Infectious Diseases Watch

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General Infectious Diseases

Complexity of Infectious Diseases Compared to Other Cognitive Medical Subspecialties

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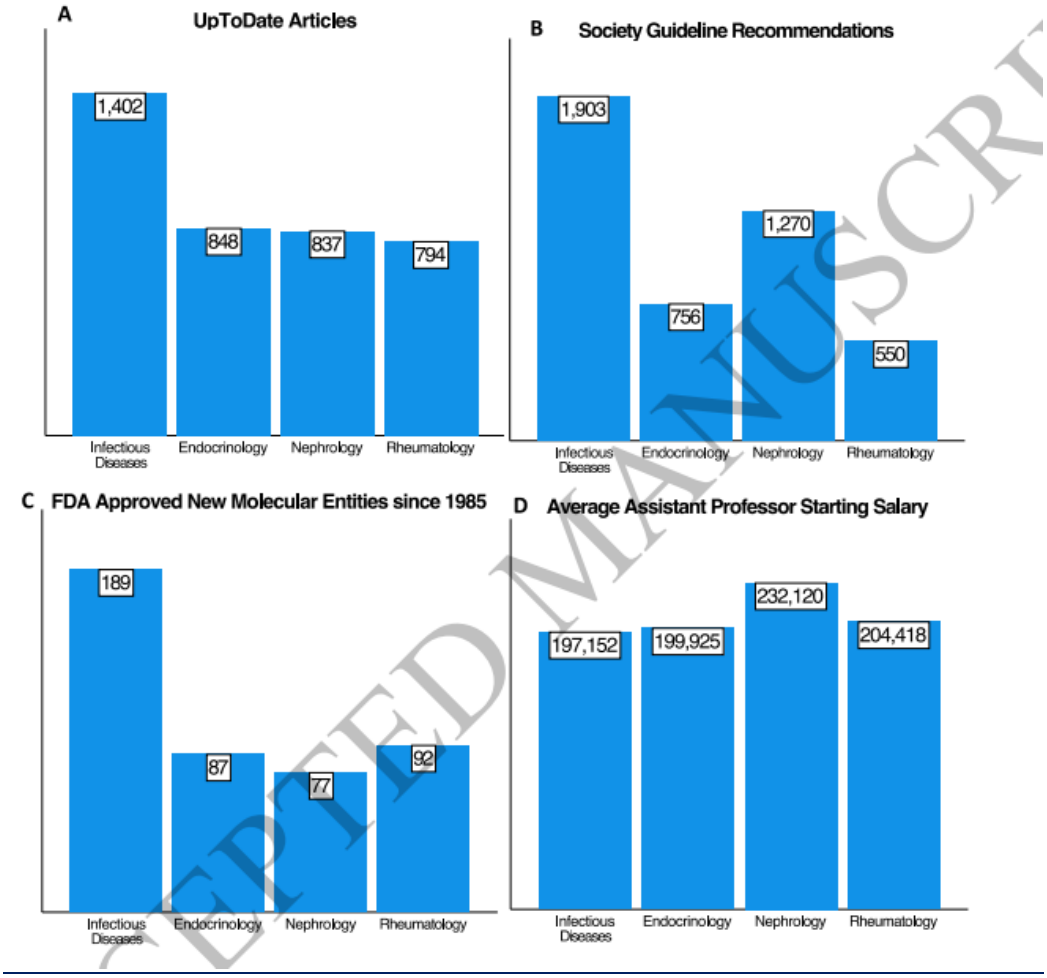
The authors sought to compare the field of Infectious Diseases (ID) with endocrinology, nephrology, and rheumatology using available metrics. They chose to compare these other specialties because they are also primarily cognitive specialties without procedures and similar in size to ID.

Since Up To Date is the most widely used clinical resource, they reviewed its Infectious Disease content. Up To Date is organized into specialties, sections, subsections, and articles. They examined the number of articles across the four specialties. This revealed that ID contained between 65 and 77% more articles than those of the other 3 specialties (n=1402 articles vs. 794 to 848 articles). Likewise, professional societies produce practice guidelines which establish standards of care. Each guideline is distilled into evidence based and graded recommendations. The authors enumerated the number of recommendations from active guidelines. This revealed that the Infectious Diseases Society of America (IDSA) guidelines (n=1903 recommendations) contained between 50 and 346% more recommendations than those of the Endocrine Society, the kidney disease - Improving Global Outcomes (KDIGO), and the American College of Rheumatology. They also noted that the complexity of many guidelines has increased with time. Lastly, they reviewed the new molecular entities or drugs approved by the FDA and assigned them to specialties based on their initial approved indication. Of 1199 new entities approved by the FDA from 1985 through 2021, 189 (16%) have an infectious diseases indication, substantially more than the number ascribable to endocrinology, nephrology, or rheumatology.



Comment: First the authors concede that the specialties of endocrinology, nephrology, and rheumatology are also not always simple. Their knowledge bases are also large, and we all take care of patients with complicated disease processes and comorbidities. Rather, their argument is that the knowledge base required of the ID physician is increasingly complex especially during the pandemic and beyond. ID is primarily hospital based. The complexity of ID clinical decision-making is not adequately appreciated or compensated by payers. The physician work RVU is supposed to reflect the time and intensity associated with furnishing a service, however there is no additional intensity that can be assigned because of the complexity of our field or decision-making. IDSA is aware of this and has authored letters to Congress stating that ID reimbursement does not adequately reflect the value and complexity of care provided by ID clinicians. Despite their efforts in the CMS proposed update in compensation **ID physicians will face a 2.25% reduction in reimbursement**! I hope data such as presented in this paper can be used to advocate for the complexity of ID decision-making and enhanced compensation. While the complexity of the field of infectious diseases may be appealing for some of us that entered the specialty, it may present an unattractive lifestyle choice for others, particularly when coupled with the low compensation of the field. Difficulty in mastering a field and low compensation have been noted as a reason for declining interest in ID. New trainees are looking for a more balanced lifestyle. Lastly, they point out ID divisions and subspecialty groups may need to evolve. It has become harder for the general ID specialist to stay abreast of

the latest information and evidence in all areas. Large infectious disease groups and divisions may need to further develop subspecialties within ID for optimal clinical care. Transplant ID and HIV are examples.

