data provide strong support for SARS-CoV-2 brain entry across the BBB resulting in increased interferon signaling.	attraversare la barriera emato-encefalica e aumentare il signaling dell'interferone, giustificando in parte le manifestazioni neurologiche comunemente riportare nel COVID-19.
Petersen EL et al Multi-organ assessment in mainly non-hospitalized individuals after SARS-CoV-2 infection: The Hamburg City Health Study COVID programme *European Heart Journal*	Aims Long-term sequelae may occur after SARS-CoV-2 infection. We comprehensively assessed organ-specific functions in individuals after mild to moderate SARS-CoV-2 infection compared with controls from the general population. Methods and results Four hundred and forty-three mainly non-hospitalized individuals were examined in median 9.6 months after the first positive SARS-CoV-2 test and matched for age, sex, and education with 1328 controls from a population-based German cohort. We assessed pulmonary, cardiac, vascular, renal, and neurological status, as well as patient-related outcomes. Bodyplethysmography documented mildly lower total lung volume (regression coefficient −3.24,	Studio volto a valutare lo status polmonare, cardiaco, vascolare, renale e neurologico dopo una media di 9 mesi dall'infezione da SARS-CoV-2, in pazienti con forme da lievi a moderate di infezione e prevalentemente non ospedalizzati. Gli autori dimostrano che soggetti apparentemenți guariti riportano comunque sequele multi-organo a lungo termine, quali lieve riduzione del volume polmonare totale e aumento delle resistenze delle vie aeree, misure di funzione ventricolare destra e sinistra lievemente più basse e aumento delle concentrazioni di biomarkers cardiaci, maggiore incidenza di trombosi venosa profonda e riduzione della capacità di filtrazione glomerulare.

https://academic.oup.com/eurheartj/advance-article/doi/10.1093/eurheartj/ehab914/6499078	adjusted *P*=0.014) and higher specific airway resistance (regression coefficient 8.11, adjusted *P*=0.001) after SARS-CoV-2 infection. Cardiac assessment revealed slightly lower measures of left (regression coefficient for left ventricular ejection fraction on transthoracic echocardiography −0.93, adjusted *P*=0.015) and right ventricular function and higher concentrations of cardiac biomarkers (factor 1.14 for high-sensitivity troponin, 1.41 for N-terminal pro-B-type natriuretic peptide, adjusted *P*≤0.01) in post-SARS-CoV-2 patients compared with matched controls, but no significant differences in cardiac magnetic resonance imaging findings. Sonographically non-compressible femoral veins, suggesting deep vein thrombosis, were substantially more frequent after SARS-CoV-2 infection (odds ratio 2.68, adjusted *P*<0.001). Glomerular filtration rate (regression coefficient −2.35, adjusted *P*=0.019) was lower in post-SARS-CoV-2 cases. Relative brain volume, prevalence of cerebral microbleeds, and infarct residuals were similar, while the mean cortical thickness was higher in post-SARS-CoV-2 cases. Cognitive function was not impaired. Similarly, patient-related outcomes did not differ. Conclusion Subjects who apparently recovered from mild to moderate SARS-CoV-2 infection show signs of subclinical multi-organ affection related to pulmonary, cardiac, thrombotic, and renal function without signs of structural brain damage, neurocognitive, or quality-of-life impairment. Respective screening may guide further patient management.	

Shoji K et al Clinical characteristics and outcomes of COVID-19 in pregnant women: a propensity score matched analysis of the data from the COVID-19 Registry Japan Clinical Infectious Diseases https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciac028/6509063	Background Several studies have investigated whether pregnancy is a risk factor for developing severe COVID-19; however, the results remain controversial. In addition, the information regarding risk factors for developing severe COVID-19 in pregnant women is limited. Methods A retrospective cohort study analyzing the data from the nationwide COVID-19 registry in Japan was conducted. Propensity score matched analysis was performed to compare COVID-19 severity between pregnant and nonpregnant women. Multivariate analysis was also conducted to evaluate risk factors for developing moderate-to-severe COVID-19 in pregnant women. Results During the study period, 254 pregnant and 3752 nonpregnant women of reproductive age were identified. After propensity score matching, 187 pregnant women and 935 nonpregnant women were selected. A composite outcome of moderate-to-severe COVID-19 was more frequently observed in pregnant women than that of nonpregnant women (n=18, 9.6% vs. n=46, 4.9%; *P*=0.0155). In multivariate analysis, the presence of underlying diseases and being in the second-to-third trimester of pregnancy were recognized as risk factors for moderate-to-severe COVID-19 in pregnant women (odds ratio [95% confidence interval]: 5.295 [1.21-23.069] and 3.871 [1.201-12.477], respectively).	Studio retrospettivo di coorte condotto utilizzando i dati del registro COVID-19 nazionale giapponese in cui 187 donne in gravidanza sono state matchate per gravità con 935 donne non in gravidanza per valutare i fattori di rischio di sviluppare malattia moderato-severa nelle donne in gravidanza. I risultati hanno dimostrato che la gravidanza in sè rappresenta un fattore di rischio per forme moderato-severe e che nelle donne in gravidanza la presenza di comorbidità e le fasi avanzate di gravidanza (secondo e terzo trimestre) rappresentano fattori di rischio per forme moderato-severe di COVID-19.

	Conclusions Pregnancy could be a risk factor for moderate-to-severe COVID-19 for women in Japan. In addition to the presence of comorbidities, advanced pregnancy stages may contribute to greater risks for developing moderate-to-severe COVID-19 in pregnant women.	

