Infectious Diseases Watch

July 11, 2022

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General Infectious Diseases

Patterns, Predictors, and Intercenter Variability in Empiric Gram-Negative Antibiotic Use Across 928 United States Hospitals Clin Infect Dis published online June 23, 2022

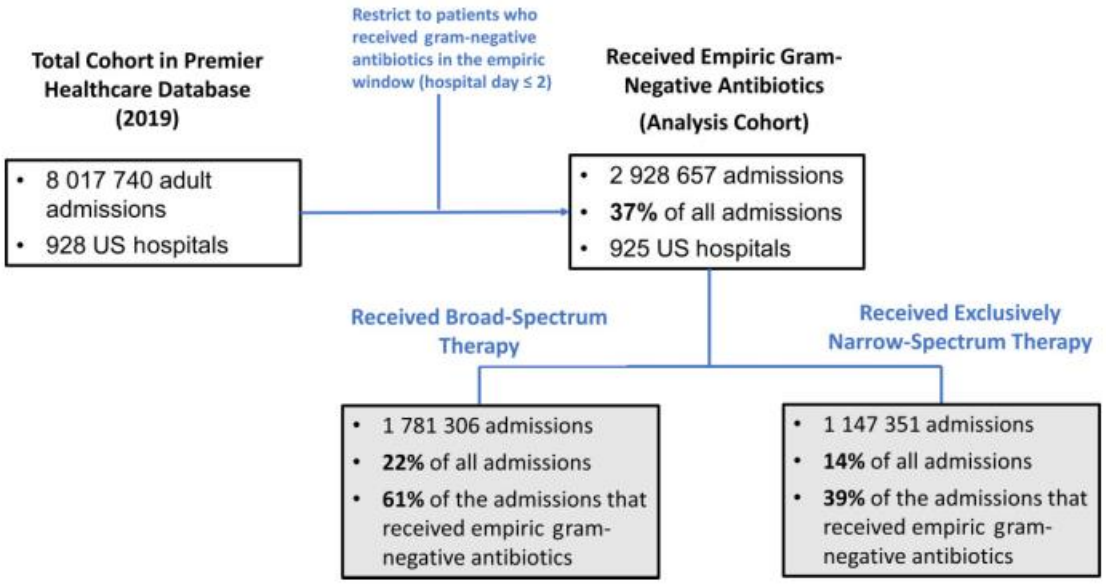
doi/10.1093/cid/ciac504/6614628

The investigators performed a retrospective cohort study of adults discharged in 2019 from 928 hospitals in the Premier Healthcare Database. “Empiric” gram-negative antibiotics were defined by administration before day 3 of hospitalization. Multivariable logistic regression models with random effects by hospital were used to evaluate associations between patient and hospital characteristics and empiric receipt of broad-spectrum, compared to narrow-spectrum, gram-negative antibiotics. See table below

NARROW SPECTRUM		BROAD SPECTRUM	
Narrowest-Spectrum	**Narrower-Spectrum**	**Extended-Spectrum**	**Extremely Broad-Spectrum**
• 2nd-generation cephalosporins • Amoxicillin • Ampicillin • Metronidazole	• Ceftriaxone • Third-generation oral cephalosporins • Amoxicillin-clavulanate • Ampicillin-sulbactam	• Antipseudomonal penicillins • Fluoroquinolones • Aminoglycosides • Cefepime • Ceftazidime • Carbapenems • Aztreonam • Colistin • Ceftaroline	• Imipenem/cilastatin/relebactam • Meropenem-vaborbactam • Tigecycline • Ceftolozane-tazobactam • Ceftazidime-avibactam • Cefiderocol

Of 8,017,740 hospitalized adults, 2,928,657 (37%) received empiric gram-negative antibiotics. Among 1,781,306 who received broad-spectrum therapy, 30% did not have a common infectious syndrome present on admission (pneumonia, UTI, sepsis, or bacteremia), surgery, or an ICU stay in the empiric window. This suggests that a subset of these patients may have been exposed unnecessarily to broad-spectrum empiric therapy which could result in unintended consequences. Holding other factors constant, males were 22% more likely (adjusted odds ratio [aOR], 1.22 [95% confidence interval, 1.22–1.23]), and all non-White

racial groups 6%–13% less likely (aOR range, 0.87–0.94), to receive broad-spectrum therapy. There were significant prescribing differences by region, with the highest adjusted odds of broad-spectrum therapy in the US West South-Central division. Even after model adjustment, there remained substantial interhospital variability: Among patients receiving empiric therapy, the probability of receiving broad-spectrum antibiotics varied as much as 34+ percentage points due solely to the admitting hospital (95% interval of probabilities: 43%–77%).



Narrow-Spectrum Gram-Negative Antibiotics*	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]	Broad-Spectrum Gram-Negative Antibiotics**	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]	Extremely Broad-Spectrum Gram-Negative Antibiotics***	Total Empiric Days of Therapy (DOTs) in Cohort (n, % of total empiric DOTs)[a]
Ceftriaxone	1 883 838 (60.1%)	Piperacillin-tazobactam	1 495 491 (43.0%)	Tigecycline	2268 (40.0%)
Metronidazole	654 142 (20.9%)	Cefepime	778 853 (22.4%)	Ceftolozane/ tazobactam	1690 (29.8%)
Ampicillin/ sulbactam	172 720 (5.5%)	Levofloxacin	419 586 (12.1%)	Ceftazidime/ avibactam	1432 (25.8%)
Ampicillin	166 724 (5.3%)	Ciprofloxacin	211 415 (6.1%)	Meropenem/ vaborbactam	252 (4.4%)
Cefoxitin	79 590 (2.5%)	Meropenem	207 012 (6.0%)		

