COVID-19 Research Review™

Making Education Easy

Issue 8 - 2022

In this issue:

Abbreviations used in this issue:

Ad26.COV2.S = Johnson & Johnson vaccine;
BNT162b2 = Pfizer–BioNTech COVID-19 vaccine;
COVID-19 = coronavirus disease 19; **mRNA-1273** = Moderna vaccine;
PCR = polymerase chain reaction; **PCS** = post covid syndrome;
RT = reverse transcription;
SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Welcome to issue 8 of COVID-19 Research Review.

In this issue, a Chinese study assesses previously hospitalised patients' symptoms 2-years post-COVID-19 infection. An objective study observes the reduction of COVID-19 hospitalisation and death following the vaccination booster. Also included in this issue, is a longitudinal study analysing the causes of death in Mexico during the 2020-21 period of the COVID-19 pandemic. Another notable study included is the use of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period.

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

Kind Regards,

Dr Minh Cuong Duong
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Two-year health outcomes in hospitalised COVID-19 survivors in China

Authors: Yang X et al.

Summary: The objective of this study is to assess the health outcomes of those hospitalised with COVID-19 over 2 years and identify the factors associated with increased risk of persistent symptoms. This longitudinal cohort study investigated patients who survived COVID-19 hospitalisation in Wuhan, China. All patients completed a symptom questionnaire for evaluation, as well as a chronic obstructive pulmonary disease assessment test post-discharge over 1- and 2-year follow-up visits. The results of this study concluded that 2 years post-discharge, 370 patients still had symptoms, including 224 being persistent, and 146 being new-onset or worse. The most common symptoms included dyspnoea, which showed no significant change over time. A total of 116 patients had chronic obstructive pulmonary disease assessment scores of at least 10 at 2 years post-discharge. Patients who had been admitted to the intensive care unit had higher risks of persistent symptoms.

Comment: Most published studies on long COVID-19 followed up patients for a short period. The presenting longitudinal cohort study was among the few studies examining the 2-year health outcomes of COVID-19 hospitalised patients. The investigators found that symptoms including the new-onset ones persisted after 2 years in 19.8% of 1,864 study participants. In addition to the most reported symptoms persisting after 1 year (Pathogens, 2022;11:269), such as fatigue, anxiety, and dyspnoea, they found other symptoms including chest tightness and myalgia. They also found that although most symptoms resolved, dyspnoea could persist over time. The study reconfirmed an association between the severity of the initial illness and risks of persistent symptoms, and higher chronic obstructive pulmonary disease assessment test scores. Some important limitations may affect the study validity and include selection bias (i.e., less than half of the eligible population was enrolled, and patients completing the study were younger than those lost to follow-up) and measurement bias (i.e., the use of a self-reported symptom questionnaire). In addition to the need of longer follow-up studies, a universal, validated instrument measuring patients' persisting symptoms is needed to better explore this health issue, and allow a more reliable comparison between the different populations.

Reference: JAMA Netw Open. 2022;5(9):e2231790

Abstract

COVID-19 Research Review™

Independent commentary by Dr Minh Cuong Duong

Dr Minh Cuong Duong (MD, MMed, PhD), an infectious disease specialist and epidemiologist, is a Lecturer at the School of Population Health, University of New South Wales. Minh teaches epidemiology and infectious disease control and is convenor of the courses, PHCM2001 Epidemiology and PHCM9784 Communicable Disease Control in Global Heath. His research aims to improve the prevention and control of infectious diseases with a special focus on low-resource settings. Minh has conducted the Australian Alumni Grands Fund (AAGF) projects to increase the prevention and control of malaria and COVID-19 in Vietnam.

Incidence of severe COVID-19 illness following vaccination and booster with BNT162b2, mRNA-1273, and Ad26.COV2.S vaccines

Authors: JD Kelly et al.

