COVID-19 Evidence Bulletin

14th December 2022

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**clinical management**

**title:** Cardiac and vascular serious adverse events following tixagevimab–cilgavimab [Correspondence]

The Lancet Respiratory Medicine | 12th december 2022

On July 8, 2022, ACTIV-3–TICO study group published a randomised controlled trial (RCT; ACTIV-3)…that evaluated tixagevimab–cilgavimab for the treatment of severe COVID-19 in hospitalised patients. This study follows the TACKLE trial by Hugh Montgomery and colleagues…of tixagevimab–cilgavimab for treatment in mild-moderate disease, and one by Levin and colleagues, the authors of PROVENT,..which studied tixagevimab–cilgavimab for prevention of COVID-19 in unvaccinated individuals. In all studies, more patients treated with tixagevimab–cilgavimab experienced events such as myocardial infarction, thrombosis, or heart failure, leading to a monograph warning of an association with cardiac and thromboembolic serious adverse events. Serious adverse events, by definition, are events that result in hospitalisation or death. We conducted a meta-analysis of published and unpublished RCTs of tixagevimab–cilgavimab versus placebo to characterise its relationship to such serious adverse events. Number of cardiac and vascular serious adverse events were obtained from appendices of published trials, and unpublished data were obtained from clinicaltrials.gov. Whenever possible, events were confirmed with the manufacturer; in cases of discrepancy, the manufacturer-provided data were used.

Four trials totalling 8738 patients from full-analysis sets were included…The results, produced by Review Manager (version 5.4.1) using a fixed-effects model and inverse-variance weighting, showed an increased odds of cardiac and vascular serious adverse events in tixagevimab–cilgavimab-treated patients (odds ratio [OR] 1·90, 95% CI 1·05–3·43; p=0·03;..). A random-effects model produced concordant results. We conducted a sensitivity analysis using updated event rates collected by the manufacturer that are not in the public domain. This analysis, which included two additional serious adverse events in each of the treatment and placebo groups of STORM CHASER, produced similar results (OR 1·87, 95% CI 1·08–3·22; p=0·02). The test for heterogeneity generated an I2 value of 0% suggesting consistency between studies. Of the serious adverse events reported, six led to cardiac-related deaths in the tixagevimab–cilgavimab group and none in placebo group (0·11% vs 0; p=0·15).

Various monoclonal antibodies have been linked to cardiac and vascular serious adverse events through platelet activation participating in the allergic thrombosis process…Although a causal relationship between tixagevimab–cilgavimab has not been established, a sign of increased serious adverse events found in well conducted RCTs is important for post-marketing safety monitoring. While there are limitations of reporting standards of serious adverse events, which capture thrombotic-related events as both cardiac and vascular, potentially leading to misclassification, this analysis represents best-available data using triangulated sources. Furthermore, these trials examined tixagevimab–cilgavimab across different clinical scenarios, including prevention, treatment of mild disease, and treatment of severe COVID-19 in hospitalised patients. However, baseline characteristics were similar across trials; the median ages were between 46·1 years and 58·7 years and many participants had a single cardiovascular risk factor such as obesity, smoking, or hypertension but few had known heart or thrombotic disease. Since these comorbidities are common in the general population, these results might help inform clinical and policy decisions regarding the benefit versus risk of tixagevimab–cilgavimab…

<https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00452-0/fulltext>

**title:** Cardiac and vascular serious adverse events following tixagevimab–cilgavimab – Author's reply [Correspondence]

the lancet respiratory medicine | 12th December 2022

We thank Jolanta Piszczek and colleagues for their meta-analysis of cardiac and vascular serious adverse events; however, this definition differs from how they were reported in the cited clinical studies, which refer to separate system organ class terms for “cardiac disorders” and “vascular disorders” (defined by Medical Dictionary for Regulatory Activities [MedDRA] 24.0) and should not be combined in an analysis.

We report further on cardiac and vascular serious adverse events from ongoing AstraZeneca-sponsored phase 3 trials with updated data cutoffs, showing distribution across individual events and lack of common pathology... Most vascular events were not thrombosis-related. Although more participants in PROVENT experienced cardiac serious adverse events with 300 mg tixagevimab–cilgavimab versus placebo, this imbalance was not observed in STORM CHASER, nor with the higher 600 mg dose in TACKLE in the treatment group, with no clear temporal pattern following dosing. All participants who experienced cardiac serious adverse events were high-risk and had at least one baseline cardiovascular risk factor, or history of cardiac events. No cardiac serious adverse events were observed in a phase 1 study (doses up to 3000 mg), indicating absence of dose association. No causal relationship was established…

Safety evaluation continues in ongoing trials and post-marketing surveillance. We searched the AstraZeneca safety database (the largest tixagevimab–cilgavimab post-marketing surveillance safety dataset) up to June 30, 2022, using MedDRA (version 25.0), system organ class term “cardiac disorder”. With an estimated 1 515 812 doses of 300 mg tixagevimab–cilgavimab distributed for COVID-19 prevention in immunocompromised individuals, cardiac serious adverse events were reported in 34 individuals, of whom 15 (44%) were aged 65 years or older and 30 (88%) had increased risk or alternate aetiology for cardiac events. These data support the absence of causal relationship.

Tixagevimab–cilgavimab contains three amino acid substitutions (L234F, L235E, P331S) that decrease Fc receptor binding; there is no evidence that it causes platelet activation… Presently, there is no plausible mechanism for cardiac and vascular events given that tixagevimab–cilgavimab does not bind endogenous proteins.

Risk of severe COVID-19 outcomes, including hospitalisation and death in immunocompromised individuals with reduced protective options, persists… Tixagevimab–cilgavimab benefit–risk remains in favour in these vulnerable individuals, and will be continually monitored.

SM, AK, AT, and MTE are employees of, and hold or might hold stock in, AstraZeneca…

<https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(22)00450-7/fulltext>

**title:** Association of Glucose-Lowering Drugs With Outcomes in Patients With Diabetes Before Hospitalization for COVID-19: A Systematic Review and Network Meta-analysis

jama network open | 6th december 2022

Key Points

Question What is the difference in the association between COVID-19–related adverse outcomes and 8 routine glucose-lowering therapies in hospitalized patients with diabetes?

Findings In this network meta-analysis of 31 observational studies with more than 3.6 million patients, sodium-glucose cotransporter-2 inhibitors were associated with lower risk of COVID-19–related adverse outcomes in diabetes, followed by glucagon-like peptide-1 receptor agonists and metformin, compared with insulin, dipeptidyl peptidase-4 inhibitors, secretagogues, and glucosidase inhibitors.

Meaning The findings of this meta-analysis provide information regarding routine antihyperglycemic medications and COVID-19–related adverse outcomes.

Abstract

Importance Patients with COVID-19 have a high prevalence of diabetes, and diabetes and blood glucose control are determinants of intensive care unit admission and mortality.

Objective To evaluate the association between COVID-19–related adverse outcomes and 8 antihyperglycemic drugs in patients with diabetes who were subsequently diagnosed and hospitalized with COVID-19.

Data Sources Data were retrieved and collected in PubMed, Embase, Cochrane Central Register, Web of Science, and ClinicalTrials.gov from database inception to September 5, 2022.

Study Selection For this systematic review and network meta-analysis, randomized clinical trials and observational studies conducted among patients with diabetes while receiving glucose-lowering therapies for at least 14 days before the confirmation of COVID-19 infection were included after blinded review by 2 independent reviewers and consultations of disagreement by a third independent reviewer. Of 1802 studies initially identified, 31 observational studies met the criteria for further analysis.

Data Extraction and Synthesis This study follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses reporting guideline. Bayesian network meta-analyses were performed with random effects.

Main Outcomes and Measures A composite adverse outcome, including the need for intensive care unit admission, invasive and noninvasive mechanical ventilation, or in-hospital death.

Results Thirty-one distinct observational studies (3 689 010 patients with diabetes hospitalized for COVID-19) were included. The sodium-glucose cotransporter-2 inhibitors (SGLT-2is) were associated with relatively lower risks of adverse outcomes compared with insulin (log of odds ratio [logOR], 0.91; 95% credible interval [CrI], 0.57-1.26), dipeptidyl peptidase-4 inhibitors (logOR, 0.61; 95% CrI, 0.28-0.93), secretagogues (logOR, 0.37; 95% CrI, 0.02-0.72), and glucosidase inhibitors (logOR, 0.50; 95% CrI, 0.00-1.01). Based on the surface under the cumulative ranking curves value, SGLT-2is were associated with the lowest probability for adverse outcomes (6%), followed by glucagon-like peptide-1 receptor agonists (25%) and metformin (28%). A sensitivity analysis revealed that the study was reliable.

Conclusions and Relevance These findings suggest that the use of an SGLT-2i before COVID-19 infection is associated with lower COVID-19–related adverse outcomes. In addition to SGLT-2is, glucagon-like peptide-1 receptor agonists and metformin were also associated with relatively low risk of adverse outcomes.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799219>

**title:** Incidence of Viral Rebound After Treatment With Nirmatrelvir-Ritonavir and Molnupiravir

jama network open | 6th december 2022

Key Points

Question What is the incidence of viral rebound after treatment with nirmatrelvir-ritonavir and molnupiravir?

Findings In this cohort study of 12 629 adults in Hong Kong with COVID-19 who were hospitalized and had serial cycle threshold values measured, viral rebound (defined as a cycle threshold value >40 that decreased to ≤40) occurred in 68 antiviral nonusers (0.6%), 2 (1.0%) nirmatrelvir-ritonavir users, and 6 (0.8%) molnupiravir users.

Meaning In this study, viral rebound was uncommon in adults with COVID-19 after treatment with nirmatrelvir-ritonavir and molnupiravir, suggesting that these novel oral antivirals should be prescribed to more patients with COVID-19 in the early phase of the infection.

Abstract

Importance Some patients treated with nirmatrelvir-ritonavir have experienced rebound of COVID-19 infections and symptoms; however, data are scarce on whether viral rebound also occurs in patients with COVID-19 receiving or not receiving molnupiravir.

Objective To examine the incidence of viral rebound in patients with COVID-19 who were treated with the oral antiviral agents nirmatrelvir-ritonavir and molnupiravir.

Design, Setting, and Participants This cohort study identified 41 255 patients with COVID-19 who were hospitalized from January 1, 2022, to March 31, 2022, in Hong Kong and assessed 12 629 patients with serial cycle threshold (Ct) values measured. Patients were followed up until the occurrence of the clinical end point of interest, death, date of data retrieval (July 31, 2022), or up to 30 days of follow-up, whichever came first.

Exposures Molnupiravir or nirmatrelvir-ritonavir treatment.

Main Outcomes and Measures Viral rebound, defined as a Ct value greater than 40 that decreased to 40 or less.