Comment: This study found that >1 of every 5 US hospitalized patients received broad-spectrum gram-negative antibiotics in the first 2 days of hospitalization. There was high variability in the receipt of broad-spectrum therapy across geographic regions and high unexplained variance between individual hospitals. The potential overuse of broad-spectrum therapy when not indicated is well known, but the potential underuse of broad-spectrum therapy when it is indicated is also of concern. In this study, 23% of patients with sepsis did not receive broad-spectrum empiric gram-negative therapy. Taken together, both the potential overtreating of patients without clear risk factors and the potential undertreating of patients with invasive infections underscores the need for the development of real time validated risk-assessment tools, to guide optimal empiric therapy selection. In a study from 2020 both inadequate and unnecessarily broad antibiotics was associated with higher morality. [JAMA Netw Open. 2020;3:e202899] The Inspire trial provide just such a tool using smart prompts to predict

the risk of MDROs for patients admitted with pneumonia and UTIs. [ID Week October 2021]. These studies have shown that most clinicians overestimate the risk of MDROs. The investigators did not have microbiological data, and therefore, they could not adjust for hospitals' local susceptibility patterns, which may influence empiric prescribing. [I doubt this would have made much difference] They did find that patient severity-of-illness markers were independent predictors of receipt of broad-spectrum empiric therapy, as were invasive infections at admission and receipt of broad-spectrum gram-negative antibiotics in the 3 months preceding admission. The study used diagnostic claims codes to identify POA infections, and they did not have laboratory or vital signs data. The study did not evaluate clinical outcomes. Lastly, a common perception is that a few days of antibiotic exposure will not cause harm. However, data indicate that each day of therapy can increase the risk of adverse events. [Pharmacotherapy 2019; 39:261–70; JAMA Surg 2019; 154:590–8] In addition many patients initiated on empiric therapy are not de-escalated even when cultures are negative [BMC Infect Dis 2016; 16:751]. These findings underscore the need for better tools and stewardship to improve empiric antibiotic prescribing in US inpatients.

Temporal Trends in Antimicrobial Prescribing During Hospitalization for Potential Infection and Sepsis JAMA Intern Med published online June 27, 2022

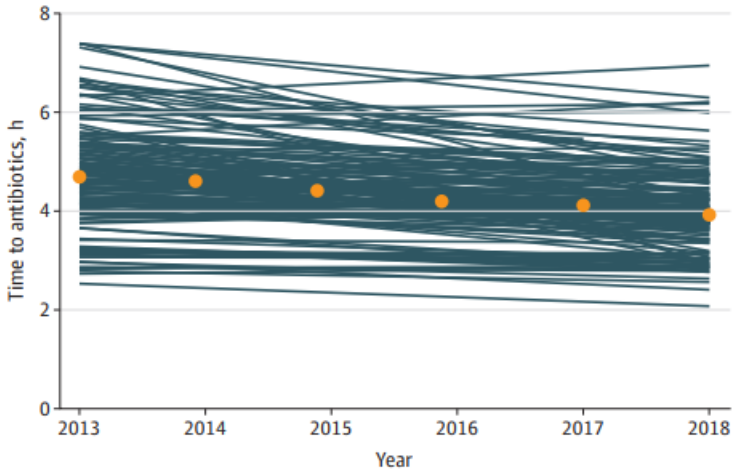
doi:10.1001/jamainternmed.2022.2291

This is an observational cohort study of hospitalized patients at 152 hospitals in 2 health care systems [at the US Veterans Affairs (VA) and Kaiser Permanente Northern California (KPNC)] health care systems during 2013 to 2018, admitted via the ED with 2 or more SIRS criteria. Patient and hospitalization characteristics, including demographics, race, comorbidities, laboratory values, and hospital treatments, were extracted from the VA and KPNC electronic health records. They classified patients as having sepsis on the basis of objective evidence of suspected infection and acute organ dysfunction, similar to the CDC's Adult Sepsis Event definition.[identified by antimicrobial therapy administered within 12 hours of emergency department presentation, antimicrobial therapy continued for 4 or more consecutive days, and objective evidence of acute organ dysfunction within 48 hours of arrival] They measured hospital-level temporal trends in time to first antimicrobial administration among patients with sepsis using multilevel linear regression models. Antimicrobial outcomes included antimicrobial use, days of therapy, and broadness of antibacterial coverage. Clinical outcomes included in-hospital mortality, 30-day mortality, length of hospitalization, and new multidrug-resistant (MDR) organism culture positivity.

Among 1,559,523 patients admitted to the hospital via the ED with 2 or more SIRS criteria (1,269,998 male patients [81.4%]; median [IQR] age, 67 [59-77] years), only 273,255 (17.5%) met objective criteria for sepsis. In multivariable models adjusted for patient characteristics, the adjusted median (IQR) time to first antimicrobial administration to patients with sepsis decreased by 37 minutes, from 4.7 (4.1-5.3) hours in 2013 to 3.9 (3.6-4.4) hours in 2018, although the slope of decrease varied across hospitals. During the same period, antimicrobial use within 48 hours, days of antimicrobial therapy, and receipt of broad-spectrum coverage decreased among the broader cohort of patients with SIRS. In-hospital mortality, 30-day mortality, length of hospitalization, new MDR culture positivity, and new MDR blood culture positivity decreased over the study period among both patients with sepsis and those with SIRS. When examining hospital-specific trends, decreases in antimicrobial use, days of therapy, and broadness of antibacterial coverage for patients with SIRS did not differ by hospital antimicrobial timing trend for sepsis, however, among all patients with SIRS, receipt of an antimicrobial

within 12 hours of emergency department arrival increased from 49.1% in 2013 to 50.5% in 2018. Overall, there was no evidence that decreasing antimicrobial timing for sepsis was associated with increasing antimicrobial use or impaired antimicrobial stewardship.

Figure 1. Temporal Trends in Time to First Antimicrobial Administration Among Patients With Sepsis, by Hospital



Orange dots indicate median time to first antimicrobial by year; blue lines denote temporal trend in median time to first antimicrobial per hospital. Median time to first antimicrobial, after adjustment for patient characteristics, decreased by 7.3 minutes per year (from a median [IQR] of 4.7 [4.1-5.3] hours in 2013 to 3.9 [3.6-4.4] hours in 2018).

Comment: These findings suggest that shortening the time to antibiotics administration for sepsis is feasible without leading to indiscriminate antimicrobial use in VA and KPNC which both have robust antimicrobial stewardship program. Therefore, this finding may not be generalizable to the average US hospital. In fact, an interrupted time series of hospitalized patients at 111 hospitals, the investigators found that days of broad-spectrum antimicrobial therapy per 100 000 patient-days increased immediately after SEP 1 rollout among patients hospitalized for severe sepsis and septic shock. [Clin Infect Dis 2021; 72:556-565] In the current study changes in antimicrobial prescribing over time were small. (See graph above) Therefore, at best we can say antimicrobial utilization was stable and no worse. Lastly, if you look at percent of patients who had SIRS, but did not meet the sepsis definition, ~1/3 may have received unnecessary antibiotics. Bottom line, this is a very nice study, but the results may not be generalizable since other studies have shown increased use of broad-spectrum antibiotics when SEP-1 was implemented. See article above

Monkeypox Update

The Monkeypox cases are continuing to increase in the US and elsewhere, with CDC now reporting over 700 cases in 34 states, the District of Columbia, and Puerto Rico.

