Infectious Diseases Watch

July 4, 2022

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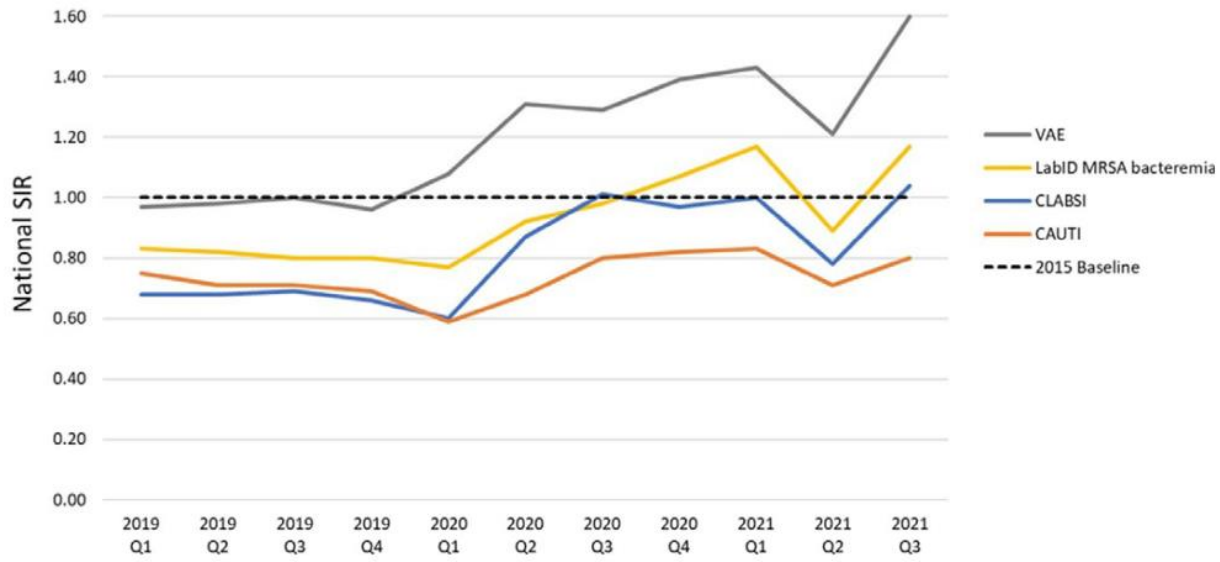
Continued increases in the incidence of healthcare-associated infection (HAI) during the second year of the coronavirus disease 2019 (COVID-19) pandemic.
Infect Control Hosp Epidemiol published online May 20, 2022

doi:10.1017/ice.2022.116

This analysis followed the same methodology published for 2020 data which demonstrated increases in most HAIs except CDIs. Quarterly national standardized infection ratios (SIRs) and standardized utilization ratios (SURs) were calculated for the first 3 quarters of 2021 (2021-Q1 through 2021-Q3) for CLABSIs, CAUTIs, VAEs, select SSIs, LabID MRSA bacteremia, and LabID CDI events as applicable. The 2021 quarterly results were compared to the same quarters from 2019.

This analysis revealed elevated incidence of CLABSIs, CAUTIs, VAEs, and MRSA bacteremia infections during 2021, especially during the first and third quarters of the year.
During 2021-Q1, all-time highs of COVID-19–associated hospitalizations were recorded throughout the country. Although large increases were noted in CLABSI, VAE, and MRSA bacteremia in 2021-Q1, the increase in the CAUTI SIR was modest. Improvements in CLABSI, CAUTI, VAE, and MRSA bacteremia SIRs were observed in 2021-Q2, coincident with the dramatic reduction in nationwide COVID-19 hospitalizations. However, as the severe acute SARS-CoV-2 delta variant emerged in 2021-Q3, dramatic increases in SIRs were observed again. PPE practices, and environmental cleaning may have contributed to the decreases observed in the CDI SIR.



Comment: These increases corresponded with periods of high COVID-19 hospitalizations and were especially elevated during the first and third quarters of 2021. Data also revealed declines in CDIs, likely due to pandemic-related improvements in hand hygiene, personal protective equipment (PPE) practices, and environmental cleaning in healthcare settings. This underscores the continued challenges experienced in infection prevention. This is certainly multi-factorial including turnover (both nursing and IPs), visiting nurses, burnout, staffing etc. My hope now is with Covid hospitalizations decreasing, we now have the opportunity to get back to "basics." The Compendium is being updated with CLABSI and VAP/HAP guidelines already published.