Results Of 12 629 patients (mean [SD] age, 65.4 [20.9] years; 6624 [52.5%] male), 11 688 (92.5%) were oral antiviral nonusers, 746 (5.9%) were molnupiravir users, and 195 (1.5%) were nirmatrelvir-ritonavir users. Compared with nonusers, oral antiviral users were older, had more comorbidities, and had lower complete vaccination rates. The mean (SD) baseline Ct value was slightly higher in nirmatrelvir-ritonavir users (22.2 [6.0]) than nonusers (21.0 [5.4]) and molnupiravir users (20.9 [5.4]) (P = .04). Viral rebound occurred in 68 nonusers (0.6%), 2 nirmatrelvir-ritonavir users (1.0%), and 6 molnupiravir users (0.8%). Among 76 patients with viral rebound, 12 of 68 nonusers, 1 of 6 molnupiravir users, and neither of the nirmatrelvir-ritonavir users died of COVID-19.

Conclusions and Relevance In this cohort study, viral rebound was uncommon in patients taking molnupiravir or nirmatrelvir-ritonavir and was not associated with increased risk of mortality. Given these findings, novel oral antivirals should be considered as a treatment for more patients with COVID-19 in the early phase of the infection.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799218>

**title:** Efficacy and Safety of Pacritinib vs Placebo for Patients With Severe COVID-19: A Phase 2 Randomized Clinical Trial

jama network open| 5th december 2022

Key Points

Question Is the oral JAK2/IRAK1 inhibitor pacritinib superior to placebo in patients hospitalized with severe COVID-19?

Findings In this phase 2 randomized clinical trial of 200 patients, the rate of progression to invasive mechanical ventilation, extracorporeal membrane oxygenation, or death by day 28 was 17.2% with pacritinib vs 22.8% with placebo. Among patients with elevated interleukin 6, the rate was 17.5% vs 30.4%.

Meaning Pacritinib did not demonstrate a significant benefit over placebo in patients with severe COVID-19.

Abstract

Importance The morbidity and mortality associated with COVID-19 remain high despite advances in standard of care therapy, and the role of anti-inflammatory agents that inhibit the interleukin 6/JAK2 pathway is still being elucidated.

Objective To evaluate the efficacy and safety of the oral JAK2/IRAK1 inhibitor pacritinib vs placebo in the treatment of adults with severe COVID-19.

Design, Setting, and Participants This phase 2, double-blind, placebo-controlled, randomized clinical trial enrolled hospitalized adult patients with severe COVID-19 at 21 centers across the US between June 2020 and February 2021, with approximately 1.5 months of safety follow-up per patient. Data analysis was performed from September 2021 to July 2022.

Interventions Patients were randomized 1:1 to standard of care plus pacritinib (400 mg per os on day 1 followed by 200 mg twice daily on days 2-14) vs placebo, for 14 days.

Main Outcomes and Measures The primary end point was death or need for invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO) by day 28. All-cause mortality and safety were also assessed.

Results A total of 200 patients were randomized to pacritinib (99 patients; 56 men [56.6%]; median [range] age, 60 [19-87] years) or placebo (101 patients; 64 men [63.4%]; median [range] age 59 [28-94] years). The percentage requiring supplementary oxygen was 99.0% (98 patients) in the pacritinib group vs 98.0% (99 patients) in the placebo group. The percentage who progressed to IMV, ECMO, or death was 17.2% (17 patients) in the pacritinib group vs 22.8% (23 patients) in the placebo group (odds ratio, 0.62; 95% CI, 0.28-1.35; P = .23). Among patients with elevated interleukin 6, the rate was 17.5% (11 of 63 patients) in the pacritinib group vs 30.4% (21 of 96 patients) in the placebo group. The adverse event rate was similar for pacritinib vs placebo (78.1% [75 patients] vs 80.2% [81 patients]), with no excess in infection (14.6% [14 patients] vs 19.8% [20 patients]), bleeding (8.3% [8 patients] vs 10.9% [11 patients]), or thrombosis (8.3% [8 patients] vs 7.9% [8 patients]). Rates of grade 3 or higher adverse events were lower with pacritinib than placebo (29.2% [28 patients] vs 40.6% [41 patients]).

Conclusions and Relevance The study did not meet its primary end point in patients with severe COVID-19. Subgroup analyses may indicate specific populations with hyperinflammation that could benefit from pacritinib, although further clinical trials would be needed to confirm these effects.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799198>

**long-****term effects**

**title:** Seeing Blue Dots After COVID-19 Infection

jama ophthalmology | 8th december 2022

A healthy 12-year-old female individual received a diagnosis of SARS-CoV-2 and reported visual symptoms 2 days later, with bilateral blurry vision, large blue paracentral scotomata, and a migraine without a scintillating scotoma. On clinical examination, visual acuity measured 20/70 + 1 in the right eye and 20/100 in the left eye, while she previously had visual acuity of 20/25 in each eye on examination 8 years prior. Motility, visual fields, and anterior segment examination results were normal. Dilated fundus examination revealed subtle reddish geographic irregularities at the level of the retinal pigment epithelial at a nasal juxtafoveal location in both eyes. The optic discs, vessels, and periphery were normal. Near-infrared (IR) imaging highlighted the irregularities in both eyes…

Full text requires subscription.

<https://jamanetwork.com/journals/jamaophthalmology/article-abstract/2799529>

**title:** Report on Long COVID Urges Actions to Address Needs of Patients, Caregivers

jama health forum | 6th december 2022

As part of a broader effort to address the long-term effects of COVID-19, or long COVID, the US Department of Health and Human Services (HHS) has released a new report drawn from the experiences of patients, their caregivers, and clinicians, with recommendations for actions to address these individuals’ concerns.

The Health+ Long COVID report, based on information gathered from workshops and more than 1000 hours of interviews, is intended to “ensure the lived experiences and perspectives of people impacted by Long COVID are integrated into the social, public health, and economic solutions being created to support the Long COVID community,” HHS notes.

The precise number of people in the US who are affected by long COVID is unknown, and estimates vary widely. According to a March 2022 federal government report, findings from US studies suggest that 10% to 30% of people with COVID-19 will develop symptoms that last longer than 4 weeks, with some resulting in significant disability. Based on these estimates, 7.7 million to 23 million people in the US may have developed long COVID as of February 2022.

More recently, according to a Centers for Disease Control and Prevention analysis of data from a US Census Bureau survey administered in June and July 2022, 18% to 19% of US adults who reported having had COVID-19 currently had symptoms of long COVID, defined as symptoms lasting 3 months or longer that were not present before these individuals became ill with COVID-19.

The new report builds on a presidential memorandum issued in April 2022, in which the Biden administration ordered the secretary of HHS to create a national action plan to coordinate research on long COVID and support for patients with the condition. In August 2022, as mandated in the memorandum, HHS released the National Research Action Plan on Long COVID, as well a guide on federal programs, supports, and services that can help individuals with long COVID and their families and caregivers.

The Health+ Long COVID report is intended to complement the findings and recommendations of these previous reports by “broadening the conversation and elevating what is often underrepresented in Long COVID statistics, scientific literature, and policy making—the narratives and expertise of people with Long COVID and what they want and need to live better, healthier lives.” To accomplish this, the 88-page report—commissioned by HHS and produced by Coforma, an independent research firm—is based on human-centered design, a collaborative approach that includes the people affected by a problem as active participants to help craft solutions that address their most urgent concerns.

The report explores how and why the effects of long COVID, which can range from mild to severely debilitating, differ from person to person. It also notes that various social determinants of health influence how profoundly long COVID affects an individual’s life. These determinants include where people live (which affects factors such as housing quality, access to transportation, and availability of healthy foods), health care access and quality, economic stability, and insurance status, as well as other factors such as disparities in quality of care associated with a patient’s race, ethnicity, age, gender, or sexual orientation.

Although data on long COVID’s disproportionate effects across different communities is incomplete, the report says, “it is strongly believed that people of color are more likely to be affected by Long COVID, as a result of their increased likelihood to become infected with COVID-19 and lower access to health care.” It also notes that long COVID is more common among bisexual and transgender people because of lower access to health care, as well as stigma related to their gender or sexuality.

Based on information about common experiences shared by patients with long COVID in interviews and workshops, as well as input from caregivers, clinicians, and others, the report offers a number of recommendations. For example, to increase access to disability benefits and assistance programs, the report calls for increasing funding for community-based organizations and programs that can help patients and caregivers apply for such benefits; it also urges health care professionals and others who support and assist people with long COVID to provide referrals to these resources.

Longer-term recommendations include creating Social Security credits for people with long COVID and their caregivers, as well as consolidating—under 1 roof—treatment and professional help for navigating and understanding existing support services.

A common concern expressed by patients with long COVID is long wait times for appointments with clinicians. “A scarcity of medical specialists equipped with knowledge relevant to Long COVID means people with Long COVID often wait for months just to be seen,” the report notes. “This is true across the medical field, as well as at Long COVID clinics.”

To increase the capacity of health care and assistance programs to offer support to people with long COVID, a system to rate the quality of care at long COVID clinics should be developed and ratings shared with the public, the report says. It also advised improving data tracking for long COVID to better target responses and allocation of resources where they are needed, as well as establishing care managers in clinicians’ offices and hospitals to help people with long COVID and their caregivers with scheduling and preparing for appointments and in managing issues with billing and insurance.

Another issue is that many clinicians, especially in the primary care community, “do not have the knowledge base that would enable them to link a constellation of potential symptoms to Long COVID,” the report notes. “As a result, instead of being able to provide a diagnosis and initiate a care pathway during an initial appointment, health care providers may send people with Long COVID to a string of other specialists, delaying diagnosis, treatment, and the ability to apply for disability.”

To address this issue, the report urges sending clinicians the latest information on findings, testing, and treatments in the form of “Long COVID digests,” as well as enlisting academic partners to launch an “expansive outreach campaign” to train clinicians about long COVID and suggested care pathways through in-person and virtual presentations. In the longer term, it advised medical schools to increase training on long COVID and other infection-associated chronic conditions.

Other recommendations, based on experiences reported by patients, are aimed at nonclinicians. For example, the report said that educators and employers should develop and support accommodations that allow people with long COVID to continue to study and work.

The report also stresses that people with long COVID and those who care for them “feel marginalized, misunderstood, and isolated by a general public that is impatient for a return to business as usual.” It urged public messaging campaigns in multiple languages and formats to increase the public’s literacy and awareness regarding long COVID and said that government agency leaders should be encouraged “to amplify and share that Long COVID is real and a serious public health issue.”

<https://jamanetwork.com/journals/jama-health-forum/fullarticle/2799427>

**title:** Myopericarditis After COVID-19 mRNA Vaccination Among Adolescents and Young Adults: A Systematic Review and Meta-analysis

jama pediatrics | 5th december 2022

Key Points

Question What are the frequency, clinical features, and early outcomes associated with myopericarditis after COVID-19 mRNA vaccination in adolescents and young adults?

Findings In this systematic review and meta-analysis of 23 studies, including 854 patients aged 12 to 20 years with vaccine-associated myopericarditis, the incidence of myopericarditis was higher in males after the second dose. Although 15.6% of patients had left ventricular (LV) systolic dysfunction, only 1.3% had severe LV systolic dysfunction (ejection fraction <35%); late gadolinium enhancement was found in 87.2% and 23.2% required intensive care unit admission; however, no in-hospital mortality was observed.