New York has the most cases, with 122, followed by California with 116 and Florida with 64.

According to the latest situation update from the WHO published July 6th, global cases increased 77% in the past week. The global total stands at 8,127 cases from 59 countries. There have been 3 deaths, all in African nations. In non-endemic countries, the United Kingdom has the most cases, with 1,235, followed by 1,054 in Germany.

The WHO update also noted that among monkeypox patients with known HIV status, 41% were HIV-positive. Among cases with reported sexual orientation, 60% (1,214 of 2,025) identified as gay, bisexual, and other men who have sex with men. The most often suspected and reported route of transmission, among known contacts, has been through sexual contact. Due to sensitivity in reporting a full list of sexual contacts, identification of all contacts of probable and confirmed cases has proven to be very challenging. The European Centre for Disease Prevention and Control (ECDC) published its first update to its rapid risk assessment of monkeypox, saying that the likelihood of disease spread in people with multiple sexual partners in Europe is high, but the risk to the broader population is very low. The outbreak in Europe is still mostly contained to MSM, and several parties, bath houses, saunas, and other mass-gathering sites have been implicated in transmission events.

Widespread rash remains the most common symptom among patients in the current outbreak. Among the cases who reported at least one symptom, 81% presented with systemic rash (widespread rash on the body), 50% presented with fever and 41% presented with genital rash.

The WHO also warned that 25 cases have been detected so far among healthcare workers and said transmission in this setting cannot be ruled out.

Comment: During a meeting last week, the WHO decided the outbreak to date does not yet warrant a public health emergency of international concern. The European Centre for Disease Prevention and Control (ECDC) and the WHO released a new toolkit aimed at event organizers who wish to minimize the spread of monkeypox at large gatherings. The document states that mass gatherings do not amplify transmission by themselves—it is the behavior during events that matters. As events may be a conducive environment for the transmission of monkeypox if they entail close, prolonged, and frequent interactions, especially sexual activity.

The emerging theory is that the monkeypox virus is evolving 6-12 times faster than would be expected, according to a report of a new study. [not yet published] The virus is thought to have a single origin, the genetic data suggests, and is a likely descendant of the strain involved in the 2017-2018 monkeypox outbreak in Nigeria. In the study, investigators analyzed 15 monkeypox DNA sequences made available by Portugal and the National Center for Biotechnology Information in Bethesda, Maryland, between May 20 and May 27, 2022. The analysis revealed that this most recent strain differed by 50 single-nucleotide polymorphisms compared with previous strains of the virus in 2017-2018. However, it is not known if these mutations have clinical implications. In another study the 2022 monkeypox virus does appear to behave

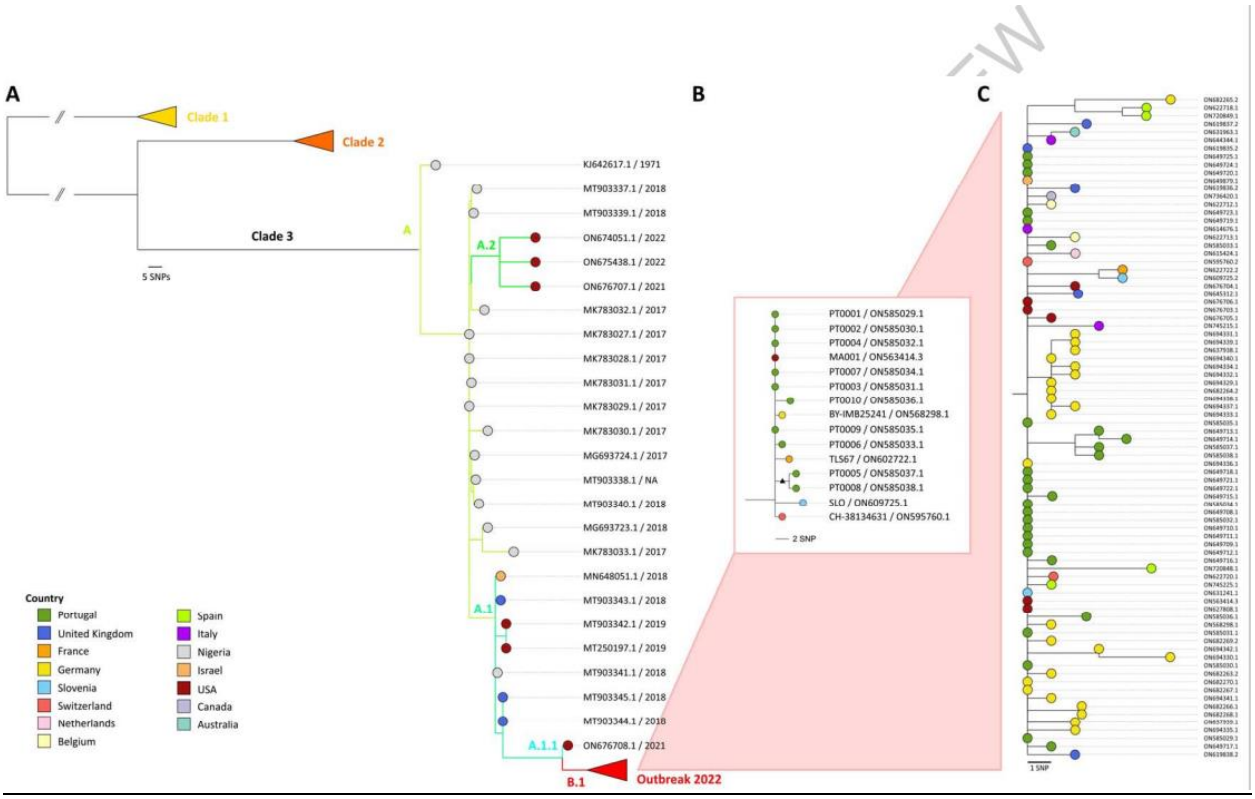
differently than previous strains of the virus. (See article below) In the current outbreak, sexual transmission appears to be very common, which is not the case for previous outbreaks. Also, while monkeypox traditionally presents with a rash that can spread to all parts of the body, there have been several instances of patients presenting with just a few very innocuous lesions.