Prevalence and Characterization of the Cefazolin Inoculum Effect in North American Methicillin-Susceptible Staphylococcus aureus Isolates

J Clin Microbiol published online June 2022

Doi:10.1128/jcm.02495-21

Ant staphylococcal penicillins and cefazolin remain the primary treatments for serious MSSA infections. The cefazolin inoculum effect (CzIE) causes the cefazolin (CZ) MIC to be elevated in proportion to the number of bacteria in the inoculum. Although CZ has shown better tolerability with similar treatment outcomes, some MSSA demonstrate this "inoculum effect," where raising the inoculum above the standard concentration results in CZ resistance due to beta-lactamase hydrolysis. CZ treatment failure in such settings has been documented primarily in endocarditis. MSSA isolates were tested by broth microdilution at a standard inoculum equivalent to a final concentration of 5 X 10^5 CFU/mL and at a high bacterial inoculum of 5 X 10^7 CFU/mL.

Investigators in this study tested clinical MSSA isolates from several US and Canadian microbiology laboratories for presence of the "inoculum effect." A positive inoculum effect was defined in MSSA with a CZ minimum inhibitory concentration (MIC) ≥16 mg/L under high-inoculum testing and a MIC ≤8 mg/L under standard inoculum testing. Isolates were also

characterized by whole genome sequencing. A positive inoculum effect was seen in 19% of MSSA tested (range, 0%–28%). The MSSA ST8 and ST30 genetic backgrounds were most common among inoculum-effect–positive strains. Type C (54%) and type A (44%) were the most common beta-lactamase types in inoculum-effect–positive MSSA.

Comment: This study demonstrated that under conditions of high inoculum, up to ~25% of MSSA demonstrate CZ MIC ≥16mg/L raising concern about use of monotherapy with CZ when treating high inoculum infections such as endocarditis. Until CZ inoculum testing becomes available, it is important that clinicians assure adequate source control before using CZ monotherapy to treat high-risk MSSA infections. One approach for serious MSSA infections with bacteremia is to start with an antistaph penicillin and then consider changing to CZ only after good source control and negative blood cultures.

Intravenous Vitamin C in Adults with Sepsis in the Intensive Care Unit N Engl J Med 2022;386:2387-98.

DOI: 10.1056/NEJMoa2200644

This is a randomized, placebo-controlled trial, which included adults who had been in the ICU for no longer than 24 hours, who had proven or suspected infection as the main diagnosis, and who were receiving a vasopressor. They were randomized to receive an infusion of either vitamin C (at a dose of 50 mg per kilogram of body weight) or matched placebo administered every 6 hours for up to 96 hours. The primary outcome was a composite of death or persistent organ dysfunction (defined by the use of vasopressors, invasive mechanical ventilation, or new renal-replacement therapy) on day 28. They prespecified the subgroup analyses of the primary outcome according to age (<65 years or ≥65 years), sex, frailty (according to a score on the Clinical Frailty Scale25 of 1 to 4 or ≥5), severity of illness (the quartile of predicted risk of death on the basis of the baseline APACHE II score), presence of septic shock (defined as the use of a vasopressor infusion to maintain a mean arterial pressure of ≥65 mm Hg and the presence of a lactate level of ≥2 mmol per liter1 vs. the use of vasopressor infusion alone).

A total of 872 patients underwent randomization (435 to the vitamin C group and 437 to the control group). The primary outcome occurred in 191 of 429 patients (44.5%) in the vitamin C group and in 167 of 434 patients (38.5%) in the control group (risk ratio, 1.21; 95% confidence interval [CI], 1.04 to 1.40; P=0.01). In addition, at 28 days, death had occurred in 152 of 429 patients (35.4%) in the vitamin C group and in 137 of 434 patients (31.6%) in the placebo group (risk ratio, 1.17; 95% CI, 0.98 to 1.40) and persistent organ dysfunction in 39 of 429 patients (9.1%) and 30 of 434 patients (6.9%), respectively (risk ratio, 1.30; 95% CI, 0.83 to 2.05). Findings were similar in the two groups regarding organ-dysfunction scores, biomarkers, 6-month survival, health-related quality of life, stage 3 acute kidney injury, and hypoglycemic episodes. In the vitamin C group, one patient had a severe hypoglycemic episode, and another had a serious anaphylaxis event.

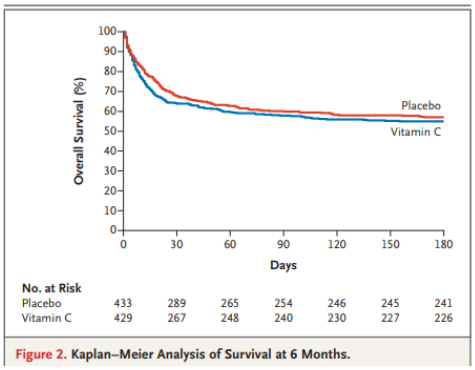


Figure 2. Kaplan–Meier Analysis of Survival at 6 Months.