Meaning These findings suggest largely favorable outcomes of COVID-19 vaccine-associated myopericarditis in adolescents and young adults.

Abstract

Importance Published data on COVID-19 mRNA vaccine–associated myopericarditis in adolescents and young adults have been derived from small case series, national population-based studies, or passive reporting systems. Pooled evidence from a larger, international cohort is scarce.

Objective To investigate the clinical features and early outcomes associated with myopericarditis after COVID-19 mRNA vaccination in a heterogeneous population of adolescents and young adults.

Data Sources PubMed and EMBASE were searched through August 2022. Language restrictions were not applied.

Study Selection Observational studies and case series describing COVID-19 vaccine–associated myopericarditis in adolescents and young adults aged 12 to 20 years and reporting clinical characteristics and early outcomes were included.

Data Extraction and Synthesis Two independent investigators extracted relevant data from each study. One-group meta-analysis in a random effects model was performed. The Preferred Reporting Items for Systematic Reviews and Meta-analysis and Meta-analysis of Observational Studies in Epidemiology reporting guidelines were followed.

Main Outcomes and Measures The primary outcomes were clinical features and early outcomes for COVID-19 mRNA vaccine–associated myopericarditis, including incident rate, cardiac findings, hospitalization, intensive care unit (ICU) admission, and in-hospital mortality.

Results A total of 23 observational studies were identified, including 854 individuals (mean age, 15.9 [95% CI, 15.5-16.2] years) with COVID-19 vaccine–associated myopericarditis. Male sex was predominant, at 90.3% (95% CI, 87.3%-93.2%) of individuals. The incident rate was higher after the second dose than the first dose, with 74.4% (95% CI, 58.2%-90.5%) of events occurring after the second dose. Most patients (84.4% [95% CI, 80.5%-88.3%] of patients) had preserved left ventricular (LV) function. Of the 15.6% (95% CI, 11.7%-19.5%) of patients with LV systolic dysfunction (LV ejection fraction [LVEF] <55%), most (14.1% [95% CI, 10.2%-18.1%]) were mild (ie, LVEF 45%-54%), and only 1.3% (95% CI, 0%-2.6%) of patients had severe LV systolic dysfunction (ie, LVEF<35%). Interestingly, cardiac magnetic resonance imaging revealed late gadolinium enhancement in 87.2% (95% CI, 79.8%-94.7%) of patients. Although 92.6% (95% CI, 87.8%-97.3%) of patients were hospitalized and 23.2% (95% CI, 11.7%-34.7%) of patients required ICU admission, inotropes were used in only 1.3% (95% CI, 0%-2.7%) of patients, no patients died or required mechanical support, and the hospital length of stay was 2.8 (95% CI, 2.1-3.5) days.

Conclusions and Relevance This systematic review and meta-analysis found low incidence rate and largely favorable early outcomes of COVID-19 mRNA vaccine–associated myopericarditis in adolescents and young adults from a wide range of populations. These findings are reassuring but continued follow-up is warranted.

<https://jamanetwork.com/journals/jamapediatrics/fullarticle/2798866>

**infection control**

**title:** Effectiveness of BNT162b2 and CoronaVac COVID-19 vaccination against asymptomatic and symptomatic infection of SARS-CoV-2 omicron BA.2 in Hong Kong: a prospective cohort study

the lancet infectious diseases | 12th december 2022

Summary

Background

COVID-19 vaccines provide protection against symptomatic infection that might require medical attention and against severe outcomes; however, there is a paucity of evidence regarding the effectiveness of the BNT162b2 and CoronaVac vaccines and their booster regimens against asymptomatic or mild omicron infections in the community. We aimed to measure the effectiveness of BNT162b2 and CoronaVac vaccines against asymptomatic and symptomatic SARS-CoV-2 omicron infections, during a period of omicron BA.2 predominance in Hong Kong.

Methods

In this prospective cohort study in a population that was generally infection-naive before the large omicron BA.2 wave between January and late May, 2022, we established a public health surveillance platform to monitor the evolving activity of SARS-CoV-2 infections in the community. We recruited a cohort of individuals aged 5 years and older between March 1 and March 7, 2022, from the general population. Individuals were enrolled from all 18 districts of Hong Kong, according to a predefined age-stratified quota, primarily by random digit dialing (generating suitable eight-digit local telephone numbers by randomly picking sets of the first four digits from a sampling frame, and randomly generating the last four digits), and supplemented by our existing cohorts (which included cohorts for studying influenza vaccination from school-based vaccination programmes and cohorts for SARS-CoV-2 seroprevalence from the community), to ensure representativeness of the population in Hong Kong. Participants did weekly rapid antigen testing with a self-collected pooled nasal and throat swab, regardless of symptom and exposure status, from March 1 to April 15, 2022. Individuals reporting a history of SARS-CoV-2 infection confirmed by laboratory PCR testing before enrolment were excluded from the vaccine effectiveness analysis to avoid potential bias due to infection-induced immunity. The primary outcomes of the study were the incidence of SARS-CoV-2 infection, including asymptomatic and symptomatic infections, and the vaccine effectiveness of BNT162b2 and CoronaVac vaccines. The effectiveness of one, two, and three doses of vaccination was estimated with a Cox proportional hazards regression model with time-dependent covariates, allowing for changes in vaccination status over time, after adjustment for demographic factors and pre-existing medical conditions.

Findings

Of the 8636 individuals included in the analysis, 7233 (84%) received at least two doses of vaccine, 3993 (46%) received booster doses, and 903 (10%) reported SARS-CoV-2 infection. Among these infections 589 (65·2%) were symptomatic and 314 (34·8%) were asymptomatic at the time of testing. Statistically significant protection against asymptomatic and symptomatic SARS-CoV-2 omicron infection was found only for those who received a BNT162b2 or CoronaVac booster dose, with a vaccine effectiveness of 41·4% (23·2 to 55·2; p=0·0001) and 32·4% (9·0 to 49·8; p=0·0098), respectively. The vaccine effectiveness of BNT162b2 and CoronaVac boosters was further increased to 50·9% (95% CI 31·0–65·0; p<0·0001) and 41·6% (15·0–59·8; p=0·0049), respectively, for symptomatic omicron infections. A similar pattern of vaccine effectiveness (55·8%, 22·9–74·6; p=0·0040) was also conferred after receipt of a BNT162b2 booster by individuals who received a CoronaVac primary vaccination series.

Interpretation

Two doses of either vaccine did not provide significant protection against COVID-19 infection. However, receipt of a BNT162b2 booster or CoronaVac booster was associated with a significantly lower risk of omicron BA.2 infection and symptomatic infection. Our findings confirm the effectiveness of booster doses to protect against mild and asymptomatic infection.

Funding

Henry Fok Foundation and Hong Kong Health Bureau…

<https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00732-0/fulltext>

**title:** Rapid emergence of omicron sublineages expressing spike protein R346T [Correspondence]

The Lancet regional health - europe | 9th december 2022

Although vaccinations and SARS-CoV-2 infections have resulted in a high level of antibody-positive individuals, SARS-CoV-2 omicron variants continue to spread, including with high infection rates in triple-vaccinated individuals…The first waves of SARS-CoV-2 infections were caused by distinct variants of concern (VOC), each dominating until being replaced by a novel VOC. Since the emergence of omicron in late 2021, new subvariants exhibiting increased capacity for immune escape have emerged… Currently, various BA.2/4/5 sublineages circulate in the population, strongly dominated by BA.5.

Recently, sequencing data has revealed the emergence of new circulating omicron variants in e.g. the United Kingdom,..with indication of accelerated convergent evolution…resulting in shared phenotypes between variants. This marks a possible shift in the transmission landscape; rather than one specific sublineage dominating, several distinct subvariants with a specific phenotype may together form a dominating cluster. One of such important mutations is R346X, in particular R346T, situated in the receptor binding domain (RBD) of the spike protein, with an enhanced capacity to escape neutralizing antibodies… Current sequencing data is largely generated from group-specific testing, possibly delaying detection of novel variants and transmission patterns in society…

To estimate the prevalence of SARS-CoV-2 infection and to identify variants causing them, we invited individuals being part of a Swedish nationwide probability-based web panel to participate in a survey taking place September 26–29, 2022. Enrolled participants (n = 1774) received material for self-sampling of upper respiratory tract for PCR-analysis for presence of SARS-CoV-2 and of blood for serological analysis…

In total, 1524 of 1554 participants were positive for anti-spike IgG. Ongoing SARS-CoV-2-infection was detected in 31 out of 1687 participants, resulting in an age-, sex- and region-adjusted estimated overall point-prevalence of 1·5% (95% CI: 0·9–2·5%). Of the 31 positive samples, 30 were successfully sequenced. In total, 13 different omicron sublineages were identified, among which BA.5.2 (n = 7) and BF.7 (n = 7) were the most common ones... Strikingly, 40% of infections were caused by R346X-mutated variants represented by six different sublineages. Moreover, five of these sublineages showed an identical pattern of RBD mutations...

To conclude, these results show a rapid emergence of several R346T expressing sublineages with identical or very similar RBD, indicating that the next wave of SARS-CoV-2 infections may be caused by a group of sublineages sharing a phenotype, rather than by one specific sublineage.

<https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00260-5/fulltext>

**title:** Urgent Need for Next-Generation COVID-19 Vaccines [viewpoint]

jama | 9th december 2022

Despite the availability of safe and effective vaccines, SARS-CoV-2 continues to circulate rampantly across the globe. Problems with vaccine access and hesitancy present throughout the pandemic are partially responsible. However, the seemingly ceaseless progression of increasingly transmissible variants, recently including BF.7 and BQ.1.1, presents a major challenge to medical interventions, particularly vaccines.

Attempting to address the continued genetic evolution of SARS-CoV-2, the US Food and Drug Administration authorized bivalent boosters (original plus BA.4/BA.5 Omicron variant) for the 2 available messenger RNA (mRNA) COVID-19 vaccines to address the waves of disease leading to hospitalization and death. These updated vaccines may also reduce the amount of symptomatic disease and associated heath care use. However, introduction of these bivalent boosters likely only represents a temporizing measure until variants emerge that necessitate additional booster vaccination or modification of the current generation of vaccines.

The existing COVID-19 vaccines have had a profoundly positive effect during the pandemic, reducing both hospitalization and death. However, those at risk of severe outcomes from COVID-19, especially older individuals, have required booster vaccination even to maintain this level of protection. The need to repeatedly vaccinate at-risk populations, combined with the documented emergence of a new dominant SARS-CoV-2 variant approximately every 3 to 4 months, presents a public health dilemma… Continuing along the current path of the generation and administration of variant-specific vaccine boosters is inadequate as a long-term strategy for addressing COVID-19 in populations globally.

There is also a risk that eventually a variant will emerge that will escape the protection provided by the current generation of vaccines against severe disease. Experience with SARS-CoV-2 infection to date in older individuals indicates that higher antibody titers tend to correlate better with prevention of severe COVID-19. Therefore, older individuals may be at risk for becoming the initial group most susceptible to such novel variants that lack adequate antibody coverage. Serious consideration therefore needs to be given to the development of a distinctly improved generation of SARS-CoV-2 vaccines offering longer protection with greater scope.