Beginning this week, Labcorp will be able to test for monkeypox virus, doubling the nationwide capacity for testing, according to CDC. Labcorp said it will be able to process 10,000 tests weekly. HHS said the federal administration will make 144,000 doses of the Jynneos vaccine available to states beginning July 11th.

Phylogenomic characterization and signs of microevolution in the 2022 multi-country outbreak of monkeypox virus Nature Med published online June 24, 2022

doi.org/10.1038/ s41591-022-01907-y

The investigators used shotgun metagenomics which allowed for rapid reconstruction and phylogenomic characterization of the first MPXV outbreak genome sequences, showing that this MPXV belongs to clade 3 and that the outbreak most likely has a single origin. Although 2022 MPXV (lineage B.1) clustered with 2018-2019 cases linked to an endemic country, it segregates in a divergent phylogenetic branch, likely reflecting continuous accelerated evolution. An in-depth mutational analysis suggests the action of host APOBEC3 (apolipoprotein B mRNA editing catalytic polypeptide-like 3) in viral evolution as well as signs of potential MPXV human adaptation in ongoing microevolution. Their findings also indicate that genome sequencing may provide resolution to track the spread and transmission of this presumably slow-evolving dsDNA virus.



Comment: The genomic and phylogenomic data in this article provide potential insights into the evolutionary trajectory of the 2022 MPVX outbreak strain, and sheds light on potential mechanisms and targets of human adaptation. The observed accelerated evolution of this human MPVX, potentially driven by the APOBEC3 action, suggests that viral genome sequencing might provide sufficient resolution to track the transmission dynamics and outbreak spread, which seemed to be challenging for a presumably slow-evolving dsDNA virus. Together with the adopted strategy of real-time data sharing, this study may help guide novel outbreak control measures and subsequent research direction.

COVID-19

COVID-19 News

FDA Authorizes Pharmacists to Prescribe Nirmatrelvir/Ritonavir for Some Patients at High Risk for Severe COVID-19

The FDA revised the EUA for nirmatrelvir/ritonavir (Paxlovid) to authorize state-licensed pharmacists to prescribe nirmatrelvir/ritonavir to eligible patients who are at high risk for progression to severe coronavirus disease 2019 (COVID-19), with certain limitations.

Patients in the authorized population who report a positive home test result from a rapid antigen diagnostic test or a positive polymerase chain reaction (PCR) test, to their provider are eligible for nirmatrelvir/ritonavir under the EUA. Confirmation of a positive home rapid antigen diagnostic test with additional direct SARS-CoV-2 viral testing, such as a PCR, is not required.

Patients who have tested positive for COVID-19 and are seeking to determine their eligibility for receiving nirmatrelvir/ritonavir at locations where prescribing by state-licensed pharmacists is available should bring the following information to ensure that the state-licensed pharmacist has sufficient information to determine their eligibility to receive nirmatrelvir/ritonavir:

- Electronic or printed health records less than 12 months old, including the most recent reports of laboratory blood work for the state-licensed pharmacist to review for kidney or liver problems. State-licensed pharmacists could also receive this information through a consultation with the patient's healthcare provider.
- A list of all medications they are taking, including over-the-counter medications so the state-licensed pharmacist can screen for drugs with potentially serious interactions with nirmatrelvir/ritonavir.

Under the limitations outlined in the authorization, the state-licensed pharmacist should refer patients for clinical evaluation with a physician, advanced practice registered nurse, or physician assistant licensed or authorized under state law to prescribe drugs, if any of the following apply:

- Sufficient information is not available to assess renal and hepatic function.
- Sufficient information is not available to assess for a potential drug interaction.
- Modification of other medications is needed due to a potential drug interaction.
- Nirmatrelvir/ritonavir is not an appropriate therapeutic option based on the current Fact Sheet for Healthcare Providers or due to potential drug interactions for which recommended monitoring would not be feasible.

Comment: Since nirmatrelvir/ritonavir must be taken within 5 days after symptoms begin, authorizing state-licensed pharmacists to prescribe nirmatrelvir/ritonavir could expand access to timely treatment for some patients who are eligible to receive this drug for the treatment of COVID-19. The key will be to make sure the pharmacist has access to medication list and certain laboratory parameters such as serum creatinine.

