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Infectious Diseases Watch

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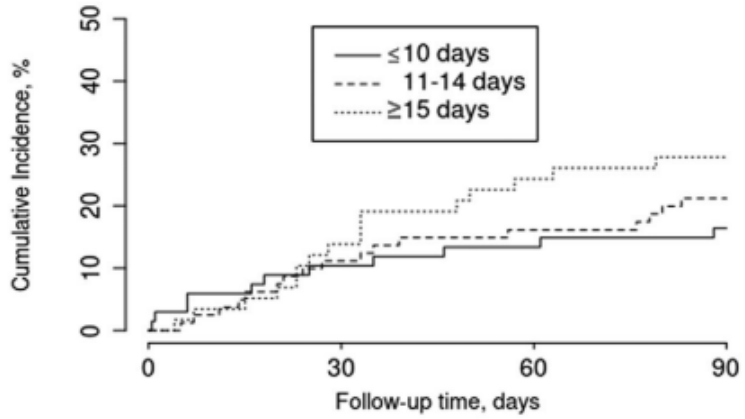
General Infectious Diseases

Evaluating antimicrobial duration for Gram-negative bacteremia in patients with neutropenia due to hematologic malignancy or hematopoietic stem cell transplantation Transplant Infect Dis published online June 6, 2023

https://doi.org/10.1111/tid.14085

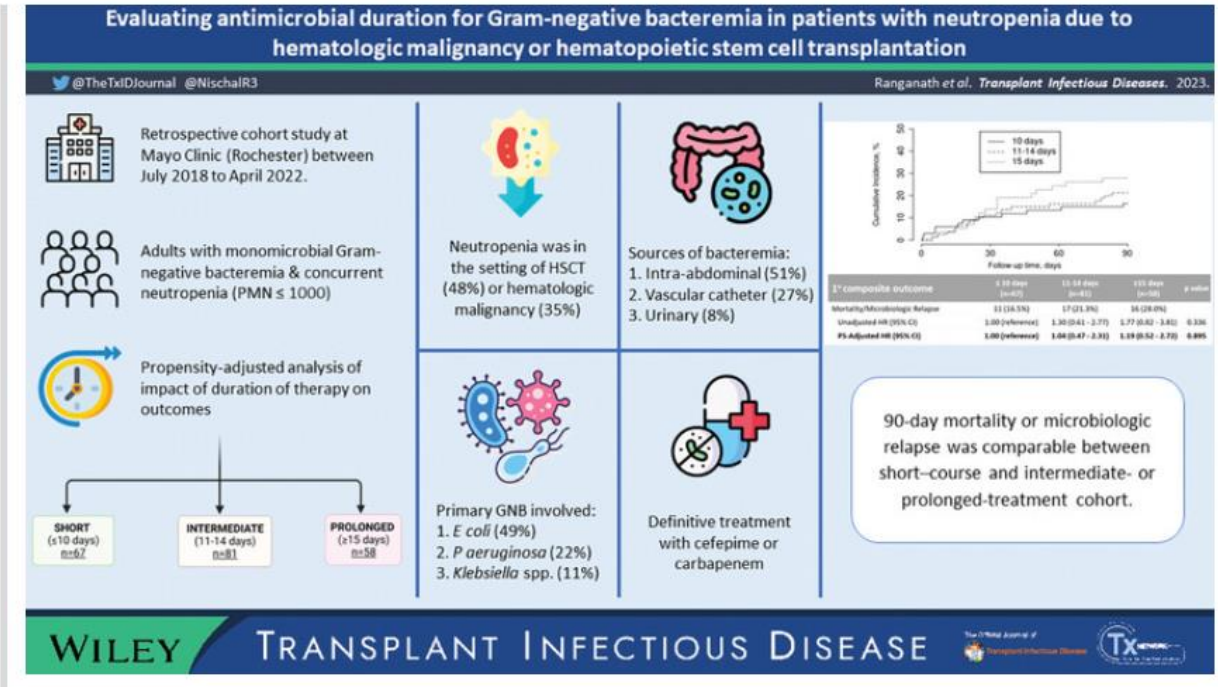
In the management of Gram-negative bloodstream infection (GN-BSI), short antimicrobial courses have been increasingly demonstrated to be non-inferior to prolonged therapy, with lower risk of CDI and emergence MDR organisms. However, immunocompromised hosts were excluded from these studies. Therefore, the investigators set out to study outcomes of short (≤10 days), intermediate (11–14 days), and prolonged (≥15 days) antimicrobial durations for GN-BSI in neutropenic patients.

GN-BSI developed in 206 patients with neutropenia and cancer between 2018 and 2022. Most patients were stem-cell transplant recipients (48%) or had other hematologic malignancies (35%) or solid tumors (10%). In all, 67 patients received antimicrobial therapy for ≤10 days, 81 for 11–14 days, and 58 for ≥15 days. Most patients were on antibacterial prophylaxis at the onset of GN-BSI, and 66% resumed such prophylaxis after completing their treatment course. The primary composite endpoint (all-cause mortality and/or microbiologic relapse at 90 days) occurred in 21.6% of patients across all groups, with no significant differences among groups. Emergence of MDROs or CDI, while less likely in the short-course group, was not significantly different between groups. Most patients received definitive therapy with cefepime or a carbapenem. The most common pathogens were E coli, P aeruginosa, and Klebsiella sp.



1° composite outcome	≤10 days (n=67)	11-14 days (n=81)	≥15 days (n=58)	p value
Mortality/Microbiologic Relapse	11 (16.5%)	17 (21.3%)	16 (28.0%)	
Unadjusted HR (95% CI)	1.00 (reference)	1.30 (0.61 - 2.77)	1.77 (0.82 - 3.81)	0.336
PS-Adjusted HR (95% CI)	**1.00 (reference)**	**0.89 (0.39 - 2.03)**	**1.20 (0.52 - 2.74)**	**0.722**

Comment: Most studies to date have excluded immunosuppressed patients. We have all struggled if shorter courses of antimicrobial therapy also apply to immunocompromised patients. This study supports decreasing duration of therapy for GN-BSI even in immunocompromised patients. It should be mentioned that a plurality of patients continued some form of prophylaxis which may have been active against the blood culture pathogen. Some centers resume prophylaxis until neutropenia resolves. The numbers are modest and there are confounders which may influence results.



Clinical burden of invasive *Escherichia coli* disease among older adult patients treated in hospitals in the United States BMC Infectious Diseases 2023 23:550

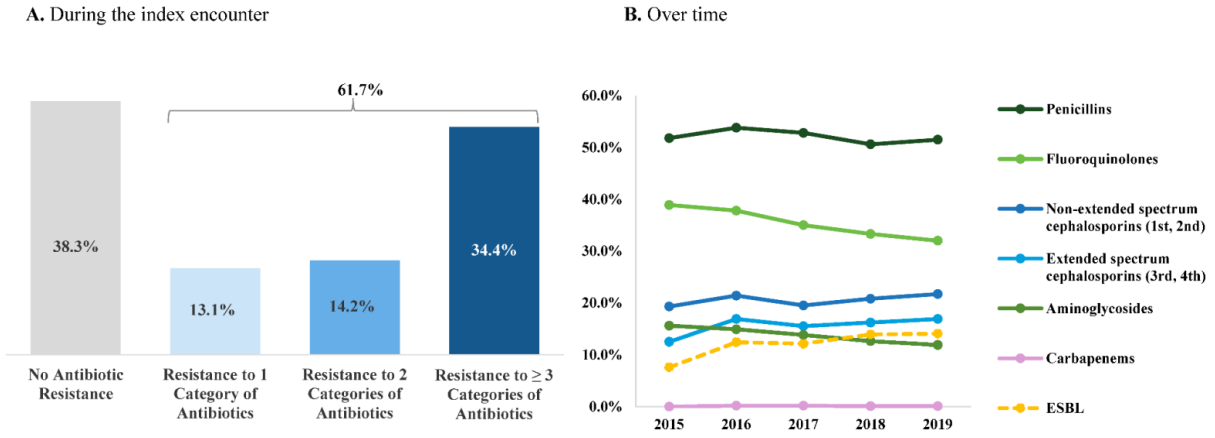
doi.org/10.1186/s12879-023-08479-3

This study analyzed retrospectively invasive extraintestinal pathogenic *E coli* disease (IED) in an older population. They used data from the PINC AI™ Healthcare Database (PHD). The PHD comprises detailed inpatient services from patients admitted to a representative set of >1,000 US hospitals nationwide and includes admission-level information (e.g., patient characteristics, primary and secondary admitting diagnoses), detailed day-of-service billing information during hospitalizations (e.g., inpatient procedures and medications used by day of stay), and discharge-level data (e.g., length of stay, discharge status) They described and characterized the short- and long-term impacts of IED, which comprises sepsis, bacteremia, peritonitis, meningitis, and other infectious syndromes. Investigators analyzed data only on patients aged 60 and older. The primary outcomes analyzed were clinical outcomes, medical resource use, and *E coli* isolate characteristics. Patient and hospital characteristics were recorded, as well as the characteristics and course of the index encounter which included the point of origin (e.g., clinic, transfer from another hospital), the IED onset (hospital or community, defined respectively based on the date of the positive *E. coli* culture≥ 3 days vs. ≤2 days after hospital admission, and whether community onset IED was healthcare-associated, the type of encounter (inpatient stay, emergency room visit, or outpatient hospital visit), the type of IED, infection type (e.g., urosepsis with/without bacteremia, meningitis, IED-related treatments, and discharge status. Trends in antibiotic resistance over time between 2015 and 2019 were also assessed. Statistical comparisons for variables were conducted using Wilcoxon rank-sum and Chi-square tests.

Overall, 19,773 patients with IED from October 2015 through March 2020 were included (mean age, 76.8 years; 67.4% female; 78.5% with signs of sepsis). Most encounters involved community-onset IED (94.3%) and required hospitalization (96.5%; mean duration, 6.9 days), with 32.4% of patients being admitted to the intensive care unit (mean duration, 3.7 days) and

8.6% requiring mechanical ventilation. Nearly all patients (99.3%) were treated with antibiotics and typically received several antibiotic courses, with a mean of 2.9 different antibiotics. Notably, 30.1% of patients received ≥4 antibiotics. The most frequently observed antibiotics were ceftriaxone (66.2%), vancomycin (36.3%), and piperacillin (35.0%).

Nearly two thirds (61.7%) of *E coli* isolates were resistant to one or more antibiotic categories, and 34.4% were resistant to three or more antibiotic categories. Following their first IED encounter, 34.8% of patients were transferred to a skilled nursing/intermediate care facility, and 6.8% had died. During the 12-month observation period, 36.8% of IED patients were re-hospitalized, 2.4% had IED recurrence, and in-hospital death increased to 10.9%. Patients with MDR isolates tended to have a more severe comorbidity profile compared to those with non-MDR isolates (CCI score ≥3: 46.7% vs. 40.3%, p <0.001). Encounters with MDR isolates were more likely to be associated with hospital-onset IED (6.5% vs. 5.3%, p<0.001), occur in hospitals of ≥500 beds (33.2% vs. 29.1%, p <0.001), and originate from a SNF/LTC (5.2% vs. 3.6%, p<0.001) compared to non-MDR isolates.



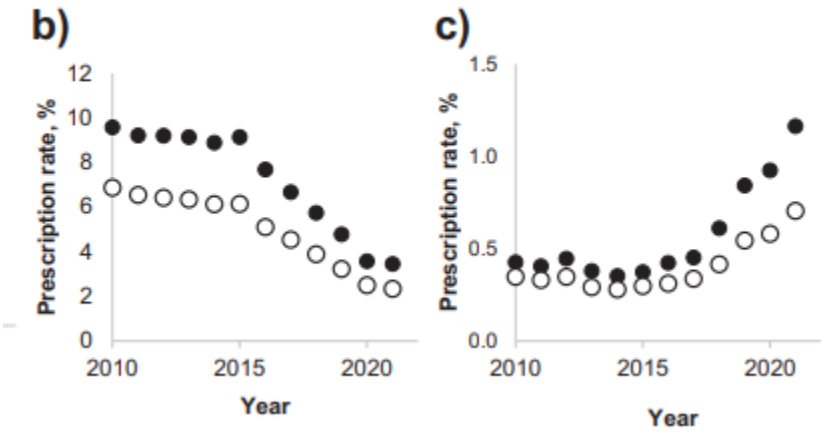
Comment: An analysis of invasive extraintestinal pathogenic IED in older patients found a substantial clinical burden, with considerable long-term consequences. The burden was particularly high in the presence of antibiotic resistance. The findings are important given the global increase in *E coli* infections and rising rates of antibiotic resistance. Of interest there was a decrease in AR to FQ which may reflect decreased use associated with ASP. [but still fairly high] [see next review] Since this was a retrospective study, it is subject to inherent limitations. IED encounters were identified based on microbiological data from laboratory records and diagnosis and procedure codes in claims data; therefore, some patients may have been misidentified as having IED due to any limitations in the various data sources (e.g., coding errors, etc.). Furthermore, the definition of IED used in this study included sepsis, for which a range of definitions exist in the literature; these may affect epidemiological estimates of sepsis.

Increase in the community circulation of ciprofloxacin-resistant Escherichia coli despite reduction in antibiotic prescriptions. Comm Med 2023 3:110 (August 12, 2023)

doi.org/10.1038/s43856-023-00337-2

The investigators wanted to determine the frequency of isolation and other characteristics of E. coli resistant to ciprofloxacin in 515 and 1604 E. coli-positive fecal samples collected in 2015 and 2021, respectively. The samples were obtained from non-antibiotic-taking women of age 50+ receiving care in the Kaiser Permanente Washington healthcare system.

They were able to show that despite a nearly three-fold drop in the prescription of ciprofloxacin between 2015 and 2021, the rates of gut carriage of ciprofloxacin-resistant E. coli increased from 14.2 % to 19.8% (P = .004). This is driven by a significant increase of isolates from the pandemic multi-drug resistant clonal group ST1193 (1.7% to 4.2%; P = .009) and isolates with relatively few ciprofloxacin-resistance determining chromosomal mutations (2.3% to 7.4%; P = .00003). Though prevalence of isolates with the plasmid-associated ciprofloxacin resistance dropped (59.0% to 30.9%; P = 2.7E-06), the isolates co-resistance to third generation cephalosporins has increased from 14.1% to 31.5% (P = .002).



b FQ yearly prescription rates. c 3GC yearly prescription rates.

Comment: Despite decrease in ciprofloxacin use, community circulation of the resistant uropathogenic E. coli increased with a rise of co-resistance to third generation cephalosporins. Thus, to reduce the rates of urinary tract infections refractory to antibiotic treatment, greater focus should be on controlling the resistant bacteria in gut microbiota. There was an increase in gut carriage of FQREC strains that are also resistant to 3GC. The primary but not exclusive mechanism of 3GC resistance in E. coli is the production of ESBL dominated by the CTX-M family typically coded by plasmid-associated genes. In their analysis, 3GC resistance increased across all FQREC categories and clonal groups, suggesting that this had happened under a generally imposed selective pressure. Especially troublesome is the doubling of 3GC resistance among the isolates with ≥3 QRDR mutations, i.e., highly resistant to FQ. Notably, the prescription of 3GC was significantly increased in KPWA enrollees between 2015–2021, especially among women 50+ years old. My guess is the reason for the increase may potentially be associated with 3GC being used more often as a replacement choice for FQ. This study still supports the efforts of antimicrobial stewardship to decrease the overuse of antibiotics, but a reduction in a specific antibiotic may not alone be a sufficient measure to reduce the spread of resistance. Another factor to consider is the use of FQ in animals like poultry farming and its spread into the environment, that was not accounted for in this study but might have a significant effect on the circulation of resistant bacteria in the community. In the end, they propose that there is a need to expand the role of antimicrobial stewardship programs from

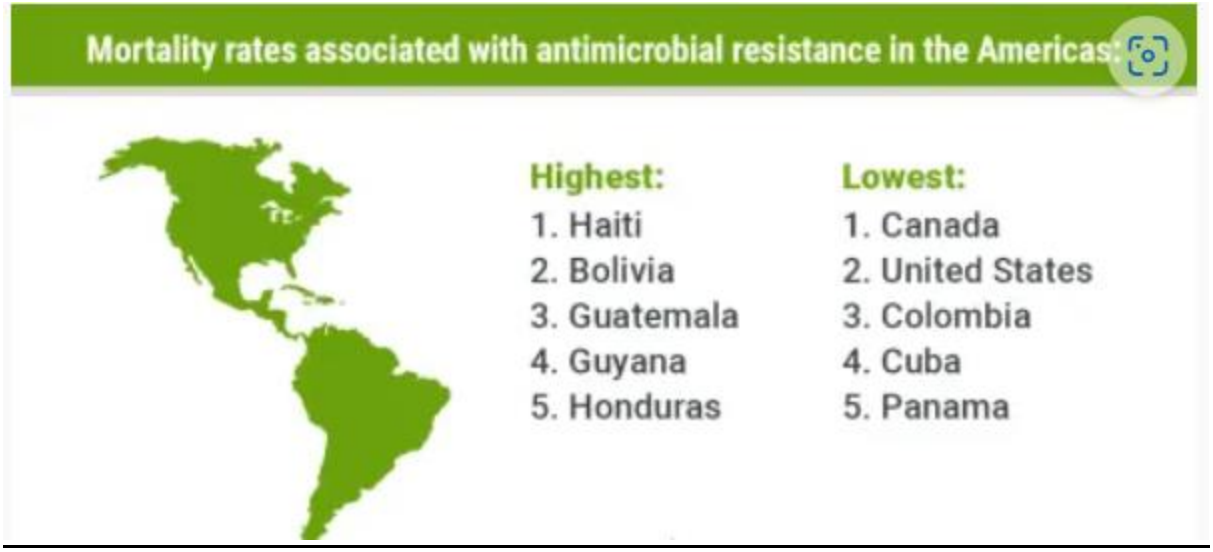
being focused only on antibiotic use in clinical settings to being also oriented towards screening for and decolonization of commensal carriage of antibiotic-resistant strains in the most vulnerable individuals. I would add diagnostic and antimicrobial stewardship needs to be robust across the continuum of care. See next review.