Based on experience to date with COVID-19 and other vaccines, a variety of approaches to the development of new vaccines will need to be explored by academic and industrial researchers and sponsors, as well as government agencies. One potential model for approaching such development was used successfully at the beginning of the pandemic when Operation Warp Speed evaluated numerous global vaccine types and focused on advancing several promising candidates, knowing full well that most would ultimately not be found to meet the criteria set forth for a safe vaccine with adequate efficacy… Such focused effort, along with technical and financial resources, will likely be required to overcome the significant challenges intrinsic to efforts to develop a vaccine having the needed extent and duration of protection.

Developing the next generation of vaccines addressing SARS-CoV-2 will be demanding. This work will almost certainly require more than simply making incremental modifications on the current generation of vaccines. Although experience with the mRNA vaccine platforms has enabled authorization of updated versions of vaccines without large clinical trials, when more significant modifications are made to a vaccine, the clinical effects are often unexpected. Biological properties that may plausibly have beneficial effects often have unanticipated consequences. Therefore, unless correlates of protection that are strongly associated with duration of protection against COVID-19 can be identified, it is likely that rather than relying on immunobridging to infer vaccine effectiveness, large randomized clinical trials similar to the initial trials of the currently authorized or licensed vaccines for COVID-19 will be required to ascertain the effectiveness of these new vaccines.

Simply updating the existing vaccine constructs with new variant sequences or even making trivalent or quadrivalent vaccines covering several variants is not likely to provide the depth and breadth of protection needed to interrupt viral transmission during a prolonged period. It is also not at all clear from well-controlled clinical trials that administering existing vaccines by the intranasal route (as some countries have already even approved) will provide truly meaningful benefit over the existing generation of COVID-19 vaccines. Such limitations were recently illustrated by the disappointing results with a viral-vectored vaccine administered intranasally in an early-phase clinical trial…

However, the situation is far from hopeless because there are other approaches to future COVID-19 vaccine development currently under investigation, including potentially effective means of achieving improved mucosal immunity with or without intranasal administration. These approaches might include, among many other methods, targeting S protein viral sequences that are immutable, immunogenic, and accessible to neutralizing antibodies; including other targets from the virus such as portions of the membrane, envelope, or nucleocapsid proteins; targeting conserved or occluded (structurally hidden) epitopes using nanoparticles of randomly arrayed receptor binding domains; and developing vaccines based on T-cell receptor constructs that specifically recognize the SARS-CoV-2 RNA-dependent RNA polymerase…

So what would define success for these new vaccines? To truly represent a significant advance in this area, the protection provided by vaccination would need to apply across a wide range of potential variants that might emerge. In terms of the actual level of effectiveness, the minimum expectations for such a vaccine might be adopted from the criteria used in the search for an acceptable “universal” influenza vaccine. The National Institute of Allergy and Infectious Diseases defines the threshold for influenza vaccine as at least 75% effectiveness in preventing influenza-like illness, achieving durable protection that lasts at least 1 year, and suitability for use in all age groups… Aiming even further, the vaccines would ideally not only protect against hospitalization, death, and symptomatic disease leading to increased health care use but would also reduce viral transmission. Even using the criterion for success of a moderate 40% to 60% reduction in transmission is predicted to have a notable positive impact on outbreak control…

The continued adverse effects of SARS-CoV-2 on individuals and populations necessitate the urgent development of the next generation of vaccines. The adverse effects wrought by SARS-CoV-2 extend far beyond the acute complications of COVID-19 to post–COVID-19 conditions. Achieving success in developing improved vaccines will obviously be a major challenge, given all that we have learned to date about this virus, the human response to infection, and the immune correlates of protection after vaccination. However, an attempt to produce vaccines that lead to broad long-lasting immunity is clearly needed. Additionally, although reducing viral transmission is a difficult objective, the potential benefits to global public health are profound enough to merit acceptance of the challenge. Particularly, if immunity that reduced disease transmission could be elicited by a relatively inexpensive, easily administered vaccine stored at room temperature, a much greater fraction of the world’s population could be readily immunized, perhaps slowing the emergence of troubling variants.

What we learn as we address the challenges posed by SARS-CoV-2 and COVID-19 about virology and immunology, along with the accompanying advances in technology and manufacturing that will come from developing the next generation of vaccines, may broadly benefit public health during our current era of constantly emerging and reemerging infectious diseases…

<https://jamanetwork.com/journals/jama/fullarticle/2799600>

**title:** Trends in Risk Factors and Symptoms Associated With SARS-CoV-2 and Rhinovirus Test Positivity in King County, Washington, June 2020 to July 2022

jama network open | 9th december 2022  
  
Key Points

Question What are the risk factors associated with symptomatic SARS-CoV-2 and rhinovirus infection in King County, Washington, from June 2020 to July 2022?

Findings In this case control study with a test-negative design of 23 498 participants, reporting close contact with a SARS-CoV-2 case was the strongest risk factor associated with a positive SARS-CoV-2 test, while young age was associated with a positive rhinovirus test. Sociodemographic disparities were present for both SARS-CoV-2 and rhinovirus.

Meaning These findings suggest that monitoring risk factors associated with respiratory pathogen test positivity remains important to identify at-risk populations in the post–SARS-CoV-2 pandemic period.

Abstract

Importance Few US studies have reexamined risk factors for SARS-CoV-2 positivity in the context of widespread vaccination and new variants or considered risk factors for cocirculating endemic viruses, such as rhinovirus.

Objectives To evaluate how risk factors and symptoms associated with SARS-CoV-2 test positivity changed over the course of the pandemic and to compare these with the risk factors associated with rhinovirus test positivity.

Design, Setting, and Participants This case-control study used a test-negative design with multivariable logistic regression to assess associations between SARS-CoV-2 and rhinovirus test positivity and self-reported demographic and symptom variables over a 25-month period. The study was conducted among symptomatic individuals of all ages enrolled in a cross-sectional community surveillance study in King County, Washington, from June 2020 to July 2022.

Exposures Self-reported data for 15 demographic and health behavior variables and 16 symptoms.

Main Outcomes and Measures Reverse transcription–polymerase chain reaction–confirmed SARS-CoV-2 or rhinovirus infection.

Results Analyses included data from 23 498 individuals. The median (IQR) age of participants was 34.33 (22.42-45.08) years, 13 878 (59.06%) were female, 4018 (17.10%) identified as Asian, 654 (2.78%) identified as Black, and 2193 (9.33%) identified as Hispanic. Close contact with an individual with SARS-CoV-2 (adjusted odds ratio [aOR], 3.89; 95% CI, 3.34-4.57) and loss of smell or taste (aOR, 3.49; 95% CI, 2.77-4.41) were the variables most associated with SARS-CoV-2 test positivity, but both attenuated during the Omicron period. Contact with a vaccinated individual with SARS-CoV-2 (aOR, 2.03; 95% CI, 1.56-2.79) was associated with lower odds of testing positive than contact with an unvaccinated individual with SARS-CoV-2 (aOR, 4.04; 95% CI, 2.39-7.23). Sore throat was associated with Omicron infection (aOR, 2.27; 95% CI, 1.68-3.20) but not Delta infection. Vaccine effectiveness for participants fully vaccinated with a booster dose was 93% (95% CI, 73%-100%) for Delta, but not significant for Omicron. Variables associated with rhinovirus test positivity included being younger than 12 years (aOR, 3.92; 95% CI, 3.42-4.51) and experiencing a runny or stuffy nose (aOR, 4.58; 95% CI, 4.07-5.21). Black race, residing in south King County, and households with 5 or more people were significantly associated with both SARS-CoV-2 and rhinovirus test positivity.

Conclusions and Relevance In this case-control study of 23 498 symptomatic individuals, estimated risk factors and symptoms associated with SARS-CoV-2 infection changed over time. There was a shift in reported symptoms between the Delta and Omicron variants as well as reductions in the protection provided by vaccines. Racial and sociodemographic disparities persisted in the third year of SARS-CoV-2 circulation and were also present in rhinovirus infection. Trends in testing behavior and availability may influence these results.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799348>

**title:** Effectiveness of BNT162b2 COVID-19 vaccination in prevention of hospitalisations and severe disease in adults with SARS-CoV-2 Delta (B.1.617.2) and Omicron (B.1.1.529) variant between June 2021 and July 2022: A prospective test negative case–control study

the lancet regional health - europe| 7th december 2022

Summary

Background

Whilst other studies have reported the effectiveness of mRNA vaccination against hospitalisation, including emergency department or intensive care admission, few have assessed effectiveness against other more clinically robust indices of COVID-19 severity.

Methods

A prospective single-centre test-negative design case–control study of adults hospitalised with COVID-19 disease or other acute respiratory disease between 1 June 2021 and 20 July 2022. We assessed VE (vaccine effectiveness) against hospitalisation, length of stay [LOS] >3 days, WHO COVID Score >5 and supplementary oxygen FiO2 (fraction inspired oxygen) >28%, conducting regression analyses controlling for age, gender, index of multiple deprivation, Charlson comorbidity index, time, and community infection prevalence.

Findings

935 controls and 546 cases were hospitalised during the Delta period, with 721 controls and 372 cases hospitalised during the Omicron study period. Two-dose BNT162b2 was associated with VE 82.5% [95% confidence interval 76.2%–87.2%] against hospitalisation following Delta infection, 63.3% [26.9–81.8%], 58.5% [24.8–77.3%], and 51.5% [16.7–72.1%] against LOS >3 days, WHO COVID Score >5, and requirement for FiO2 >28% respectively. Three-dose BNT162b2 protection against hospitalisation with Omicron infection was 30.9% [5.9–49.3%], with sensitivity analyses ranging from 28.8–72.6%. Protection against LOS >3 days, WHO COVID Score >5 and requirement for FiO2 >28% was 56.1% [20.6–76.5%], 58.8% [31.2–75.8%], and 41.5% [−0.4–66.3%], respectively. In the UK, BNT162b2 was prioritised for high-risk individuals and those aged >75 years. In the latter group we found a higher estimate of VE against hospitalisation of 47.2% [16.8–66.6%].

Interpretation

BNT162b2 vaccination results in risk reductions for hospitalisation and multiple patient outcomes following Delta and Omicron COVID-19 infection, particularly in older adults. BNT162b2 remains effective against severe SARS-CoV-2 disease.