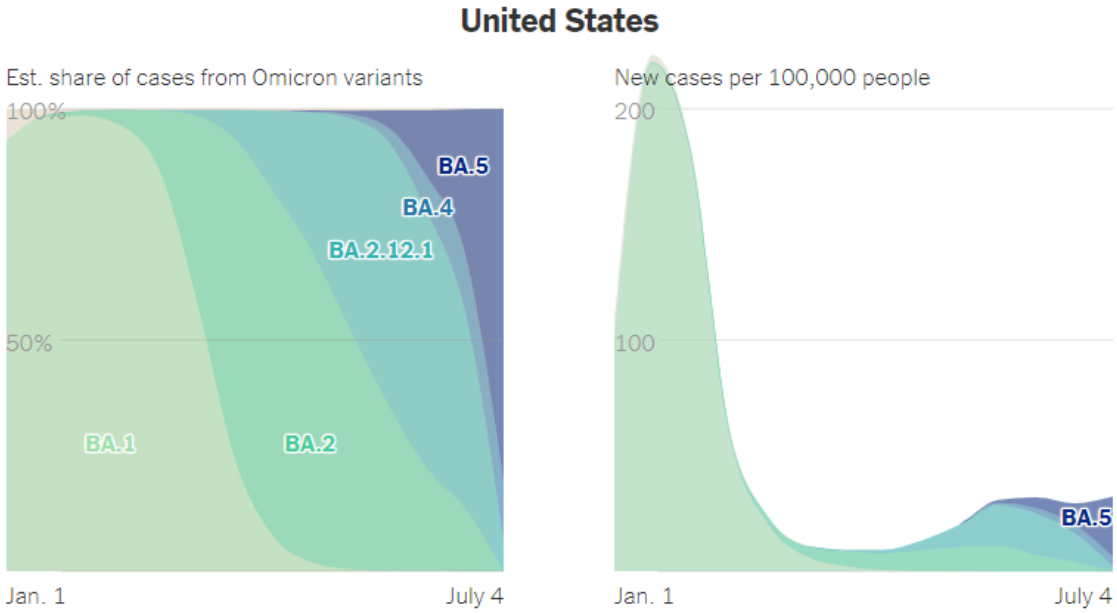
Omicron mutations, BA.2.75

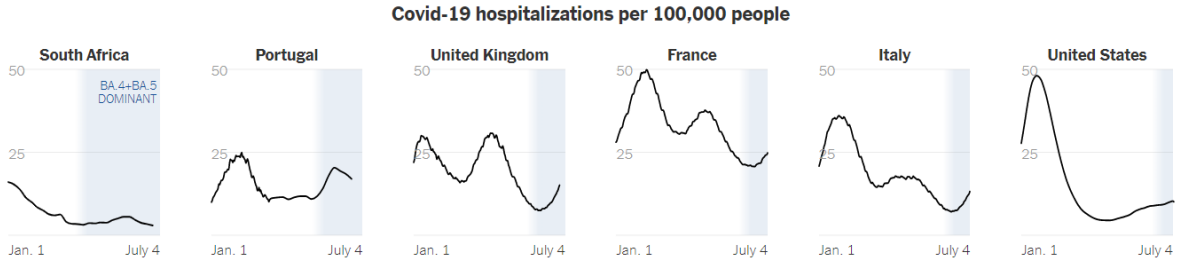
The U.S. has identified cases of the latest Omicron subvariant, dubbed "Centaurus" and known as BA.2.75. Two cases have been detected in the U.S. so far, with the first identified on June 14, per the CDC.

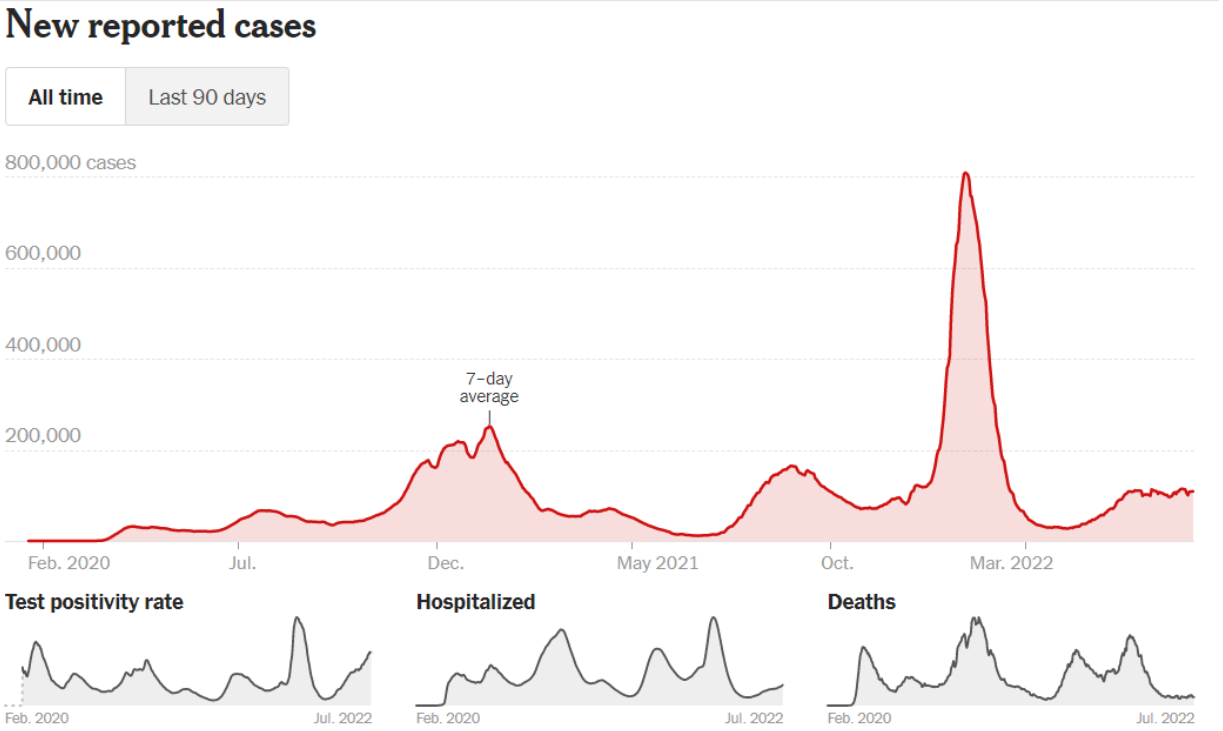
The WHO announced this week that it has begun tracking the subvariant, which was identified in India in early June and has been reported in several other countries. BA.2.75 hasn't yet been declared a variant of concern yet by WHO, and researchers are still learning about the transmissibility, severity, and potential for immune evasion. Along with the usual Omicron mutations, BA.2.75 has nine additional changes, which could help the subvariant to spread more quickly and more broadly than previous Omicron subtypes.

Comment: Currently public health officials cannot say whether BA.2.75 will out compete in countries where BA.5 is dominant, such as the US. Stay tuned.

COVID-19 by the Numbers







Comment: More than half the states are seeing higher daily cases than two weeks ago. Even New York and New Jersey, where conditions had been improving throughout June, are now in the midst of modest increases. Hospitalizations have increased steadily in recent weeks, but far below the omicron surge earlier this year. Fewer than 400 deaths are currently reported each day, down from more than 2,600 a day at the height of the Omicron surge. BA.5 is responsible for over 50% of new cases. The Ro is close to measles.