The burden of antimicrobial resistance in the Americas in 2019: a cross-country systematic analysis The Lancet Regional Health – Americas published online August 2023

doi.org/10. 1016/j.lana.2023. 100561

The investigators estimated deaths and disability-adjusted life-years (DALYs) attributable to and associated with AMR for 23 bacterial pathogens and 88 pathogen–drug combinations for countries in the WHO Region of the Americas in 2019.[pre-pandemic] We obtained data from mortality registries, surveillance systems, hospital systems, systematic literature reviews, and other sources, and applied predictive statistical modelling to produce estimates of AMR burden for all countries in the Americas. Five broad components were the mainstay of their approach: the number of deaths where infection had a role, the proportion of infectious deaths attributable to a given infectious syndrome, the proportion of infectious syndrome deaths attributable to a given pathogen, the percentage of pathogens resistant to an antibiotic class, and the excess risk of mortality (or duration of an infection) associated with this resistance. They then used these components to estimate the disease burden by applying two counterfactual scenarios: deaths attributable to AMR (compared to an alternative scenario where resistant infections are replaced with susceptible ones), and deaths associated with AMR (compared to an alternative scenario where resistant infections would not occur at all). They generated 95% uncertainty intervals (UIs) for final estimates as the 25th and 975th ordered values across 1000 posterior draws, and models were cross-validated for out-of-sample predictive validity.

They estimated 569,000 deaths (95% UI 406,000–771,000) associated with bacterial AMR and 141,000 deaths (99,900–196,000) attributable to bacterial AMR among the 35 countries in the WHO Region of the Americas in 2019. Lower respiratory and chest infections, as a syndrome, were responsible for the largest fatal burden of AMR in the region, with 189,000 deaths (149,000–241,000) associated with resistance, followed by bloodstream infections (169,000 deaths [94,200–278,000]) and peritoneal/intra-abdominal infections (118,000 deaths [78,600–168,000]). The six leading pathogens (by order of number of deaths associated with resistance) were *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Together, these pathogens were responsible for 452,000 deaths (326,000–608,000) associated with AMR. MRSA predominated as the leading pathogen–drug combination in 34 countries for deaths attributable to AMR, while aminopenicillin-resistant *E. coli* was the leading pathogen–drug combination in 15 countries for deaths associated with AMR.



Comments: In 2019, 569,000 deaths were associated with AMR in the Americas. Deaths attributable to AMR made up more than 11% of the total global deaths attributable to resistant infections. Antimicrobial Resistance Surveillance System has documented that the rate of MRSA infections has been increasing steadily since 2012. This study confirms that MRSA is the combination with the highest age-standardized mortality rate in Canada, where this pathogen–drug combination was responsible for 490 deaths (95% UI 200–870), an age-standardized mortality rate of 0.69 (0.27–1.24), and 8000 DALYs (3000–15,000) attributable to AMR. The large burden of E. coli coincides with high burden of resistant Enterobacterales in this region more broadly, and echoes results from Karlowsky and colleagues that showed resistance to third generation cephalosporins among E. coli species increased substantially in Latin America from 2015 to 2019, while K. pneumoniae resistant to third generation cephalosporins increased substantially in Canada, Latin America, and the USA during the same time period. [Int J Antimicrob Agents 2022; 59:106535] Carbapenem-resistant E. coli and K. pneumoniae are particularly serious health threats in Latin America and the Caribbean. [Expert Rev Anti Infect Ther 2017; 15:272-297] CDC published a 2019 report on AMR infections and deaths in the USA for 18 AMR threats by using surveillance data and showed that more than 2.8 million AMR infections occur in the US every year, resulting in more than 35,000 deaths. This study estimates for the US indicate that 42,000 deaths (28,000–60,000) are attributable to and 173,000 deaths (120,000–243,000) associated with AMR for the 88 pathogen–drug combinations and 23 bacterial pathogens. However, the CDC analysis also included resistant fungi. Other than as a component of multidrug-resistant P. aeruginosa, fluoroquinolone resistance was not identified as a major threat or concern in the CDC report. By contrast, this study found substantial burden attributable to fluoroquinolone resistance in the US (with 9400 deaths [6200–13,900]) and fluoroquinolone-resistant E. coli is the pathogen–drug combination with the third greatest attributable burden in the country. On average fluoroquinolone-resistant E coli is in the range of 30% in most hospitals that I have observed during site visits for clinical trials.

Comment: There was a paucity of data for several pathogen–drug combinations, particularly for Cuba, Paraguay, and Uruguay. Limited data in some countries was important for the prevalence of resistance and relative risk modelling components of their work. Additionally, these two components were not stratified by age and sex groups nor by infectious syndromes. When data for a specific country is lacking, their estimates relied on regional patterns, covariates, and out-

of-sample predictive validity. Even though they tried to account for various biases, they admit that selection bias may occur in passive microbial surveillance data, while potential bias and misclassification can arise. Lastly, despite their use of the most recent CLSI breakpoint guidelines whenever possible, there are no universal laboratory standards to distinguish resistance versus susceptibility, and deferring to source laboratory interpretation for classifying the isolates in their study may have resulted in dissimilar classification.

This study was pre-pandemic and based on recent studies, AMR in the US and globally rose during the pandemic. We need effective strategies combining antimicrobial and diagnostic stewardship along with infection prevention that holds providers accountable.

Reduction in urinary tract infections in patients treated with fecal microbiota transplantation for recurrent Clostridioides difficile infection. European Journal of Clinical Microbiology & Infectious Diseases 2023; 42:1037–1041

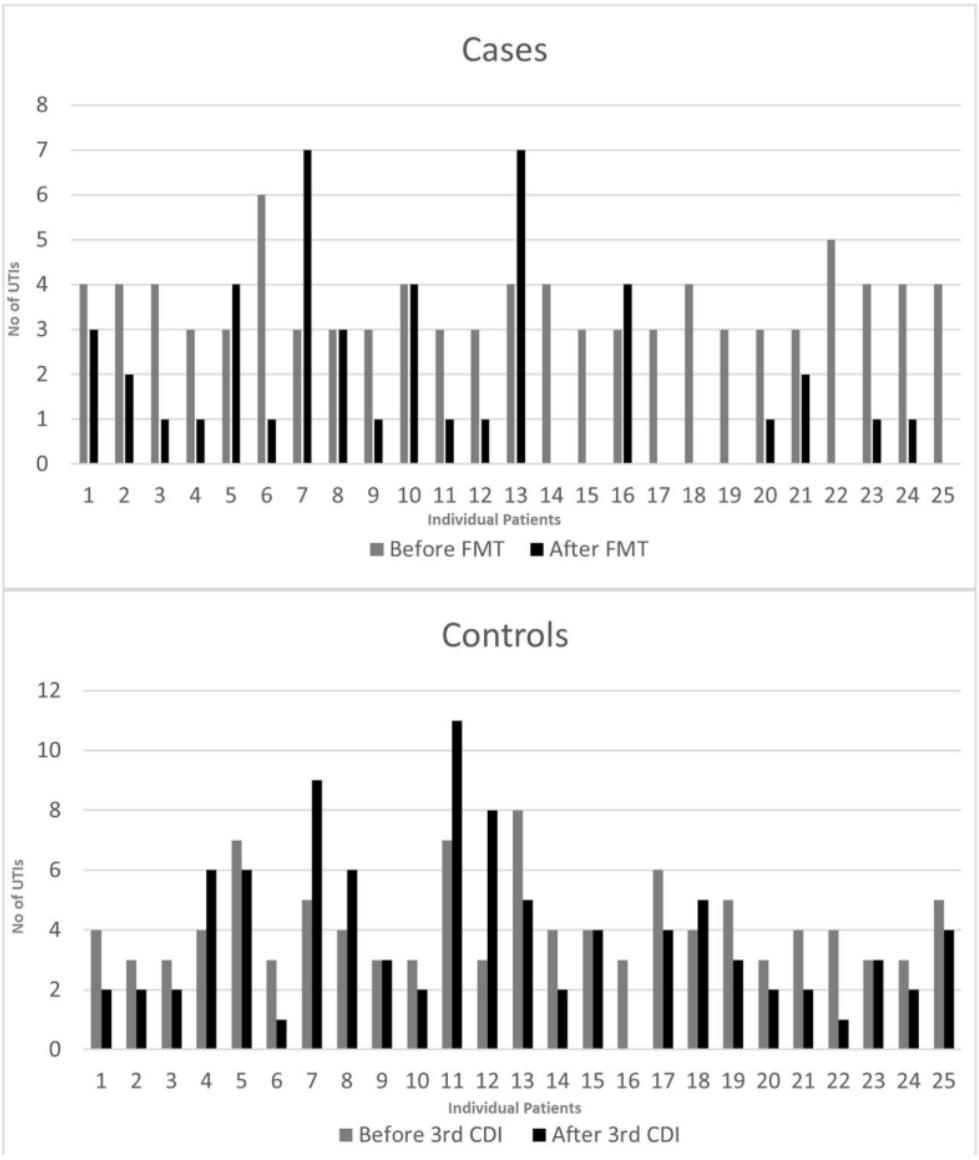
doi.org/10.1007/s10096-023-04635-4

The investigators performed a retrospective chart review to identify patients with 3 or more UTIs in the year prior to FMT for CDI from May 2012 to April 2022. Patients were selected for FMT for recurrent CDI if they had 3 or more CDI episodes with positive stool test (most commonly polymerase chain reaction) in the presence of diarrhea. For comparison, they identified patients with 3 episodes of CDI managed with standard of care antibiotics (PO vancomycin, fidaxomicin, and metronidazole) and 3 or more UTIs in the year prior to the 3rd episode of CDI. Patients with urinary symptoms and with a single bacterial colony count $>10^5$ colony-forming units/mL were considered positive. Data including patient demographics, CDI history, and frequency of UTIs in 1 year before and after FMT (3rd CDI episode date for the comparator group) were collected. Data were also collected for all the organism and antimicrobial resistance patterns from positive urine cultures. They compared the rate of antimicrobial resistance to one of more antibiotics for the most common organism before and after FMT (or 3rd CDI episode for controls). Demographic and clinical variables were summarized using descriptive statistics.

A total of 25 patients were managed with FMT for rCDI and 25 patients received standard antibiotics for rCDI. Both groups had similar age of 67 years (range 24–92) for cases compared to 75 years (range 38–87) for controls and 84% were female in both groups. For cases (patients undergoing FMT for rCDI), the median number of CDI episodes prior to FMT was 3 (range 3–6). After FMT, 21 patients had complete resolution of CDI and had no recurrences within in 1 year of follow-up despite future antibiotic exposure for recurrent UTIs. Four patients had CDI recurrence, 2 were managed with antibiotics followed by repeat FMT, and 2 had CDI resolution with PO vancomycin. For patients managed with FMT, there was a statistically significant decrease in the frequency of UTIs from a median of 4 (range 3–9) episodes in the year before FMT to median of 1 (range 0–7) ($p < 0.001$).

Among the patients treated with FMT, a total of 107 positive urine samples were identified in the year before FMT and 45 positive samples the year after. *Escherichia coli* was the most common organism cultured from pre- and post-FMT urine samples followed by *Klebsiella* species. There was a numerical decrease in the antimicrobial resistance for *E. coli* (pre-FMT 40% vs post-FMT

22.2%, p = 0.18). For *Klebsiella* species, there was a decrease in antimicrobial resistance (35.4% vs 15.3%, p = 0.18).



Comment: The investigators found a significant reduction in number of UTIs after FMT compared to patients who received antibiotics for CDI treatment. After FMT, they also observed a trend towards reduction of antibiotic resistance in organisms causing UTI. The origin of most bacterial infections in urinary tract has been presumed to be the gut. A prior study suggested that gut abundance of uropathogens (*E. coli* and *Enterococcus*) is associated with UTI. [Nat Commun 10(1):5521] Similar strains of uropathogens have been found in the urinary tract and gut supporting a gut pathobiont-UTI link. The notion that the gut microbiota might influence susceptibility to UTIs is an intriguing hypothesis that is supported by emerging evidence. Repletion of healthy gut microbiome with FMT may also decrease the concentration of gut MDROs (colonization resistance) responsible for recurrent UTIs and, hence, reduce symptomatic UTIs. FMTs are now being considered in decolonization of MDR-GN. There was no microbiome profiling, and the sample size was small. See next review

A Phase 2 Extension Study Evaluating the Immunogenicity, Safety, and Tolerability of 3 or 4 Doses of a Clostridioides difficile Vaccine in Healthy US Adults 65 to 85 Years of Age J Infect Dis published online August 2, 2023

DOI: 10.1093/infdis/jiad307

Vaccination is one approach for preventing *Clostridioides difficile* infection (CDI). A previous study of a three-dose *C. difficile* vaccine using inactivated toxins A and B demonstrated immunogenicity for both monthly (0, 1, and 6 months) and daily (1, 8, and 30 days) regimens among healthy participants aged 65–85 without a prior history of CDI. Now, investigators report the results of a study extension in 300 participants randomized to receive a booster vaccination 12 months after primary immunization. This study was designed to investigate antibody persistence up to 48 months after a 3-dose primary series of a *C difficile* vaccine candidate and the immune response and antibody persistence up to 36 months after a fourth dose.

Although immune responses in the 200-µg/placebo and 100-µg/placebo groups were similar for both month and day regimens at 48 months after Dose 3, higher responses were observed with the 200-µg/placebo month regimen. For the three-dose, 200-µg primary monthly regimen without boosting, neutralizing antibody to both toxin A and toxin B were detectable 48 months after the third immunization, with 24% of subjects remaining above a prespecified antibody level against toxin A and 26% above a prespecified level against toxin B. For those receiving the fourth dose, 100% reached prespecified antibody levels to toxin A and 97% to toxin B one month after boosting, and this response persisted above that in participants not boosted for 36 months. Antibody responses among those receiving primary daily injections were lower than in those receiving the monthly regimen. Injection-site reactions were more common in vaccine than placebo recipients; however, systemic reactions were similar with vaccine and placebo, and none were deemed Grade 4 in severity.

Comment: The results of this study complement the safety, tolerability, and immunogenicity findings from the primary stage of this study, as well as a recent study in older Japanese adults [Vaccine 2019; 37:2600-7]. In addition, although the phase 3 CLOVER trial did not meet its pre-specified primary endpoint of prevention of primary CDI, *C difficile* vaccine efficacy was demonstrated to be 100% for CDI requiring medical attention compared with placebo and was also associated with 75–80% reduction in CDI duration [Pfizer. Phase 3 CLOVER trial for Pfizer's investigational *Clostridioides Difficile* vaccine-press release]. These studies provide additional support for the investigational *C difficile* vaccine for the prevention of CDI in adults. However, a general limitation of the extension stage of this study was small sample sizes, particularly in the day regimen. Antibody responses did wane over time indicating possible loss of immunity. The article did not present data on reducing the risk of acquiring CDI.

Risk of Misleading Conclusions in Observational Studies of Time-to-Antibiotics and Mortality in Suspected Sepsis Clin Infect Dis published online August 2023

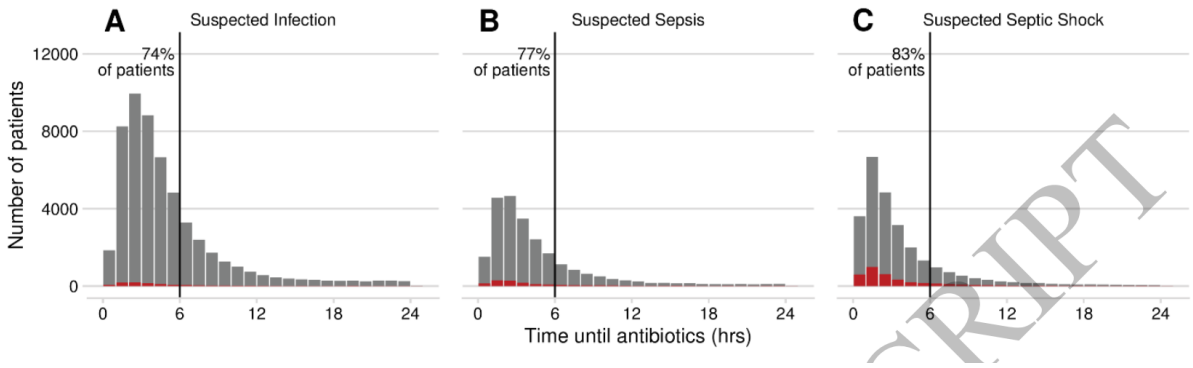
DOI: 10.1093/cid/ciad450

Influential studies conclude that each hour until antibiotics increases mortality in sepsis. However, these analyses often 1) adjusted for limited covariates, 2) included patients with long delays until antibiotics, 3) combined sepsis and septic shock, and 4) used linear models presuming each hour delay has equal impact. The investigators evaluated the effect of these analytic choices on associations between time-to-antibiotics and mortality.

The investigators retrospectively identified 104,248 adults admitted to five hospitals from 2015–2022 with suspected infection (blood culture collection and intravenous antibiotics within 24h of arrival), including 25,990 with suspected septic shock and 23,619 with sepsis without shock. They defined "suspected infection" as the collection of ≥1 blood culture (regardless of result) and administration of IV antibiotics within 24 hours from ED arrival. They defined "suspected sepsis" as suspected infection plus organ dysfunction within 12 hours of ED arrival, defined as ≥1 of: lactate >2.0mmol/L; initiation of non-invasive or invasive mechanical ventilation; creatinine >2.0mg/dL and an increase of ≥50% from baseline; total bilirubin >2.0mg/dL and an increase of ≥50% from baseline; or platelets <100,000/μL and a decrease of ≥50% from baseline. They defined "suspected septic shock" as suspected infection plus either hypotension (systolic blood pressure [SBP] <90mmHg) or lactate ≥4.0mmol/L within 12 hours of ED arrival. [Sepsis-3] They used ED arrival time as time zero for antibiotic timing. The investigators used multivariable regression to calculate associations between time-to-antibiotics and in-hospital mortality under successively broader confounding-adjustment, shorter maximum time-to-antibiotic intervals, stratification by illness severity, and removing assumptions of linear hourly associations.

In a fully adjusted model of patients treated within 6 hours, each hour associated with higher mortality for septic shock (aOR 1.07; 95% CI 1.04–1.11), but not sepsis without shock (aOR 1.03; 0.98–1.09) or suspected infection alone (aOR 0.99; 0.94–1.05). Modeling each hour separately confirmed that every hour delay was associated with increased mortality for septic shock, but only delays of >6 hours were associated with higher mortality for sepsis without shock.

