I BEST OF THE WEEK (21 mar – 27 mar 2022)

Articolo	Abstract	Contenuto e Commento
Markov PV et al. Nat Rev Microbiol. Antigenic evolution will lead to new SARS-CoV-2 variants with unpredictable severity. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8919145/pdf/41579_2022_Article_722.pdf	Abstract The comparatively milder infections with the Omicron variant and higher levels of population immunity have raised hopes for a weakening of the pandemic. We argue that the lower severity of Omicron is a coincidence and that ongoing rapid antigenic evolution is likely to produce new variants that may escape immunity and be more severe.	In questo articolo della sezione « comment » della prestigiosa rivista « Nature Reviews Microbiology » viene analizzata la relazione fra l'evoluzione antigenica del virus SARS-CoV-2 e la potenziale formazione di nuovi varianti virali in grado di generare sindromi di severità clinica imprevedibile. Secondo gli autori il concetto secondo cui l'evoluzione dei virus tenderebbe a produrre ceppi sempre meno virulenti al fine di poter aumentare la sua trasmissibilità non ha fondamento : la relativa bassa virulenza della più recente « variant-of-concern » Omicron sarebbe solamente una coincidenza. La virulenza sarebbe infatti del tutto indipendente dalla trasmissibilità del virus e pertanto potrebbero generarsi varianti virali non solo più trasmissibili ma contemporaneamente anche più aggressive. Un altro concetto da accantonare secondo gli autori sarebbe quello per cui la diffusione dell'immunità vaccinale o post-infezione garantirebbe in caso di reinfezione delle forme cliniche meno severe : l'evoluzione antigenica del virus potrebbe rendere infatti le nuove varianti in grado di evadere completamente la risposta immunitaria, dando luogo quindi a forme cliniche di invariata o superiore severità. Le conoscenze dell'evoluzione antigenica dei virus sono ancora estremamente limitate e pertanto risulta

		estremamente difficile predire efficacemente quali nuove varianti potranno generarsi nel prossimo futuro e quali caratteristiche potranno avere. Dovrebbe essere attivamente promossa un'attenta e costante analisi dei meccanismi dell'evoluzione antigenica, specialmente in popolazioni bersaglio dove tale processo è massimizzato come gli immunodepressi o specie animali « permissive » in stretto contatto con l'uomo.

Allotey J et al The BMJ SARS-CoV-2 positivity in offspring and timing of mother-to-child transmission: living systematic review and meta-analysis https://www.bmj.com/content/376/bmj-2021-067696	Objectives To assess the rates of SARS-CoV-2 positivity in babies born to mothers with SARS-CoV-2 infection, the timing of mother-to-child transmission and perinatal outcomes, and factors associated with SARS-CoV-2 status in offspring. Design Living systematic review and meta-analysis. Data sources Major databases between 1 December 2019 and 3 August 2021. Study selection Cohort studies of pregnant and recently pregnant women (including after abortion or miscarriage) who sought hospital care for any reason and had a diagnosis of SARS-CoV-2 infection, and also provided data on offspring	Ampia revisione sistematica di quasi 500 lavori sulla trasmissione verticale di SARS-CoV-2 dalla madre al feto, oppure al neonato durante il parto o in epoca perinatale; il fenomeno è descritto in tutti e tre i casi, ma appare estremamente raro e associato alla gravità dell'infezione materna.

	SARS-CoV-2 status and risk factors for positivity. Case series and case reports were also included to assess the timing and likelihood of mother-to-child transmission in SARS-CoV-2 positive babies. Data extraction Two reviewers independently extracted data and assessed study quality. A random effects model was used to synthesise data for rates, with associations reported using odds ratios and 95% confidence intervals. Narrative syntheses were performed when meta-analysis was inappropriate. The World Health Organization classification was used to categorise the timing of mother-to-child transmission (in utero, intrapartum, early postnatal). Results 472 studies (206 cohort studies, 266 case series and case reports; 28952 mothers, 18237 babies) were included. Overall, 1.8% (95% confidence interval 1.2% to 2.5%; 140 studies) of the 14271 babies born to mothers with SARS-CoV-2 infection tested positive for the virus with reverse transcriptase polymerase chain reaction (RT-PCR). Of the 592 SARS-CoV-2 positive babies with data on the timing of exposure and type and timing of tests, 14 had confirmed mother-to-child transmission: seven in utero (448 assessed), two intrapartum (18 assessed), and five during the early postnatal period (70 assessed). Of the 800 SARS-CoV-2	

