COVID-19 Research Review™

Making Education Easy

Issue 6 - 2022

In this issue:

Abbreviations used in this issue:

HR = hazard ratio; **DMT** = disease modifying therapies; **OR** = odds ratio; **S1PRM** = sohingosine-1-phosphate receptor modulator; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2.

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Welcome to issue 6 of COVID-19 Research Review.

In this issue a multinational study pinpoints the epicentre for the COVID-19 pandemic, a related study discusses the epidemiology of the zoonotic origins of SARS-CoV-2 and a UK study identifies the risk trajectories associated with post-SARS-CoV-2 infection, whilst a US study discusses the epidemiology of the zoonotic origins of SARS-CoV-2. Also, in this issue, myocarditis and pericarditis post-COVID-19 in unvaccinated patients and clinical characteristics with inflammation profiling of long COVID 1-year post-recovery are presented.

We hope you find these and the other selected studies interesting and we look forward to receiving your comments and feedback.

Kind Regards,

Professor Tania Sorrell
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The Huanan Seafood Wholesale Market in Wuhan was the early epicentre of the COVID-19 pandemic.

Authors: Worobey M, et al.

Summary: This study outlines how understanding how SARS-CoV-2 emerged in 2019 is critical to preventing future zoonotic outbreaks before they become pandemics. The Huanan Seafood Wholesale Market in Wuhan, China was originally identified as the source of early COVID-19 cases, however this conclusion became controversial. Live SARS-CoV-2 susceptible mammals were sold at this market in late 2019 and, SARS-CoV-2-positive environmental samples were concentrated in the same area of the market. Whilst the study identifies that samples from live animals were not available, the evidence suggests that the emergence of SARS-CoV-2 occurred via wildlife trade in China and demonstrating that the Huanan market was the epicentre of the pandemic.

Comment: In this companion report spatial relative risk analyses were applied to the early human cases of COVID-19 and to environmental samples of SARS-CoV-2 and combined with human mobility data, to infer that the earliest known COVID-19 cases were geographically centred on The Huanan Seafood Wholesale Market in Wuhan, China. Live animals were not sampled directly, but SARS-CoV-2-positive samples from cages, water drains and other sewage were concentrated in the section housing vendors selling live or freshly butchered SARS-CoV-2 susceptible mammals immediately prior to the pandemic. The almost concurrent emergence of two SARS-CoV-2 lineages in relation to this market (see companion report), strongly suggests that SARS-CoV-2 occurred via the live wildlife trade in China and that the Huanan market was the epicentre of the COVID-19 pandemic. These two publications highlight the need to limit relevant trade and transmission routes and opportunities for virus spill over events to reduce the risk of future pandemics.

Reference: Science 2022; 377:951
Abstract

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COVID-19 Research Review™

Independent commentary by Professor Tania Sorrell

Professor Tania Sorrell is Professor of Clinical Infectious Diseases, and the previous Co-director of the University of Sydney Institute for Infectious Diseases and Director of the NSW Biocontainment Centre. She is one of the NSW and National leaders in research and clinical responses to COVID-19. Prof Sorrell chairs the COVID Expert Committee of the Australian Academy of Health and Medical Sciences and has served on the national Genomics Health Futures Mission Expert Advisory Committee (2019-21), state and national advisory committees in Infectious Diseases (including COVID-19) and therapeutics and the Research and Human Ethics Committees of the National Health and Medical Research Council of Australia.

The molecular epidemiology of multiple zoonotic origins of SARS-CoV-2

Authors: Pekar J et al.

Summary: Understanding the circumstances that lead to a pandemic is important for their prevention. In this study the genomic diversity of SARS-Cov-2 before February 2020 is analysed in Wuhan, China. This study provides evidence that it is likely that SARS-CoV-2 is comprised of two distinct viral lineages, denoted as A and B. These lineages are the result of two separate cross-species transmission events into humans, where the first zoonotic transmission likely involved lineage B viruses around 18 November 2019, whilst separate lineage A likely occurred within weeks of this event. These findings suggest that it is unlikely SARS-CoV-2 circulated widely in humans prior to November 2019, until the first cases of COVID-19 were reported. As with other coronaviruses, SARS-CoV-2's emergence likely resulted from multiple zoonotic events.

Comment: Epidemics of new infectious diseases most commonly originate from zoonotic transmission especially between humans and wild animal reservoirs. Based on analyses of SARS-CoV-2 genomic diversity, this manuscript presents strong evidence that infection of humans first occurred because of separate, but almost contemporaneous, zoonotic transmission events in Wuhan, China. By coupling genomics-based phylodynamic rooting methods with epidemic simulations, the models indicated that two successful viral lineages (A and B) were established in humans, with lineage B causing 65% of early infections. As with other coronaviruses, there were likely multiple zoonotic spills over events, with most not sustained in humans. Although putative, non-human, mammalian hosts were not identified, the data indicated a high probability that human lineage A and B infections originated in proximity to the Huanan Seafood Wholesale Market and that lineage B originated from the wild animal section (see companion paper above). Appropriate regulation of wild-life supply chains and markets will be key to prevention of future pandemics.