Figure 1. Distribution of Time to Antibiotics in Each Cohort



Comment: Sepsis guidelines, quality metrics, and quality improvement initiatives recommend immediate broad-spectrum antibiotics for all patients with possible sepsis based on observational studies. When they included patients treated >6 hours from arrival, each additional hour until antibiotics was associated with increased mortality for both sepsis and septic shock, whereas restricting the analytic cohort just to patients treated within 6 hours of ED arrival generated a significant estimated hourly effect only for patients with septic shock. The investigators were limited to structured covariates extracted from electronic medical records. It is possible that qualitative information in clinical notes could further reduce confounding, such as vague vs explicit presenting symptoms. They did not evaluate whether patients had confirmed infections in retrospect or assess the appropriateness of ordered antibiotics. They were not able to adjust for concomitant sepsis treatments such as source control or fluid resuscitation. They used ED arrival time as time zero for antibiotic timing rather than trying to define time zero on physiologic grounds; some patients may have had sepsis for prolonged times prior to or after ED arrival. Despite some limitations, they found that in maximally-adjusted non-linear models, each hour until antibiotics from 1–6 hours were associated with significantly higher mortality in patients with suspected septic shock, but not in patients with suspected sepsis or infection alone. This study confirms earlier observational trials which showed the association between each hour of delay until broad-spectrum antibiotics only applied to patients with septic shock. [N Engl J Med 2017; 376:2235-2244; AJRCCM 2017; 146:856-863] These findings have important implications for sepsis treatment guidelines, quality metrics, and quality improvement initiatives. For organizations that now require antibiotics to be administered within one hour for all suspected septic patients, I recommend they reassess current practice and separate septic shock from other forms of sepsis. The “one hour” rule has led to overuse and misuse of broad-spectrum antibiotics which has been shown to lead to unintended consequences including AKI, CDI, ADE, and AR which can lead to increased mortality. [JAMA Netw Open 2020;3(4): e2028] See next review.

The Centers for Disease Control and Prevention's Hospital Sepsis Program Core Elements JAMA published online August 24, 2023

doi:10.1001/jama.2023.16693

This month, the CDC released the Hospital Sepsis Program Core Elements to assist hospitals with developing multiprofessional programs to monitor and optimize management and outcomes of sepsis. The Sepsis Core Elements complement existing sepsis guidelines and facilitate implementation of best practices across a range of patient populations (adults, children, and people who are pregnant or postpartum) and in a range of hospital settings. The guidance does not provide a specific guidance for treating sepsis, but rather a "manager's guide" for developing a comprehensive program to monitor and improve outcomes from sepsis. The guidance conceptualizes sepsis performance improvement as a continual process and highlights the importance of using quality improvement tools and implementation science principles to drive ongoing improvement in sepsis management and outcomes.

Modeled after the CDC's Core Elements of Antibiotic Stewardship, the Hospital Sepsis Program Core Elements aim to help hospitals organize staff, identify resources, and structure their sepsis programs so they can rapidly identify and provide effective care for all types of patients with sepsis, which is a complex condition that can manifest in a variety of ways and isn't easy to recognize. The Sepsis Core Elements build on prior large-scale efforts to improve sepsis outcomes, such as the Surviving Sepsis Campaign, the New York state sepsis regulations, and the CMS Severe Sepsis/Septic Shock Early Management Bundle. These initiatives have focused on recognition and early management of sepsis in hospitals. While measuring the impact of such programs is especially difficult, some studies have suggested that these programs may have improved sepsis outcomes, however, morbidity and mortality from sepsis remain unacceptably high, indicating more work is needed.

First, the Sepsis Core Elements emphasize the importance of hospital leadership in directing that clinicians leading the program have the time, resources (including data analytics), and support structures needed to succeed. Second, the Sepsis Core Elements address all hospital-based sepsis activities—including education, tracking of sepsis management, and reporting of sepsis outcomes—while prior sepsis initiatives have focused on improving select processes of care. Third, the Sepsis Core Elements address management of sepsis throughout hospitalization, while prior initiatives have often focused on the first 6 to 24 hours of sepsis management, or the so-called "golden hours" of sepsis resuscitation. Early recognition and management are critical and are points of emphasis in the Sepsis Core Elements, but subsequent management is also important to optimizing longer-term recovery from sepsis and is an area for improvement.

Table. Core Elements of Hospital Sepsis Programs[4]

Core element	Description
Hospital leadership commitment	Support from hospital leadership to ensure that hospital sepsis efforts have the necessary human, financial, and information technology resources.
Accountability	Appointment of 1 leader or 2 co-leaders responsible for program goals and outcomes.
Multiprofessional expertise	Engagement of key partners throughout the hospital and health system to support sepsis measurement and quality improvement efforts.
Action	Implementation of structures and processes to improve the identification of, management of, and recovery from sepsis (eg, hospital guidelines, care pathways, screening protocols, and order sets).
Tracking	Measurement of hospital sepsis epidemiology, management, and outcomes to assess the impact of sepsis initiatives and progress toward program goals.
Reporting	Provision of data on sepsis management and outcomes to relevant partners.
Education	Education on sepsis for clinicians, patients, and family/caregivers.

Comment: CMS has begun developing a 30-day mortality measure for community-onset sepsis that will leverage electronic health record data for both sepsis identification and risk adjustment. [JAMA. 2023; 329:535-536] The CDC estimates that at least 1.7 million Americans develop sepsis each year, and at least 350,000 adults who develop sepsis during their hospitalization die or are moved into hospice. There are far more who survive and suffer from cognitive and other quality of life issues long after discharge from sepsis. Survival and recovery from sepsis requires rapid identification, action, and coordination from multiple hospital departments. Much more work is needed to reduce mortality in hospital-onset sepsis and reducing the long-term consequences in survivors. See next review.

Sepsis Program Activities in Acute Care Hospitals — National Healthcare Safety Network, United States, 2022 MMWR 2023; 72: 907-911

The 2022 NHSN annual survey evaluated the prevalence and characteristics of sepsis programs in acute care hospitals. Among 5,221 hospitals, 3,787 (73%) reported having a committee that monitors and reviews sepsis care. Prevalence of these committees varied by hospital size, ranging from 53% among hospitals with 0–25 beds to 95% among hospitals with >500 beds. Fifty-five percent of all hospitals provided dedicated time (including assigned protected time or job description requirements) for leaders of these committees to manage a program and conduct daily activities, and 55% of committees reported involvement with antibiotic stewardship programs.

Comment: These data highlight opportunities, particularly in smaller hospitals, to improve the care and outcomes of patients with sepsis in the US by ensuring that all hospitals have sepsis programs with protected time for program leaders, engagement of medical specialists, and integration with antimicrobial stewardship programs. The NHSN survey is limited to acute care hospitals enrolled in NHSN and might not reflect practices among all US acute care hospitals; however, hospitals enrolled in NHSN represent at least 88% of U.S. acute care hospitals. Second, although hospitals reported whether specialty services such as pediatrics and labor and delivery were included in sepsis committees, these services are not within the scope of practice at all hospitals, and thus conclusions cannot be made regarding the frequency with which these services might be missing from sepsis committees. Third, although many sepsis

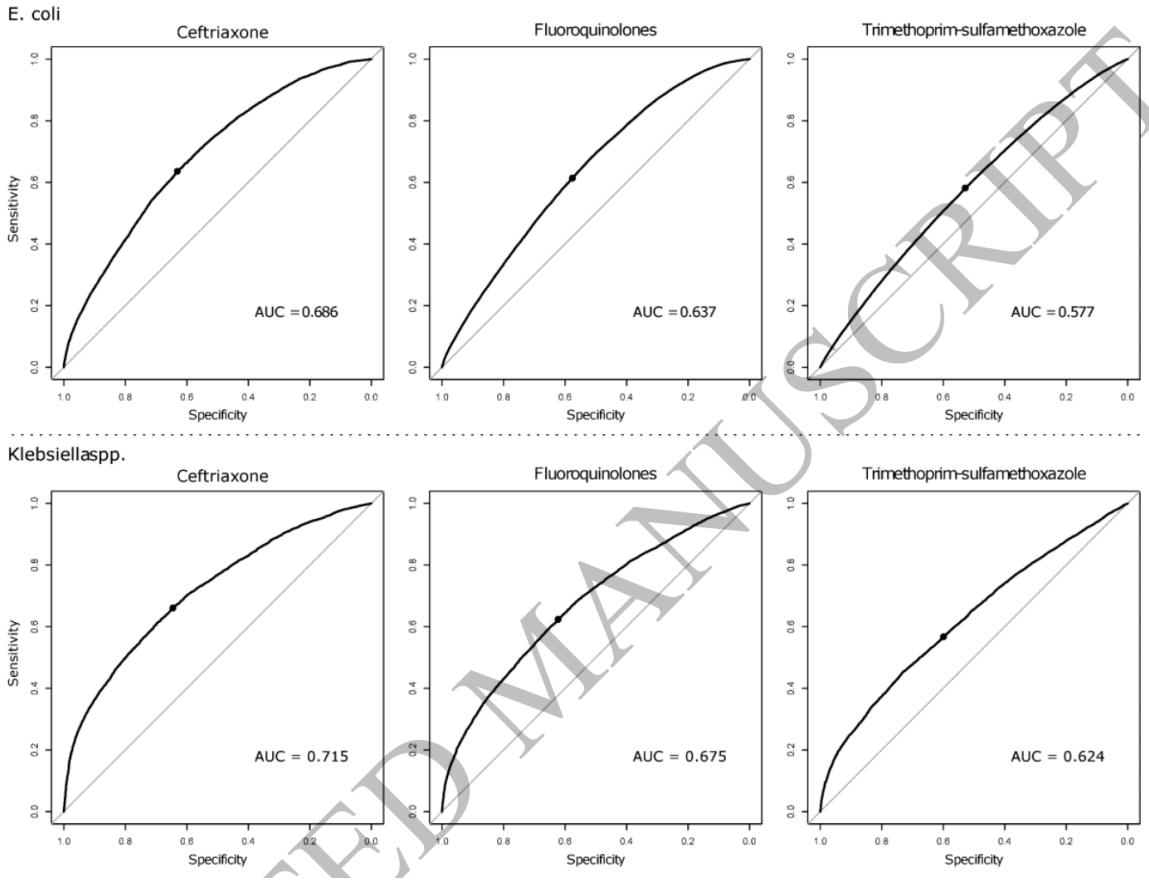
committees do not monitor antimicrobial use in sepsis, these responsibilities overlap with those of ASPs. Lastly, this survey did not define criteria for a sepsis program or if it was effective and is subject to respondent interpretation. I think it is critical to integrate diagnostic and antimicrobial stewardship, and infection prevention with sepsis.

Diagnostic Accuracy of Hospital Antibiograms in Predicting the Risk of Antimicrobial Resistance in Enterobacteriaceae Isolates: A Nationwide Multicenter Evaluation at the Veterans Health Administration Clin Infect Dis published online August 10, 2023

DOI: 10.1093/cid/ciad467

Hospital antibiograms are typically generated by aggregation of microbiologic data, and little is known about an antibiogram's reliability in predicting antimicrobial resistance (AMR) risk at the patient-level. The investigators aimed to assess the diagnostic accuracy of antibiograms as a tool for selecting empiric therapy for *E. coli* and *Klebsiella spp*. for individual patients. They retrospectively generated hospital antibiograms for the nationwide Veterans Health Administration (VHA) facilities from 2000 to 2019 using all clinical culture specimens positive for *E. coli* and *Klebsiella* spp., then assessed the diagnostic accuracy of an antibiogram to predict resistance for isolates in the following calendar year using logistic regression models and predefined 5-step interpretation thresholds.[predefined interpretation thresholds with five step-wise increments at <80%, <85%, <90%, <95%, and <98% (i.e., 2-20% prevalence of AMR)]. *K. aerogenes* was excluded because some facilities reported *Enterobacter* spp. only at the genus level before 2017, when *K. aerogenes* was reclassified from *Enterobacter* spp. to *Klebsiella* spp. Following CLSI guidelines, they included only the first isolate per patient in each calendar year and facility for *E. coli* and *Klebsiella* spp. They then created standardized antibiograms from 2000 to 2019 at all facilities, based on phenotypic susceptibility (susceptible vs. non-susceptible) for antimicrobial categories for each calendar year and facility, where ≥30 isolate-antimicrobial combinations a year were available. To assess prediction performance, they generated 2x2 contingency tables and reported sensitivities and specificities for all antimicrobial groups. They also created receiver operating characteristic (ROC) curves for the three commonly used antimicrobial classes for GNR infections, ceftriaxone, fluoroquinolones, and trimethoprim-sulfamethoxazole, to visualize the prediction performances and estimate the area under the curve of ROC (AUC). They interpreted AUC at 0.5- 0.7 as poor, 0.7-0.8 as moderate, 0.8-0.9 as good, and >0.9 as excellent discriminative abilities.

Among 127 VHA facilities, 1,484,038 isolates from 704,779 patients for *E. coli* and 671,035 isolates from 340,504 patients for *Klebsiella* spp. were available for analysis. For *E. coli* and *Klebsiella* spp., the discrimination abilities of hospital-level antibiograms in predicting individual patient AMR were mostly poor, with the areas under the receiver operating curve at 0.686 and 0.715 for ceftriaxone, 0.637 and 0.675 for fluoroquinolones, and 0.576 and 0.624 for trimethoprim-sulfamethoxazole, respectively. The sensitivity and specificity of the antibiogram varied widely by antimicrobial groups and interpretation thresholds with substantial trade-offs.



Comment: Several previous studies proposed stratified antibiograms according to the setting (e.g., inpatient vs. outpatient), clinical syndromes, or age. The CLSI guideline includes these approaches as an "enhanced antibiogram." While enhanced antibiograms are reported to have improved diagnostic accuracies in single-center studies conducted at academic institutions, it is difficult for a stratified antibiogram to present data for patients with multiple risk factors, and it may underestimate the risk of resistance for medically complex patients. In addition, their generalizability, applicability, and practicality are questionable at smaller hospitals. On the other hand, antibiograms may overestimate the risk of AMR in relatively healthy patients with fewer risk factors and sway clinicians to choose more broad-spectrum agents for those patients. Mostly poor prediction capabilities and drastic trade-offs between sensitivity and specificity also raise a concern that antibiograms may be contributing to the overuse of broad-spectrum antimicrobials among patients with low risks of AMR. More than 80% of patients were adult males, and this gender imbalance might result in a small proportion of isolates from uncomplicated urinary tract infections, of which the most common pathogens are *E. coli* and *Klebsiella* spp. This may potentially limit the generalizability to populations outside the VHA systems. The investigators in this study focused on assessing standardized antibiograms based on the CLSI guidelines. Their results do not necessarily negate the usefulness of "enhanced antibiograms," such as stratified antibiograms by clinical locations, patient populations, or clinical syndromes. With the advent of advanced predictive analytics (e.g., machine learning-Inspire Trials), providing absolute risk of AMR for each patient should provide more useful guidance to clinicians.

Association Between Fluoroquinolone Use and Hospitalization With Aortic Aneurysm or Aortic Dissection JAMA Cardiol published online August 16, 2023

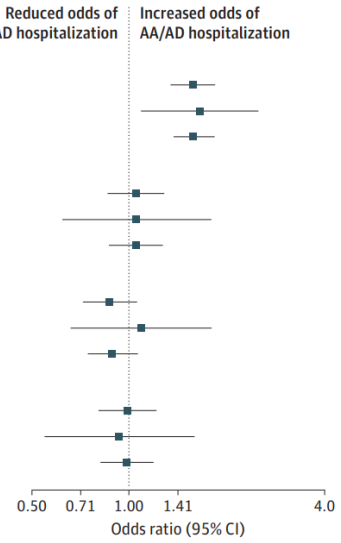
doi:10.1001/jamacardio.2023.2418

Cohort and case-crossover studies were conducted separately in 2 databases of UK primary care records. Clinical Practice Research Datalink Aurum and GOLD primary care records were linked to hospital admissions data. Adults with a systemic fluoroquinolone or cephalosporin prescription between April 1997 and December 2019 were included in the cohort study. Adults hospitalized with aortic aneurysm or dissection within the eligibility period were included in the case-crossover study. Individuals meeting inclusion criteria in the case-crossover study were matched 1:3 to control individuals on age, sex, index date, and clinical practice to adjust for calendar trends in prescribing. Data were analyzed from January to July 2022.

In this cohort study, the investigators identified 3,134,121 adults in Aurum (mean [SD] age, 52.5 [20.3] years; 1 969 257 [62.8%] female) and 452,086 in GOLD (mean [SD] age, 53.9 [20.2] years; 286 502 [63.4%] female) who were prescribed fluoroquinolones or cephalosporins. In crude analyses, fluoroquinolone relative to cephalosporin use was associated with increased hospitalization with aortic aneurysm or dissection (pooled HR, 1.28; 95% CI, 1.13-1.44; P < .001) but after adjustment for potential confounders, this association disappeared (pooled adjusted HR, 1.03; 95% CI, 0.91-1.17; P = .65). In the case-crossover study, they identified 84, 841 individuals hospitalized with aortic aneurysm or dissection in Aurum (mean [SD] age, 75.5 [10.9]; 23,551 [27.8%] female) and 10,357 in GOLD (mean [SD] age, 75.6 [10.5]; 2809 [27.1%] female). Relative to nonuse, fluoroquinolone use was associated with an increase in hospitalization with aortic aneurysm or dissection, but no association was found relative to other antibiotics (vs cephalosporin pooled OR, 1.05; 95% CI, 0.87-1.27; vs trimethoprim, 0.89; 95% CI, 0.75-1.06; vs co-amoxiclav, 0.98; 95% CI, 0.82-1.18). However, in the case-crossover study, increased hospitalization with aortic aneurysm or dissection was observed relative to nonuse for multiple antibiotics across different drug classes, including fluoroquinolones.