Funding

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<https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00248-4/fulltext>

**title:** Humoral immune evasion of the omicron subvariants BQ.1.1 and XBB [Correspondence]

the lancet infectious diseases | 7th december 2022

The omicron (B.1.1.529) variant of SARS-CoV-2 evolved into several sublineages, three of which (BA.1, BA.2, and BA.5) became globally dominant. Currently, the prevalence of omicron subvariants BQ.1 (a subvariant of BA.5), its sublineage BQ.1.1, and XBB (a recombinant of two different BA.2 subvariants) is increasing rapidly in the USA, France, Singapore, India, and elsewhere. BQ.1.1 and XBB possess substitutions relative to BA.5 and BA.2, respectively, in the receptor-binding domain of their spike protein..,which is the major target for vaccines and therapeutic monoclonal antibodies (mAbs) for COVID-19. Both variants have the substitution R346T, which confers resistance to certain therapeutic antibodies,..raising concerns that mAbs or vaccines might be less effective against BQ.1.1 and XBB than against other omicron strains. We showed that BQ.1.1 and XBB have enhanced immune evasion capabilities compared with earlier omicron variants, including BA.5 and BA.2, by evaluating the efficacy of therapeutic mAbs against BQ.1.1 and XBB... However, the neutralising ability of plasma from convalescent individuals and COVID-19 vaccinees against BQ.1.1 and XBB clinical isolates remained unknown.

Accordingly, we evaluated the neutralising ability of antibodies in plasma from three different groups against BQ.1.1 and XBB clinical isolates: individuals (180–189 days after the third dose; n=20) who received three doses of the monovalent mRNA vaccine BNT162b2 (Pfizer–BioNTech) or mRNA-1273 (Moderna), or both; individuals (33–57 days after the fourth dose; n=20) who received four doses of the monovalent mRNA vaccine BNT162b2 or mRNA-1273, or both; and individuals (29–89 days after the infection; n=10) who received three doses of monovalent BNT162b2 or mRNA-1273 before the BA.2 breakthrough infection. Using a live-virus neutralisation assay, we determined the 50% focus reduction neutralisation titre (FRNT50) of the plasma samples against BA.2 (hCoV-19/Japan/UT-NCD1288-2N/2022), BA.5 (hCoV-19/Japan/TY41-702/2022), BQ.1.1 (hCoV-19/Japan/TY41-796/2022), and XBB (hCoV-19/Japan/TY41-795/2022). For plasma from individuals who received a third dose of the mRNA vaccine, 17 (85%) of 20 samples or 18 (90%) of 20 samples had FRNT50 values that were below the limit of detection (<10-fold dilution) against BQ.1.1 or XBB, respectively. To calculate the geometric mean titre of each group, we assigned samples that were under the limit of detection of an FRNT50 value of ten. The FRNT50 geometric mean titres against BQ.1.1 and XBB were 21·1-fold and 21·6-fold lower, respectively, than those against the ancestral strain (SARS-CoV-2/UT-NC002-1T/Human/2020/Tokyo)... In addition, the geometric mean titres aganst BQ.1.1 and XBB were 1·7-fold and 2·6-fold lower, respectively, than those against BA.5 and BA.2. Similar results were obtained with samples from individuals who received four doses of mRNA vaccine...the FRNT50 geometric mean titres against BQ.1.1 and XBB were 43·3-fold and 51·6-fold lower, respectively, than those against the ancestral strain, and were 3·7-fold and 6·2-fold lower than those against BA.5 and BA.2, respectively… In contrast, most of the samples from vaccinees with BA.2 breakthrough infection neutralised BQ.1.1 and XBB; however, the FRNT50 geometric mean titres against BQ.1.1 and XBB were 35·2-fold and 61·7-fold lower, respectively, than those against the ancestral strain, and were 4·9-fold and 15·1-fold lower than those against BA.5 and BA.2, respectively…

Our data suggest that the omicron sublineages BQ.1.1 and XBB effectively evade current humoral immunity induced by mRNA vaccines or natural infection. A previous study using pseudotyped viruses reported that BQ.1.1 and XBB were less well recognised than BA.2 and BA.4/5 by plasma from convalescent individuals and mRNA vaccinees… These findings show that BQ.1.1 and XBB clinical isolates have higher immune evasion abilities than earlier omicron variants, including BA.5 and BA.2…

<https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(22)00816-7/fulltext>

**title:** Infections, Hospitalizations, and Deaths Among US Nursing Home Residents With vs Without a SARS-CoV-2 Vaccine Booster

jama network open | 7th december 2022

Key Points

Question What is the estimated vaccine effectiveness up to 12 weeks for the first COVID-19 mRNA booster vaccines administered in US nursing homes?

Findings In this cohort study of 10 949 residents of 202 community nursing homes and 4321 residents of 128 Veterans Health Administration community living centers, booster vaccination was associated with significant reductions in SARS-CoV-2 infections, hospitalizations, and the combined end point of hospitalizations or deaths.

Meaning These findings suggest that administration of a SARS-CoV-2 mRNA vaccine booster among nursing home residents may have played an important role in preventing COVID-19–associated morbidity and mortality.

Abstract

Importance A SARS-CoV-2 vaccine booster dose has been recommended for all nursing home residents. However, data on the effectiveness of an mRNA vaccine booster in preventing infection, hospitalization, and death in this vulnerable population are lacking.

Objective To evaluate the association between receipt of a SARS-CoV-2 mRNA vaccine booster and prevention of infection, hospitalization, or death among nursing home residents.

Design, Setting, and Participants This cohort study emulated sequentially nested target trials for vaccination using data from 2 large multistate US nursing home systems: Genesis HealthCare, a community nursing home operator (system 1) and Veterans Health Administration community living centers (VHA CLCs; system 2). The cohort included long-term (≥100 days) nursing home residents (10 949 residents from 202 community nursing homes and 4321 residents from 128 VHA CLCs) who completed a 2-dose series of an mRNA vaccine (either BNT162b2 [Pfizer-BioNTech] or mRNA-1273 [Moderna]) and were eligible for a booster dose between September 22 and November 30, 2021. Residents were followed up until March 8, 2022.

Exposures Receipt of a third mRNA vaccine dose, defined as a booster dose (boosted group), or nonreceipt of a booster dose (unboosted group) on an eligible target trial date. If participants in the unboosted group received a booster dose on a later target trial date, they were included in the booster group for that target trial; thus, participants could be included in both the boosted and unboosted groups.

Main Outcomes and Measures Test-confirmed SARS-CoV-2 infection, hospitalization, or death was followed up to 12 weeks after booster vaccination. The primary measure of estimated vaccine effectiveness was the ratio of cumulative incidences in the boosted group vs the unboosted group at week 12, adjusted with inverse probability weights for treatment and censoring.

Results System 1 included 202 community nursing homes; among 8332 boosted residents (5325 [63.9%] female; 6685 [80.2%] White) vs 10 886 unboosted residents (6865 [63.1%] female; 8651 [79.5%] White), the median age was 78 (IQR, 68-87) years vs 78 (IQR, 68-86) years. System 2 included 128 VHA CLCs; among 3289 boosted residents (3157 [96.0%] male; 1950 [59.3%] White) vs 4317 unboosted residents (4151 [96.2%] male; 2434 [56.4%] White), the median age was 74 (IQR, 70-80) vs 74 (IQR, 69-80) years. Booster vaccination was associated with reductions in SARS-CoV-2 infections of 37.7% (95% CI, 25.4%-44.2%) in system 1 and 57.7% (95% CI, 43.5%-67.8%) in system 2. For hospitalization, reductions of 74.4% (95% CI, 44.6%-86.2%) in system 1 and 64.1% (95% CI, 41.3%-76.0%) in system 2 were observed. Estimated vaccine effectiveness for death associated with SARS-CoV-2 was 87.9% (95% CI, 75.9%-93.9%) in system 1; however, although a reduction in death was observed in system 2 (46.6%; 95% CI, −34.6% to 94.8%), this reduction was not statistically significant. A total of 45 SARS-CoV-2–associated deaths occurred in system 1 and 18 deaths occurred in system 2. For the combined end point of SARS-CoV-2–associated hospitalization or death, boosted residents in system 1 had an 80.3% (95% CI, 65.7%-88.5%) reduction, and boosted residents in system 2 had a 63.8% (95% CI, 41.4%-76.1%) reduction.

Conclusions and Relevance In this study, during a period in which both the Delta and Omicron variants were circulating, SARS-CoV-2 booster vaccination was associated with significant reductions in SARS-CoV-2 infections, hospitalizations, and the combined end point of hospitalization or death among residents of 2 US nursing home systems. These findings suggest that administration of vaccine boosters to nursing home residents may have an important role in preventing COVID-19–associated morbidity and mortality.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799266>

**title:** Novavax COVID-19 Vaccine Booster Authorized

jama | 6th december 2022

The Novavax COVID-19 vaccine, adjuvanted received FDA Emergency Use Authorization for use as a first booster dose.

The Novavax booster dose is intended for individuals aged 18 years or older for whom an FDA-authorized messenger RNA bivalent COVID-19 booster vaccine is not accessible or clinically appropriate and for individuals aged 18 years or older who would otherwise not receive a COVID-19 vaccine booster. The 0.5-mL booster dose may be administered intramuscularly at least 6 months after completion of primary vaccination with an authorized or approved COVID-19 vaccine.

The vaccine previously received Emergency Use Authorization for a 2-dose primary series for individuals aged 12 years or older. The two 0.5-mL intramuscular doses are given 3 weeks apart.

<https://jamanetwork.com/journals/jama/fullarticle/2799175>

**title:** Omicron sublineage recombinant XBB evades neutralising antibodies in recipients of BNT162b2 or CoronaVac vaccines [Correspondence]

the lancet microbe | 6th december 2022

The SARS-CoV-2 omicron variant XBB sublineage, a BA.2.10.1–BA.2.75 recombinant classified as variant under monitoring by WHO, has been found in 35 countries,..and has become the dominant strain in Singapore. There is early evidence suggesting that XBB might be associated with a higher risk of reinfection…A previous study using a pseudovirus neutralisation test and sera from individuals who received CoronaVac (Sinovac) found that XBB is the most immunoevasive sublineage…

We assessed the neutralisation of XBB.1 and XBB.3 compared with BA.5.2 (a widely circulating strain since July, 2022) and the ancestral strain, using a live virus neutralisation test… XBB.1 differs from XBB.3 due to an extra spike mutation: Gly252Val. We included sera specimens from 30 individuals who received two to four doses of BNT16b2 (Pfizer-BioNtech) or CoronaVac with or without previous SARS-CoV-2 infection (seven [23%] individuals who received two vaccinations and had a previous BA.2 infection; seven [23%] who received three vaccinations and had a previous BA.2 infection; nine [30%] who received three vaccinations and had no previous SARS-CoV-2 infections; and seven [23%] who received four vaccinations and had no previous SARS-CoV-2 infections…). Overall, the geometric mean 50% neutralising antibody titre (NT50 GMT) was lower for XBB strains (XBB.1, 26.0; XBB.3, 19.4) than the ancestral strain (436.1; XBB.1 16·8-fold, p<0.0001; XBB.3: 22·5-fold, p<0·0001) or BA.5.2 strain (87.4; XBB.1 3·4-fold, p=0·0191; XBB.3 4·5-fold, p<0·0001), but the difference between XBB.1 and XBB.3 was not statistically significant (p=0·17…). All subgroups with different history of vaccination or infection had a statistically significantly lower GMT against XBB.1 or XBB.3 than those against the ancestral strain…