Comment: After a single-center study by Marik spurred interest in the use of intravenous vitamin C, administered with hydrocortisone and thiamine [Chest 2017;151:1229-1238], subsequent randomized, controlled trials evaluating this combination treatment did not show benefits. [Intensive Care Med 2022;48:16-24; JAMA 2021; 325:742-750] In contrast, in a randomized, controlled trial, patients with sepsis and acute lung injury who received a higher dose of vitamin C (50 mg per kilogram of body weight every 6 hours) had a lower 28-day risk of death than those who received placebo.[JAMA 2019;322:1261-1270] However, recent meta-analyses suggest that the overall evidence supporting the use of vitamin C therapy in patients with sepsis is of low certainty. [Intensive Care Med 2022;48:16-24]

In this clinical trial involving adults with sepsis who were receiving vasopressors in the ICU, the composite primary outcome (death or persistent organ dysfunction at trial day 28) occurred more frequently in patients who had received intravenous vitamin C than in those who had received placebo. This was a surprise finding to me, and the secondary analyses — which included the evaluation of five biomarkers of tissue dysoxia, inflammation, and endothelial injury measured up to day 7 — did not determine an explanation for harm. For now, the evidence for IV vitamin C in patients with sepsis remains weak.

Monkeypox Update

Europe cases have grown to over 4000 cases in less than 2 months with the UK accounting for 25% of cases. In the US cases now stand at over 350 from 28 states. The Texas Department of State Health Services said there was evidence of local, community spread of the virus involved in international travel, but recent cases did not travel in the last 3 weeks before becoming ill. So far none of the more than 5000 cases seen in non-endemic countries have been fatal.

COVID-19

COVID-19 News

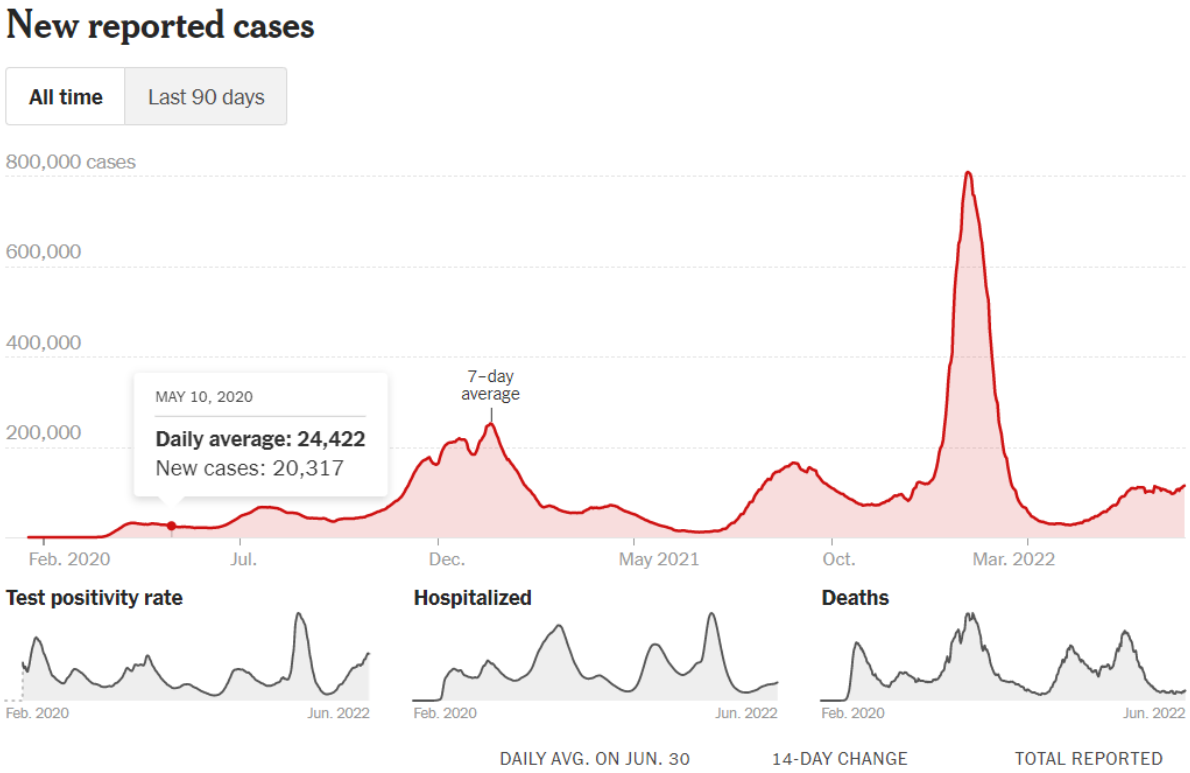
FDA Advisors Endorse update Covid Vaccine

The FDA outside advisory panel by a vote of 19-2 endorsed last Tuesday to include vaccines better able to protect against the Omicron variants. Exact formulation to be determined.