B Fluoroquinolone vs comparator antibiotics (case-crossover study)

Comparison	Database	Odds ratio (95% CI)	P value
Fluoroquinolone vs nonuse			
	Aurum	1.57 (1.35-1.84)	<.001
	GOLD	1.65 (1.09-2.50)	.02
	Pooled	1.58 (1.37-1.83)	<.001
Fluoroquinolone vs cephalosporin			
	Aurum	1.05 (0.86-1.28)	.61
	GOLD	1.05 (0.62-1.79)	.85
	Pooled	1.05 (0.87-1.27)	.59
Fluoroquinolone vs trimethoprim			
	Aurum	0.87 (0.72-1.05)	.14
	GOLD	1.09 (0.66-1.79)	.74
	Pooled	0.89 (0.75-1.06)	.20
Fluoroquinolone vs co-amoxiclav			
	Aurum	0.99 (0.81-1.21)	.92
	GOLD	0.93 (0.55-1.59)	.79
	Pooled	0.98 (0.82-1.18)	.85



Comment: The results in this study suggest that estimates of association of fluoroquinolones with aortic aneurysm or dissection may be affected by confounders. When such confounders are accounted for, they found no association, providing reassurance on the safety of fluoroquinolones with respect to aortic aneurysm or dissection. The investigators in this study suggest the increased risk of aortic aneurysm or dissection that's been observed in previous studies and led FDA to add a warning to fluoroquinolone packaging in 2018—may be related to infection itself. In a nested case-control study, genitourinary and lower respiratory tract infections were associated with increased risk of hospitalization with aortic aneurysm or dissection after adjustment for antibiotic usage. [JAMA Intern Med. 2020;180: 1587-1595] The findings are noteworthy because aortic aneurysm and dissection are just one of several potential side effects that have been identified for fluoroquinolones, which cover a broad range of gram-positive and gram-negative bacteria and are one of the most prescribed and overused and misused antibiotic class. Other side effects that have been added to fluoroquinolone packaging include tendinitis, tendon rupture, and peripheral neuropathy. Ruptured aneurysms and dissections leading to death before hospitalization was not identified. Most fluoroquinolone prescriptions (88.1%) were for ciprofloxacin and most fluoroquinolone prescriptions in the UK are for UTIs, potentially limiting generalizability of findings to other fluoroquinolones and other indication.

Staphylococcus epidermidis bloodstream infections (SE-BSI) are a cause of septic shock in ICU patients

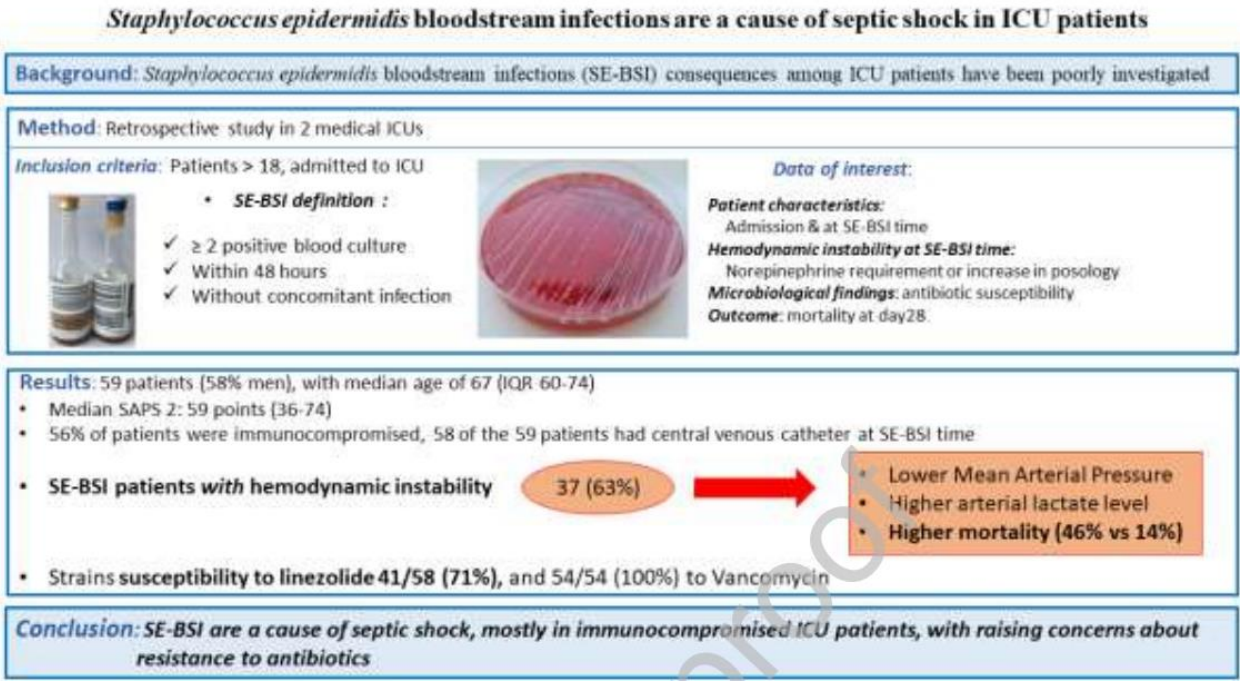
Int J Infect Dis published online July 2023

doi.org/10.1016/j.ijid.2023.07.014

The investigators conducted a retrospective cohort in two medical ICUs. SE-BSI were defined by two or more independent SE-positive blood cultures of the same strain, within 48 hours, without concurrent infection.

They included 59 patients, 58% men (n=34), with median age of 67 (IQR 60-74) and SAPS II of 59 points (36-74), 56% being immunocompromised (n=33). Among the 37 patients (63%) requiring norepinephrine initiation or increase at the onset of SE-BSI versus patients not requiring vasopressors (37%; n=22), concomitant arterial lactate levels reached 2.8 (1.9-5.8) vs. 1.5 (1.3-2.2) mmol/L (p<0.01) while mean blood pressure was 49 (42-54) vs. 61 (56-65) mmHg (p=0.01), and mortality attained 46% (n=17) vs. 14% (n=3) at day 28 (p=0.01), respectively. Percent susceptibility for linezolid and vancomycin were 71% (n=41/58), and 100% (n=54/54), respectively. At the time of SE-BSI, all but one patient had a central venous device during their ICU stay, mostly inserted into the jugular vein (IJ) (76%; n=45). Forty-seven percent (n=28) had a dialysis catheter. Central venous catheter was removed in 53 patients, among which 25% (n=13) were implantable venous access devices (IVADs) and PICC lines.

Comment: This study highlights SE-BSI can cause septic shock, primarily in immunocompromised ICU patients. This study also raises concerns about resistance to antibiotics and the importance of prevention of CLABSIs. SE is a low virulent organism, and is therefore it is usually considered a contaminant when found in microbiological samples, leading to make the diagnosis of CoNS(coagulase negative staphylococcus) BSI only if two or more independent blood cultures are positive for the same species of CoNS within 5 days, in the absence of another concomitant infection. CoNS is implicated in 31 to 38% of catheter-related BSIs. [Front Microbiol 2017; 8: 1401] SE infections have been documented in neutropenic cancer patients. [Cancer Treat Res 2014; 161: 43-89] The literature is limited on critically ill patients suffering from BSI caused by SE (SE-BSI), particularly regarding clinical morbidity and prognosis, despite the high proportion of immunocompromised patients and the frequent use of invasive devices in the ICU. The updated Compendium on Prevention of CLSBSI in Acute Care recommends that the subclavian site is preferred in ICU settings. In this study IJ was the most common site for insertion. We are not told what preventive practices were employed during this study.

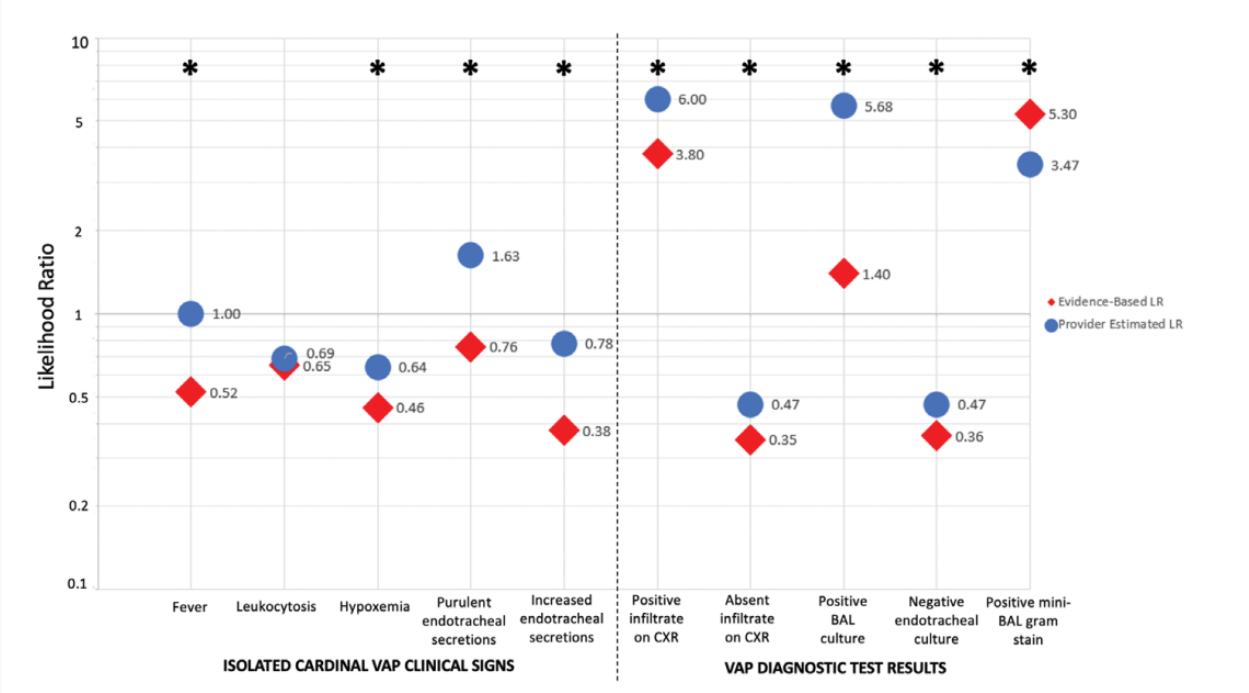


Healthcare providers consistently overestimate the diagnostic probability of ventilator-associated pneumonia Infect Control Hosp Epidemiol published online June 24, 2023

doi.org/10.1017/ice.2023.62

Investigators performed a clinical survey of ICU physicians to evaluate provider estimates of VAP diagnostic probability before and after isolated cardinal VAP clinical changes and VAP diagnostic test results at Michigan Medicine University Hospital. In total, the investigators collected 133 survey responses, 30% of which were from attending physicians and 70% from residents or fellows and 66% of whom reported being “moderately” to “extremely confident” in their ability to accurately diagnose VAP.

The study showed that provider estimates of VAP diagnostic probability were consistently higher than evidence-based diagnostic probabilities, with data showing that survey respondents overestimated the baseline probability of VAP with a median estimated probability of 20% relative to evidence-based baseline probability of 16%. These rates were similar following presented isolated cardinal VAP clinical changes and VAP diagnostic test results with the median provider-estimated pretest probability of VAP following patient development of isolated purulent endotracheal secretions being 34% relative to an evidence-based pretest probability of 12.6%. The median provider-estimated post-test VAP probability then rose to 80% relative to an evidence-based post-test probability of 16.5% after receipt of a positive bronchoalveolar lavage culture. The study also showed that imputed likelihood ratios (LRs) from provider-estimated diagnostic probabilities were consistently higher than evidence-based LRs — with the differences being most notable for positive bronchoalveolar lavage culture (provider-estimated LR = 5.7 vs. evidence-based LR = 1.4; $P < .01$), chest radiograph with air bronchogram (6 vs. 3.6; $P < .01$), and isolated purulent endotracheal secretions (1.6 vs. 0.8; $P < .01$). Finally, the study showed that attending physicians and infectious disease physicians were more accurate in their LR estimates than trainees ($P = .04$) and non-ID physicians ($P = .03$).



Comment: I think we can all agree that VAP is very challenging to accurately diagnose, and we tend to over diagnose and overtreat. To try and be more objective, VAE was created years ago and can be a first step in meeting criteria for VAP. It's important to ensure that the diagnostic probabilities we implicitly or explicitly use in clinical practice are consistent with available evidence. Diagnostic stewardship initiatives, including educational outreach and clinical decision support systems are needed in minimizing VAP overdiagnosis and ICU antibiotic overuse.

FDA Gives 510(k) Clearance to Respiratory Viral Panel Test for Rapid RSV, COVID-19 Detection

The FDA granted 510(k) clearance to Becton, Dickinson and Company's (BD) Respiratory Viral Panel (RVP) test, a novel PCR assay that can quickly determine whether a patient has Covid-19, influenza A, influenza B, or RSV. The test is a single molecular diagnostic combination test that uses a single nasal swab/NP(nasopharyngeal) swab sample to detect or determine the presence of Covid-19, influenza A, influenza B, or RSV in about 2 hours.

Comment: The test, which has been available in the US since February through an Emergency Use Authorization (EUA) from FDA, uses a single nasal swab or a single NP swab sample to determine if a patient has Covid-19 or the flu or RSV. The hope is this test will help eliminate the need for multiple individual tests or doctor visits and can help clinicians implement the right treatment plan quickly. I do not have any cost on this new test, but if actionable may help determine the right diagnosis and intervention in real time.

Infants Admitted to US Intensive Care Units for RSV Infection During the 2022 Seasonal Peak *JAMA Netw Open.* 2023;6(8):e2328950

doi:10.1001/jamanetworkopen.2023.28950

This was a cross-sectional study using a public health prospective surveillance registry surveillance of infants admitted to an ICU or other high-acuity unit for RSV at 39 hospitals in 27 states from October 17 to December 16, 2022.

Data were captured on demographics, clinical characteristics, signs and symptoms, laboratory values, severity measures, and clinical outcomes, including receipt of noninvasive respiratory support, invasive mechanical ventilation, vasopressors or extracorporeal membrane oxygenation, and death. Mixed-effects multivariable log-binomial regression models were used to assess associations between intubation status and demographic factors, gestational age, and underlying conditions, including hospital as a random effect to account for between-site heterogeneity.

The first 15 to 20 consecutive eligible infants from each site were included for a target sample size of 600. Among the 600 infants, the median (IQR) age was 2.6 (1.4-6.0) months; 361 (60.2%) were male, 169 (28.9%) were born prematurely, and 487 (81.2%) had no underlying medical conditions. Primary reasons for admission included LRTI (594 infants [99.0%]) and apnea or bradycardia (77 infants [12.8%]). Overall, 143 infants (23.8%) received invasive mechanical ventilation (median [IQR], 6.0 [4.0-10.0] days). The highest level of respiratory support for nonintubated infants was high-flow nasal cannula (243 infants [40.5%]), followed by bilevel positive airway pressure (150 infants [25.0%]) and continuous positive airway pressure (52 infants [8.7%]). Infants younger than 3 months, those born prematurely (gestational age <37 weeks), or those publicly insured were at higher risk for intubation. Four infants (0.7%) received extracorporeal membrane oxygenation, and 2 died. The median (IQR) length of hospitalization for survivors was 5 (4-10) days.

Comment: They noted that RSV is the leading cause of respiratory disease–related hospital admissions in young children around the world. In this cross-sectional study, most US infants who required intensive care for RSV LRTIs were young, healthy, and born at term. The investigators did not include all cases of severe RSV admitted to the ICU during the 2-month study period, which also did not encompass the full RSV season at these centers. In addition, including only clinician-ordered, laboratory-confirmed RSV cases may have resulted in missing cases that were not tested for RSV. Although most infants were tested for influenza and SARS-CoV-2, only half were tested with a respiratory viral panel, so they were unable to systematically assess the influence of viral codetection on disease severity. In addition, not all intubated infants were tested for bacterial coinfection and it was not possible to acquire bacterial lower respiratory samples in nonintubated patients, so the role of bacterial coinfection may be underestimated. RSV vaccination during pregnancy may be a new approach. In addition, the recent experience during the Covid-19 pandemic has shown that community mitigation measures are effective in decreasing the circulation of non–Covid-19 respiratory viral pathogens, including RSV. The resurgence of RSV when these measures were lifted suggests that studies of nonpharmaceutical interventions may be important for future surges, but also underscores the need for therapeutic interventions and vaccination to target all infants to reduce the overall

burden of severe RSV disease. The FDA recently approved nirsevimab, a longer acting mAb that neutralizes RSV and a maternal vaccine to prevent RSV. See next review.

FDA approves first vaccine to protect infants from RSV

The FDA on August 21st announced its approval for the use of Pfizer's RSV vaccine in pregnant women to help protect infants as old as 6 months old, marking a new way to protect babies—a group that is at higher risk for complications from the virus. FDA's approval is for use of the vaccine at 32 to 36 weeks gestational age of pregnancy. The vaccine is administered as a single intramuscular dose.

Comment: Last week's approval announcement follows recommendations earlier in May from the FDA's vaccine advisory group, which unanimously approved a vote on efficacy, but raised some concerns about preterm births in a safety vote that passed by a tighter margin. The prescribing information includes information about a numerical imbalance in preterm births among vaccine recipients (5.7%) compared to those who received placebo (4.7%). The FDA, however, said the data aren't sufficient to establish or exclude a relationship between vaccine and preterm birth. Also, the warning urged healthcare providers to avoid using the vaccine in women before 32 weeks gestation. CDC vaccine advisory group will discuss the recommendation, which will require a final sign-off by the CDC.

COVID-19

The plasma metabolome of long COVID patients two years after infection

Sc Rep 2023; 13**,** 12420

doi.org/10.1038/s41598-023-39049-x

Researchers at the Autonomous University of Zacatecas in Mexico led the study, which involved assessment of the plasma metabolome (set of metabolites) in 100 samples obtained from healthy controls, COVID-19 patients, and long-COVID patients in Mexico from 2020 and 2022.