COVID-19 Journal Review

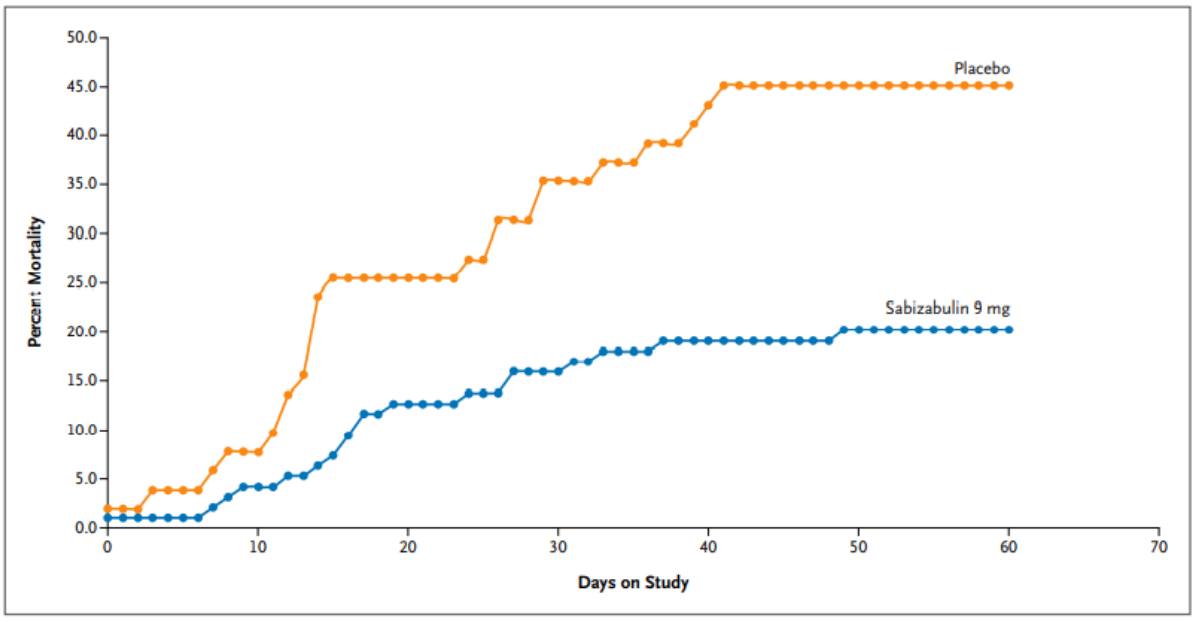
Oral Sabizabulin for High-Risk, Hospitalized Adults with Covid-19: Interim Analysis NEJM Evidence published online July 6, 2022

DOI: 10.1056/EVIDoa2200145

Investigators conducted a multicenter trial of sabizabulin, which showed both antiviral and anti-inflammatory properties in preclinical models. The drug binds to the microtubules critical for SARS-CoV-2 cell entry and replication and for the outsized inflammatory response leading to acute respiratory distress syndrome (ARDS) and death.

A total of 204 adults with moderate to severe COVID-19 at high risk for poor outcomes were randomly assigned to receive either 9 milligrams of sabizabulin or a placebo daily for up to 21 days. Patients were randomly assigned to receive Sabizabulin or placebo in a 2:1 ratio. Randomization was stratified by WHO COVID-19 ordinal clinical severity score (0 to 8). ~80% in both groups received dexamethasone and ~30% received RDV, and ~20% received either tocilizumab or baricitinib. The trial was stopped early owing to demonstrated drug efficacy, resulting in inclusion of 150 patients (98 assigned to sabizabulin and 52 to placebo) in the analysis, 145 of whom completed the study and had a known status at 60 days.

Sabizabulin led to a 24.9-percentage-point absolute reduction and a 55.2% relative reduction in deaths over placebo (odds ratio, 3.23; 95% confidence interval, 1.45 to 7.22). Nineteen of 94 sabizabulin recipients (20.2%) died, compared with 23 of 51 placebo recipients (45.1%). Relative to placebo recipients, the sabizabulin group also saw a 43% relative reduction in average days in an intensive care unit (-13.4 days), a 49% relative reduction in days on mechanical ventilation (-14.1), and a 26% relative reduction in days in the hospital (-8.4). Adverse events occurred less often in sabizabulin recipients (61.5%) than in the placebo group (78.3%).



Comment: These data demonstrate that sabizabulin treatment significantly reduced mortality with an acceptable side-effect and safety profile in hospitalized patients with moderate to severe COVID-19 at high risk for ARDS. This trial was relatively small, with just 134 patients receiving sabizabulin. The patients were allowed to simultaneously receive other treatments that have been shown to be effective in hospitalized Covid patients. The 45% mortality rate in the control group seems high to me.

Leading Causes of Death in the US During the COVID-19 Pandemic, March 2020 to October 2021 JAMA Intern Med published online July 5, 2022

doi:10.1001/jamainternmed.2022.2476

National Cancer Institute researchers analyzed national death certificate data and provisional 2021 data from the CDC. Data beyond October 2021 were excluded because they were incomplete; thus, the analysis doesn't include deaths from the Omicron variant period.

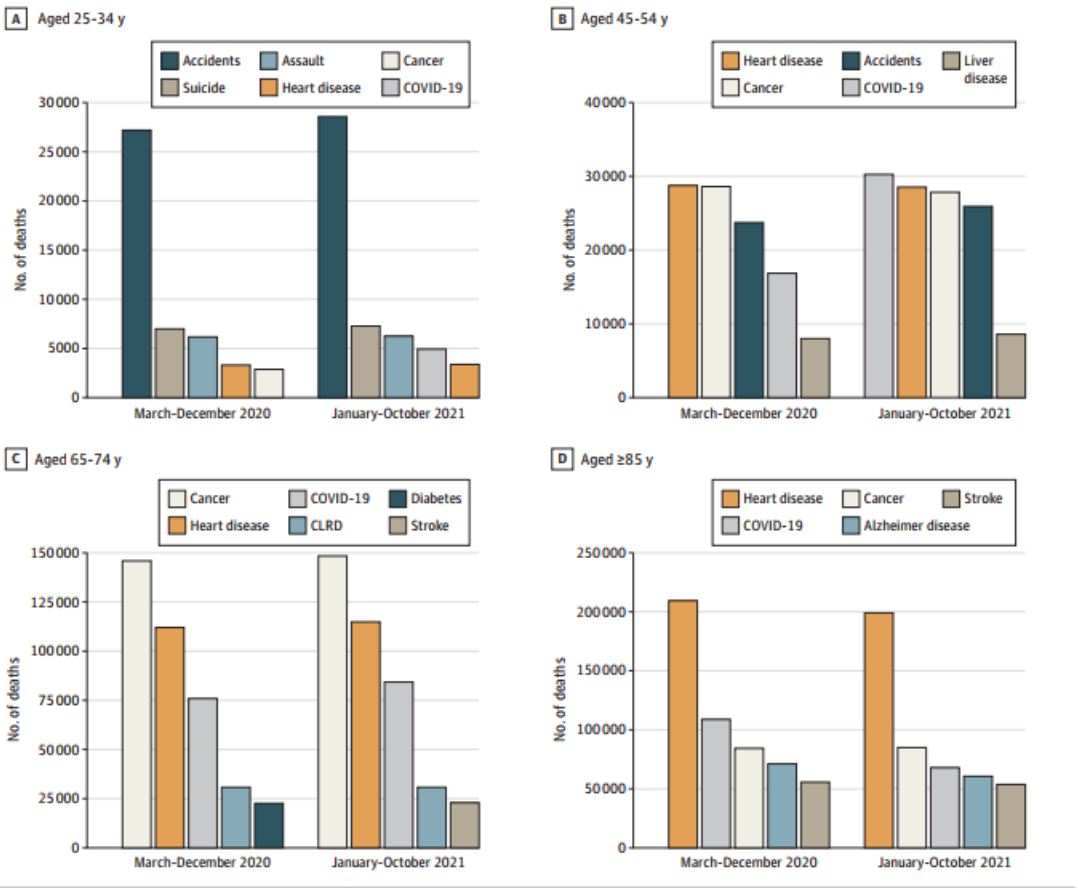
Over the entire study period, the leading causes of death were heart disease (20.1%), cancer (17.5%), COVID-19 (12.2%), accidents (6.2%), and stroke (4.7%). From March to December 2020, 2.88 million people died in the US, slightly more than the 2.86 million who died from January to October 2021. The number of deaths rose across all age-groups except for those younger than 1 year.