Reference: Science 2022; 337:960-6
Abstract

Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients

Authors: Taquet M, et al.

Summary: This study addresses the association of COVID-19 and the increased risk of neurological and psychiatric sequelae. The study aims to determine how long these risks remain, whether adults and children are similarly affected and if the different SARS-CoV-2 variants are associated with different relative risks. The cohort study included patients with COVID-19 diagnosed between January 20, 2020, and April 13, 2022, matched using propensity scores. The analysis was stratified by age group and date of diagnosis. The findings of the study included: most outcomes having HRs significantly increased after 1-6 months. Risks of the common psychiatric disorders returned to baseline after 1-2 months. By contrast risks of cognitive deficit were still increased at the end of the 2-year period. Children were not at an increased risk of mood or anxiety disorders. However, they did have an increased risk of cognitive deficit, insomnia, and intracranial haemorrhage. These differing trajectories suggest different pathogeneses.

Comment: In this study electronic health records of individuals with COVID-19 and a matched control group with other respiratory infections, were accessed from the extensive TriNetX database. The duration of neurological and psychiatric disorders was determined. An increased risk of five of 14 disorders (cognitive deficit (brain fog), dementia, psychotic disorders, and epilepsy or seizures) was still present 2 years post-COVID. Potential biases in results may have resulted from pre-existing but undiagnosed dementia and as noted in an accompanying editorial, the assumption that the diagnosis of psychosis in routinely collected data, is valid. That the risk of mood and anxiety disorders returned to baseline within 2 months is encouraging, as is the generally more benign course in children. However, compared with adults, the cumulative incidence of epilepsy or seizures, encephalitis, and nerve, nerve root, and plexus disorder at 2 years was significantly higher in children (albeit with small absolute risks). Prospective studies are needed to confirm these findings. If similar neurological and psychiatric outcomes noted during the delta and omicron waves are confirmed, the burden on health-care systems might continue even with variants that otherwise cause less severe disease.

Reference: Lancet Psychiatry published online Aug, 17 2022
Abstract

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References: 1. LAGEVRIO® Approved Product Information. 22 April 2022. **2.** Pharmaceutical Benefits Scheme (PBS). www.pbs.gov.au. Accessed 11 July 2022.

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MSD

Long-term cardiovascular outcomes of COVID-19

Authors: Xie Y, et al.

Summary: This study identifies that the long-term cardiovascular manifestations of COVID-19 have not yet been comprehensively characterised. This cohort study includes 153,760 individuals with COVID-19 as well as two control cohorts with 5,637,647 contemporary controls and 5,859,411 historical controls to estimate the risks and burdens on cardiovascular outcomes 1-year post-COVID-19 infection. The study concludes that beyond the first 30 days after infection individuals with COVID-19 have an increased risk of cardiovascular disease spanning across several categories. These can include dysrhythmias, ischaemic and non-ischaemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease. The study identifies that care pathways of those surviving with acute COVID-19 should include attention to cardiovascular and health disease.

Reference: Nat Med 2022;28:583-590
Abstract

The Incidence of Myocarditis and Pericarditis in Post COVID-19 Unvaccinated Patients - A Large Population-Based Study

Authors: Tuvali O, et al.

Summary: This retrospective cohort study evaluates the incidence of myocarditis and pericarditis in post COVID-19 patients from March 2020 and February 2021. Both of which are potential post-acute cardiac sequalae of COVID-19 arising from the adaptive immune response. 196,992 adults were included in the cohort study, and diagnosis of either myocarditis or pericarditis was retrieved day 10 after a positive PCR. A follow up was then conducted in February 2021 over the course of 18 days. The study's findings included 9 patients diagnosed with myocarditis and 11 with pericarditis. In the control cohort 27 patients had myocarditis and 52 had pericarditis. Age and male sex were also associated with myocarditis proven by a 95% CI. Male sex and peripheral vascular disease were also associated with pericarditis.

Reference: J Clin Med. 2022; 11;2219
Abstract

Comment: Viral myocarditis and pericarditis are recognised though uncommon, manifestations of acute COVID-19. Both syndromes are also rare adverse effects of vaccination with the BNT162b2mRNA COVID-19 vaccine, especially in young males; in this setting the pathogenesis is most likely driven by the adaptive immune response. Two recent studies in Israel and the USA respectively, addressed whether myocarditis and pericarditis (or other cardiovascular complications) are part of a post-SARS-CoV-2 infection syndrome. Both utilised data from large observational patient databases and included context-relevant control groups.