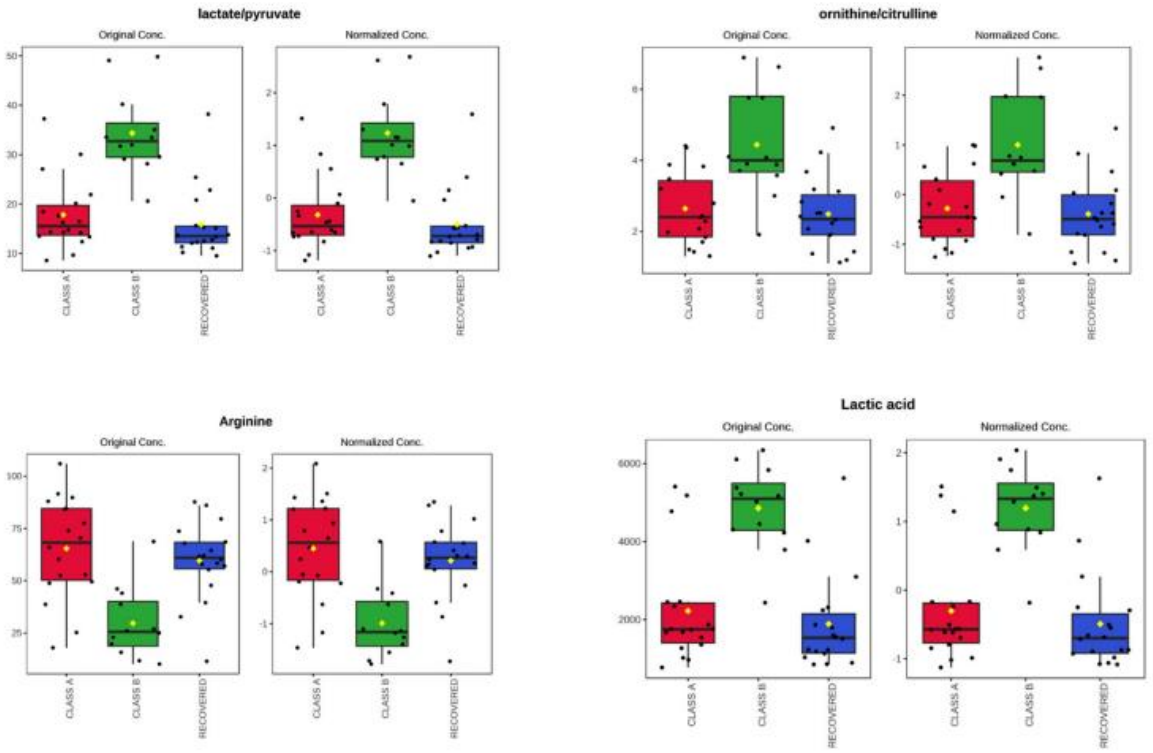
The team measured concentrations of 108 metabolites using liquid chromatography and flow injection analysis with tandem mass spectrometry. They also asked participants to complete symptom questionnaires and used an immunoenzymatic assay to measure the levels of the protein interleukin 17 (IL-17) and the weight-maintenance hormone leptin in long-COVID patients.

All patients were fully vaccinated in 2021 and 2022. Six patients (12.5%) had mild COVID-19, 37 (77%) had moderate or severe infections, and 5 (10.4%) had critical cases.

A comparison of paired samples from 15 COVID-19 and long-COVID patients showed significant differences in 53 metabolites, with 13 upregulated and 32 downregulated in long-COVID patients.

Twenty-seven metabolites were still dysregulated in long-COVID patients compared with controls after 2 years. Long-COVID patients had different concentrations of lactic acid and arginine, altered lactate-pyruvate and ornithine-citrulline ratios, and significantly higher levels of IL-17.

The most common long-COVID symptoms included memory loss (73.3%); sleep disorders, joint pain, fatigue, exercise intolerance, and muscle pain (66.7%); and anxiety (60.0%).



Class A patients (< five symptoms), class B patients (> than five symptoms), and recovered patients

Comment: Mitochondrial dysfunction, redox state imbalance, impaired energy metabolism, and chronic immune dysregulation are likely to be the main hallmarks of long COVID even two years after acute COVID-19 infection. NIH launched and is opening enrollment for phase 2 clinical trials that will evaluate at least four potential treatments for long COVID, with additional clinical trials to test at least seven more treatments expected in the coming months. Treatments will

include drugs, biologics, medical devices and other therapies. The trials are designed to evaluate multiple treatments simultaneously to identify more swiftly those that are effective.

SARS-CoV-2 — No Increased Islet Autoimmunity or Type 1 Diabetes in Teens N Engl J Med published online August 3, 2023

DOI: 10.1056/NEJMc2216477

The investigators conducted a study involving 4586 children 9 to 15 years of age from the United States, Sweden, Finland, and Germany.5 The children were followed from January 2020 (prepandemic) through December 2021 (pandemic) and were tested every 3 months for type 1 diabetes if they had islet autoantibodies (440 participants) and every 6 months if they did not (4146 participants). The children were tested for SARS-CoV-2 nucleocapsid (infection) and spike (vaccination) antibodies at each follow-up visit.

Of the 4586 children, 705 (15.4%) had a positive test for SARS-CoV-2 nucleocapsid antibodies — 623 of the 4146 children without islet autoantibodies (15.0%; 95% confidence interval [CI], 13.9 to 16.1) and 82 of the 440 children with islet autoantibodies (18.6%; 95% CI, 15.0 to 22.3). Among the 4146 children without islet autoantibodies, seroconversion to persistent, confirmed positivity for islet autoantibodies occurred in 40 (1.0%; 95% CI, 0.7 to 1.3).

A total of 45 children received a diagnosis of type 1 diabetes during the 24-month follow-up. Five children received a diagnosis before they had a positive test for SARS-CoV-2 nucleocapsid antibodies. One child received a diagnosis of type 1 diabetes after the detection of SARS-CoV-2 infection. The remaining 39 children with type 1 diabetes never had a positive test for nucleocapsid antibodies: 30 were never vaccinated, 2 were vaccinated before the diagnosis of type 1 diabetes, and 4 were vaccinated after the diagnosis; 3 were not tested.

There was no evidence showing that the number of children in whom seroconversion to persistent islet-autoantibody positivity occurred was greater among those with SARS-CoV-2 infection, even with the inclusion of samples obtained after the study period if the last sample within the study period was positive for Covid-19 or islet autoantibodies.

Comment: An increased incidence of pediatric type 1 diabetes during the Covid-19 pandemic has been widely reported including several publications reviewed in ID Watch. [Pediatr Diabetes 2022; 23:433-8; JAMA Netw Open 2022;5(9):e2233014] Despite the plausibility of a biologic connection, systematic testing for the virus and type 1 diabetes in this prospective, multinational cohort of children before and during the pandemic did not show that Covid-19 triggered type 1 diabetes. The investigators wrote: “These findings must be tempered somewhat because they reflect a narrow age range among children with an increased genetic risk of type 1 diabetes.” They recommend longer follow-up.

Impact of the COVID-19 Pandemic on Inpatient Antibiotic Use in the United States, January 2019 through July 2022 Clin Infect Dis published online August 3, 2023

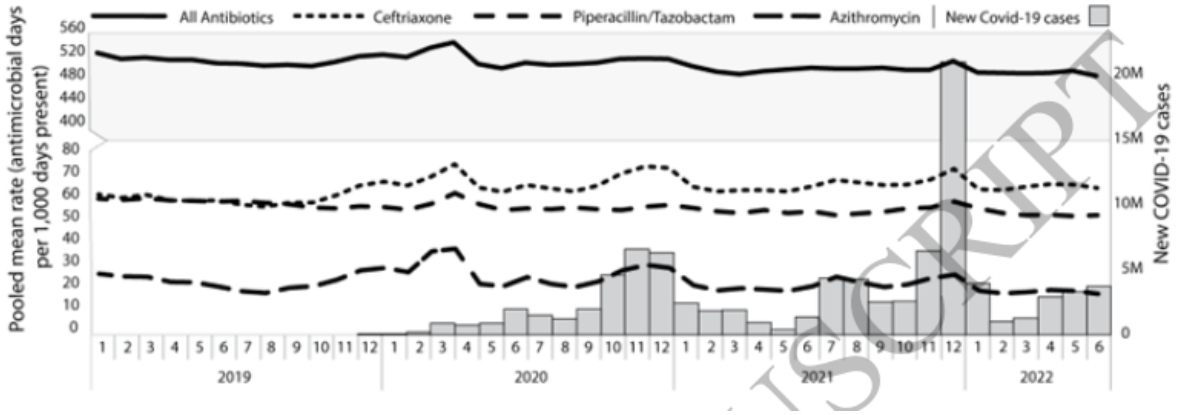
doi.org/10.1093/cid/ciad453

Early in the pandemic of Covid-19, rates of inpatient antimicrobial use (AU) increased due to uncertainty about the optimal treatment of hospitalized patients with Covid-19. Studies published during year one of the pandemic showed that bacterial co-infections in hospitalized patients were uncommon at the time of presentation. The investigators described rates of antibiotics administered to hospitalized patients, as reported to the NHSN AU Option, to characterize changes in AU during the Covid-19 pandemic.

They analyzed antibiotics administered via oral, parenteral, inhaled, and intramuscular routes. They calculated monthly pooled mean rates as antimicrobial days of therapy (DOT) per 1,000 days present for all antibiotics (combined) reported to the AU Option during the study period. They also reported monthly pooled AU rates for specific antibiotic agents: azithromycin and ceftriaxone because they are commonly used agents for treating CAP and piperacillin with tazobactam because of its broad-spectrum coverage and use in treating hospital-onset infections. They summed the number of new daily cases of Covid-19 in the US, reported by the CDC, to the month-level to highlight changes in Covid-19 case counts during the study period.

The final analysis included 553 acute care hospitals (440 general acute care, 52 critical access, 41 Veterans Affairs, 12 children's, 3 women's, 2 women's and children's, 2 military, 1 oncology). Median hospital bed size was 178 (interquartile range: 80-317), median number of Intensive Care Unit (ICU) beds was 20 (interquartile range: 8-49), 78% of facilities were teaching hospitals and 49% were major teaching hospitals.

Increases in pooled mean rates for total antibiotics, azithromycin, ceftriaxone, and piperacillin/ tazobactam were observed in April 2020, during this first major wave. Compared to April 2019, the total AU rate in April 2020 increased by 7%, azithromycin by 64%, ceftriaxone by 27%, and piperacillin with tazobactam by 5%. Rates of use of azithromycin and ceftriaxone increased during each subsequent rise in Covid-19 cases reported, with larger increases observed in November and December of 2020 and 2021. However, these increases were smaller than those observed in April 2020. Rates of piperacillin/ tazobactam and total antibiotics also increased in December 2021, though rises in use were less pronounced than those reported with ceftriaxone and azithromycin.



Comment: This evaluation of inpatient antimicrobial use in US hospitals showed an increase in total AU and in use of azithromycin, ceftriaxone, and piperacillin with tazobactam in April 2020. This was likely due to diagnostic uncertainty, knowledge gaps, and limited data about risk of secondary bacterial infection during the early months of the Covid-19 pandemic and may also have been impacted by a higher acuity of illness in hospitalized patients early in the pandemic. During early months of the pandemic azithromycin was used because of reports on the potential effectiveness of azithromycin against severe disease early in the pandemic which was later disproven. Though the use of ceftriaxone and azithromycin increased during each subsequent COVID-19 wave, the magnitude was not as large as the initial increase reported during the spring of 2020, despite subsequent COVID-19 waves being considerably larger. This finding was probably due to a combination of factors including increased availability of diagnostic testing, introduction of vaccines and therapeutics for Covid-19, release of clinical treatment guidelines for managing Covid-19, increased studies demonstrating the rarity of bacterial co-infections on hospital admission and focus on antibiotic stewardship efforts.

The use of piperacillin/ tazobactam increased the most during the initial Covid-19 wave and then again during the largest winter 2022 wave. It is likely that the rise in April 2020 was due both to a drop in total days present and a rise in the severity of illness in hospitals, as elective admissions were cancelled leaving a larger proportion of hospitalized patients at relatively higher risk of developing drug-resistant infections and HAIs, which increased during the pandemic. The rise in AU during the winter 2022 surge was mostly likely driven by high rates of hospitalization and secondary infections among patients with Covid-19 as hospital days present were stable during that time.

The AU Option does not collect patient- or encounter-level data; thus Covid-19 burden, rates of co-morbid conditions and co-infections among hospitalized patients, and appropriateness of treatment could not be assessed. Additionally, larger facilities that see more patients and have larger denominators (days present) contributed more data to pooled rates, therefore, larger facilities may be over-represented when reporting the pooled mean metric.

Pediatric Hospitalizations and ICU Admissions Due to COVID-19 and Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2 in England JAMA Pediatr published online July 31, 2023

doi:10.1001/jamapediatrics.2023.2357

The researchers conducted a population-level analysis of hospitalizations after COVID-19 infection in England among youth 0 to 17 years old from February 1, 2020, to January 31, 2022. They linked national hospital data with data on COVID-19 testing, vaccination, PICU admissions, and death.

A total of 10,540 hospitalizations due to COVID-19 and 997 due to MIS-C were identified, with numbers of both declining during the second year of the pandemic. Of 10,540 hospitalized children and adolescents, 4.3% required PICU admission for COVID-19, falling from 9.9% in wild-type cases to 6.1% with Alpha variant infections, 3.4% with Delta, and 1.7% with Omicron.

Overall, 62.1% of hospitalizations for COVID-19 were among children younger than 5 years. The age distribution varied over time, with those aged 0 to 5 making up a higher proportion during Omicron than during previous variants.

Youth from deprived neighborhoods and those who were Asian, Black, or multiracial were overrepresented in hospitalizations throughout the pandemic. Medical comorbidities were noted in 43.9% of children hospitalized with COVID-19, ranging from 29.1% among children younger than 5 to 69.5% among those 12 to 17 years old.

Of children and adolescents with chronic conditions hospitalized with COVID-19, 8.6% required PICU admission, compared with 0.9% in those without comorbidities. PICU admission increased from 3.9% with underlying conditions affecting one body system to 12.2% in those with more chronic conditions and 17.0% for those with life-limiting neurodisabilities. The proportion of children requiring PICU admission fell as the pandemic progressed among those with and without comorbidities.

After adjusting for the presence of any chronic condition, youth aged 5 to 17 years were at significantly greater odds of PICU admission for COVID-19 than those younger than 5, as were children who were Asian, Black, or of unspecified race compared with their White peers.

From May 2021 to January 2022, there were fewer than 20 hospitalizations a month due to MIS-C per 100,000 COVID-19 cases. A total of 61.6% of hospitalizations with MIS-C occurred among boys, 58.5% were among children aged 5 to 11 years, and 29.2% were among those aged 12 to 17. A total of 69.7% of MIS-C hospitalizations occurred among youth with an underlying disease, but a high proportion of these cases may have been acute complications. After excluding hematologic and noncongenital cardiac conditions (common acute manifestations of MIS-C), 35.6% of hospitalized patients had a previous comorbidity. Overall, 54.8% of MIS-C hospitalizations occurred among never-before-hospitalized children. A total of 43.8% MIS-C patients required PICU admission, 46.4% of them aged 12 to 17 and 34.1% younger than 5. This proportion declined over time, from 58.8% during wild-type dominance to 51.8% during Alpha, 45.3% during Delta, and 31.1% amid Omicron. After adjusting for the presence of any comorbidity, girls were linked to a higher likelihood of PICU admission, as were youth aged 12 to 17 years versus those younger than 5 and Asian and White children.

Forty-eight children and adolescents died of COVID-19 within 28 days of hospitalization, but none died of MIS-C (data on MIS-C deaths were available only from November 2020 onward). The risk of severe COVID-19 was tied to underlying medical conditions and neurodisabilities, regardless of variant. Results were similar when the analysis excluded previously infected or vaccinated children.

Comment: In this study of data across the first 2 years of the Covid-19 pandemic, risk of severe disease from SARS-CoV-2 infection in children and adolescents in England remained low. Children and adolescents with multiple medical problems, particularly neurodisability, were at increased risk. In addition, severe illness defined by the need for PICU admission among children hospitalized with Covid-19 declined over the course of the pandemic with PICU admission occurring in nearly 10% of hospitalized pediatric patients during the wild-type period, 3.4% in the Delta period, and 1.7% in the Omicron period. Similar declines in PICU admissions during the Omicron period relative to earlier variants have been reported in the US. [MMWR 2022;71(16):574-581; MMWR; 2022;71(11):429-436] This may be due to increasing immunity and/or milder variants. Although SARS-CoV-2 testing of all emergency hospitalizations was introduced from the end of April 2020, limited testing availability earlier in the pandemic may have affected identification of Covid19 hospitalizations, and children and adolescents with multiple comorbidities may have been more likely to have been tested. They used PICU admission as a proxy for disease severity but did not have data on the level of intensive support required. Their estimate for Covid-19 deaths after hospitalization is likely an overestimate, as we were unable to attribute cause of death in this analysis.

In an editorial, the authors point out what was not measured in this report may represents our greatest challenge: “addressing the decrement in child physical and mental health indirectly related to the Covid-19 pandemic and the resulting mitigation strategies.”

Use of Wastewater Metrics to Track COVID-19 in the US JAMA Netw Open JAMA Network Open. 2023;6(7):e2325591.

doi:10.1001/jamanetworkopen.2023.25591

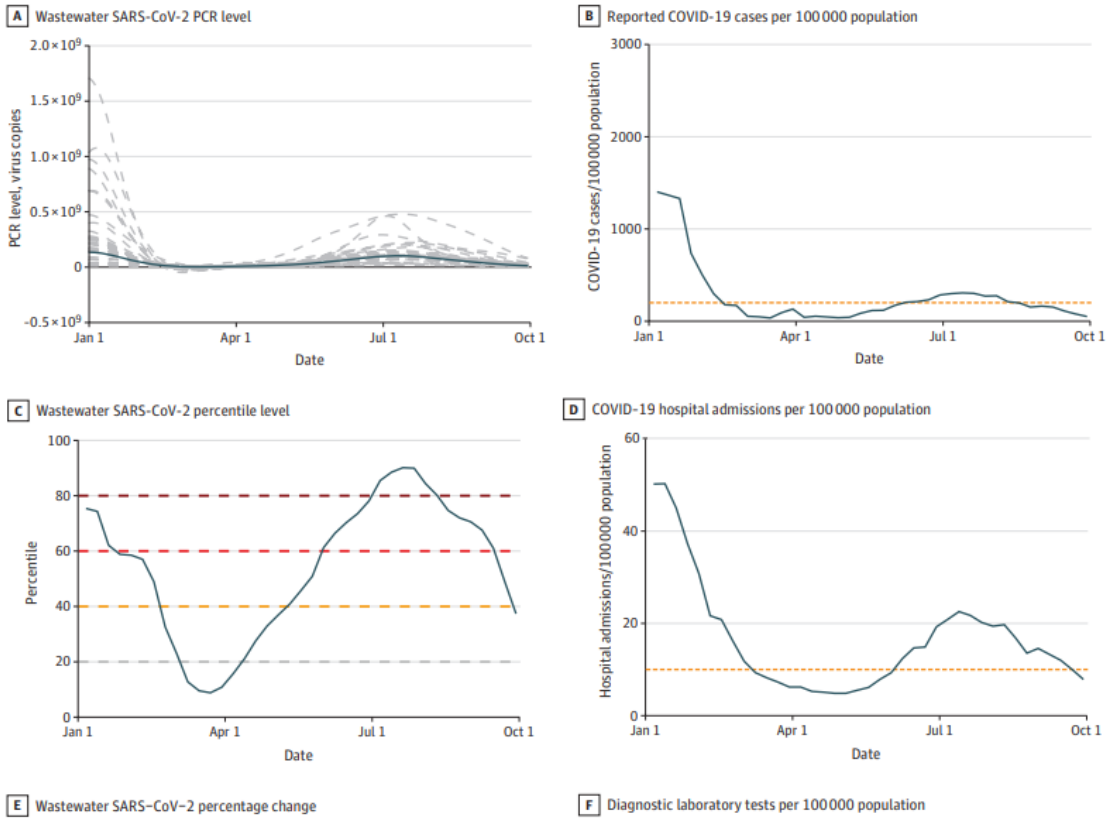
The investigators conducted a time series analysis of wastewater surveillance data from 268 counties in 22 US states from January to September 2022 and offer a strategy for communities to use SARS-CoV-2 wastewater metrics amid declining reliability of conventional surveillance methods. The study period took place during SARS-CoV-2 Omicron variant predominance.