Paired acute and convalescent serum specimens were available for one patient with BA.5.2 and two patients with XBB. The patient who had previously had a BA.5.2 infection, had a 16·2 times higher NT50 GMT against the ancestral strain and a 16·5 times higher GMT NT50 against BA.5.2 for the convalescent serum than the acute serum, but the acute and convalescent sera had similar NT50 against XBB.1 or XBB.3... The patient who had previously had an XBB.1 infection had an increase in their NT50 GMT against the ancestral strain by 7·9 times, BA.5.2 by 29·6 times, XBB.1 by 21·3 times, and XBB.3 by 28·1 times... The patient who had previously had an XBB.3 infection had an increase in their NT50 GMT against XBB.1 by 10·8 times and XBB.3 by 6·9 times; this patient had a 2·1 times increase in their NT50 GMT against the ancestral strain and a 3·2 times increase against BA.5.2. In summary, our data showed that both XBB.1 and XBB.3 were much more immunoevasive than ancestral strain and BA.5.2. This immunoevasion is consistently seen in patients with different history of vaccination or infection. Since patients infected with BA.5.2 might not elicit neutralising antibody against XBB sublineage, patients who have been infected with BA.5 or those with bivalent vaccine might have a higher risk of reinfection or vaccine breakthrough infection from XBB sublineage than previous sublineages…

<https://www.thelancet.com/journals/lanmic/article/PIIS2666-5247(22)00335-4/fulltext>

**title:** Neutralising antibody potency against SARS-CoV-2 wild-type and omicron BA.1 and BA.4/5 variants in patients with inflammatory bowel disease treated with infliximab and vedolizumab after three doses of COVID-19 vaccine (CLARITY IBD): an analysis of a prospective multicentre cohort study

the lancet gastroenterology & hepatology| 5th december 2022

Summary

Background

Anti-TNF drugs, such as infliximab, are associated with attenuated antibody responses after SARS-CoV-2 vaccination. We aimed to determine how the anti-TNF drug infliximab and the anti-integrin drug vedolizumab affect vaccine-induced neutralising antibodies against highly transmissible omicron (B.1.1.529) BA.1, and BA.4 and BA.5 (hereafter BA.4/5) SARS-CoV-2 variants, which possess the ability to evade host immunity and, together with emerging sublineages, are now the dominating variants causing current waves of infection.

Methods

CLARITY IBD is a prospective, multicentre, observational cohort study investigating the effect of infliximab and vedolizumab on SARS-CoV-2 infection and vaccination in patients with inflammatory bowel disease (IBD). Patients aged 5 years and older with a diagnosis of IBD and being treated with infliximab or vedolizumab for 6 weeks or longer were recruited from infusion units at 92 hospitals in the UK. In this analysis, we included participants who had received uninterrupted biological therapy since recruitment and without a previous SARS-CoV-2 infection. The primary outcome was neutralising antibody responses against SARS-CoV-2 wild-type and omicron subvariants BA.1 and BA.4/5 after three doses of SARS-CoV-2 vaccine. We constructed Cox proportional hazards models to investigate the risk of breakthrough infection in relation to neutralising antibody titres. The study is registered with the ISRCTN registry, ISRCTN45176516, and is closed to accrual.

Findings

Between Sept 22 and Dec 23, 2020, 7224 patients with IBD were recruited to the CLARITY IBD study, of whom 1288 had no previous SARS-CoV-2 infection after three doses of SARS-CoV-2 vaccine and were established on either infliximab (n=871) or vedolizumab (n=417) and included in this study (median age was 46·1 years [IQR 33·6–58·2], 610 [47·4%] were female, 671 [52·1%] were male, 1209 [93·9%] were White, and 46 [3·6%] were Asian). After three doses of SARS-CoV-2 vaccine, 50% neutralising titres (NT50s) were significantly lower in patients treated with infliximab than in those treated with vedolizumab, against wild-type (geometric mean 2062 [95% CI 1720–2473] vs 3440 [2939–4026]; p<0·0001), BA.1 (107·3 [86·40–133·2] vs 648·9 [523·5–804·5]; p<0·0001), and BA.4/5 (40·63 [31·99–51·60] vs 223·0 [183·1–271·4]; p<0·0001) variants. Breakthrough infection was significantly more frequent in patients treated with infliximab (119 [13·7%; 95% CI 11·5–16·2] of 871) than in those treated with vedolizumab (29 [7·0% [4·8–10·0] of 417; p=0·00040). Cox proportional hazards models of time to breakthrough infection after the third dose of vaccine showed infliximab treatment to be associated with a higher hazard risk than treatment with vedolizumab (hazard ratio [HR] 1·71 [95% CI 1·08–2·71]; p=0·022). Among participants who had a breakthrough infection, we found that higher neutralising antibody titres against BA.4/5 were associated with a lower hazard risk and, hence, a longer time to breakthrough infection (HR 0·87 [0·79–0·95]; p=0·0028).

Interpretation

Our findings underline the importance of continued SARS-CoV-2 vaccination programmes, including second-generation bivalent vaccines, especially in patient subgroups where vaccine immunogenicity and efficacy might be reduced, such as those on anti-TNF therapies…

<https://www.thelancet.com/journals/langas/article/PIIS2468-1253(22)00389-2/fulltext>

**title:** Working towards a comprehensive appraisal of vaccine-induced immunity against SARS-CoV-2 in IBD [Comment]

The Lancet Gastroenterology & Hepatology | 5th december 2022

In The Lancet Gastroenterology & Hepatology, Zhigang Liu and colleagues…on behalf of the CLARITY-IBD study investigators, report on the effect of different immunomodulating treatments commonly prescribed to patients with inflammatory bowel disease (IBD) on serological responses against the highly transmissible SARS-CoV-2 omicron (B.1.1.529) variants (BA.1 and BA.4 and BA.5 [hereafter BA.4/5]). In this prospective, multicentre, cohort study, functional neutralising antibody responses against SARS-CoV-2 wild-type and omicron BA.1 and BA.4/5 variants after three doses of SARS-CoV-2 vaccine were investigated in 1288 patients with IBD without previous SARS-CoV-2 infection, and who were treated with either infliximab (n=871) or vedolizumab (n=417) recruited from infusion units across the UK. The median age of patients was 46·1 years (IQR 33·6–58·2) and 612 (47·5%) of 1288 were female, 663 (51·5%) were male, 1209 (93·9%) were White, and 46 (3·6%) were Asian. The investigators found that patients treated with infliximab had significantly lower neutralising antibodies against all investigated SARS-CoV-2 variants than did those being treated with vedolizumab, irrespective of the primary vaccination schedule. Additionally, they found that breakthrough SARS-CoV-2 infections were associated with lower neutralising antibody titres against the BA.4/5 variant in patients being treated with infliximab and in those being treated with vedolizumab. These trends remained present after adjusting for potentially confounding patient characteristics (eg, age, concomitant use of immunomodulators and corticosteroids, and comorbidities) with inverse probability of treatment weighting, a statistical method used to correct for such characteristics by reducing the bias of potentially unweighted estimators… The findings of this study have important implications for patients with IBD, supporting the prioritisation of second-generation, bivalent booster vaccinations for patients who are treated with infliximab, who generally have lower neutralising antibody titres against the SARS-CoV-2 BA.1 and BA.4/5 omicron variants than those treated with vedolizumab.

Continued assessment of the effect of immunomodulating treatment on the antiviral immune response is essential, especially when considering the ongoing spread of novel dominant SARS-CoV-2 variants caused by viral mutation drift driving global infection rates. The study of Liu and colleagues…highlights the consequences of infliximab and vedolizumab therapy for neutralising antibody responses against omicron BA.1 and BA.4/5 variants for patients with IBD; however, similar efforts for other immunosuppressive agents like methotrexate and JAK inhibitors are also important, because these treatments are likely to affect vaccine-induced immunity against SARS-CoV-2… More real-world evidence is required to inform vaccine prioritisation in the foreseeable future. Such information would aid in substantiating personalised vaccination strategies for specific subgroups of patients with IBD—eg, across different disease activity states, disease complications, and the presence of relevant comorbidities.

An important point of discussion relates to focusing on specific immunological domains when assessing the immune response after vaccination. Liu and colleagues…focused on the humoral immune response through examination of functional neutralising antibody responses. Although this functional neutralising capacity reflects efficient protection against SARS-CoV-2 infection, it only partially informs on immunological protection…T-cell-mediated immunity against SARS-CoV-2 is at least equally important in combating the infection when neutralising antibody concentrations decay. Further study of cellular immune responses could provide important additional insights. A flow cytometry approach could already be sufficient to enumerate and phenotypically characterise variant-specific T cells (eg, using IFN-γ release assays or ELISpot assays on cryopreserved peripheral blood mononuclear cells). Previously, the CLARITY-IBD study investigators reported no significant differences in quantities of anti-spike T-cell fractions or IFN-γ-producing T cells in patients with IBD treated with infliximab versus vedolizumab after one or two doses of SARS-CoV-2 vaccine… Similarly, the VIP study reported similar T-cell concentrations among patients with IBD treated with infliximab or vedolizumab,..and some other studies have found augmented anti-SARS-CoV-2 T-cell fractions in patients with IBD treated with TNF antagonists… By contrast, a study investigating anti-SARS-CoV-2 serological responses after a third vaccine dose in patients with IBD treated with biologics reported reduced T-cell-mediated IFN-γ concentrations in those treated with TNF antagonists compared with those not treated with such agents… Likewise, two other studies reported reduced IFN-γ secretion in vaccinated patients treated with TNF antagonists, whereas those not treated with TNF antagonists had T-cell responses similar to controls without IBD… These observations could be explained by a potential reduction in T-cell functionality or specificity in the absence of quantitative alterations in relevant T-cell subsets. As such, a comprehensive appraisal of qualitative T-cell responses, neutralising antibody responses, and the risk of breakthrough infections deserves attention in future studies, assessing which domains are most relevant for guiding vaccination prioritisation in patients with IBD receiving immunomodulating treatment.

The efforts of Liu and colleagues in identifying patient subgroups at risk of reduced neutralising capacity against the dominating SARS-CoV-2 omicron variants are important and can only be applauded. However, more in-depth and mechanistic assessment of waning vaccine-induced immunity is warranted to secure improved vaccine immunogenicity for patients with IBD…

<https://www.thelancet.com/journals/langas/article/PIIS2468-1253(22)00404-6/fulltext>

**title:** Estimated SARS-CoV-2 antibody seroprevalence trends and relationship to reported case prevalence from a repeated, cross-sectional study in the 50 states and the District of Columbia, United States—October 25, 2020–February 26, 2022

The Lancet Regional Health – Americas | 3rd december 2022

Summary

Background

Sero-surveillance of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can reveal trends and differences in subgroups and capture undetected or unreported infections that are not included in case-based surveillance systems.

Methods

Cross-sectional, convenience samples of remnant sera from clinical laboratories from 51 U.S. jurisdictions were assayed for infection-induced SARS-CoV-2 antibodies biweekly from October 25, 2020, to July 11, 2021, and monthly from September 6, 2021, to February 26, 2022. Test results were analyzed for trends in infection-induced, nucleocapsid-protein seroprevalence using mixed effects models that adjusted for demographic variables and assay type.