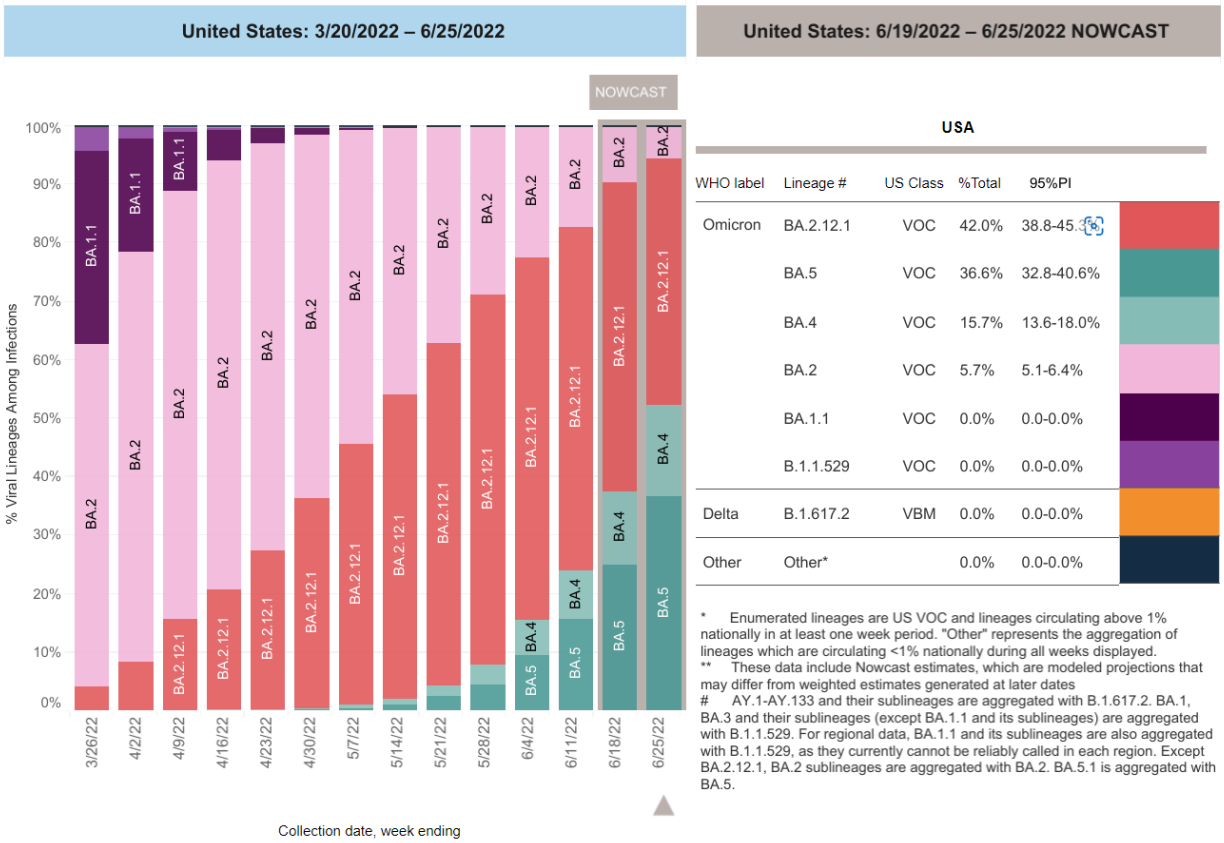
Omicron Subvariants BA.4 and BA.5

The CDC reports together subvariants BA.4 an BA.5 has become the dominant variants. As of the end of June 2022, BA.4 cases make up ~16% of new cases and BA.5 make up almost 40% of new cases.

COVID-19 by the Numbers



- **Comment:** The average number of cases announced each day in the US has stayed relatively consistent in June. Regional differences are significant. In most of the Northeast, cases have decreased continuously throughout the month of June. In the South, many states have seen cases double or triple in the same time. Hospitalizations have increased modestly throughout the month, though they remain low. Reports of new deaths remain below 400 a day, down from more than 2,600 a day at the height of the Omicron surge. BA.4 and BA.5 together constitute the majority of cases. See below



Commonwealth Fund Report: Meeting America's Public Health Challenge June 2022

<u>Summary</u>

- Public health efforts are not organized for success. Despite dozens of federal health agencies and nearly 3,000 state, local, tribal, and territorial health departments, there is no single person or office at the U.S. Department of Health and Human Services to lead and coordinate the nation's public health efforts.
- Public health funding is not sufficient or reliable. The chronic underfunding of public health has left behind a weak infrastructure, with antiquated data systems, an overworked and stressed workforce, laboratories in disrepair, and other major gaps.
- Expectations for health agencies are minimal. Funding is not tied to a set of basic standards for the capabilities of state, local, tribal, and territorial health departments.
- The health care system is missing opportunities to support health improvement. It is difficult to convert collaboration with public health agencies during emergencies into sustainable work to address day-to-day health challenges.
- The public health enterprise is facing a crisis in trust. This crisis relates to experiences with racism and discrimination, ideological opposition, and misinformation.