Summary: The objective of this study is to describe the incidence of severe COVID-19 illness among a cohort that received a vaccination and a booster vaccination. This retrospective cohort study of 1,610,719 adults observed a breakthrough COVID-19 hospitalisation and hospitalisation with severe COVID-19 pneumonia and/or death. The results of this study conclude that over 24 weeks, 125 per 10,000 participants had breakthrough COVID-19, 8.9 per 10,000 participants were hospitalised with COVID-19 pneumonia or died, and 3.4 per 10,000 were hospitalised with severe pneumonia or died. For high-risk populations, hospitalisation with COVID-19 pneumonia or death included: aged 65 years or older 1.9 in 10,000 persons, immunocompromising conditions 29.6 in 10,000 persons and high-risk comorbid conditions 6.7 in 10,000 persons. Therefore, the study concludes that vaccination against COVID-19 is highly effective at reducing hospitalisations.

Comment: Given the emergence of omicron, a third dose of an mRNA vaccine is recommended to reduce the risks of reinfection with COVID-19 and severe outcomes. The presenting retrospective cohort study conducted on 1,610,719 adults receiving care at Veterans Health Administration facilities across the US, demonstrated the effectiveness of a booster dose with any of BNT162b2, mRNA-1273, or Ad26.COV2.S vaccines against delta and omicron variants with a relatively low incidence of hospitalisation or death of 8.9 per 10,000 persons. However, among study participants, most of them were male (91.8%) and more than two-thirds of them were aged 65 years or older (68.4%) and had high-risk comorbid conditions (70.4%) which may confound the generalisation of the study findings.

Reference: JAMA. 2022;328(14):1427-1437
Abstract

Diagnostic accuracy of COVID -19 rapid antigen tests with unsupervised self-sampling in people with symptoms in the omicron period

Authors: Schuit E et al.

Summary: The objective of this study is to assess the performance of rapid antigen tests with unsupervised nasal and combined oropharyngeal and nasal self-sampling tests. This prospective, cross-sectional study included 6497 participants who presented with COVID-19 symptoms. The study evaluates the use of Flowflex (Acon Laboratories; phase 1 only), MPBio (MP Biomedicals), and Clinitest (Siemens-Healthineers) tests. The main outcomes of this study assessed the sensitivity, specificity and positive and negative values of the self-tests. Overall, the sensitivities for Flowflex were 79%, for MPBio 69.9% and 70.2% for Clinitest. When combined, oropharyngeal and nasal self-sampling were compared with nasal self-sampling, sensitivities were slightly higher in confirmatory testers (87%), and substantially higher in those testing for other reasons (69.3%). The study discovers that during the omicron outbreak nasal self-sampling decreased but that was only statistically significant for Clinitest.

Comment: Without the need of a trained professional's supervision or laboratory setting, COVID-19 antigen rapid self-tests could enable widespread testing and thus, improve the control of the pandemic through early detection and self-isolation of infectious people. However, this is subject to their real-world clinical performance which could be influenced by the alterations in SARS-CoV-2 viral proteins and infection dynamics. By using RT-PCR testing as a reference to examine the performance of three rapid antigen tests (Flowflex - Acon Laboratories; MPBio - MP Biomedicals, and Clinitest - Siemens-Healthineers), this large-scale study from the Netherlands found a statistically insignificant absolute decrease in the sensitivity of Clinitest during the emergence of omicron. They also found that a combination of oropharyngeal and nasal self-sampling would enhance the sensitivities of MPBio and Clinitest. In general, positive predictive values of these tests were high, while their negative predictive values were lower. Notably this study was conducted on only three rapid tests during the emergence of omicron and may yield different data with other rapid tests and newly emerging variants. In addition, self-testers' deviations of sampling and testing as well as levels of knowledge regarding the self-testing results may influence the test's performance.

Reference: BMJ. 2022;378:e071215
Abstract

Estimated effectiveness of COVID-19 vaccines against omicron or delta symptomatic infection and severe outcomes

Authors: Buchan SA et al.

