I BEST OF THE WEEK (07 mar – 13 mar 2022)

Articolo	Abstract	Contenuto e Commento
Fragkou PC et al. Clin Microbiol Infect. ESCMID COVID-19 guidelines: diagnostic testing for SARS-CoV-2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8863949/pdf/main.pdf	Abstract **Scope:** The objective of these guidelines is to identify the most appropriate diagnostic test and/or diagnostic approach for SARS-CoV-2. The recommendations are intended to provide guidance to clinicians, clinical microbiologists, other health care personnel, and decision makers. **Methods:** An ESCMID COVID-19 guidelines task force was established by the ESCMID Executive Committee. A small group was established, half appointed by the chair, and the remaining selected with an open call. Each panel met virtually once a week. For all decisions, a simple majority vote was used. A list of clinical questions using the PICO (population, intervention, comparison, outcome) format was developed at the beginning of the process. For each PICO, two panel members performed a literature search focusing on systematic reviews with a third panelist involved in case of inconsistent results. Quality of evidence assessment was based on the GRADE-ADOLOPMENT approach. **Questions addressed by the guideline and recommendations:** A total of 43 PICO questions were selected that involve the following types of populations: 1) patients with signs and symptoms of COVID-19; 2) travelers, healthcare workers, and	

	other individuals at risk for exposure to SARS-CoV-2; 3) asymptomatic individuals and 4) close contacts of patients infected with SARS-CoV-2. The type of diagnostic test (commercial rapid nucleic acid amplification tests, and rapid antigen detection), biomaterial, time since onset of symptoms/contact with an infectious case, age, disease severity, and risk of developing severe disease are also taken into consideration.	
Bar-On Y. M. et al. Preprint not peer reviewed Protection by 4th dose of BNT162b2 against Omicron in Israel https://www.medrxiv.org/content/10.1101/2022.02.01.22270232v1	BACKGROUND: On January 2, 2022, Israel began administering a fourth dose of BNT162b2 vaccine (Pfizer-BioNTech) to people aged over 60 years and at-risk populations, who had received a third dose of vaccine at least 4 months earlier. The effect of the fourth dose on confirmed coronavirus 2019 disease (Covid-19) and severe illness are still unclear. METHODS: We extracted data for the Omicron-dominated period January 15 through January 27, 2022, from the Israeli Ministry of Health database regarding 1,138,681 persons aged over 60 years and eligible for the fourth dose. We compared the rate of confirmed Covid-19 and severe illness between those who had received a fourth dose at least 12 days earlier, those who had received only three doses, and those 3 to 7 days after receiving the fourth dose. We used Poisson regression after adjusting for possible confounding factors. RESULTS : The rate of confirmed infection was lower in people 12 or more days after their fourth dose than among those who received only three doses and those 3 to 7 days after vaccination by factors of 2.0 (95% confidence interval	COMMENTO : analisi condotta in Israele su partecipanti dai 60 anni in su che abbiano ricevuto 3 dosi di vaccino BNT162b2 da almeno 4 prima dell'inizio dello studio nel periodo tra il 15 e il 27 gennaio 2022 (periodo a prevalenza omicron) per indagare infezione da SARS-CoV2 e patologia severa, studiando stato vaccinale, variabili demografiche e area di residenza. Sui 1 138 681 soggetti studiati, si e' effettuata una regressione di Poisson per calcolare i tassi di infezione e patologia severa per 100 000 persone-giorni di rischio in ogni gruppo (3 gruppi : individui eleggibili per non abbiano ricevuto la quarta dose, individui a 3-7 giorni dalla quarta dose, individui a 12 giorni o piu' dalla quarta dose). Il tasso di infezione confermata nel gruppo vaccinato da 12 giorni o piu' era piu' basso di 2 volte (95% confidence interval [CI], 2.0 a 2.1) rispetto al gruppo eleggibile non vaccinato e di 1,9 (95% CI, 1.8 a 1.9) rispetto a coloro che avevano ricevuto la quarta dose 3-7 giorni prima. Le differenze aggiustate dei tassi erano 279 (95% CI, 271 a 287) e 234 (95% CI, 219 a 247) casi per 100,000 persone-