Tuvali et al. extracted data from inpatient codes for myocarditis or pericarditis 10 days to 6 months post-infection whereas Xie et al. used US Department of Veterans Affairs national healthcare databases to identify survivors at 30 days post-acute COVID-19 with follow up for 12 months (young white males predominated in this data set). In the Tuvali study, rates of myo- and pericarditis were very low and post-COVID infection was not associated with an increased rate of either syndrome, although some cases may have been missed due to the study design. In contrast, the Xie study showed a relative increase in pericarditis and myocarditis as well as multiple other cardiovascular complications (cerebrovascular, cardiac, and thrombotic), for up to 12-months post-acute COVID-19. There was a graded increase in the rate of these complications with severity of acute COVID-19.

Discrepancies in outcomes of the two studies may reflect different populations and methodologies, although long-term post-COVID-19 consequences have been reported from smaller studies that lacked controls. Further research and monitoring for preventable and treatable post-COVID-19 cardiovascular complications will be essential to our understanding and management of this complex disease.

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Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study

Authors: The PHOSP-COVID Collaborative Group

Summary: This study aims to identify factors associated with perceived recovery 1 year after hospital discharge of patients with COVID-19. The study also suggests potential therapeutic targets through underlying inflammatory profiles of the previous recovery clusters at 5 million after hospital discharge. This post-hospitalisation COVID-19 study is a prospective, longitudinal cohort study in the UK. The study assessed the recovery of COVID-19 patients between March 2020 and April 2021. From the 2320 participants the study found that those who were less likely to report full recovery at 1 year were female, obese and/or had been on a ventilator. The study concludes that there were minimal improvements across all measured outcomes 1 year after discharge.

Comment: This British longitudinal cohort study assessed patients with COVID-19 at 5- and 12-months post-hospital discharge. It is concerning that full recovery across patient-reported symptoms, mental health, exercise capacity, organ impairment and quality-of-life, at each time point, was only 25% and 28% respectively and was further reduced in females, obese patients and those requiring invasive mechanical ventilation. Furthermore, obesity, reduced exercise capacity, a greater number of symptoms, and an increase in the serum inflammatory marker, C-reactive protein, were associated with severe physical and mental health impairment or moderate physical health impairment with cognitive impairment.

Systematic inflammation and obesity are potential treatable traits amenable to further investigation in clinical trials.

Regarding potential generalisability of the findings, it should be noted that only hospitalised people, a relatively high proportion of whom (28%) were ventilated, were included, there was no control group, and only ~800/2000+ participated in the 12-month assessment, raising the possibility of selection bias. In addition, as the study was conducted in 2020, the effect of current acute care, newer SARS-CoV-2 variants including Omicron and vaccination status before and after contracting COVID-19 remain to be determined.

Reference: LANCET 2022; 22:127-8
Abstract

Beneficial and harmful effects of monoclonal antibodies for the treatment and prophylaxis of COVID-19: a systematic review and meta-analysis of randomized controlled trials

Authors: Hernandez A, et al.

Summary: This study systematically assessed RCTs evaluating monoclonal antibodies vs. control in hospitalised or non-hospitalised adult COVID-19 patients. Primary outcomes of the study include all-cause mortality, COVID-19 related death, serious adverse effects, hospitalisation of non-hospitalised patients and a development of symptomatic COVID-19 for prophylaxis. In hospitalised patients, monoclonal antibodies reduced patient respiratory rate and bacteraemia. However, the study acknowledges the uncertainty of the effect on adverse events. In hospitalised patients, monoclonal antibodies lowered the number of hospitalisations and may reduce some serious adverse events. The study concludes that there are limited effects from monoclonal antibodies on COVID-19 patients and additional data are needed to determine patient efficacy and safety.

Comment: This methodologically rigorous systematic review and meta-analysis assessed the relative value of antiviral therapies in non-severe COVID 19, recognising that there are no head-to-head trials of newer antivirals now marketed for COVID-19. The authors concluded that molnupiravir and nirmatrelvir–ritonavir each reduced risk of hospital admissions and death with moderate certainty, when compared with molnupiravir, nirmatrelvir–ritonavir reduced the risk of hospital admission with moderate certainty and remdesivir probably has no effect on risk of death, but may reduce hospital admissions, with low certainty.

The authors provide relevant caveats in relation to their findings. Perhaps the one most pertinent to the current stage of the pandemic is that most trials were conducted with unvaccinated patients and before the emergence of the Omicron variant; hence the effectiveness of these drugs needs testing in vaccinated patients and against newer variants. Furthermore, as estimates of absolute effects are dependent on the baseline risk, which may vary across populations, clinicians should consider the anticipated baseline risk in their own patients when applying the evidence provided in this manuscript.