The main study outcomes were county-high COVID-19 cases (at least 200 cases per 100,000 people) and hospitalizations (10 or more per 100,000 2 weeks after case reports) by quarter in 2022. More than 70 countries and 3,500 sites report COVID-19 data to a global dashboard. In the US, most communities with populations of at least 3,000 people that conduct wastewater surveillance report metrics to the CDC's National Wastewater Surveillance System (NWSS).

In the first quarter 2022, use of the wastewater percentile (viral wastewater concentration relative to the county maximum) accurately detected high reported rates of Covid-19 cases (area under the curve [AUC], 0.95) and hospitalization (AUC, 0.86). But the 15-day percentage change in SARS-CoV-2 (percentage change metric) performed less well, with AUCs of 0.51 to 0.57 for new cases and 0.50 to 0.55 for hospitalizations in the first three quarters. The Youden

index score (another measure of test accuracy) for wastewater surveillance of high county incidence was 51% (sensitivity, 0.82; specificity, 0.93), and a model that used both AUC and Youden index scores performed no better than the wastewater percentile alone. The performance of wastewater percentile declined over time for cases in the second quarter (AUC, 0.84; 95% CI, 0.82-0.86) and third quarter (AUC, 0.72; 95% CI, 0.70-0.75) of 2022. The investigators postulated this could be due to case underreporting due to home testing, lower virulence of infection, vaccines and/or natural disease, and treatments.

Figure 3. Time History of Wastewater Surveillance Data and Clinical Case Metrics From Harris County, Texas, January 2022 and September 2022

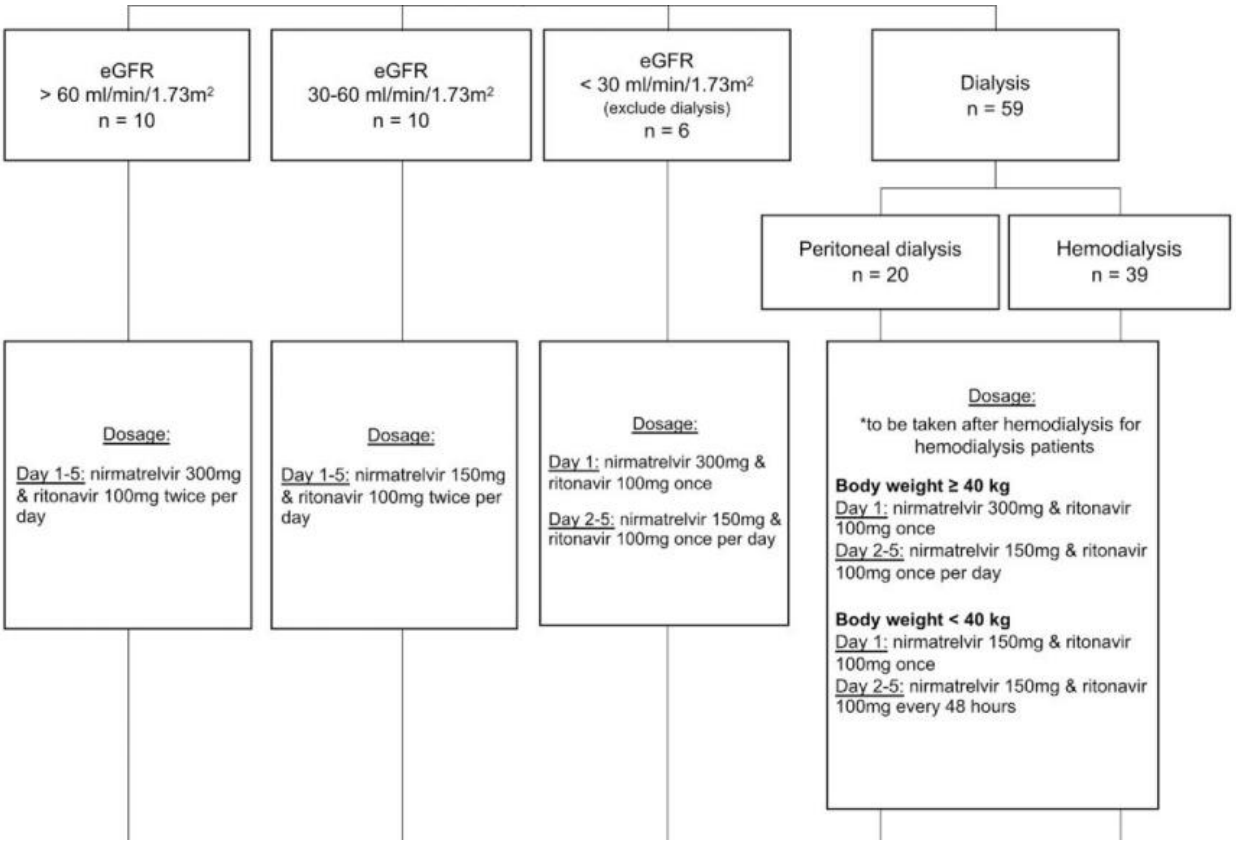


Comment: In this cohort study with a time series analysis of 268 counties in 22 states from January to September 2022, SARS-CoV-2 wastewater metrics accurately reflected high clinical rates of disease early in 2022, but this association declined over time as home testing and vaccination increased. However, these findings suggest that wastewater surveillance can provide an accurate assessment of county SARS-CoV-2 incidence and may be the best metric for monitoring amount of circulating virus as home testing increases and disease acuity decreases because of immunity and treatment. Their analysis is limited by the need to rely on a subset of facilities with sufficient data to not only track back to a true community peak, but also to allow a relatively stable percentile value assigned to an absolute viral concentration over time evaluated metrics available within NWSS, rather than generating de novo metrics using raw or normalized wastewater data. The counties in this wastewater cohort are larger than the average US county.

Safety Profile and Clinical and Virological Outcomes of Nirmatrelvir-Ritonavir Treatment in Patients With Advanced Chronic Kidney Disease and Coronavirus Disease 2019 (COVID-19) Clin Infect Dis published online August 2, 2023

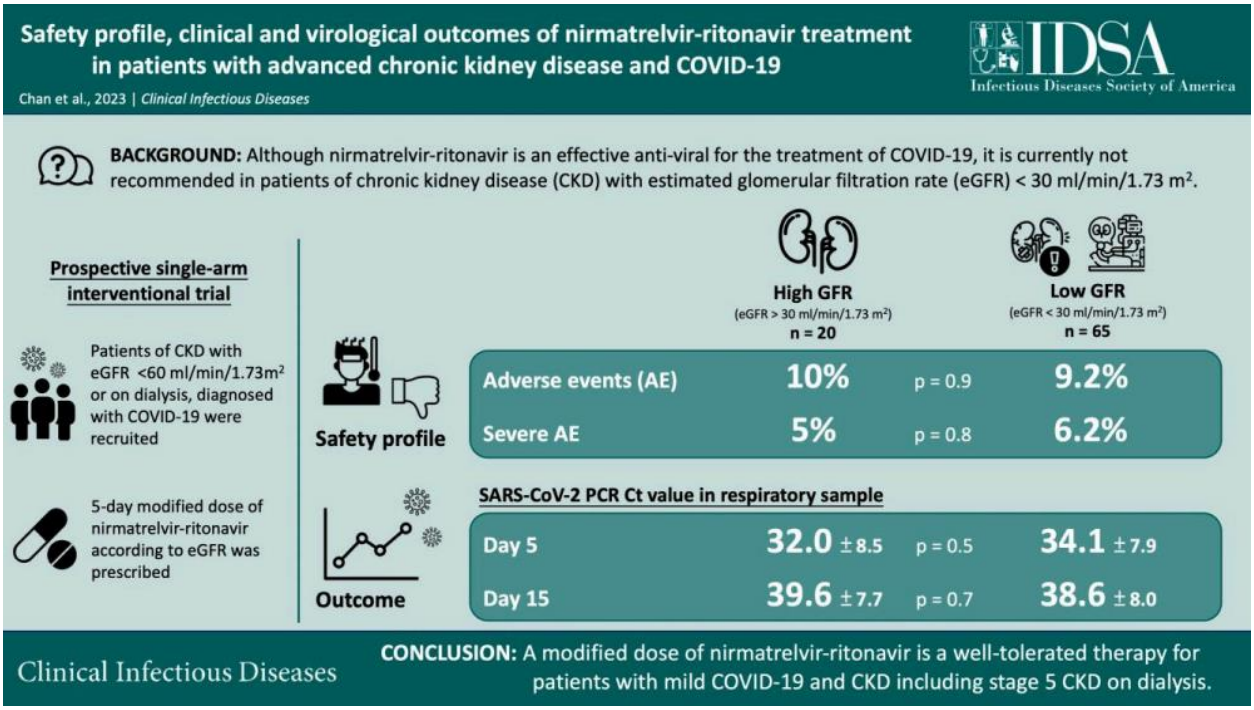
doi.org/10.1093/cid/ciad371

The investigators set out to determine the safety profile and clinical and virological outcomes of nirmatrelvir-ritonavir use at a modified dosage in adults with chronic kidney disease (CKD). This was a prospective, single-arm, interventional trial recruited patients with eGFR < 30 mL/minute/1.73 m2 and on dialysis. Primary outcomes included safety profile, adverse/serious adverse events, and events leading to drug discontinuation. Disease symptoms, virological outcomes by serial SARS-CoV-2 PCR tests, rapid antigen tests, and virological and symptomatic rebound were also recorded. Adut patients with CKD who had Covid-19 infection with symptom onset at less than 5 days were recruited from November 1, 2022 to January 31, 2023. Patients who had severe disease, including patients who require supplemental oxygen therapy, and those with contraindications to nirmatrelvir-ritonavir were excluded. Patients with an eGFR above 60 mL/minute/1.75 m^2 were recruited as controls. The proportions of patients vaccinated with 0, 1, 2, and at least 3 doses of COVID-19 vaccines were 4.7%, 1.2%, 5.9%, and 88.2%, respectively. Fifty-nine patients (69.4%) had stage 5 CKD and were on dialysis. Treatment dose was done per their eGFR calculated by the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation. See below.



Eighty (94.1%) completed the full treatment course; 9.4% and 5.9% had adverse and serious adverse events, and these were comparable between those with eGFR < or >30

mL/minute/1.73 m^2. The viral load significantly decreased on days 5, 15, and 30 ($P < .001$ for all), and the reduction was consistent in the subgroup with eGFR < 30 mL/minute/1.73 m^2. Ten patients had virological rebound, which was transient and asymptomatic. With treatment, the disease symptoms resolved in 18.3 ± 11.1 days, with no difference in resolution time between GFR groups (19.4 ± 11.1 vs 17.9 ± 11.2 days; $P = .7$). 48 (56.5%) and 85 (100%) patients were asymptomatic on day 15 and 30, respectively. With treatment, the participants' rapid Ag tests were negative after a mean period of 5.4 ± 3.3 days. The PCR Ct value increased by 12.2 ± 7.4 to 33.6 ± 8.0 ($P < .001$), when over half of the participants (63.8%) had a PCR Ct value above 30 by day 5.



Comment: Patients with CKD, especially those on dialysis, are at higher risk of severe Covid-19. Antivirals such as nirmatrelvir-ritonavir can effectively prevent disease progression and is the only approved oral antiviral treatment for Covid -19 in some countries. However, most trials have excluded patients with CKD. The present study is the first prospective study to document the safety and virological and clinical outcome in patients with CKD prescribed with a modified dose of nirmatrelvir-ritonavir with Covid-19. They demonstrated that nirmatrelvir-ritonavir can effectively suppress the viral load with a favorable safety profile and low rates of viral and symptom rebound. The sample size is small, and an untreated control group was unavailable for comparison. They also did not analyze the drug level of nirmatrelvir-ritonavir. A recent study that investigated the pharmacokinetics of more frequent dosing of nirmatrelvir/ritonavir in patients undergoing HD found a peak plasma concentration at the higher end of the level. [Antimicrob Agents Chemother 2022; 66: e0122922] Because urinary excretion is the primary excretion route for nirmatrelvir, further dedicated pharmacokinetic studies should be undertaken to explore the optimal dosing to be used in patients at advanced stages of CKD.

Impact of SARS-CoV-2 Prevention Measures on Non-SARS-Cov-2 Hospital-Onset Respiratory Viral Infections: An Incidence Trend Analysis from 2015-2023 Clin Infect Dis published online August 2, 2023

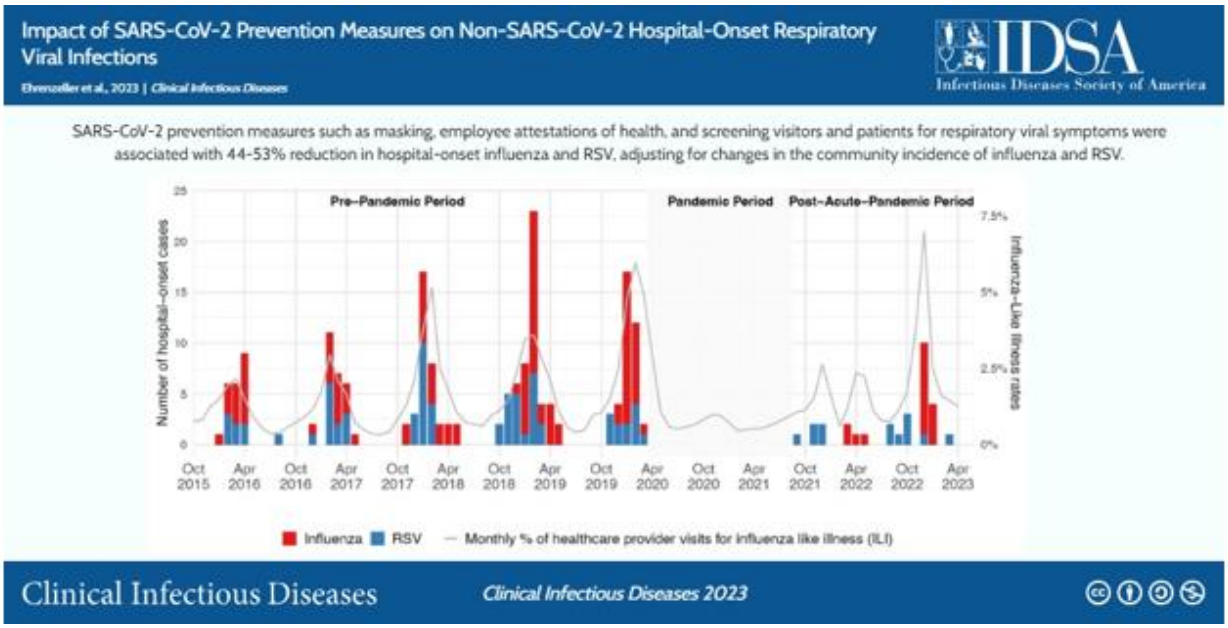
DOI: 10.1093/cid/ciad451

The investigators used data from Brigham and Woman's Hospital, an 803-bed academic hospital in Boston. They assessed monthly counts of patients with incident positive influenza, parainfluenza, adenovirus, human metapneumovirus (HMPV), rhinovirus, and respiratory syncytial virus (RSV) PCR or antigen tests between October 2015 and April 2023. Cases were categorized as community-onset if detected on hospital days 1-3 and hospital-onset (HO) if first detected on hospital day 4 or later.

They calculated the monthly frequency of HO respiratory viral infection per 1,000 admissions. They used an interrupted time-series analysis to assess for changes in the incidence of HO respiratory viral infections following the implementation of infection control measures to reduce in-hospital transmission of SARS-CoV-2 starting in March 2020. Measures included universal masking of patients and providers (with surgical masks), requiring employees to attest to lack of respiratory viral symptoms before each shift, visitor restrictions, and regularly screening patients for new respiratory viral symptoms. Influenza vaccines were required for all employees in all seasons. They limited the statistical assessment for changes in non-SARS-CoV-2 incidence rates to influenza and RSV because access to testing for these pathogens has been stable over time whereas testing for other respiratory viruses (HMPV, rhinovirus, parainfluenza, adenovirus) has increased due to a combination of greater awareness and the introduction of in-house multiplex PCR testing.

The incidence of hospital-acquired respiratory viral infections is closely associated with community incidence rates; they therefore adjusted monthly estimates of hospital-onset influenza and RSV using one of two different measures of community incidence rates: 1) the count of patients admitted with community-onset influenza or RSV, and 2) CDC's weekly estimates of influenza-like-illness (ILI) activity for Massachusetts, expressed as the percentage of healthcare provider visits for ILI. They divided the analysis into three periods: pre-pandemic (October 2015 to March 2020), the intra-pandemic period during which the community incidence of influenza and RSV was near zero (April 2020 to August 2021), and the post-acute-pandemic period when the community incidence of influenza and RSV rose again (September 2021 to April 2023).