	[CI], 2.0 to 2.1) and 1.9 (95% CI, 1.8 to 2.0), respectively. The rate of severe illness was lower by factors of 4.3 (95% CI, 2.4 to 7.6) and 4.0 (95% CI, 2.2 to 7.5). CONCLUSIONS: Rates of confirmed Covid-19 and severe illness were lower following a fourth dose compared to only three doses.	giorni a rischio tra il gruppo di trattamento e gli altri due gruppi. Il tasso di patologia severa nel gruppo di persone che avevano ricevuto la quarta dose 12 o piu' giorni prima era piu' basso di 4.3 (95% CI 2.4 a 7.6) rispetto al gruppo vaccinato con 3 dosi e di 4.0 volte (95% CI 2.2 a 7.5) rispetto a coloro che avevano ricevuto la quarta dose 3-7 giorni prima. Le differenze aggiustate dei tassi erano di 3.8 (95% CI, 2.8 a 4.8) e 3.5 (95% CI, 2.1 a 5.1) casi per 100,000 persone-giorni di rischio rispetto ai due gruppi di controllo, rispettivamente. Il rapporto di incidenza durante I primi 3-7 giorni dopo la vaccinazione e' circa 1, aumentando di 2-3 volte 2 settimane dopo la vaccinazione. I dati dimostrano che una quarta dose ad almeno 4 mesi dalla terza puo' aumentare la protezione verso la patologia severa, specialmente in popolazioni a rischio. LIMITAZIONI : differenze di comorbidita' nei gruppi non analizzate in quanto dati non disponibili ; non analizzate differenze comportamentali (richiesta di supporto medico ecc) ; modifica delle linee guida nazionali per il testing nello stesso periodo che puo' sovra o sottostimare l'effetto osservato nello studio.
Andrews N. et al. The NEJM	BACKGROUND A rapid increase in coronavirus disease 2019 (Covid-19) cases due to the omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 in highly vaccinated populations has aroused concerns about the effectiveness of current vaccines. METHODS We used a test-	CONTENUTO : studio caso controllo, a design test-negativo per valutare l'efficacia del vaccino contro la malattia sintomatica dovuta alle varianti delta ed omicron nel Regno Unito (novembre 2021-gennaio2022). Tale efficacia è stata valutata dopo due dosi di BNT162b2 (Pfizer–

Covid-19 Vaccine Effectiveness against the Omicron (B.1.1.529) Variant https://www.nejm.org/doi/pdf/10.1056/NEJMoa2119451?articleTools=true	negative case–control design to estimate vaccine effectiveness against symptomatic disease caused by the omicron and delta (B.1.617.2) variants in England. Vaccine effectiveness was calculated after primary immunization with two doses of BNT162b2 (Pfizer–BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), or mRNA-1273 (Moderna) vaccine and after a booster dose of BNT162b2, ChAdOx1 nCoV-19, or mRNA-1273. RESULTS Between November 27, 2021, and January 12, 2022, a total of 886,774 eligible persons infected with the omicron variant, 204,154 eligible persons infected with the delta variant, and 1,572,621 eligible test-negative controls were identified. At all time points investigated and for all combinations of primary course and booster vaccines, vaccine effectiveness against symptomatic disease was higher for the delta variant than for the omicron variant. No effect against the omicron variant was noted from 20 weeks after two ChAdOx1 nCoV-19 doses, whereas vaccine effectiveness after two BNT162b2 doses was 65.5% (95% confidence interval [CI], 63.9 to 67.0) at 2 to 4 weeks, dropping to 8.8% (95% CI, 7.0 to 10.5) at 25 or more weeks. Among ChAdOx1 nCoV-19 primary course recipients, vaccine effectiveness increased to 62.4% (95% CI, 61.8 to 63.0) at 2 to 4 weeks after a BNT162b2 booster before decreasing to 39.6% (95% CI, 38.0 to 41.1) at 10 or more weeks. Among BNT162b2 primary course recipients, vaccine effectiveness increased to 67.2% (95% CI, 66.5 to 67.8) at 2 to 4 weeks after a BNT162b2 booster before declining to 45.7% (95% CI, 44.7 to 46.7) at 10 or more weeks. Vaccine effectiveness	BioNTech), ChAdOx1 nCoV-19 (AstraZeneca), o mRNA-1273 (Moderna) e dopo una dose booster di BNT162b2, ChAdOx1 nCoV-19, o mRNA-1273. La popolazione di studio contava 886.774 persone con variante omicron, 204.154 con variante delta e 1.572.621 controlli test-negativi. I risultati hanno mostrato, in ogni momento dello studio, una superiorità della protezione vaccinale nei confronti della malattia sintomatica contro la variante delta rispetto alla omicron. A 20 settimane dalle due dosi di ChAdOx1 nCoV-19 non sono stati evidenziati effetti contro Omicron, mentre per BNT162b2 la protezione risultava del 65.5% fino a 4 settimane dalla seconda dose vs. 8.8% oltre le 25 settimane. Nei pazienti vaccinati con ChAdOx1 nCoV19 e riceventi il booster BNT162b2 si oscillava tra il 62.4% dopo 2-4 settimane fino al 39.6% oltre le 10 settimane. In pazienti con ciclo vaccinale omologo con BNT162b2 si riscontrava il 67.2% di protezione nel primo periodo per poi decrescere fino al 45.7% oltre le 10 settimane. Quando la dose booster considerata era mRNA-1273 nei pazienti con ciclo primario con Astrazeneca la protezione risultava maggiore, del 70.1% dopo 2-4 settimane per poi ridursi al 60.9% fino alla nona settimana dalla somministrazione booster. La combinazione con i migliori dati di protezione risulta essere quella con ciclo iniziale Pfizer e booster Moderna (73.9% nelle prime 4 settima e 64.4% fino a 9 settimane dal booster). Lo studio evidenzia come il ciclo vaccinale con due dosi, indipendentemente dal composto ricevuto, non garantisce una immunizzazione efficace nei