In 2020, heart disease and cancer were the two top causes of death in the country, leading to 1.29 million deaths, followed by COVID-19, at 350,000 deaths.

Among people aged 55 years and older, deaths from cancer, heart disease, and COVID-19 led to the most deaths in both 2020 and 2021. Among those 85 years and older, COVID-19 was the second leading cause of death in 2020, at 110,000 (12.8%) of deaths, while it was the third leading cause in 2021, at 69,000 (8.9%) of deaths.

While COVID-19 was the fourth leading cause of death among Americans 45 to 54 years in 2020 (17,000 [10.4%]), it ranked first in 2021 (30,000 [16.8%]). In both time spans, accidents were the leading cause of death among people aged 1 to 44 years.

Relative to 2020, in 2021, COVID-19 rose from the fifth (6,100 deaths) to the second (13,000) leading cause of death among people 35 to 44 years old and took the fourth-leading spot among those 25 to 34 years (5,000) and 15 to 24 (1,100).



Comment: From March 2020 to October 2021, COVID-19 accounted for 1 in 8 deaths in the US and was a top 5 cause of death in every age group aged 15 years and older. Cancer and heart disease deaths exceeded COVID-19 deaths overall and in most age groups, whereas accidents were the leading cause of death among those aged 1 to 44 years. Compared with the 2020 time period, deaths from COVID-19 in the 2021 time period decreased in ranking among those aged 85 years or older but increased in ranking among those aged 15 to 54 years and became the leading cause of death among those aged 45 to 54 years. The article correctly points out that the increased ranking of COVID-19 as a leading cause of death in some age groups is consistent with a downward shift in age in the distribution of COVID-19 deaths in the US in 2021 compared with 2020. This is probably the result of higher COVID-19 vaccination rates in 2021 in the oldest age groups. We should not forget the indirect impact of the pandemic on other causes of death in the US. From 2019 to 2020, death rates increased for heart disease, accidents, stroke, Alzheimer disease, and diabetes. Deaths due to drug overdoses, alcohol, and suicide were also up especially in younger age groups. A limitation of the study is the potential misclassification of the cause of death and incomplete death data for 2021. Moreover, this analysis only extended through October 2021, so it does not include deaths that occurred during the Omicron wave of late 2021 and early 2022.

Outcomes of SARS-CoV-2 Reinfection Research Square posted June 17, 2022

https://doi.org/10.21203/rs.3.rs-1749502/v1

The investigators use the national health care databases of the US Department of Veterans Affairs to build a cohort of people with first infection (n = 257,427), reinfection (2 or more infections, n = 38,926), and a non-infected control group (n = 5,396,855) to estimate risks and 6-month burdens of all-cause mortality, hospitalization, and a set of pre-specified incident outcomes.

They show that compared to people with first infection, reinfection contributes additional risks of all-cause mortality, hospitalization, and adverse health outcomes in the pulmonary and several extrapulmonary organ systems (cardiovascular disorders, coagulation and hematologic disorders, diabetes, fatigue, gastrointestinal disorders, kidney disorders, mental health disorders, musculoskeletal disorders, and neurologic disorders); the risks were evident in those who were unvaccinated, had 1 shot, or 2 or more shots prior to the second infection; the risks were most pronounced in the acute phase, but persisted in the post-acute phase of reinfection, and most were still evident at 6 months after reinfection. Compared to non-infected controls, assessment of the cumulative risks of repeated infection showed that the risk and burden increased in a graded fashion according to the number of infections. The constellation of findings show that reinfection adds risks of all-cause mortality, hospitalization, and adverse health outcomes in the acute and post-acute phase of the reinfection.

Outcome	HR (95% CI)	Reinfection burden per 1000 persons at 6-months (95% CI)	First infection burden per 1000 persons at 6-months (95% CI)	Excess burden per 1000 persons at 6-months (95% CI)
All-cause mortality	2.14 (1.97, 2.33)	45.08 (40.2, 50.53)	21.3 (19.57, 23.19)	23.78 (18.9, 29.23)
Hospitalization	2.98 (2.83, 3.12)	147.78 (141.48, 154.34)	52.31 (51.38, 53.26)	95.47 (89.17, 102.03)
At least one sequela	1.82 (1.78, 1.88)	553.03 (543.4, 562.71)	356.84 (355.13, 358.54)	196.2 (186.57, 205.87)
Cardiovascular	2.36 (2.23, 2.51)	88.06 (83.3, 93.09)	38.23 (37.46, 39.02)	49.83 (45.07, 54.86)
Coagulation and hematologic	2.22 (2.05, 2.41)	47.66 (44.24, 51.33)	21.73 (21.15, 22.31)	25.93 (22.51, 29.6)
Diabetes	1.62 (1.49, 1.76)	58.32 (53.9, 63.09)	36.34 (35.55, 37.14)	21.98 (17.56, 26.75)
Fatigue	2.4 (2.22, 2.58)	58.03 (54.05, 62.29)	24.64 (23.94, 25.37)	33.39 (29.41, 37.65)
Gastrointestinal	1.69 (1.58, 1.8)	68.91 (64.69, 73.39)	41.46 (40.69, 42.24)	27.45 (23.24, 31.93)
Kidney	1.7 (1.52, 1.9)	35.14 (31.52, 39.17)	20.83 (20.01, 21.68)	14.31 (10.69, 18.34)
Mental health	1.97 (1.9, 2.04)	266.74 (258.69, 274.99)	145.69 (144.38, 147)	121.05 (113, 129.31)
Musculoskeletal	1.29 (1.2, 1.38)	59.45 (55.52, 63.65)	46.48 (45.69, 47.29)	12.97 (9.04, 17.17)
Neurologic	1.39 (1.32, 1.46)	135.65 (129.79, 141.75)	99.63 (98.45, 100.83)	36.02 (30.16, 42.12)
Pulmonary	2.49 (2.34, 2.65)	85.69 (80.98, 90.66)	35.34 (34.59, 36.11)	50.35 (45.64, 55.32)