The United States should build a national public health system to promote and protect the health of every person, regardless of who they are and where they live; implement effective strategies with others in the public and private sectors; respond to both day-to-day health

priorities and crises with vigor and competence; and, in the process, earn high levels of trust. In this report, the Commission provides a detailed set of recommendations to achieve this vision, which include the following.

Congress should:

- Establish a position, such as an undersecretary for public health at the U.S. Department of Health and Human Services (HHS), to oversee and coordinate the development of the national public health system.
- Provide adequate and reliable public health infrastructure funding, paired with expectations that states, localities, tribes, and territories meet standards for protecting their communities.
- Fund a modern public health information technology system and provide HHS with the authority to make it work.

The Administration should:

- Set parameters for use of available funds to systematically build public health infrastructure, with an initial focus on workforce and data systems.
- Support revision of accreditation standards for state, local, tribal, and territorial health departments to focus on basic capabilities for public health protection.
- Establish a council to coordinate federal public health action with states, localities, tribes, and territories.
- Reconvene the National Prevention and Public Health Council to guide an all-of-government approach to the drivers of health.
- Embrace ethics, integrity, and transparency in decision-making in public health.

States, localities, tribes, and territories should:

- Assess the structural and policy changes needed to provide foundational capabilities for all their residents.
- Build connections between the health care system and public health to strengthen day-to-day health improvement efforts and better prepare for emergencies.
- Involve community partners in decision-making about public health.

Comment: More than 1 million Americans have died from COVID-19. Why have so many Americans died? The answer lies not just in the biology of SARS-CoV-2 but also in the nation's lack of funding and preparedness for a pandemic. Public health has been underfunded for decades. The warning signs were seen during the 2009 pandemic, but no one addressed these concerns. So, in 2020 particularly in the early critical months of the pandemic, there were significant gaps in tracking the disease related to delays in getting tests to people who needed them and to archaic approaches to aggregating and data sharing in real time. The local and federal response struggled to develop timely guidance and to communicate accurate information amid falsehoods and misinformation, some spread deliberately. There were missteps from CDC and other public health agencies and officials which resulted in many Americans distrusting their government/CDC and each other. These brutal truths uncovered that the US lacked a national public health system capable of protecting and responding effectively to emergencies. "The consequences of these deficiencies reach far beyond the current pandemic and undermine the nation's ability

to respond to ongoing and pressing health challenges." We must restore confidence in public health and improve communication to reduce confusion. The commonsense recommendations in this report are a good starting point. The time to act is now! See first article under Covid-19 Journal Review

COVID-19 Journal Review

Building a National Public Health System in the United States N Engl J Med published online June 21, 2022

DOI: 10.1056/NEJMp2207374

Risk of long COVID associated with delta versus omicron variants of SARS-CoV-2 Lancet published online June 9, 2022

doi.org/10.1016/ S0140-6736(22)00946-1

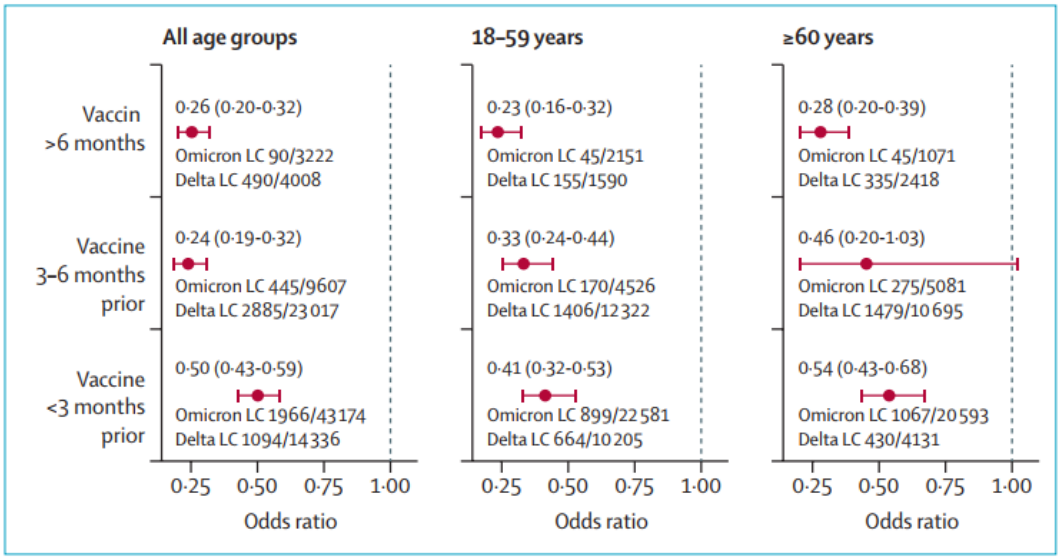
Omicron appears to cause less severe acute illness than previous variants, at least in vaccinated populations. However, the potential for large numbers of people to experience long-term symptoms remains a major concern. In this case-control observational study, the investigators set out to identify the relative odds of long-COVID (defined following the National Institute for Health and Care Excellence guidelines as having new or ongoing symptoms 4 weeks or more after the start of acute COVID-19 in the UK during the omicron period compared with the delta period.