Across eight years, they detected 436 HO respiratory viral infections. Most occurred during the fall-winter months of October to March (315/436, 72.2%). HO cases were predominantly attributable to influenza (124/436, 28.4%), RSV (84/436, 19.3%), and rhinovirus (114/436, 26.1%) but HMPV (40/436, 9.2%), parainfluenza (52/436, 11.9%), and adenovirus (22/436, 5.0%) were also detected. The incidence rate was highest in winter 2019/2020 (4.0 cases per 1,000 admissions) and lowest in 2020/2021 (0.55 cases per 1,000 admissions). On average, 14.9% of all respiratory viral infections among hospitalized patients during respiratory viral seasons (October to March) were HO, ranging from 9.8% in 2015/2016 to 20.9% in 2018/2019and 20.2% in 2019/2020.



Comment: This study supports other studies. [Clin Infect Dis 2016; 63: 999-1006; J Hosp Infect 2022; 121: 82-906] This study reports a 44-53% decrease in the incidence of hospital-onset influenza and RSV following implementation of universal masking and other measures but extends the other studies by adjusting for community incidence of respiratory viral infections using two independent measures (influenza-like illness and community-acquired influenza plus RSV hospitalizations). A common finding across all these studies is that masking healthcare workers is associated with reducing nosocomial respiratory viral infections by about half. The investigators only included data from a single hospital and so their results may not be generalizable to other settings or populations. Patients may have been discharged before nosocomial respiratory infection was diagnosed, resulting in under detection of hospital-acquired infections. The threshold for testing for respiratory viruses has likely decreased over time due to greater awareness during the pandemic. Lastly, multiple measures were implemented to control SARS-CoV-2 in the study hospital making it difficult to elucidate which change or changes were most impactful. Questions remain such as what level of community activity would merit going back to universal masking? Should we use N-95 vs surgical masks? Communities should act together to protect our patients and HCWs. See next review.

Assessment of Hospital-Onset SARS-CoV-2 Infection Rates and Testing Practices in the US, 2020-2022 JAMA Network Open. 2023;6(8):e2329441.

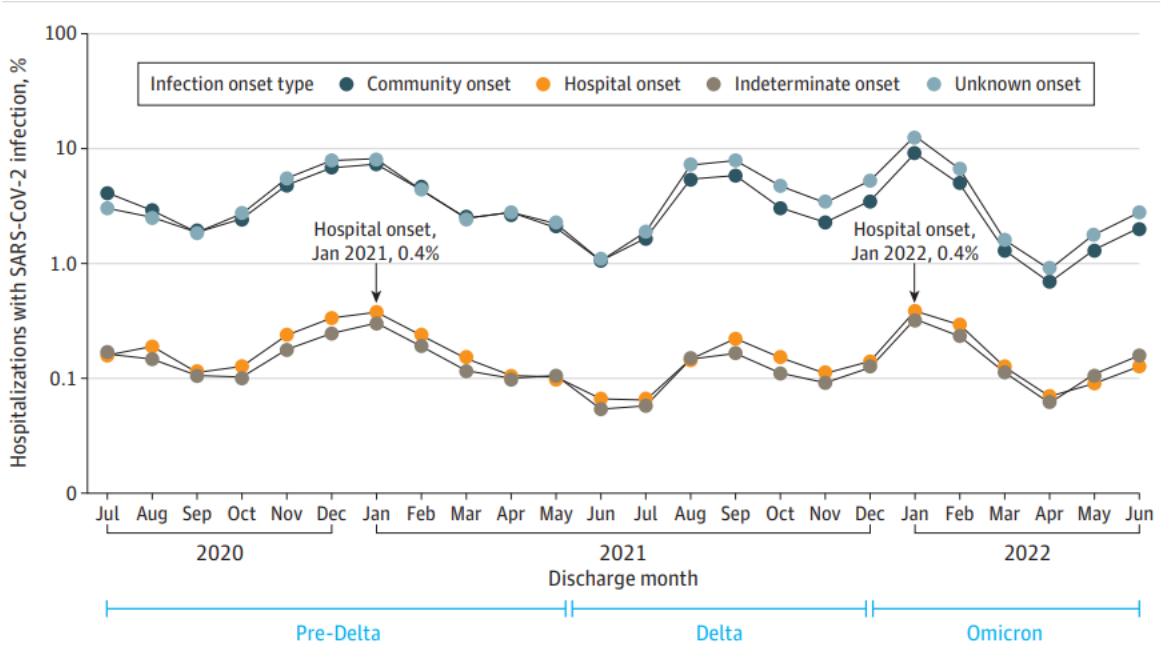
doi:10.1001/jamanetworkopen.2023.29441

This is a cohort study of US hospitals reporting SARS-CoV-2 testing data in the PINC AI Healthcare Database Covid-19 special release files conducted from July 2020 through June 2022. Data were collected from hospitals that reported at least 1 SARS-CoV-2 PCR or antigen

test during hospitalizations discharged that month. For each hospital-month where the hospital reported sufficient data, all hospitalizations discharged in that month were included in the cohort. SARS-CoV-2 viral tests and results reported in the microbiology files for all hospitalizations in the study period by discharge month were identified. Data analysis was conducted from September 2022 to March 2023.

Multivariable generalized estimating equation negative binomial regression models were used to assess associations of monthly rates of hospital-onset SARS-CoV-2 infections per 1000 patient-days (defined as a first positive SARS-CoV-2 test during after hospitalization day 7) with the phase of the pandemic (defined as the predominant SARS-CoV-2 variant in circulation), admission testing rates, and hospital characteristics (hospital bed size, teaching status, urban vs rural designation, Census region, and patient distribution variables).

The study consisted of 288 hospitals. They found that hospital-onset SARS-CoV-2 infections occurred at rates similar to those of other measured health care–associated infections; among 171,564 hospitalizations with a positive SARS-CoV-2 test, 7591 (4.4%) were found to be hospital onset and 6455 (3.8%) were indeterminate onset. In multivariable models, higher hospital-onset infection rates were associated with increases in community-onset SARS-CoV-2 infection rates, period of the COVID-19 pandemic, admission testing rate, Census region, and bed size.



Comment: In this cohort study of hospitals reporting SARS-CoV-2 infections, there was an increase of hospital-onset SARS-CoV-2 infections when community-onset infections were higher, supporting the need for ongoing and enhanced surveillance and prevention efforts to reduce in-hospital transmission of SARS-CoV-2 infections, particularly when community-incidence of SARS-CoV-2 infections is high. Hospital-onset SARS-CoV-2 infection rates were determined using the day of the first positive test. They selected a 7-day cutoff for hospital-onset categorization consistent with various definitions used in other studies, but could not couple it with additional epidemiologic, clinical, or genetic testing information to more accurately ascertain infection onset. This study spanned several different variant predominance periods and phases

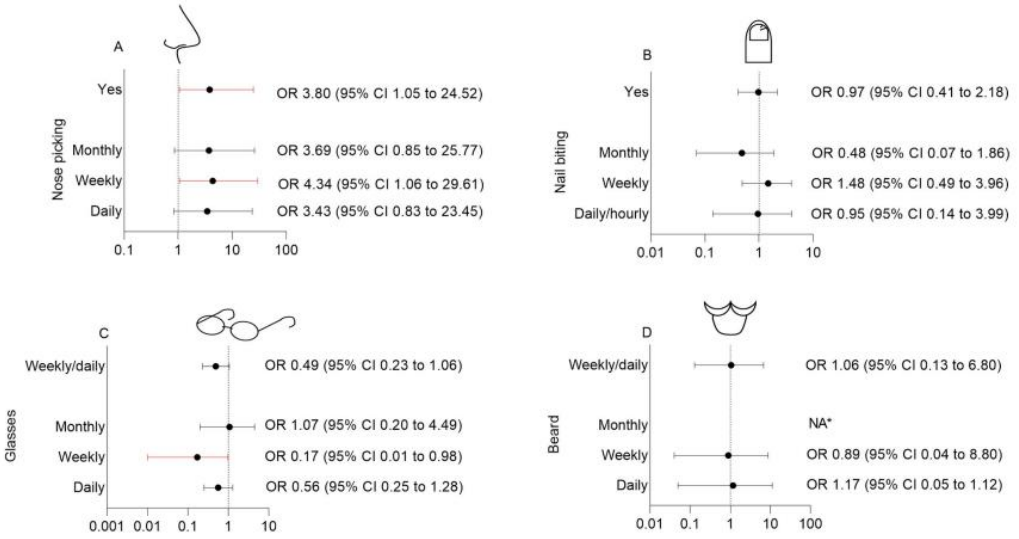
of the pandemic, and therefore, the epidemiologic characteristics of SARS-CoV-2 infections may have changed over the study period. They were unable to combine a measure of community incidence that was independent of hospital testing practice due to a lack of specific information on hospital location in the data set. Their community incidence measure was derived on hospitalized patients only and may not represent the true incidence in the community. Nonetheless, this article and the prior article suggests community level of SARS-CoV-2 correlates with increase of hospital-onset SARS-CoV-2 infections.

Why not to pick your nose: Association between nose picking and SARS-CoV-2 incidence, a cohort study in hospital health care workers PLoS ONE 2023; 18(8): e0288352.

doi.org/10.1371/journal. pone.0288352

The purpose of this analysis was to assess the association between nose picking and related behavioral or physical features (nail biting, wearing glasses, and having a beard) and the incidence of SARS-CoV-2- infection. This was a cohort study among 404 HCW in two university medical centers in the Netherlands. SARS-CoV-2-specific antibodies were prospectively measured during the first phase of the pandemic. For this study HCW received an additional retrospective survey regarding behavioral (e.g., nose picking) and physical features.

In total 219 HCW completed the survey (response rate 52%), and 34/219 (15.5%) became SARS-CoV-2 seropositive during follow-up from March 2020 till October 2020. The majority of HCW (185/219, 84.5%) reported picking their nose at least incidentally, with frequency varying between monthly, weekly and daily. SARS-CoV-2 incidence was higher in nose picking HCW compared to participants who refrained from nose picking (32/185: 17.3% vs. 2/34: 5.9%, OR 3.80, 95% CI 1.05 to 24.52), adjusted for exposure to COVID-19. No association was observed between nail biting, wearing glasses, or having a beard, and the incidence of SARS-CoV-2 infection.



ORs and 95% CI of the association between nose picking, nail biting, wearing glasses or having a beard, and the incidence of SARS-CoV-2

Comment: Surveyed hospital workers who admitted to picking their nose were three to four times more likely to wind up having a COVID infection, and the prevalent habit may be an underrecognized source of spread. The viral load in the nasal mucosa is high in the days after contracting SARS-CoV-2 and before the onset of symptoms including patients that remain asymptomatic. Nose pickers tended to be younger (mean age 44 vs 53 years for non-pickers) and were more likely to be men (90% vs 83%), with doctors being the worst offenders. Concern around glasses and beards involves the potential for less-than-ideal fitting PPE, though glasses, if anything, seemed potentially protective in the study (OR 0.49, 95% CI 0.23-1.06); prior studies have shown conflicting results as to whether eyewear confers protection against infection. This study was done pre-Omicron and pre-vaccine availability and therefore might not be generalizable to the current circulating variants or to the vaccine era. Another limitation involved the survey timing -- as it was conducted retrospectively, it may have introduced recall bias.

Vaccine-induced and hybrid immunity to SARS-CoV-2 after three or four doses of BNT162b2 - results from 22 months follow-up of a healthcare workers cohort, Israel, 2020-2022 Int J Infect Dis published online August 16, 2023

doi.org/10.1016/j.ijid.2023.08.009

The investigators periodically measured anti-spike SARS-CoV-2 IgG titers using a quantitative assay in an Israeli healthcare worker cohort who all received at least two Pfizer (BNT162b2) doses and either received further doses and/or were subsequently infected, up to 22 months post-dose two, and compared geometric mean concentrations according to number of doses received and infection status. To determine pre-vaccination infection status, they measured anti-Nucleocapsid (N) immunoglobulin G (IgG) antibodies prior to initiating vaccination among all consenting participants, using a SARS-CoV-2 IgG qualitative assay. Following the initiation of vaccination, they measured anti-SARS-CoV-2 Spike (S) IgG levels in participants every two-four months using the quantitative LIAISON Diasorin SARS-CoV-2 S1/S2 IgG assay. The assay is able to detect vaccine and virus induced anti-spike IgG antibodies, with comparable performance for measuring antibodies induced by the Omicron and wild-type strains. They included in their final analysis all participants who received at least two vaccine doses and either received further doses or, in order to compare vaccine-induced with infection-induced immunogenicity, were infected in the same time intervals they would have received subsequent doses, so that the time interval between doses were comparable to the time intervals between vaccination and infection. Participants who were unvaccinated, only received a single vaccine dose, or were infected outside of the time intervals of interest, were not included in the final analysis. Workers had their anti-S IgG levels checked up to 12 times between December 2020 and September 2022. They measured immunogenicity at nine time points starting 150 days after receipt of the second dose, just prior to receipt of the third dose: t_1: 150 days (range 121-180 days), t_2: 210 days (range 181-240); t3 270 days (range 241-300); t4 330 days (range 301-360); t5 390 days (range 361- 420); t6 450 days (range 421-480); t7 510 days (range 481-540); t8 570 days (range 541-600) and t9 630 days (range 601-660. HCWs were followed up to 14 months post dose three and up to eight months post dose four. HCWs were tested by PCR upon clinical suspicion of Covid-19 illness, with a low threshold for testing. Individuals with a positive PCR test were classified as infected post-vaccination (breakthrough infection). They also regularly asked workers about previously known SARS-CoV-2 infections, and measured

anti-Nucleocapsid (N) immunoglobulin G (IgG) antibodies among workers with unexplained rises in anti-S IgG titers.

Of 1,020 participants, 27 were unvaccinated and therefore excluded. Among the remaining 993 participants, median age was 43 years old (range 18-78) and 618 (62%) were female. Participants who received four vaccine doses were older and less likely to be female than other participants. The majority of workers (619, 62%) were triply vaccinated; 156 (16%) received two doses, 141 (14%) four doses and 77 (8%) a single dose, of which 70 were vaccinated after being infected. Of the 993 workers included in the study, 465 (47%) had evidence of infection, of which 119 were infected before vaccination and 346 after. The proportion of workers who were infected after their last dose (breakthrough infection) was not significantly different according to number of doses received (p=0.53). However, the proportion of re-infections decreased with the number of doses: while 32.4% of workers who had received a single dose of vaccine were infected more than once, the proportion fell to 1.4% among those who received four doses (p<0.001). Although natural infection after two doses of vaccine led to a higher IgG rise than the receipt of a third dose, nine months post-dose three or infection, there was no significant difference in GMC between those vaccinated with three doses and those infected six-eight months post dose two (931 vs 1158 AU/ml, p=0.8). The mean time interval between the third and fourth dose was 145 days. Receipt of a fourth dose among uninfected participants led to more than three-fold increase in anti-S IgG one-two months after dose four. Those who received three doses and were infected during the same time interval following dose three (four-six months post-dose three) had similar Ab levels one-two months post infection compared with uninfected, quadruply vaccinated individuals one-two months post dose four. (2804 vs 3131, p=0.5).

Comment: The long-follow up time in this HCW cohort and the large number of combinations in terms of number of vaccine doses received and timing of infection history, provided an opportunity to compare vaccine-induced and hybrid immunity up to almost two years after the initiation of Pfizer vaccine courses. Their data suggest that vaccination with at least three doses of vaccine or hybrid immunity with at least two doses of vaccine and a subsequent infection leads to long-term high circulating IgG antibody levels. Although the investigators were as sensitive as possible regarding ascertaining COVID-19 status and tested participants with a low threshold for suspicion, they could not completely eliminate misclassification in the case of infected individuals who were completely asymptomatic and never underwent a test. This study measured circulating anti-S IgG titers but they have not measured the response to different antigens and variants nor binding avidity/ neutralization. Antibody studies need to be complemented by functional and cellular immunity assays (B and T cell) to fully understand the adaptive immune response to SARS-CoV-2 infection and the impact of waning immunity. Nonetheless, 3-4 vaccine doses or 2 doses+infection(hybrid) provide similar long-term immunogenicity. Unfortunately, the CDC has never addressed the concept of hybrid immunity in their vaccine guidance.

UK releases recommendations for fall COVID boosters

In its announcement today, the UK's Joint Committee on Vaccination and Immunization (JCVI) detailed the people who will be eligible to receive the vaccine in the fall—those most likely to

benefit from vaccination. Aside from those ages 65 and older, the list includes people in nursing facilities and their caregivers, people ages 6 months to 64 who are in clinical risk groups (see below), people ages 12 to 64 who are family contacts of immunocompromised people, and frontline health and social care workers.

Table 3: Clinical risk groups for individuals aged 16 years and over.

Clinical risk groups	
Chronic respiratory disease	Individuals with a severe lung condition, including those with poorly controlled asthma[1] and chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema; bronchiectasis, cystic fibrosis, interstitial lung fibrosis, pneumoconiosis and bronchopulmonary dysplasia (BPD).
Chronic heart disease and vascular disease	Congenital heart disease, hypertension with cardiac complications, chronic heart failure, individuals requiring regular medication and/or follow-up for ischaemic heart disease. This includes individuals with atrial fibrillation, peripheral vascular disease or a history of venous thromboembolism.
Chronic kidney disease	Chronic kidney disease at stage 3, 4 or 5, chronic kidney failure, nephrotic syndrome, kidney transplantation.
Chronic liver disease	Cirrhosis, biliary atresia, chronic hepatitis.
Chronic neurological disease	Stroke, transient ischaemic attack (TIA). Conditions in which respiratory function may be compromised due to neurological or neuromuscular disease (e.g. polio syndrome sufferers). This group also includes individuals with cerebral palsy, severe or profound and multiple learning disabilities (PMLD) including all those on the learning disability register, Down's syndrome, multiple sclerosis, epilepsy, dementia, Parkinson's disease, motor neurone disease and related or similar conditions; or hereditary and degenerative disease of the nervous system or muscles; or severe neurological disability.
Diabetes mellitus and other endocrine disorders	Any diabetes, including diet-controlled diabetes, current gestational diabetes, and Addison's disease.
Immunosuppression	Immunosuppression due to disease or treatment, including patients undergoing chemotherapy leading to immunosuppression, patients undergoing radical radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients, HIV infection at all stages, multiple myeloma or genetic disorders affecting the immune system (e.g. IRAK-4, NEMO, complement disorder, SCID). Individuals who are receiving immunosuppressive or immunomodulating biological therapy including, but not limited to, anti-TNF, alemtuzumab, ofatumumab, rituximab, patients receiving protein kinase inhibitors or PARP inhibitors, and individuals treated with steroid sparing agents such as cyclophosphamide and mycophenolate mofetil. Individuals treated with or likely to be treated with systemic steroids for more than a month at a dose equivalent to prednisolone at 20mg or more per day for adults. Anyone with a history of haematological malignancy, including leukaemia, lymphoma, and myeloma. Those who require long term immunosuppressive treatment for conditions including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, scleroderma and psoriasis.