	after a ChAdOx1 nCoV-19 primary course increased to 70.1% (95% CI, 69.5 to 70.7) at 2 to 4 weeks after an mRNA-1273 booster and decreased to 60.9% (95% CI, 59.7 to 62.1) at 5 to 9 weeks. After a BNT162b2 primary course, the mRNA-1273 booster increased vaccine effectiveness to 73.9% (95% CI, 73.1 to 74.6) at 2 to 4 weeks; vaccine effectiveness fell to 64.4% (95% CI, 62.6 to 66.1) at 5 to 9 weeks. CONCLUSIONS Primary immunization with two doses of ChAdOx1 nCoV-19 or BNT162b2 vaccine provided limited protection against symptomatic disease caused by the omicron variant. A BNT162b2 or mRNA-1273 booster after either the ChAdOx1 nCoV-19 or BNT162b2 primary course substantially increased protection, but that protection waned over time. (Funded by the U.K. Health Security Agency.)	confronti della variante omicron ed inoltre che anche la protezione garantita da una dose booster decresce significativamente con il passare del tempo.
Shytaj I L et al **The FDA-Approved Drug Cobicistat Synergizes with Remdesivir To Inhibit SARS-CoV-2 Replication *In Vitro* and Decreases Viral Titers and Disease Progression in Syrian Hamsters** Virology	Combinations of direct-acting antivirals are needed to minimize drug resistance mutations and stably suppress replication of RNA viruses. Currently, there are limited therapeutic options against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and testing of a number of drug regimens has led to conflicting results. Here, we show that cobicistat, which is an FDA-approved drug booster that blocks the activity of the drug-metabolizing proteins cytochrome P450-3As (CYP3As) and P-glycoprotein (P-gp), inhibits SARS-CoV-2 replication. Two independent cell-to-cell membrane fusion assays showed that the antiviral effect of cobicistat is exerted through inhibition of spike protein-mediated membrane fusion. In line with this, incubation with low-micromolar concentrations of cobicistat	Secondo lo studio, il cobicistat (questo e' il nome del farmaco) potrebbe inibire la moltiplicazione del virus SARS-CoV-2 con un meccanismo diverso da quello dei farmaci ad ora utilizzati, ovvero bloccandone la fusione alle cellule bersaglio. Inoltre, lo studio dimostra che il cobicistat puó attenuare la progressione della malattia nel modello animale di criceto, potenziando in tal senso anche l´effetto di un altro farmaco anti-COVID, ovvero il remdesivir. Finora i tentativi di usare farmaci antiretrovirali contro il SARS-CoV-2 non avevano portato risultati significativi. Come spiegano gli autori dello studio, uno dei motivi principali sono i dosaggi necessari per ottenere un effetto