Findings

Analyses of 1,469,792 serum specimens revealed U.S. infection-induced SARS-CoV-2 seroprevalence increased from 8.0% (95% confidence interval (CI): 7.9%–8.1%) in November 2020 to 58.2% (CI: 57.4%–58.9%) in February 2022. The U.S. ratio of the change in estimated seroprevalence to the change in reported case prevalence was 2.8 (CI: 2.8–2.9) during winter 2020–2021, 2.3 (CI: 2.0–2.5) during summer 2021, and 3.1 (CI: 3.0–3.3) during winter 2021–2022. Change in seroprevalence to change in case prevalence ratios ranged from 2.6 (CI: 2.3–2.8) to 3.5 (CI: 3.3–3.7) by region in winter 2021–2022.

Interpretation

Ratios of the change in seroprevalence to the change in case prevalence suggest a high proportion of infections were not detected by case-based surveillance during periods of increased transmission. The largest increases in the seroprevalence to case prevalence ratios coincided with the spread of the B.1.1.529 (Omicron) variant and with increased accessibility of home testing. Ratios varied by region and season with the highest ratios in the midwestern and southern United States during winter 2021–2022. Our results demonstrate that reported case counts did not fully capture differing underlying infection rates and demonstrate the value of sero-surveillance in understanding the full burden of infection. Levels of infection-induced antibody seroprevalence, particularly spikes during periods of increased transmission, are important to contextualize vaccine effectiveness data as the susceptibility to infection of the U.S. population changes…

<https://www.thelancet.com/journals/lanam/article/PIIS2667-193X(22)00220-4/fulltext>

**pub****lic health & health inequalities**

**title:** Severity of Omicron (B.1.1.529) and Delta (B.1.617.2) SARS-CoV-2 infection among hospitalised adults: A prospective cohort study in Bristol, United Kingdom

The Lancet Regional Health – Europe | 11th December 2022

Summary

Background

There is an urgent public health need to evaluate disease severity in adults hospitalised with Delta and Omicron SARS-CoV-2 variant infections. However, limited data exist assessing severity of disease in adults hospitalised with Omicron SARS-CoV-2 infections, and to what extent patient-factors, including vaccination, age, frailty and pre-existing disease, affect variant-dependent disease severity.

Methods

A prospective cohort study of adults (≥18 years of age) hospitalised with acute lower respiratory tract disease at acute care hospitals in Bristol, UK conducted over 10-months. Delta or Omicron SARS-CoV-2 infection was defined by positive SARS-CoV-2 PCR and variant identification or inferred by dominant circulating variant. We constructed adjusted regression analyses to assess disease severity using three different measures: FiO2 >28% (fraction inspired oxygen), World Health Organization (WHO) outcome score >5 (assessing need for ventilatory support), and hospital length of stay (LOS) >3 days following admission for Omicron or Delta infection.

Findings

Independent of other variables, including vaccination, Omicron variant infection in hospitalised adults was associated with lower severity than Delta. Risk reductions were 58%, 67%, and 16% for supplementary oxygen with >28% FiO2 [Relative Risk (RR) = 0.42 (95%CI: 0.34–0.52), P < 0.001], WHO outcome score >5 [RR = 0.33 (95%CI: 0.21–0.50), P < 0.001], and to have had a LOS > 3 days [RR = 0.84 (95%CI: 0.76–0.92), P < 0.001]. Younger age and vaccination with two or three doses were also independently associated with lower COVID-19 severity.

Interpretation

We provide reassuring evidence that Omicron infection results in less serious adverse outcomes than Delta in hospitalised patients. Despite lower severity relative to Delta, Omicron infection still resulted in substantial patient and public health burden and an increased admission rate of older patients with Omicron which counteracts some of the benefit arising from less severe disease.

Funding

AvonCAP is an investigator-led project funded under a collaborative agreement by Pfizer.

<https://www.thelancet.com/journals/lanepe/article/PIIS2666-7762(22)00252-6/fulltext>

**title:** Race and Ethnicity and Sex Variation in COVID-19 Mortality Risks Among Adults Experiencing Homelessness in Los Angeles County, California

jama network open | 6th december 2022

Key Points

Question Did COVID-19 mortality differ between people experiencing homelessness (PEH) in Los Angeles and the general population by race and ethnicity and sex?

Findings In this cross-sectional study, PEH with COVID-19 infection experienced a higher risk of COVID-19 mortality than the general population among all racial and ethnic and sex groups. White PEH had greater relative risk of mortality vs their general population counterparts than Black and Hispanic PEH. Female PEH had greater relative risk than male PEH.

Meaning The findings of this study provide evidence suggesting excess risk of COVID-19 fatality among PEH with COVID-19 infection and further our understanding of the intersectional association between homelessness and race and ethnicity and sex.

Abstract

Importance Few studies have used precise age-specific data to construct age-standardized estimates of the relative risks (RRs) of COVID-19 mortality for people experiencing homelessness (PEH) vs the general population, and none to date has addressed race and ethnicity and sex variations in COVID-19 mortality among PEH with COVID-19 infection.

Objective To measure age-standardized mortality rate ratios for PEH vs the general population overall and by sex and race and ethnicity.

Design, Setting, and Participants In this cross-sectional study, crude and age-specific COVID-19 mortality rates per 100 000 people were calculated using 5-year age groups and standardized mortality ratios for PEH and the general population aged 25 years and older, assessing differences by race and ethnicity and sex, from January 1, 2020, to November 1, 2021. Mortality and population estimates came from COVID-19 mandatory case reporting conducted by the Los Angeles County Department of Public Health, the annual point-in-time homeless count, and the US Census.

Main Outcomes and Measures The main outcome was COVID-19 deaths sourced from clinician reports, death certificates, medical examiner reports, and vital records deaths. PEH status was determined using the US Department of Housing and Urban Development definitions for homelessness at the time of COVID-19 diagnosis or symptom onset.

Results The study population included 25 441 deaths among an estimated 6 382 402 general population individuals and 256 deaths among an estimated 52 015 PEH. The race and ethnicity of the PEH sample was as follows: 15 539 Black (29.9%), 18 057 Hispanic (34.7%), 14 871 female (28.6%), 37 007 male (71.3%), and 3380 aged 65 years or older (6.5%), compared with the estimated general population of 6 382 402, which was 591 003 Black (9.3%), 2 854 842 Hispanic (44.7%), 3 329 765 female (52.2%), 3 052 637 male (47.8%), and 1 190 979 aged 65 years or older (18.7%). Crude death rates were 0.49% for PEH and 0.40% for the general population, but PEH experienced age-specific COVID-19 mortality risk 2.35 (95% CI, 2.08-2.66) times higher than the general population. There was significant risk associated with PEH status compared with their counterparts in the general population for Black PEH (RR, 1.69; 95% CI, 1.31-2.18), Hispanic PEH (RR, 2.34; 95% CI, 1.96-2.79), White PEH (RR, 8.33; 95% CI, 6.37-10.88), female PEH (RR, 3.39; 95% CI, 2.56-4.48), and male PEH (RR, 1.74; 95% CI, 1.52-2.00).

Conclusions and Relevance This cross-sectional study of COVID-19 mortality among PEH with COVID-19 infection provides evidence suggesting excess risk of age-adjusted COVID-19 mortality among PEH compared with the general population. This study furthers understanding of the intersectional association between homelessness and race and ethnicity, as higher levels of mortality but narrower racial disparities among PEH than in the general population were observed.

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799217>

**title:** Sex, Racial, and Ethnic Representation in COVID-19 Clinical Trials: A Systematic Review and Meta-analysis

JAMA Internal Medicine | 5th december 2022

Key Points

Question Compared with their representation in the US population with COVID-19, are female participants and racial and ethnic minority persons underenrolled in COVID-19 prevention and treatment trials?

Findings In this systematic review and meta-analysis of 122 US-based COVID-19 clinical trials with 176 654 participants, female participants were underrepresented in treatment trials, Asian and Black participants were underrepresented in prevention trials, and Hispanic or Latino participants were overrepresented in treatment trials.

Meaning These findings show systemwide differences in representation for several key demographic groups in COVID-19 prevention and treatment trials in the US.

Abstract

Importance Since the onset of the COVID-19 pandemic, there have been calls for COVID-19 clinical trials to be fully representative of all demographic groups. However, limited evidence is available about the sex, racial, and ethnic representation among COVID-19 prevention and treatment trials.

Objective To investigate whether female participants and racial and ethnic minority individuals are adequately represented in COVID-19 prevention and treatment trials in the US.

Data Sources Identified studies were registered on ClinicalTrials.gov or published in the PubMed database from October 2019 to February 2022.

Study Selection Included studies must have provided the number of enrolled participants by sex, race, or ethnicity. Only interventional studies conducted in the US for the primary purpose of the diagnosis, prevention, or treatment of (or supportive care for) COVID-19 conditions were included.

Data Extraction and Synthesis Data on counts of enrollments by demographic variables (sex, race, and ethnicity) and location (country and state) were abstracted. Studies were broadly categorized by primary purpose as prevention (including vaccine and diagnosis studies) vs treatment (including supportive care studies). A random effects model for single proportions was used. Trial estimates were compared with corresponding estimates of representation in the US population with COVID-19.

Main Outcomes and Measures Sex, racial, and ethnic representation in COVID-19 clinical trials compared with their representation in the US population with COVID-19.

Results Overall, 122 US-based COVID-19 clinical trials comprising 176 654 participants were analyzed. Studies were predominantly randomized trials (n = 95) for treatment of COVID-19 (n = 103). Sex, race, and ethnicity were reported in 109 (89.3%), 95 (77.9%), and 87 (71.3%) trials, respectively. Estimated representation in prevention and treatment trials vs the US population with COVID-19 was 48.9% and 44.6% vs 52.4% for female participants; 23.0% and 36.6% vs 17.7% for Hispanic or Latino participants; 7.2% and 16.5% vs 14.1% for Black participants; 3.8% and 4.6% vs 3.7% for Asian participants; 0.2% and 0.9% vs 0.2% for Native Hawaiian or Other Pacific Islander participants; and 1.3% and 1.4% vs 1.1% for American Indian or Alaska Native participants. Compared with expected rates in the COVID-19 reference population, female participants were underrepresented in treatment trials (85.1% of expected; P < .001), Black participants (53.7% of expected; P = .003) and Asian participants (64.4% of expected; P = .003) were underrepresented in prevention trials, and Hispanic or Latino participants were overrepresented in treatment trials (206.8% of expected; P < .001).

Conclusions and Relevance In this systematic review and meta-analysis, aggregate differences in representation for several demographic groups in COVID-19 prevention and treatment trials in the US were found. Strategies to better ensure diverse representation in COVID-19 studies are needed, especially for prevention trials…

<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2799224>

**recovery**

**title:** WHO member states agree to draft international pandemic accord

bmj | 9th december 2022

World Health Organization member states have agreed to have the first draft of an international pandemic treaty ready for discussion by February 2023.

