I BEST OF THE WEEK (28 mar – 03 apr 2022)

Articolo	Abstract	Contenuto e Commento
Sheward DJ et al. Lancet Infect Dis. Neutralisation sensitivity of the SARS-CoV-2 omicron (B.1.1.529) variant: a cross-sectional study. https://reader.elsevier.com/reader/sd/pii/S1473309922001293?token=045A8DDD1975390F4756B9C37F35AD82438517884A3036DEB82E5326624F9E43A737A2C3C2FA357A7275844DA39C96A0&originRegion=eu-west-1&originCreation=20220325221634	Abstract 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. 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_{50} (the reciprocal dilution that produces 50% inhibition) against the omicron spike protein, and the fold-change in ID_{50} 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	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.

	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 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_{50} 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_{50} 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_{50} 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_{50} titre 369 vs 45). We found that the omicron variant was resistant to neutralisation (50% inhibitory concentration [IC_{50}] >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 SARS-CoV-2 (IC_{50} 0·1-0·2 µg/mL). 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.	

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. https://www.thelancet.com/action/showPdf?pii=S0140-6736%2821%2902796-3	**Background**: 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. **Methods**: All-cause mortality reports were collected for 74 countries and territories and 266 subnational locations (including 31 locations in low-income and middle-income 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	Questo lavoro, finanziato tra gli altri dalla Bill & 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. 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. 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

	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 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	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.

	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). Interpretation: 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.	