Summary: The objective of this study is to estimate the vaccine effectiveness against symptomatic infections of the omicron and delta variants and severe outcomes associated with those infections. This Canadian based, case-control study estimated that the effectiveness of two doses of COVID-19 vaccine was high against symptomatic delta infection (89% after 59 days and 80% after 240 or more days), and severe outcomes presented lower against symptomatic omicron infection (26% after 59 days and 1% after 240 or more days). After a third dose, the estimated vaccine effectiveness was 61% for symptomatic and 95% for severe outcomes. Specifically for delta, after a third dose the vaccine, effectiveness increased to 97%, and for omicron to 61%. The study concludes that a third dose of COVID-19 vaccine is associated with preventing infection from omicron and future variants.

Comment: Similar to the study by Kelly et al. previously discussed, based on clinical data, the effectiveness of a third dose against symptomatic infection with delta and omicron as well as severe outcomes in comparison with two doses; this important study from Canada has made a similar suggestion that a third dose is needed to protect against omicron infection and severe outcomes. In detail, a third dose provided a high protection rate against symptomatic delta infection (97% compared with 80-89% by two doses) and severe outcomes (99%). With regard to omicron, in contrast, despite a high protection rate against severe outcomes (95%), the level of protection against symptomatic infection was considerably low at 61% (compared with 1-36% by two doses). Hence, the study also emphasised the need for an improvement in non-vaccine measures to prevent symptomatic omicron infection. Nevertheless, due to the timing of the study this work probably included a high proportion of individuals who were at higher risk for COVID-19 infection, and hence, received a third dose. This may influence the generalisability of the study findings.

Reference: JAMA Netw Open. 2022;5(9):e2232760
Abstract

PBS information: LAGEVRIO® is listed on the PBS (Streamlined Authority). Please refer to www.pbs.gov.au for eligibility criteria.

LAGEVRIO® is also available via the National Medical Stockpile in accordance with the supply agreement.

▼ This medicine is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

SELECTED SAFETY INFORMATION[1]

INDICATIONS:

LAGEVRIO® has provisional approval for the treatment of adults with COVID-19 who do not require initiation of oxygen due to COVID-19 and who are at increased risk for hospitalisation or death. The decision to approve this indication is based on the efficacy and safety data from a Phase 3 trial. Continued approval of this indication depends on additional data.

PRECAUTIONS:

Pregnancy Category D: The use of LAGEVRIO® is not recommended during pregnancy. In women of childbearing potential, health care providers should discuss the chance that they may be pregnant and consider the need for a pregnancy test.

Contraception: Advise women of childbearing potential to use effective contraception for the duration of treatment and for 4 days after the last dose of LAGEVRIO®. Sexually active men with a partner of childbearing potential should use contraception during and for 3 months after treatment. Based on animal data, LAGEVRIO® may cause foetal harm when administered to pregnant women.

Breastfeeding: Based on the potential for adverse reactions on the infant from LAGEVRIO®, breastfeeding is not recommended during treatment and for 4 days after the last dose of LAGEVRIO®.

Paediatric patients: Use in patients under the age of 18 years is not recommended.

Use in elderly: No dose adjustment of LAGEVRIO® is recommended based on age. In the MOVe-OUT study there was no difference in the safety and tolerability between patients >65 years of age and younger who were treated with LAGEVRIO®.

Hypersensitivity: Hypersensitivity reactions have been reported with LAGEVRIO®. If signs or symptoms of a clinically significant hypersensitivity reaction occur, immediately discontinue LAGEVRIO® and initiate appropriate medications and/or supportive care.

CONTRAINDICATIONS: Hypersensitivity to the active substance or any of the excipients.