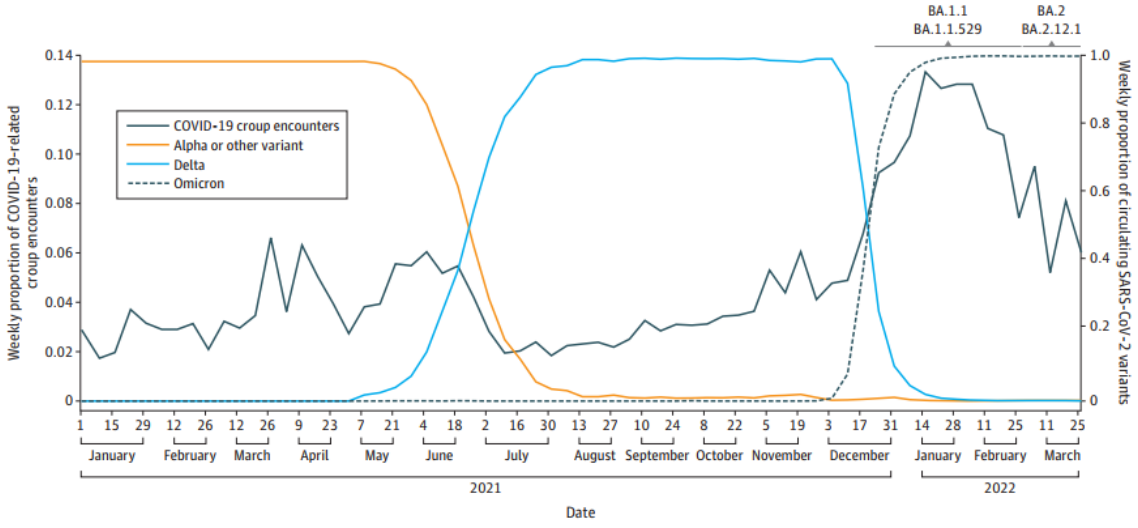
Comment: The mechanisms leading to the increased risks of death and adverse health outcomes in reinfection are not entirely clear. Prior infection has been shown to reduce risk of reinfection and its severity; however, SARS-CoV-2 is mutating rapidly, and new variants are replacing older ones now every few months. Evidence suggests that the reinfection risk is especially higher with the Omicron variant which was shown to have a marked ability to be immune evasive especially the BA.4 and BA.5. And any protection from infection also wanes over time. Therefore, protection from reinfection declined over time. A new study reported by Tel Aviv University, Ben Gurion University and the Health Ministry finds that a fourth dose of the Pfizer COVID-19 vaccine is effective in protecting senior citizens living in care homes from the effects of COVID. [not published] They report a 34% reduced risk of contracting the Omicron variant, a 64-67% reduced risk of being hospitalized due to COVID, and a 72% reduced risk of death from the virus. This report does not specify which Omicron variant(s) was circulating. Reducing overall burden of death and disease due to SARS-CoV-2 will require new strategies for reinfection prevention including vaccinations.

Analysis of COVID-19–Related Croup and SARS-CoV-2 Variant Predominance in the US JAMA Netw Open 2022;5(7):e2220060

doi:10.1001/jamanetworkopen.2022.20060

This is a cross-sectional study which included children aged 3 months to 8 years with ICD-10 diagnoses of COVID-19 and croup between January 1, 2021, and March 26, 2022, using data from 43 US children's hospitals in the Pediatric Health Information System. They excluded children with croup-mimicking (e.g., tracheitis) or complex chronic conditions. SARS-CoV-2 variant predominance (i.e., Alpha or other variant, Delta, and Omicron) was determined from the CDC COVID Data Tracker and defined as more than 50% of SARS-CoV-2 diagnoses attributable to a particular variant The primary outcome was encounters for COVID-19–related croup, summarized by week and variant predominance. Secondary outcomes included hospital and ICU admissions and racemic epinephrine (RE) treatment. They used mixed-effects logistic regression to evaluate the association of variant predominance with hospitalization and RE use after adjusting for age, sex, race and ethnicity, insurance, and census region.

They identified 5152 children with COVID-19–related croup (3329 [64.6%] boys; median [IQR] age, 17 [9-31] months) (Table). The proportion of children with COVID-19–related croup was significantly increased during Omicron (10.9%) compared with Alpha or other variant (4.1%) and Delta (3.6%) periods ($P < .001$). Odds of hospitalization during Alpha or other variant (adjusted odds ratio [aOR], 1.28; 95% CI, 0.97-1.70) or Delta (aOR, 0.92; 95% CI, 0.74-1.15) periods were not significantly different compared with the period of Omicron predominance. Treatment with RE was less likely during the Delta period (aOR, 0.73; 95% CI, 0.61-0.87) and did not differ in the Alpha or other variant periods (aOR, 1.03; 95% CI, 0.81-1.31) compared with the period of Omicron predominance. The frequency of ICU admission was not statistically different across time periods.



Comment: The proportion of children with COVID-19-related croup increased during the period in which Omicron was the predominant variant in the United States. The authors point out that hospital practice may have changed, including limitation of aerosol generating procedures early in the pandemic, which may have influenced RE administration. It is also possible that conditions other than croup influenced hospitalization rates. Since COVID-19 is likely to continue to be with us and become endemic, the findings in this paper suggest that pediatric

health systems should consider variation in SARS-CoV-2 phenotypes and their association with respiratory complications such as croup. This may be especially true when other viral infections may lead to surges in patient volume as we have seen with RSV.