The study used self-reported data from the COVID Symptom Study app, with the inclusion criteria in both periods being a positive real-time PCR or lateral flow antigen test for SARS-CoV-2 after vaccination, at least one log per week in the app for at least 28 days after testing positive, and no previous SARS-CoV-2 infections before vaccination.

A total of 56,003 UK adults first testing positive between December 20, 2021, and March 9, 2022 who satisfied the inclusion criteria were identified. These cases were referred to as omicron cases as more than 70% of UK cases were attributable to the omicron variant during that time. Using identical selection criteria, 41,361 UK adult cases first testing positive between June 1, 2021, and November 27, 2021, were identified. These cases were referred to as delta cases as more than 70% of cases were attributable to the delta variant at the time. Both symptomatic and asymptomatic infections were considered, and, for the omicron period, only participants testing positive before February 10, 2022, were included to ensure all participants had at least 28 days for symptom reporting after testing positive. They then stratified the analysis according to the time elapsed between infection and most recent vaccination considering three groups, 3 months, 3–6 months, and more than 6 months, to allow for potential waning of immunity from vaccination. In both periods, female participation was higher than male participation (55% for omicron and 59% for delta cases). Delta and omicron cases had similar age (mean age 53 years) and prevalence of comorbidities (around 19%).

Among omicron cases, 2,501 (4·5%) of 56,003 individuals experienced long COVID compared to 4,469 (10·8%) of 41,361 individuals among delta cases. After adjusting for age, sex, body-mass index, Index of Multiple Deprivation, presence of comorbidities, and vaccination status (one, two, or three vaccine doses), omicron cases were less likely to experience long COVID for

all vaccine timings, with an odds ratio ranging from 0·24 (95% confidence interval [CI] 0·20–0·32) to 0·50 (0·43–0·59). These results were also confirmed when the analysis was stratified by age group.



Comment: This is the first peer reviewed study to report on long COVID risk associated with infection by the omicron variant. Overall, they found a reduction in odds of long COVID with the omicron variant versus the delta variant of 0·24–0·50 depending on age and time since vaccination. Limitations of the self-reported data include no direct testing of infectious variants and no objective measures of illness duration. They had insufficient data to estimate the odds of long COVID in unvaccinated individuals and did not estimate effects in children. The period of assessment of omicron cases was slightly shorter than for the delta variant, and assessment of longer durations of long COVID (e.g., >12 weeks) was not possible.

Effectiveness of Paxlovid in Reducing Severe COVID-19 and Mortality in High Risk Patients

Clin Infect Dis published online June 2, 2022

doi/10.1093/cid/ciac443/6599020

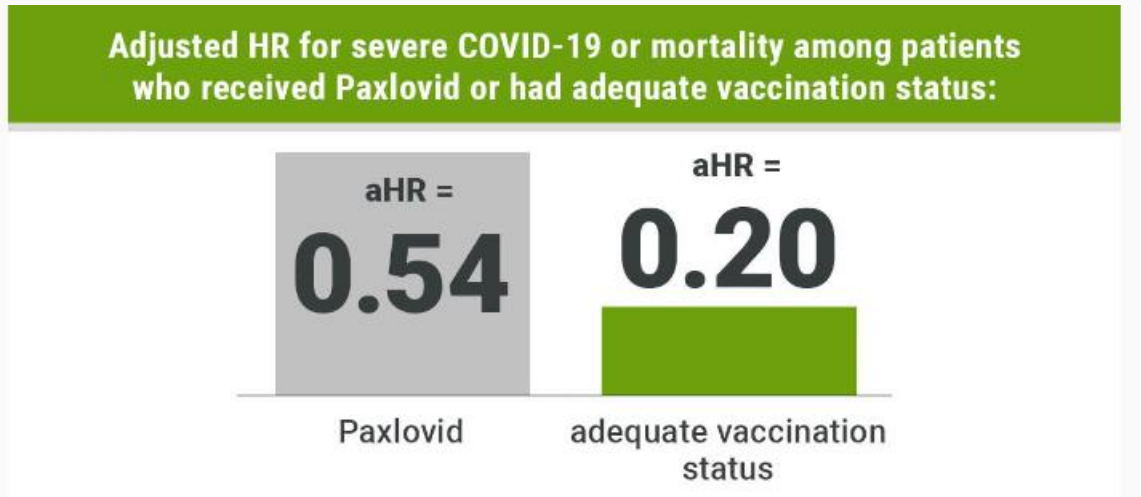
Najjar-Debbiny and colleagues used the database of the largest health care provider in Israel to identify adults with a first-time positive test for SARS-CoV-2 between January and February 2022. They included in their study patients at high risk for severe COVID-19 with no contraindications for Paxlovid, regardless of vaccination status, and estimated their 28-day HR for severe COVID-19 or death with Paxlovid, which has been authorized for use in the United States since December.