ADVERSE REACTIONS: The most common adverse reactions occurring in ≥1% of subjects in the LAGEVRIO® treatment group in the Phase 3 double-blind MOVe-OUT study were diarrhoea (2% versus placebo at 2%), nausea (1% versus placebo at 1%), and dizziness (1% versus placebo at 1%) all of which were Grade 1 (mild) or Grade 2 (moderate). Serious adverse events occurred in 7% of subjects receiving LAGEVRIO® and 10% receiving placebo; most serious adverse events were COVID-19 related. Adverse events leading to death occurred in <1% of the subjects receiving LAGEVRIO® and 2% of subjects receiving placebo.

COVID-19 = coronavirus disease 2019

References: 1-LAGEVRIO® Product Information. 22 April 2022.

Lagevrio® molnupiravir

MSD

***No known drug interactions** based on limited data available[1]

***No dose adjustments required** in patients with renal and/or hepatic impairment[1]

Before prescribing, please review the full Product Information available at www.msdinfo.com.au/lagevriopi or by scanning the QR code

Efficacy and safety of a single dose of casirivimab and imdevimab for the prevention of COVID-19 over an 8-month period

Authors: Herman GA et al.

Summary: This randomised, double-blind, placebo-controlled trial, allocated uninfected and unvaccinated participants to receive 1200mg casirivimab and imdevimab or placebo subcutaneously. The objective of this study is to discover if the use of casirivimab and imdevimab effectively prevents symptomatic SARS-CoV-2 infections. Findings of this study resulted in the reduction of COVID-19 infection by 81.2%, versus placebo. During the 7-month follow up period, protection from casirivimab and imdevimab was greatest during months 2-5, with a 100% relative risk reduction in COVID-19. This efficacy waned during months 6-8. Seroconversion occurred in 38 of participants in casirivimab and imdevimab and 181 in the placebo group. The study occurred before the emergence of omicron-lineage variants and determines that casirivimab and imdevimab is not active against the omicron variant.

Comment: Based on the available short-term efficacy and safety data, the human monoclonal antibodies including casirivimab and imdevimab have been provisionally approved for use in some countries including Australia to treat COVID-19 and could be administered monthly for ongoing need for prophylaxis. This multi-country randomised, double-blind, placebo-controlled trial provided important data on the long-term efficacy and safety of these investigational medications as a prophylaxis. With an 8-month follow-up of a total of 1,683 uninfected, unvaccinated, and healthy household contacts of infected individuals equally assigned to receive subcutaneous casirivimab and imdevimab 1200mg or placebo; the study found that casirivimab and imdevimab reduced the risk of COVID-19 infection by 81.2%. Nevertheless, the study was conducted in the period in which the predominant variant was delta and thus, more evidence is needed to confirm the efficacy and safety of casirivimab and imdevimab against omicron and newly emerging variants.

Reference: Lancet Infect Dis. 2022;10:1444-1454
Abstract

COVID-19 mortality and excess mortality among working-age residents in California, USA, by occupational sector

Authors: Chen YH et al.

Summary: This longitudinal cohort study obtained data from the California Department of Health to calculate the number of COVID-19 deaths in total, and per-capita that occurred in each employment sector. The estimated number of COVID-19 associated deaths in Californian residents aged 18-65 was 28,751. People who worked in essential sectors were associated with higher COVID-19 deaths and excess deaths than those working in non-essential sectors. The notable sectors analysed in this study included agriculture workers who had the highest COVID-19 mortality rate of 131.8 per 100,000, transportation or logistics had a rate of 107.1 per 100,000, and manufacturing had a rate of 103.3 per 100,000. During the delta dominated surge of infections during November 2020 and February 2021 emergency workers had the highest COVID-19 mortality rate of 113.7 per 100,000. The study concluded that workers in essential sectors had the highest COVID-19 mortality in countries with low vaccination rates, this was increased during the delta dominated infection period.