Reference: Am J Med; Published online July 22, 2022
Abstract

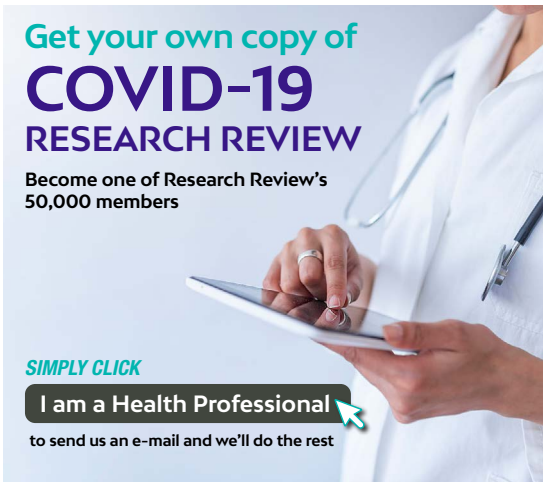
Effect of Molnupiravir on Biomarkers, Respiratory Interventions, and Medical Services in COVID-19

Authors: Johnson M, et al.

Summary: This study aims to identify clinical benefits of molnupiravir versus placebo drugs in addition to reduced mortality and hospitalisation. The authors conducted a secondary analysis of the randomised, double-blind, placebo-controlled phase 3 component of MOVe-OUT clinical trials, people receiving molnupiravir showed faster normalisation of CRP and SpO_2. Further improvements were observed on day 3 of therapy. Compared to placebo interventions molnupiravir treated patients required less respiratory interventions by 34% with a 95% CI. Patients hospitalised and treated with molnupiravir were discharged from hospital 3 days earlier demonstrating that there are additional important clinical benefits to molnupiravir beyond the reduction of hospitalisation and death.

Comment: The parent phase 3, randomised controlled trial, "MOVe-OUT", demonstrated that early initiation of the antiviral drug molnupiravir reduced hospitalisation and mortality in unvaccinated adults who had mild-to-moderate COVID-19 and risk factors for severe disease. Acknowledging biases inherent in post-hoc analyses, the current Pharma-funded study provides an informative secondary analysis of key laboratory and health care access or intervention parameters, which support the benefit of molnupiravir for COVID-19. In treated participants, CRP and SpO_2 improved and normalised more rapidly, fewer respiratory interventions were needed and patients requiring hospitalisation were discharged three days earlier than those receiving placebo. Similarly, acute care and COVID-19–related acute care visits were significantly less frequent in molnupiravir-treated participants. At this stage, further work to understand the impact of antiviral use in vaccinated individuals with breakthrough infections and emerging viral variant disease is important. Health system use and economic analyses would inform overall cost-benefit analyses of therapeutic interventions.

Reference: Ann Intern Med. 2022;175:1126–34
Abstract



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Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections

Authors: Heba N et al.

Summary: This study is a national, matched, test-negative, case control study in Qatar, which evaluated the effectiveness of vaccination Pfizer-BioNTech or Moderna, and/or natural immunity to previous infection with variants other than Omicron and hybrid immunity against symptomatic Omicron infection and severe, critical, or fatal COVID-19. The effectiveness of previous infection alone against symptomatic omicron variant BA2 was 46.1%. The effectiveness of vaccination with three Pfizer doses and no previous infection was 52.2%, however, with previous infection was 77.3%. Previous infection alone, Pfizer vaccination alone and hybrid immunity all demonstrated >70% effectiveness against severe, critical, or fatal COVID-19 due to Omicron variant BA1 infection and of vaccination with mRNA-1273.

Comment: This retrospective, national, matched, PCR test-negative case-control study of thousands of Qatar residents offers reassurance that previous SARS-CoV-2 infection, vaccination with the Pfizer or Moderna RNA vaccines and hybrid immunity provide similar levels of protection against symptomatic infection with BA.1 and BA.2 sub-lineages of the Omicron variant (B.1.1.529). Hybrid immunity due to previous infection and recent booster vaccination conferred the strongest protection (77%). Previous infection, vaccination alone, and hybrid immunity were >70% effective against severe, critical, or fatal infection due to either variant. The authors utilised several strategies to minimise bias but acknowledge that it could have arisen unexpectedly, for example, due to subtle changes in test-seeking behaviour. This seems unlikely as PCR testing is done on a massive scale in Qatar. Noting that the general population is predominantly under 50 years of age and male, the results may not be generalisable to countries with different demographics.

Reference: N Engl J Med 2022; 387:21-34

Abstract

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