REPORT COVID-19 (SETTIMANA 24-30 GENNAIO 2022)

SANITA' PUBBLICA, EPIDEMIOLOGIA, EPIDEMIOLOGIA BIOMOLECOLARE ESTENSORI : DOTT. SSA PAOLA DEL GIACOMO- DOTT. FRANCESCO V. SEGALA		
ARTICOLO	ABSTRACT	CONTENUTO
Sood N et al. JAMA Seroprevalence of Antibodies Specific to Receptor Binding Domain of SARS-CoV-2 and Vaccination Coverage Among Adults in Los Angeles County, April 2021: The LA Pandemic	This cross-sectional study estimates the seroprevalence of antibodies specific to the receptor binding domain of the spike protein of SARS-CoV-2 and vaccination coverage among adults in Los Angeles County, California, in April 2021.	Studio cross-sectional esplorante la sieroprevalenza di anticorpi diretti contro il receptor-binding domain (RBD) su un campione di popolazione residente a Los Angeles statisticamente rappresentativo. Sulla base di questa analisi è risultato che il 72% degli adulti residenti a LA possiedono una potenziale immunità protettiva nei confronti di SARS-CoV2, con percentuali significativamente inferiori per afroamericani e comunità economicamente deprivate.

Surveillance Cohort Study https://jamanetwork.com/journals/jama/fullarticle/2788408		
Henry NJ et al. Scientific Reports Variation in excess all-cause mortality by age, sex, and province during the first wave of the COVID-19 pandemic in Italy https://www.nature.com/articles/s41598-022-04993-7	Although previous evidence suggests that the infection fatality rate from COVID-19 varies by age and sex, and that transmission intensity varies geographically within countries, no study has yet explored the age-sex-space distribution of excess mortality associated with the COVID pandemic. By applying the principles of small-area estimation to existing model formulations for excess mortality, this study develops a novel method for assessing excess mortality across small populations and assesses the pattern of COVID excess mortality by province, year, week, age group, and sex in Italy from March through May 2020. We estimate that 53,200 excess deaths occurred across Italy during this time period, compared to just 35,500 deaths where COVID-19 was registered as the underlying cause of death. Out of the total excess mortality burden, 97% of excess deaths occurred among adults over age 60, and 68% of excess deaths were concentrated among adults over age 80. The burden of excess mortality was unevenly distributed across the country, with just three of Italy's 107 provinces accounting for 32% of all excess mortality. This method for estimating excess mortality can be adapted to other countries	Primo studio applicante un nuovo modello di calcolo dell'eccesso di mortalità, aggiustata, sesso, area geografica ed età, durante i mesi della prima ondata in Italia (marzo-maggio 2020). Tale studio stima che in questo periodo di tempo sia deceduto un eccesso di 53,200 individui, a confronto delle 35,500 morti registrate come COVID-associate. Inoltre, il 97% di questi decessi ha riguardato individui con età al di sopra dei 60 anni.

	where COVID-19 diagnostic capacity is still insufficient, and could be incorporated into public health rapid response systems..	
De Nadai et al. Nature Scientific Reports The impact of control and mitigation strategies during the second wave of coronavirus infections in Spain and Italy https://www.nature.com/articles/s41598-022-05041-0	European countries struggled to fight against the second and the third waves of the COVID-19 pandemic, as the Test-Trace-Isolate (TTI) strategy widely adopted over the summer and early fall 2020 failed to contain the spread of the disease effectively. This paper sheds light on the effectiveness of such a strategy in two European countries (Spain and Italy) by analysing data from June to December 2020, collected via a large-scale online citizen survey with 95,251 and 43,393 answers in Spain and Italy, respectively. Our analysis describes several weaknesses in each of the three pillars of the TTI strategy: Test, Trace, and Isolate. We find that 40% of respondents had to wait more than 48 hours to obtain coronavirus tests results, while literature has shown that a delay of more than one day might make tracing all cases inefficient. We also identify limitations in the manual contact tracing capabilities in both countries, as only 29% of respondents in close contact with a confirmed infected individual reported having been contact traced. Moreover, our analysis shows that more than 45% of respondents report being unable to self-isolate if needed. We also analyse the mitigation strategies deployed to contain	Survey sull'efficacia della strategia « Test, Trace and Isolate » in Italia e Spagna durante la seconda ondata della pandemia (giugno – dicembre 2020). Tale analisi ha rilevato diverse debolezze critiche : il 40% degli intervistati ha dovuto attendere almeno 48h per ricevere un test diagnostico, solo 29% dei contatti stretti ha riportato di essere stato contattato, e più del 45% degli intervistati ha riportato di non essere in grado di implementare l'isolamento domiciliare. Tuttavia, in Italia, nonostante queste criticità, il 20% dei contatti stretti sono stati efficacemente prevenuti.

	the second wave of coronavirus. We find that these interventions were particularly effective in Italy, where close contacts were reduced by more than 20% in the general population. Finally, we analyse the participants' perceptions about the coronavirus risk associated with different daily activities. We observe that they are often gender- and age-dependent, and not aligned with the actual risk identified by the literature. This finding emphasises the importance of deploying public-health communication campaigns to debunk misconceptions about SARS-CoV-2. Overall, our work illustrates the value of online citizen surveys to quickly and efficiently collect large-scale population data to support and evaluate policy decisions to combat the spread of infectious diseases, such as coronavirus.	