Comment: This study aimed to address the limited data on the occupational sector disparities in COVID-19 mortality. Compared with working-age residents in the non-essential sectors, a higher per-capita COVID-19 mortality rate was found among those in the essential sectors including agriculture, transportation or logistics, facilities, emergency, and manufacturing during the periods of the delta surge and vaccine availability. In the essential sectors, the lowest rate (87.8 per 100,000) was documented in people in the emergency sector compared with rates of >100 per 100,000 in the remaining non-health sectors, despite their established high risk of COVID-19 infection through frequent contact with other infected cases. Although there were some important study limitations such as the potential misclassification of occupation, these important findings implied that the occupational risk of COVID-19 death may not only be attributable to social contact, and thus could be further reduced by enforcing workplace safety, worker protections, and worker empowerment.

Reference: Lancet Public Health. 2022;9:744-753
Abstract

Severity, predictors, and clinical correlates of post-COVID syndrome in Germany

Authors: Bahmer T et al.

Summary: COVIDOM is a population-based cohort study of PCR-confirmed cases of SARS-CoV-2 infection in Germany. A PCS score was developed upon 12 long-term symptom complexes and was used to identify clinically meaningful predictors. In Kiel, 90% of participants received outpatient treatment for acute COVID-19. The most frequent persisting symptoms at 6-12 months post-infection included fatigue (61.5%) and sleep disturbance (57%). Across the sub-cohorts, higher PCS scores were associated with lower health-related quality of life. 18.8% of the Keil sub-cohort obtained severe PCS scores, 48.2% experienced moderate scores and 32.9% experienced mild/no scores. This study concludes PCS severity can be quantified to reflect the acute phase disease burden and general psychological predisposition of COVID-19 on participants in Germany.

Comment: This study was based on COVIDOM – a large German population-based cohort study conducted on PCR-confirmed cases in which one of its original objectives was to examine the magnitude of long COVID-19 and associated predictors. The presenting study developed and validated the PCS severity score through quantifying 35 COVID-19 long-term symptoms grouped into 12 non-overlapping symptom complexes. Including chemosensory deficits, fatigue, exercise intolerance, joint or muscle pain, ear-nose-throat ailments, coughing or wheezing, chest pain, gastrointestinal alignments, neurological ailments, dermatological ailments, infection signs and sleep disturbance. Despite the possibility of an incomplete symptom spectrum listed in the PCS score, in the context of an increase in the burden of long COVID-19, the work provided a promising, easy-to-use, time-saving tool to enable assessment of the presence and severity of this syndrome in the general community.

Reference: EClinicalMedicine 2022;51:101549
Abstract

Observed protection against SARS-CoV-2 reinfection following a primary infection

Authors: Michlmayr D et al.

Summary: This cohort study analyses Danish data to compare SARS-CoV-2 infection rates before and after primary infection among unvaccinated individuals. This study also assesses the protection against each of the main viral variants after a primary infection with an earlier variant. During the delta dominated period of September 2021 the estimated protection following a recent first infection was 91.3% compared to 71.4% after a first infection over a year earlier. During omicron periods, a first infection after earlier infection of alpha or delta within 1 year yielded 51% protection. Compared to a first infection longer than 12 months prior provided only 19% protection. Protection by an earlier variant-infection against hospitalisation due to a new infection was estimated at 86.6% for alpha, 97.2% for delta and 69.8% for omicron variants.

Comment: Infection-induced immunity in several non-COVID-19 respiratory viral infections, such as influenza, wanes over time resulting in individuals being at risk of reinfection. However, little has been known about this phenomenon in COVID-19. Whilst examining a large, unvaccinated population, the researchers found that the levels of protection against reinfection, and possibly severe disease after a natural infection may be comparable to those created by vaccines. However, they are reduced with the introduction of new variants. The estimated protection rate was 83.4% among those infected during the period when the alpha variant was predominant, and 91.3% in the case of delta. During the omicron period, the estimated protection rates documented in patients with previous infection with other variants were low at 51% and 25% after 3 and 6 months, respectively, between the two infections. These results suggest the potential important role of the evolution of COVID-19 in inducing reinfection rather than the waning of the infection-induced immunity. Nevertheless, the study population included two specific groups, i.e., adults refusing to get vaccinated for unknown reasons and children who were not eligible for vaccination. The characteristics and behaviours of these sub-populations which may differ with those of the vaccinated group could influence the risk of reinfection.