	positive babies with outcome data, 20 were stillbirths, 23 were neonatal deaths, and eight were early pregnancy losses; 749 babies were alive at the end of follow-up. Severe maternal covid-19 (odds ratio 2.4, 95% confidence interval 1.3 to 4.4), maternal death (14.1, 4.1 to 48.0), maternal admission to an intensive care unit (3.5, 1.7 to 6.9), and maternal postnatal infection (5.0, 1.2 to 20.1) were associated with SARS-CoV-2 positivity in offspring. Positivity rates using RT-PCR varied between regions, ranging from 0.1% (95% confidence interval 0.0% to 0.3%) in studies from North America to 5.7% (3.2% to 8.7%) in studies from Latin America and the Caribbean. Conclusion SARS-CoV-2 positivity rates were found to be low in babies born to mothers with SARS-CoV-2 infection. Evidence suggests confirmed vertical transmission of SARS-CoV-2, although this is likely to be rare. Severity of maternal covid-19 appears to be associated with SARS-CoV-2 positivity in offspring. Systematic review registration PROSPERO CRD42020178076. Readers' note This article is a living systematic review that will be updated to reflect emerging evidence. Updates may	

	occur for up to two years from the date of original publication.	

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/journals/lancet/article/PIIS0140-6736(21)02796-3/fulltext	**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 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	L'eccesso di mortalità – definito come la differenza netta tra il numero di morti (per tutte le cause) registrato e/o stimato durante la pandemia, e il numero di morti "attese" sulla base dei trend di mortalità registrati negli anni precedenti – è un indicatore cruciale per stimare l'impatto della pandemia in termini di sanità pubblica. Tale valore si scosta dalla mortalità registrata perché, da un lato, non è influenzato dalla sottostima diagnostica (differenza tra numero di casi diagnosticati e reale numero di infezioni) e, dall'altro, tiene in considerazione anche dell'eccesso di mortalità determinato dallo stravolgimento dei sistemi sanitari secondario alla pandemia, e quindi del numero dei morti in eccesso per patologie diverse dalla COVID-19 che non sono state prese correttamente in carico nel periodo di pandemia. I dati per questa analisi sono stati raccolti dai registri nazionali di 74, da gennaio 2008 fino a dicembre 2021, normalizzando le anomalie di mortalità dovute, ad esempio, ad ondate di calore. La mortalità attesa è stata quindi calcolata estrapolata dall'utilizzo di 6 modelli matematici differenti, applicando il modello predittivo anche a nazioni che non forniscono dati di mortalità. Sulla base di tale analisi, sebbene le morti COVID-relate riportate ufficialmente nel periodo di tempo intercorrente tra il 1 gennaio 2020 e il 31 dicembre 2021 sono state 5,94 milioni, gli autori stimano che l'eccesso di mortalità rispetto

	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 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	all'atteso sia stato, in tutto il mondo, di 18 milioni di morti. L'eccesso di mortalità per 100.000 unità di popolazione è risultato eterogeno, a seconda delle aree geografiche, raggiungendo i valori più alti in Asia Meridionale, Nord Africa, Medio Oriente e Est Europa. Le nazioni che hanno assistito all'eccesso di mortalità per 100.000 individui più elevato sono inoltre state, nell'ordine: Russia, Messico, Brasile e USA. Questo studio mette in evidenzia il reale impatto della pandemia sulla mortalità mondiale, stimandolo circa 3 volte superiore ai report ufficiali.

	COVID-19 pandemic was 120·3 deaths (113·1–129·3) per 100000 of the population, and excess mortality rate exceeded 300 deaths per 100000 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 (798000 [741000–867000]), Brazil (792000 [730000–847000]), Indonesia (736000 [594000–955000]), and Pakistan (664000 [498000–847000]). Among these countries, the excess mortality rate was highest in Russia (374·6 deaths [369·7–378·4] per 100000) 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 100000). **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.	