Among the 180,351 eligible patients included in the study, 4,737 were treated with Paxlovid and 135,482 had an adequate COVID-19 vaccination status.

The study demonstrated that both Paxlovid and adequate COVID-19 vaccination status were associated with a significant decrease in the rate of severe COVID-19 or mortality (adjusted HR = 0.54; 95% CI, 0.39-0.75 and aHR = 0.20; 95% CI, 0.17-0.22, respectively). They also found

that the effect of Paxlovid was seemingly more significant among older patients, immunosuppressed patients and patients with underlying neurological or cardiovascular disease ($P < .05$).

"COVID-19 vaccination remains the most effective intervention to prevent disease progression and death among COVID-19 patients," Najjar-Debbiny said. "However, another effective intervention would be the use of Paxlovid in high-risk patients suffering from a mild to moderate disease."



Paxlovid lowered the risk for severe COVID-19 or death by 46% in a study of patients in Israel and was especially effective among older or immunosuppressed patients, or patients with underlying neurological or cardiovascular diseases.

Omicron subvariants escape antibodies elicited by vaccination and BA.2.2 infection Lancet Infect Dis published online June 20,2022

doi.org/10.1016/ S1473-3099(22)00410-8

The new BA.2.12.1, BA.2.13, BA.4, and BA.5 omicron subvariants containing Leu452 substitutions show greater transmissibility than BA.2.3 The invetsigators examined neutralizing activity against the BA.1, BA.2, BA.2.11, BA.2.12.1, BA.2.13, BA.4, and BA.5 omicron subvariants in serum from people who received BBIBP-CorV (Sinopharm) primary immunization, people who received BBIBP-CorV or ZF2001 (Anhui Zhifei Longcom) boosters, and people with omicron breakthrough infections.

Using an in-house pseudovirus neutralization assay they found that two BBIBP-CorV doses induced detectable neutralizing antibodies against spike protein mutation D614G in 21 (84%) individuals, but neutralizing activity against omicron subvariants (BA.1, BA.2, BA.2.11, BA.2.12.1, BA.2.13, and BA.4/BA.5) was only minimally detectable.

Geometric mean titers (GMTs) of neutralizing antibodies against D614G in the 25 individuals who received a BBIBP-CorV booster were 3·1-times higher than in people who received two doses of BBIBP-CorV; the 30 people who received a ZF2001 booster had a 2·9-times higher

GMT than individuals who received two doses of BBIBP-CorV. Neutralizing activity against omicron subvariants was observed in 24–48% of people who received a BBIBP-CorV booster and 30–53% of people who received a ZF2001 booster.

Comment: Completion of the primary BBIBP CorV vaccination schedule induces neutralizing antibodies in most individuals against SARS-CoV-2 variants with a D614G mutation, which is consistent with previous studies. [Nat Commun 2022; 13: 1788]. However, the spike protein mutation enables the escape of omicron subvariants from neutralization, which can be partly restored by a booster vaccination. Breakthrough omicron infections enhance sera neutralizing potential specifically against the omicron subvariants, which is consistent with two recent studies. [y. medRxiv 2022; posted online May 1. https://doi.org/ 10.1101/2022.04.29.22274477; bioRxiv 2022; posted online May 2. https://doi. org/10.1101/2022.04.30.489997]. Together, the results indicate that the new SARS-CoV-2 subvariants (e.g., BA.2.12.1 and BA.4 and BA.5) has the potential of causing a new wave of infections which in fact is occurring. In the US BA.5 as increased to 23.5% of cases, BA.4 11.4%, and BA.2.12.1 56%. (see next article)