Reference: Lancet Reg Health. 2022;20:100452
Abstract

Predictive performance and clinical application of COV50, a urinary proteomic biomarker in early COVID-19 infection

Authors: Staessen JA et al.

Summary: This prospective, multicentre, cohort study utilised COV50 in order to predict death and disease progression in SARS-CoV-2. COV50 is a urinary proteomic biomarker consisting of 50 peptides. A total of 1,012 participants were recruited, 119 died and 271 had disease progression. The odds ratio associated with COV50 for death was 1.67 when adjusted for sex, age, body mass index and comorbidities. For disease progression the odds ratio was 1.63 when adjusted. The predicted accuracy for COV50 was 74% for mortality and 67.4% for disease progression. This study demonstrates that COV50 markers may be predictive of adverse COVID-19 outcomes, and therefore may reduce days in hospital and associated costs.

Comment: There is growing interest in biomarkers to predict progression of COVID-19 infection to help healthcare professionals optimise resource allocation and clinical management. The multicentre cohort study conducted on 1,012 mild-to-moderate, PCR-confirmed, COVID-19 adult patients examined the role of COV50. COV50 is a COVID-19-specific biomarker comprising of 50 differentially regulated urinary peptides that predict death and disease progression. The study found that the thresholds of the predictive accuracy of COV50 for mortality and disease progression were 74.4% and 67.4%, respectively, even in patients with mild disease. In clinical practice, the clinical risk factors may lead to unclear prognosis in mild-to-moderate patients. Hence, the researchers suggested that an early use of this test within 4 days of a positive COVID-19 PCR test could help timely justify treatment in these patients. Nevertheless, as acknowledged by the researchers, given its observational cohort study design, randomised clinical trials are needed for applying treatments guided by COV50 risk profiling.

Reference: Lancet Digit Health. 2022;10:727-737
Abstract

Leading causes of excess mortality in Mexico during the COVID-19 pandemic 2020–2021: A death certificates study in a middle-income country

Authors: Palacio-Mejia LS et al.

Summary: This longitudinal, retrospective study analysed the leading causes of mortality and the variation, with respect to cause-specific expected deaths in Mexico during the period of January 2020 and December 2021. The study found that COVID-19 was the leading cause of death during this period with a total of 439,582 deaths. The largest increases in cause-specific mortality, occurred in diabetes with an over-expected rate of 36.8%. This was followed by respiratory infections (33.3%), ischaemic heart disease (32.5%) and hypertensive diseases (25%). Groups that caused significant decreases were infectious and parasitic diseases (20.8%), skin diseases (17.5%), non-traffic related accidents (16.7%) and malignant neoplasms (5.3%). This study justifies the increase in other causes of death due to the changes in health service utilisation patterns, caused by hospital conversion or fear of the population using them in the COVID-19 pandemic period.

Comment: By using Mexico as a study context, this study contributes important information on the magnitude of the excess mortality directly and indirectly associated with COVID-19. The study similarly confirmed that COVID-19 was the leading cause of death with 439,582 deaths between January 2020 and December 2021. Considering a weekly difference between expected and observed deaths as excess deaths, the study found that all-cause total excess mortality was 600,590 deaths with a notable increase in mortality being observed in diabetes, respiratory infections, ischaemic heart, and hypertensive diseases. In contrast, a large decrease in mortality was observed in infectious and parasitic diseases, skin diseases, non-traffic related accidents and malignant neoplasms. The findings help allocate equitable resources to care for non-COVID patients most impacted by the pandemic.

Reference: Lancet Reg Health. 2022;13:100303
Abstract

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