1 Poorly controlled asthma is defined as:
- ≥2 courses of oral corticosteroids in the preceding 24 months OR
- on maintenance oral corticosteroids OR
- ≥1 hospital admission for asthma in the preceding 24 months

	Some immunosuppressed patients may have a suboptimal immunological response to the vaccine (see Immunosuppression and HIV).
Asplenia or dysfunction of the spleen	This also includes conditions that may lead to splenic dysfunction, such as homozygous sickle cell disease, thalassemia major and coeliac syndrome.
Morbid obesity	Adults with a Body Mass Index (BMI) ≥40 kg/m².
Severe mental illness	Individuals with schizophrenia or bipolar disorder, or any mental illness that causes severe functional impairment.
Younger adults in long-stay nursing and residential care settings	Many younger adults in residential care settings will be eligible for vaccination because they fall into one of the clinical risk groups above (for example learning disabilities). Given the likely high risk of exposure in these settings, where a high proportion of the population would be considered eligible, vaccination of the whole resident population is recommended. Younger residents in care homes for the elderly will be at high risk of exposure, and although they may be at lower risk of mortality than older residents should not be excluded from vaccination programmes (see priority 1 above).
Pregnancy	All stages (first, second and third trimesters)

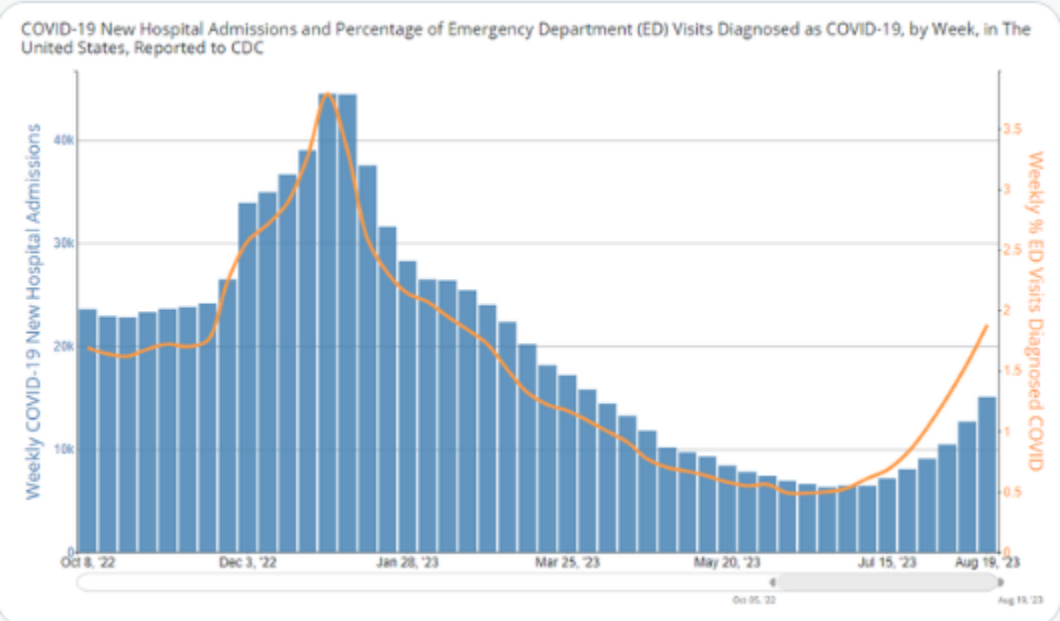
Table 4: Clinical risk groups for individuals aged under 16 years

Chronic respiratory disease	Including those with poorly controlled asthma[1] that requires continuous or repeated use of systemic steroids or with previous exacerbations requiring hospital admission, cystic fibrosis, ciliary dyskinesias and bronchopulmonary dysplasia
Chronic heart conditions	Haemodynamically significant congenital and acquired heart disease, or less severe heart disease with other co-morbidity. This includes: • single ventricle patients or those palliated with a Fontan (Total Cavopulmonary Connection) circulation • those with chronic cyanosis (oxygen saturations <85% persistently) • patients with cardiomyopathy requiring medication • patients with congenital heart disease on medication to improve heart function • patients with pulmonary hypertension (high blood pressure in the lungs) requiring medication
Chronic conditions of the kidney, liver or digestive system	Including those associated with congenital malformations of the organs, metabolic disorders and neoplasms, and conditions such as severe gastro-oesophageal reflux that may predispose to respiratory infection
Chronic neurological disease	This includes those with • neuro-disability and/or neuromuscular disease that may occur as a result of conditions such as cerebral palsy, autism, epilepsy and muscular dystrophy • hereditary and degenerative disease of the nervous system or muscles, other conditions associated with hypoventilation • severe or profound and multiple learning disabilities (PMLD), Down's syndrome, including all those on the learning disability register • neoplasm of the brain
Endocrine disorders	Including diabetes mellitus, Addison's and hypopituitary syndrome
Immunosuppression	Immunosuppression due to disease or treatment, including: • those undergoing chemotherapy or radiotherapy, solid organ transplant recipients, bone marrow or stem cell transplant recipients • genetic disorders affecting the immune system (e.g. deficiencies of IRAK-4 or NEMO, complement disorder, SCID) • those with haematological malignancy, including leukaemia and lymphoma • those receiving immunosuppressive or immunomodulating biological therapy • those treated with or likely to be treated with high or moderate dose corticosteroids • those receiving any dose of non-biological oral immune modulating drugs e.g. methotrexate, azathioprine, 6-mercaptopurine or mycophenolate • those with auto-immune diseases who may require long term immunosuppressive treatments Children who are about to receive planned immunosuppressive therapy should be considered for vaccination prior to commencing therapy.
Asplenia or dysfunction of the spleen	Including hereditary spherocytosis, homozygous sickle cell disease and thalassemia major
Serious genetic abnormalities that affect a number of systems	Including mitochondrial disease and chromosomal abnormalities
Pregnancy	All stages (first, second and third trimesters)

Comment: In the US, the FDA in the middle of June recommended a switch to a monovalent XBB.1.5 vaccine for fall immunization. Health officials are awaiting official recommendations from the FDA and CDC. The FDA will meet September 12th. Vaccine is expected to be available mid-September. I am unsure why the FDA and CDC have waited so long.

I believe President Biden misspoke earlier this week when declared that a new Covid booster shot "works" and is "necessary." He said he would ask Congress to fund it and "it will likely be recommended that everybody get it no matter whether they've gotten it before." [see UK recommendations] It is unclear what the predominant variant will be this winter. Pfizer, Moderna, and Novavax said their new boosters work on the two dominant variants in circulation today, EG.5 and FL.1.51. I think the UK recommendations are well thought out and should be a guide for the FDA and CDC.

COVID-19 by the Numbers



Total Hospitalizations 6,272,227

+18.8% in most recent week

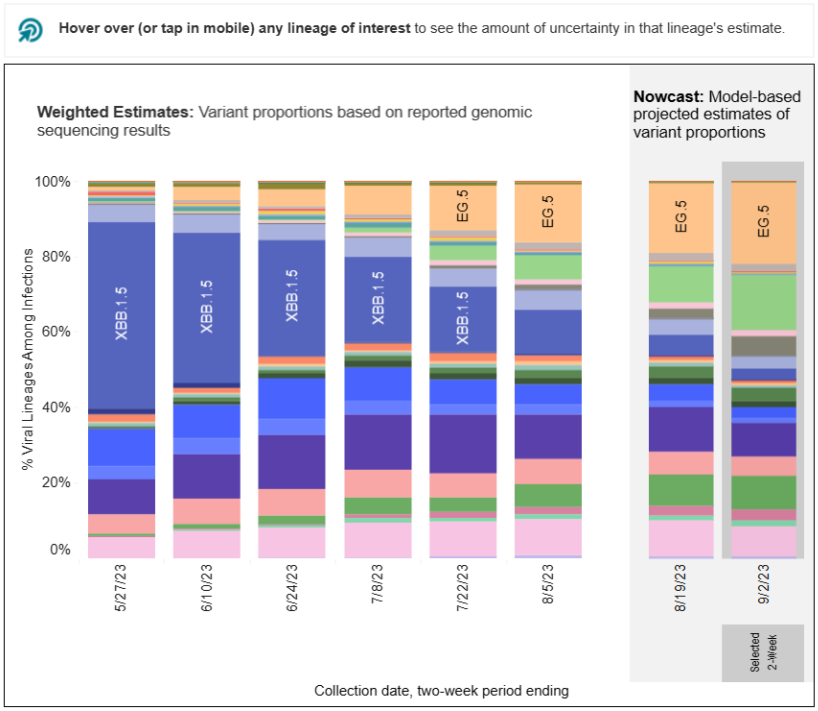
Trend in Hospital Admissions

Total Deaths 1,139,457

+17.6% in most recent week

Trend in % COVID-19 Deaths

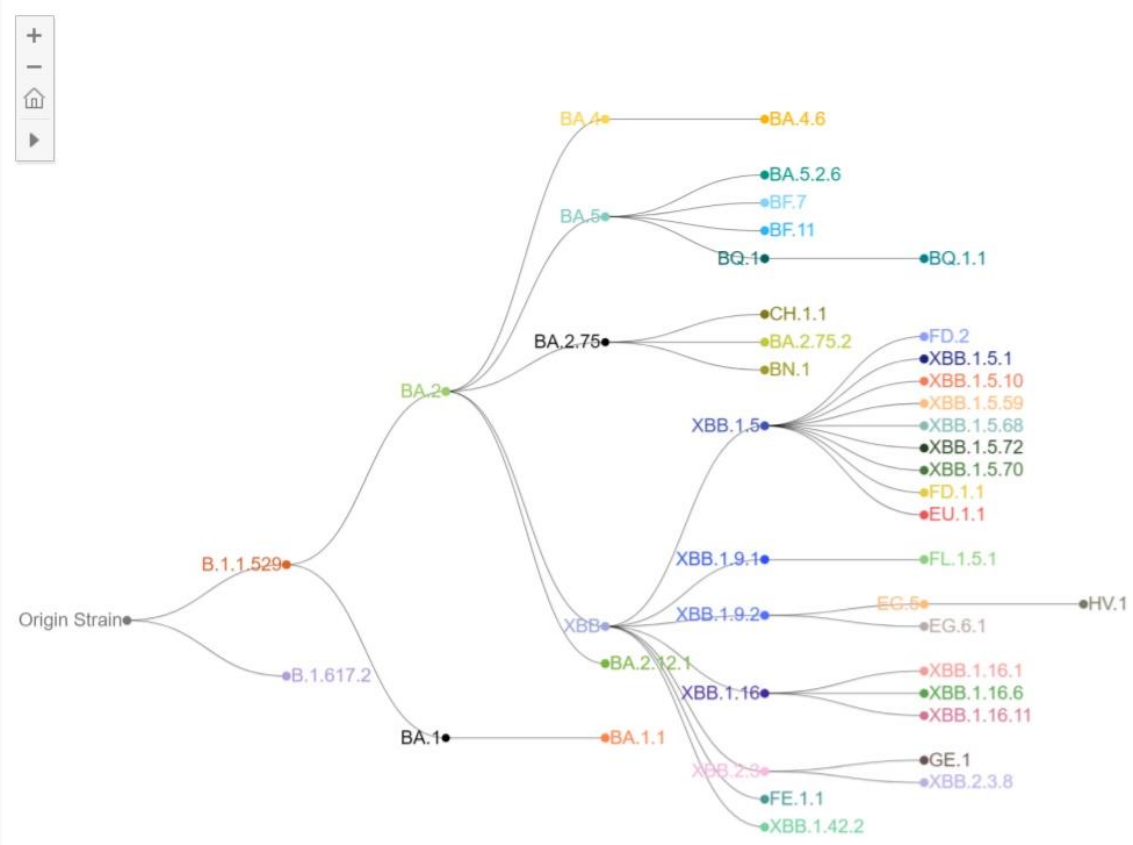
Weighted and Nowcast Estimates in United States for 2-Week Periods in 5/14/2023 – 9/2/2023



Nowcast Estimates in United States for 8/20/2023 – 9/2/2023

USA

WHO label	Lineage #	%Total	95%PI
Omicron	EG.5	21.5%	19.0-24.3%
	FL.1.5.1	14.5%	10.5-19.6%
	XBB.1.16.6	9.2%	7.6-11.0%
	XBB.1.16	8.9%	7.8-10.3%
	XBB.2.3	8.1%	7.0-9.2%
	HV.1	5.1%	3.3-7.9%
	XBB.1.16.1	5.0%	4.2-6.0%
	XBB.1.5.70	3.5%	2.6-4.7%
	XBB	3.3%	2.7-4.1%
	XBB.1.5	3.1%	2.6-3.7%
	XBB.1.9.1	3.0%	2.5-3.5%
	XBB.1.16.11	2.8%	1.8-4.5%
	EG.6.1	1.8%	1.2-2.7%
	GE.1	1.6%	1.1-2.4%
	XBB.1.5.72	1.6%	1.2-2.1%
	XBB.1.42.2	1.3%	0.7-2.3%
	XBB.1.9.2	1.1%	0.9-1.3%
	XBB.1.5.10	0.9%	0.7-1.2%
	XBB.1.5.68	0.8%	0.5-1.1%
	XBB.2.3.8	0.7%	0.4-1.2%
	FD.1.1	0.6%	0.4-0.8%
	FE.1.1	0.5%	0.3-0.8%
	XBB.1.5.59	0.4%	0.3-0.6%
	CH.1.1	0.4%	0.3-0.6%
	EU.1.1	0.1%	0.1-0.2%
	XBB.1.5.1	0.0%	0.0-0.1%
	BA.2.12.1	0.0%	0.0-0.1%
	BA.5	0.0%	0.0-0.0%
	BQ.1	0.0%	0.0-0.0%
	FD.2	0.0%	0.0-0.0%
	B.1.1.529	0.0%	0.0-0.1%
Other	Other*	0.0%	0.0-0.1%



CDC/WHO Tracking New BA.2.86 Variant Of COVID-19

The CDC is now tracking a new, highly mutated lineage of the virus that causes Covid-19. The strain is named BA.2.86, and has been detected in the US, Denmark, UK, Switzerland, and Israel. Last week the WHO has classified BA.2.86 as a 'variant under monitoring' due to the large number of mutations it carries."

The UK Health Security Agency (HSA) recently posted an initial risk assessment of the BA.2.86 Omicron subvariant, which said the rapid appearance in multiple countries in people without travel histories suggests established international transmission.

The newly identified variant has many genetic mutations and is distant from BA.2,[see above] its likely ancestor, and currently circulating XBB variants. The similarity of the sequences so far—six samples from four countries—suggests relatively recent emergence and rapid growth, but the HSA said it has low confidence in that assessment, pending the examination of further sequences.

Though predictions of the combined effect of such a large number of mutations would be unreliable now, there is enough information to expect antigenic change. The HSA also said there are mutations in the spike protein that may be associated with changes in other viral properties.

It's not possible to gauge severity based on the sample from the UK patient, but the HSA said it would share data from surveillance systems, estimates of growth rates, and virus characterization when available.

Comment: The US has already reported at least four more detections over the past few weeks. Last week the WHO added BA.2.86 to its list of variants under monitoring owing to its many mutations and detections across multiple world regions. The CDC said today that the number of genetic changes is roughly of the same magnitude as seen between the original Omicron variant and earlier variants such as Delta. One concern is whether the new virus can escape existing immunity from earlier infection or vaccination, given its large number of mutations. The CDC said so far there aren't enough virus samples for lab testing of antibodies, so it's too soon to know the real-world impacts, though most people will probably have some protection against severe disease. "This is an area of ongoing scientific investigation," the agency said.

The mutation profile suggests that treatments such as Paxlovid will be effective against the variant and that there will be little impact on the accuracy of molecular and antigen-based tests. As the US and other countries track the heavily mutated BA.2.86 variant, newer Omicron variants such as EG.5 and FL.1.5.1 are rising in proportion alongside slowly rising Covid-19 indicators, including in the US. See next review.

Risk Assessment Summary for SARS CoV-2 Sublineage BA.2.86 August 23, 2023

Based on what CDC knows now, existing tests used to detect, and medications used to treat Covid-19 appear to be effective with this variant. BA.2.86 may be more capable of causing infection in people who have previously had Covid-19 or who have received Covid-19 vaccines. Scientists are evaluating the effectiveness of the forthcoming, updated Covid-19 vaccine. CDC's current assessment is that the updated vaccine will be effective at reducing severe disease and hospitalization. At this point, there is no evidence that this variant is causing more severe illness. That assessment may change as additional scientific data are developed. CDC will share more as we know more.

The CDC Wednesday updated its initial assessment of the highly mutated BA.2.86 SARS-CoV-2 variant, which said sporadic detections continue to be reported at the global level, including in the US, where it has been picked up by at least three different genomic monitoring systems. The CDC said BA.2.86 made up less than 1% of circulating viruses over the past 2 weeks in the US [see above] and emphasized that the country's rise in Covid-19 hospitalizations is likely fueled by XBB viruses (EG.5 and FL.1.5.1) that are similar to the lineage included in the updated vaccine.

In other new developments, France and Scotland reported their first detections, and additional sequences were reported from South Africa and the US. The virus has been detected in either patient samples or wastewater from four states: Michigan, Virginia, Ohio, Texas and New York.

Comment: CDC Recommends

- Get your Covid-19 vaccines, as recommended
- Stay home if you are sick
- Get tested for COVID-19 if needed
- Seek treatment early if you have Covid-19 and are at high risk for severe disease
- If you choose to wear a mask, wear a high-quality one that fits well over your nose and mouth
- Improve ventilation
- Wash your hands

The big question remains will BA.2.86 continue to increase, and if so, what is its transmissibility and how easily will it evade immunity from earlier infection and vaccination. In my opinion, BA.2.86 is unlikely to cause a devastating surge of severe disease and death we have seen in the past given the high worldwide immunity from vaccination and/or prior infection, but we will likely see increased infections and hospitalizations. We still need to protect our most vulnerable. Let us not forget vaccinations against influenza and RSV for eligible persons as we approach the respiratory virus season.