https://journals.asm.org/doi/full/10.1128/mbio.03705-21	decreased viral replication in three different cell lines including cells of lung and gut origin. When cobicistat was used in combination with remdesivir, a synergistic effect on the inhibition of viral replication was observed in cell lines and in a primary human colon organoid. This was consistent with the effects of cobicistat on two of its known targets, CYP3A4 and P-gp, the silencing of which boosted the *in vitro* antiviral activity of remdesivir in a cobicistat-like manner. When administered *in vivo* to Syrian hamsters at a high dose, cobicistat decreased viral load and mitigated clinical progression. These data highlight cobicistat as a therapeutic candidate for treating SARS-CoV-2 infection and as a potential building block of combination therapies for COVID-19. IMPORTANCE The lack of effective antiviral treatments against SARS-CoV-2 is a significant limitation in the fight against the COVID-19 pandemic. Single-drug regimens have so far yielded limited results, indicating that combinations of antivirals might be required, as previously seen for other RNA viruses. Our work introduces the drug booster cobicistat, which is approved by the FDA and typically used to potentiate the effect of anti-HIV protease inhibitors, as a candidate inhibitor of SARS-CoV-2 replication. Beyond its direct activity as an antiviral, we show that cobicistat can enhance the effect of remdesivir, which was one of the first drugs proposed for treatment of SARS-CoV-2. Overall, the dual action of cobicistat as a direct antiviral and a drug	inibitorio contro la replicazione del virus. Lo studio infatti dimostra che il cobicistat inibisce efficacemente la moltiplicazione del virus SARS-CoV-2 a livelli circa quattro volte superiori a quelli somministrati nelle sperimentazioni cliniche iniziali. L´aspetto più importante dello studio è la dimostrazione che un composto che coadiuva l´azione di altri farmaci possa anche avere un effetto antivirale in vivo. Questo doppio effetto consente di testare una vasta gamma di combinazioni farmacologiche per arrivare ad un cocktail ottimale che possa inibire completamente la replicazione del virus.

	booster can provide a new approach to design combination therapies and rescue the activity of compounds that are only partially effective in monotherapy.	

Stegger M, et al. MedRxiv Occurrence and significance of Omicron BA.1 infection followed by BA.2 reinfection https://www.medrxiv.org/content/10.1101/2022.02.19.22271112v1	The newly found Omicron SARS-CoV-2 variant of concern has rapidly spread worldwide. Omicron carries numerous mutations in key regions and is associated with increased transmissibility and immune escape. The variant has recently been divided into four subvariants with substantial genomic differences, in particular between Omicron BA.1 and BA.2. With the surge of Omicron subvariants BA.1 and BA.2, a large number of reinfections from earlier cases has been observed, raising the question of whether BA.2 specifically can escape the natural immunity acquired shortly after a BA.1 infection. To investigate this, we selected a subset of samples from more than 1,8 million cases of infections in the period from November 22, 2021, until February 11, 2022. Here, individuals with two positive samples,	Grosso studio danese (non ancora peer-reviewed) condotto sui dati raccolti da diversi registri nazionali tra il 22 novembre 2021 e il 11 febbraio 2022. In questo lasso di tempo, su un totale di 1,8 milioni di casi di infezione, 187 individui hanno sviluppato reinfezione (definita come il riscontro di due tamponi positivi a distanza di minimo 20 - 60 giorni l'uno dall'altro) e, tra questi, 47 sono stati reinfettati dalla sottovariante BA.2 dopo infezione da BA.1. Tale studio conferma la possibilità di re-infezione precoce da BA.2 in seguito a infezione da BA.1. Inoltre, lo studio mette in risalto come la popolazione di re-infetti fosse costituita principalmente da soggetti giovani non vaccinati, e come nessuna di queste reinfezioni sia evoluta verso ricovero o malattia severa.

	more than 20 and less than 60 days apart, were selected. From a total of 187 reinfection cases, we identified 47 instances of BA.2 reinfections shortly after a BA.1 infection, mostly in young unvaccinated individuals with mild disease not resulting in hospitalization or death. In conclusion, we provide evidence that Omicron BA.2 reinfections do occur shortly after BA.1 infections but are rare.	