The agreement would legally require countries to prepare for and respond to future pandemics better and “represents a major milestone in the path towards making the world safer,” said co-chair of the Intergovernmental Negotiating Body (INB) Bureau, Roland Driece.

Driece is one of six delegates from the six WHO regions that make up the INB Bureau…

<https://www.bmj.com/content/379/bmj.o2975>

**workforce wellbeing**

**title:** Health Workforce Issues More Conspicuous After Onset of COVID-19

jama health forum | 8th december 2022

Deaths from COVID-19 are declining, but the pandemic continues to wreak havoc on the health care sector. The challenges resulting from COVID-19 are not exclusively the fault of the health care industry, but the structure of the health care industry has made them worse.

The most recent challenge is to the health care labor force. There are simply not enough workers for all the jobs that health care employers want to fill. This gap is leading to wage increases, putting pressure on hospital and physician margins and reducing access for needy patients.

The reduction in labor supply is partly due to issues related to COVID-19. In 2021 alone, more than 100 000 registered nurses left the labor force. Some workers retired rather than face COVID-19–related workplace risks and stresses. More recently, workers report leaving because of safety concerns unrelated to COVID-19 (such as workplace violence and harassment) and burnout from being asked to do more with less…The reduction in immigration begun in the Trump administration has also taken its toll by exacerbating an existing shortage of health care workers.

Overall, health care employment has increased a mere 0.5% from before the COVID-19 pandemic through October 2022, far below the 3.4% in the comparable period before the pandemic. Employment in nursing homes and residential care is down 9.7%. Hospital employment is up a mere 0.2%.

Not having enough workers causes considerable disruptions in providing health care. Patients cannot be discharged from hospitals to post-acute care facilities because there are no workers to care for them. For a similar reason, emergency department boarding is on the rise…

Health care employers have responded by raising wages. That is normal; wages always increase when demand for labor outstrips supply. The problem in health care is that prices generally do not rise with costs. Thus, rising wages cut severely into margins. Private insurance rates are set up to 3 years in advance. Medicare and Medicaid payments are set legislatively or administratively; neither adjusts automatically to changing economic conditions. Based on data from more than 900 hospitals, the typical hospital had a margin of −1.4% in the first quarter of 2022…

In an era of high input costs, larger health care systems are generally more profitable than smaller ones and can afford to pay more for labor. Thus, there is a net flow of workers from smaller health systems to their bigger competitors. That would be fine if the movement of labor was to institutions where the care was most needed. But there is no evidence that profitability is related to value…

Such disparities are also reflected in the travel nursing industry and its institutional clients. Travel nurses, typically employees of last resort, earn high wages. This, in itself, is not problematic. Emergency labor comes at a premium. But in health care, the reliance on emergency labor can be problematic. Those institutions that can afford to hire travel nurses (ie, the richer, higher-priced health care systems) are not necessarily those where nurses are most needed. Again, profitability is not correlated with value. Further, it is not clear that the extra payment is being earned by nurses themselves. Most travel nurses work through travel nursing companies, many of which are owned by private equity companies. These companies are very profitable—sufficiently so that calls for antitrust scrutiny are on the rise… At least in part, the labor shortage appears to be lining the pockets of rich investors.

The only system-wide solution to the worker shortage is to increase the supply of workers and reduce the demand for care. Here again, dysfunction in the health care system asserts itself. The easiest way to reduce demand is to care for people at home rather than in institutions. The “hospital at home” model has been around since the 1990s, but uptake has been minimal. Indeed, the use of home care after an acute stay varies enormously in different parts of the country… This variation has been known for years, but little has been done about it—and the persistence of this inaction is especially problematic when resources become scarce.

Increasing the supply of health care workers is similarly difficult. The nation’s nursing schools could turn out more nurses, but we have underinvested in training spots. Pay is also an issue, and here health care is hampered by poor policy making in other areas. The cost of living has increased markedly with economy-wide inflation, especially in areas that have been slow to build adequate housing… When the cost of living is so high, even maintaining the current workforce is challenging.

The ultimate irony of health care is that medical treatments change greatly over time, but the structure of the medical system does not. This inertia creates real problems for patients and clinicians when major change is needed. If policy makers and health system leaders cannot figure out how to address this inertia, these problems will continue to fester…

<https://jamanetwork.com/journals/jama-health-forum/fullarticle/2799565>

**health management**

**title:** Overlooked, but not overcome: smaller hospitals and the staff response to the Covid-19 pandemic [Report]

nuffield trust | 9th december 2022

How have smaller hospitals fared over the pandemic and how did it feel from the perspective of those responding during the first years of the biggest health care emergency of our times? We interviewed staff in smaller hospitals around the country during 2021 to understand their key concerns from the perspective of institutions that are sometimes overlooked when system planning gets done. We also make a set of recommendations for future crisis planning and response.

<https://www.nuffieldtrust.org.uk/research/overlooked-but-not-overcome-smaller-hospitals-and-the-staff-response-to-the-covid-19-pandemic>

**title:** Evaluation of Publication of COVID-19–Related Articles Initially Presented as Preprints [research letter]

jama network open | 8th december 2022

Since the launch of the medRxiv preprint server in 2019, the dissemination of research as preprints has grown rapidly, largely facilitated by the COVID-19 pandemic… Notwithstanding, this unprecedented increase in preprints has been subject to criticism, mainly because of reliability concerns owing to their lack of peer review. In 2020, Abdill et al…reported that 62.6% of bioRxiv preprints were later published in scientific journals, considering a time frame of at least 1 year. However, other studies…have highlighted the low percentage of medRxiv preprints subsequently published in journals, with publication rates of 14.0% after 0 to 12 months…and 10.6% after 6 to 19 months… In an analysis of COVID-19–related preprints posted on 3 servers, Añazco et al…observed that 5.7% were published in a journal 3 to 8 months after their preprint posting. To our knowledge, no recent studies have analyzed whether journal publication rates of medRxiv preprints have changed. Therefore, we conducted this study to evaluate the subsequent journal publication of COVID-19–related preprint articles posted on medRxiv in 2020.

Methods

This cross-sectional study did not require institutional review board approval or informed consent because it used publicly available data, in accordance with 45 CFR §46. The study followed the STROBE reporting guideline.

In March 2022, we searched preprints on medRxiv and included all papers on COVID-19 in the infectious diseases subject area that were posted between January 1 and December 31, 2020. We repeated this search in October 2022. Two of us (C.L. and A.M.) completed and verified both searches.

We checked whether a preprint was already published in a peer-reviewed journal by measuring the proportion of medRxiv preprints flagged as published. We recorded the journal names and obtained the journal rankings by measuring their quartile according to the updated 2021 Journal Citation Reports,..in which quartiles 1 and 4 indicate the top 25% and bottom 25% of journals in a particular category, respectively.

Results are presented as counts and percentages. Descriptive statistical analyses were conducted using Excel software, version 16.0 (Microsoft Corp).

Results

In this study, we identified 3343 COVID-19–related preprints posted on medRxiv in 2020. Our March 2022 search indicated that 1712 of those preprints (51.2%) were subsequently published in the peer-reviewed literature; this number increased to 1742 (52.1%) when we repeated the search in October 2022. Not considering January 2020, in which only 1 article on COVID-19 was posted, the rate of subsequent publication in a scientific journal ranged from 43.5% (94 of 216 preprints; observed in March 2020) to 60.6% (177 of 292 preprints posted in August 2020)…

Discussion

Researchers are able to communicate their findings immediately by posting papers on preprint servers, which has become even more important during the COVID-19 pandemic. In this cross-sectional study, we observed that slightly more than half of the preprints related to COVID-19 posted on medRxiv in 2020 were later published in peer-reviewed journals as of October 2022. This publication rate is only slightly greater than that observed 7 months earlier in March 2022, which suggests that a substantial change in the proportion of papers subsequently published in peer-reviewed journals is not expected in the future. Another notable finding of this study is the high quality of the journals in which these articles were subsequently published, as nearly half of the preprints were published in quartile 1 journals.

This study has the limitation of having analyzed only preprints related to COVID-19 posted on a single preprint server. The publication rate of preprints on other topics may be different. Future studies aimed at evaluating publication rates in other areas of medical science are needed…

<https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799314>

**title:** Funding pandemic prevention, preparedness, and response through partnership models [Correspondence]

the lancet public health | 6th december 2022

The World Bank has established the Pandemic Fund, a financial intermediary fund for pandemic prevention, preparedness, and response to strengthen the capability of low-income and middle-income countries (LMICs) to address crucial health system gaps through investments and technical support… Effective integration of the Pandemic Fund within the existing global health architecture requires that duplication of efforts be avoided, and that the function of the Fund be harmonised with that of other major funds, chiefly the Global Fund to Fight AIDS, Tuberculosis, and Malaria. We propose that the Global Fund, the world's leading financing mechanism for LMICs to fight three of the most challenging infectious diseases of our time—namely, HIV, tuberculosis, and malaria…—occupy a central position in channelling the World Bank's Pandemic Fund resources to LMICs.

Because of the Global Fund's collaborative approach to financing, it is uniquely situated among multilateral international entities to harness the power of the public, private, and civil society sectors, and does this by mobilising and deploying funds to national programmes with a high degree of accountability and impact. More than 50 million lives have been saved by programmes supported by the Global Fund…The Pandemic Fund's collaborative approach is based on a partnership model where stakeholders are represented throughout its decision-making processes. This model involves having a board with executive functions and a governance structure where donors and implementers have an equal number of seats and voting rights, as well as civil society and private sector donor seats. The model also entails engaging at the local level through its Country Coordinating Mechanisms, national committees that process funding applications and oversee grants for individual countries. These committees include representatives from all sectors involved in the response to diseases (eg, academic institutions, civil society, faith-based organisations, multilateral and bilateral agencies, non-governmental organisations, technical agencies, the private sector, and people affected by HIV, tuberculosis, and malaria).

The Global Fund has a proven record and capacity to operate beyond its original mandate. The Fund already uses many of the key strategies to help countries prevent, prepare for, and respond to the next pandemic, such as funding service delivery and health system strengthening and reducing human rights barriers to access services for key populations…The Global Fund has raised more than US$3·8 billion for its COVID-19 response mechanism, which were distributed to 109 countries and 22 multicountry programmes…

Formally moving into the pandemic prevention, preparedness, and response space is a natural progression of the Global Fund's existing activities, which could be implemented with great complementarity to the World Bank's Pandemic Fund. For successful implementation to happen, decisive action by the Global Fund's board is needed to expand its mandate…

<https://www.thelancet.com/journals/lanpub/article/PIIS2468-2667(22)00291-2/fulltext>

We

[TRFT Library & Knowledge Service](https://www.trftlibraryknowledge.com/) aim to bring together the latest guidelines, research and news on Covid-19 through our [Covid-19 portal](https://www.trftlibraryknowledge.com/coronavirus.html). For daily updates on Covid-19 visit our '[Latest Health](https://trfthealthweeklydigest.wordpress.com/)' newsfeed, or use the hashtag [#covid19rftlks](https://twitter.com/hashtag/covid19rftlks?src=hashtag_click) to see our latest tweets on Covid-19 research, guidelines and news.

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