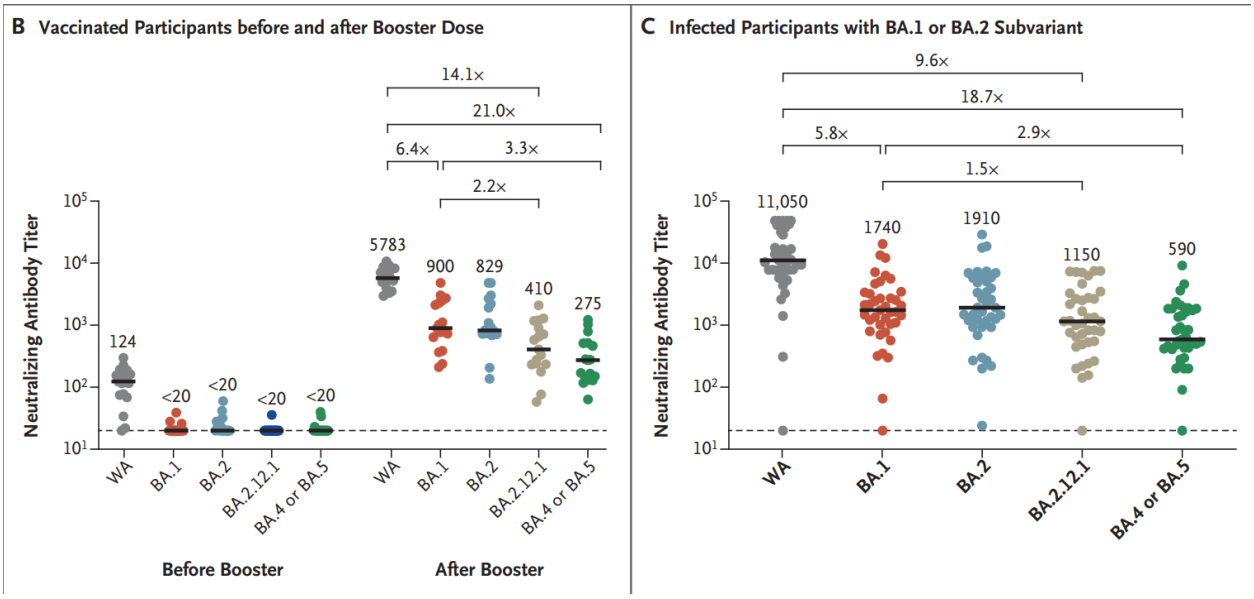
Neutralization Escape by SARS-CoV-2 Omicron Subvariants BA.2.12.1, BA.4, and BA.5

DOI: 10.1056/NEJMc2206576

The investigators evaluated neutralizing antibody titers against the reference WA1/2020 isolate of SARSCoV-2[ancestral strain] along with omicron subvariants BA.1, BA.2, BA.2.12.1, and BA.4 or BA.5 in 27 participants who had been vaccinated and boosted Pfizer vaccine and in 27 participants who had been infected with the BA.1 or BA.2 subvariant a median of 29 days earlier (range, 2 to 113).

Six months after the initial two Pfizer vaccination, the median neutralizing antibody pseudovirus titer was 124 against WA1/2020 but less than 20 against all the tested omicron subvariants. Two weeks after administration of the booster dose, the median neutralizing antibody titer increased significantly, to 5783 against the WA1/2020 isolate, 900 against the BA.1 subvariant, 829 against the BA.2 subvariant, 410 against the BA.2.12.1 subvariant, and 275 against the BA.4 or BA.5 subvariant.

Among the participants who had been infected with the BA.1 or BA.2 subvariant of omicron, all but one had been vaccinated against Covid-19. Among the participants with a history of Covid-19, the median neutralizing antibody titer was 11,050 against the WA1/2020 isolate, 1740 against the BA.1 subvariant, 1910 against the BA.2 subvariant, 1150 against the BA.2.12.1 subvariant, and 590 against the BA.4 or BA.5 subvariant.



Comment: These data show that boosted vaccinated persons when compared with the response against the WA1/2020 isolate, that the neutralizing antibody titer was lower by a factor of 6.4 against BA.1, by a factor of 7.0 against BA.2, by a factor of 14.1 against BA.2.12.1, and by a factor of 21.0 against BA.4 or BA.5. In addition, as compared with the median neutralizing antibody titer against the BA.1 subvariant, the median titer was lower by a factor of 2.2 against the BA.2.12.1 subvariant. and by a factor of 3.3 against the BA.4 or BA.5 subvariant.

These data also showed in BA.1 infected individuals compared with the WA1/2020 isolate, the median neutralizing antibody titer was lower by a factor of 6.4 against BA.1, by a factor of 5.8 against BA.2, by a factor of 9.6 against BA.2.12.1, and by a factor of 18.7 against BA.4 or BA.5.

Bottom line: This study showed that the BA.2.12.1, BA.4, and BA.5 subvariants may escape neutralizing antibodies induced by both vaccination and infection. Moreover, neutralizing antibody titers against the BA.4 or BA.5 subvariant and (to a lesser extent) against the BA.2.12.1 subvariant were lower than titers against the BA.1 and BA.2 subvariants. These findings help explain the current surge caused by the BA.2.12.1, BA.4, and BA.5 subvariants in populations even in the face of high rates of vaccination and/or prior BA.1 or BA.2 infection.