One additional fact is that multiple studies demonstrate that ID consults improve patient outcomes from S aureus BSIs, fungemia, and now gram-negative BSIs. (see next review). ID brings additional value to hospitals in supporting antimicrobial stewardship and infection prevention, some are compensated but at very low rates.

ID Watch has reported on the future challenges to ID as baby boomers retire. We need more ID physicians, especially with the growing complexity in our field. Unfortunately, we are not filling our fellowship slot which will likely continue to deteriorate without significant structural reform.

Infectious Diseases Consultation Associated With Reduced Mortality in Gram-Negative Bacteremia Clin Infect Dis published online July 4, 2023

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This is a large, multi-center retrospective observational cohort study involving 24 hospitals in the US (16 academic medical centers, 4 community hospitals, and 4 Veterans Affairs medical centers). All sites had active ASP with physician and pharmacy leadership. No site had mandatory ID consult (IDC) for GN-BSI, and sites varied in their GN-BSI epidemiology, stewardship interventions for positive blood cultures, and available guidelines for GN-BSI. Inclusion criteria consisted of all adult patients admitted to the hospital from January 2019 to December 2019 with GN-BSI, including both Enterobacterales and non-fermenting gram-negative organisms. Patients who died <48 hours were excluded from analysis. Manual chart review was conducted at each institution by personnel on site and data were entered into a standardized RedCap database. The primary exposure was IDC versus no IDC, determined by the presence of an IDC note that addressed GN-BSI management. Other data were collected to encompass clinical, host, infection, source, and organism variables. The primary outcome was 30-day mortality, defined as death from any cause documented in the electronic medical record. Secondary outcomes included 30-day readmission due to the index infection, 30-day bacteremia recurrence with the same bacterial species, and 90-day mortality. Inverse Probability of Treatment Weighting Propensity-score (PS) analysis was carried out to balance the IDC versus no IDC groups. Variables included were age ≥65 years, gender, race, comorbidities (congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, COPD, moderate or severe liver disease, diabetes, chronic kidney disease [CKD], renal replacement therapy, autoimmune conditions, malignancy and active chemotherapy, AIDS, solid organ transplant, bone marrow transplant, neutropenia), Charlson Comorbidity Index, body mass index (BMI) ≥30, Pitt bacteremia score ≥4, intensive care unit admission, Pseudomonas aeruginosa infection, multi-drug resistant organism, source of bacteremia, and achievement of source control.

There were 4861 GN-BSI episodes of which 2814 (58%) had IDC. In total, 155 (3.1%) episodes were excluded due to death <48 hours. Overall, there were 681 (14%) GN-BSI episodes that resulted in 30-day mortality (12% vs 17% in IDC and no IDC, respectively). Patients who received an IDC had a significantly decreased risk of 30-day mortality after weighting (HR 0.60, 95% CI: .47–.77). This reduction in mortality persisted at 90 days (HR 0.70 95% CI: .57–.86).

There were 869 (18%) GN-BSI episodes that resulted in 30-day readmission (20% vs 15% in IDC vs no IDC, respectively) and 85 (1.7%) that resulted in 30-day recurrent bacteremia (2.1% vs 1.3% in IDC vs no IDC, respectively). After PS-weighting, there was no difference in 30-day readmission for patients with or without an IDC (HR 1.09, 95% CI: .77–1.54). There was also no difference in 30-day recurrent bacteremia (HR 1.33, 95% CI: .70–2.52).

Comment: This study found an overall 30-day mortality rate of 14% in hospitalized patients with GN-BSI. After adjusting for differences between the IDC and no-IDC groups, there was a 40% decreased risk of 30-day mortality in patients receiving IDC. This finding is consistent with other studies evaluating the benefit of IDC on mortality in GN-BSI, candida, and MRSA, with decreased risk of mortality ranging from 49% to 89% [Open Forum Infect Dis 2020; 7: ofaa010; Sci Rep 2017; 7:12898]. In this study, patients were more likely to receive an IDC if they had more severe presentations, multiple comorbidities, or complicated infections or organisms (e.g., Pseudomonas, Acinetobacter, Stenotrophomonas, and MDRO). Limitations of the study were its retrospective study design and site heterogeneity. Their data do not account for time to IDC or frequency of IDC.

Epidemiology, Resistance Profiles, and Outcomes of Bloodstream Infections in Community-Onset Sepsis in the United States Crit Care Med 2023; 51:1148-1158

DOI: 10.1097/CCM.0000000000005870

To describe the epidemiology, frequency of blood cultures, patterns of pathogens, and antibiotic treatments initiated in patients presenting with community-acquired sepsis, the investigators retrospectively reviewed a cohort of patients with community-acquired sepsis using the Premier Healthcare Database. They defined sepsis using the CDC Adult Sepsis Event Surveillance criteria. From January 2016 to March 2020, the investigators evaluated laboratory and microbiologic data, demographics, admission type (elective vs. nonelective), hospital characteristics, ICD-10 codes, and billing records. Also included were patients who had a blood culture drawn within two days of admission, evidence of organ dysfunction within two days of admission, and exposure to a new antibiotic for at least four consecutive days.

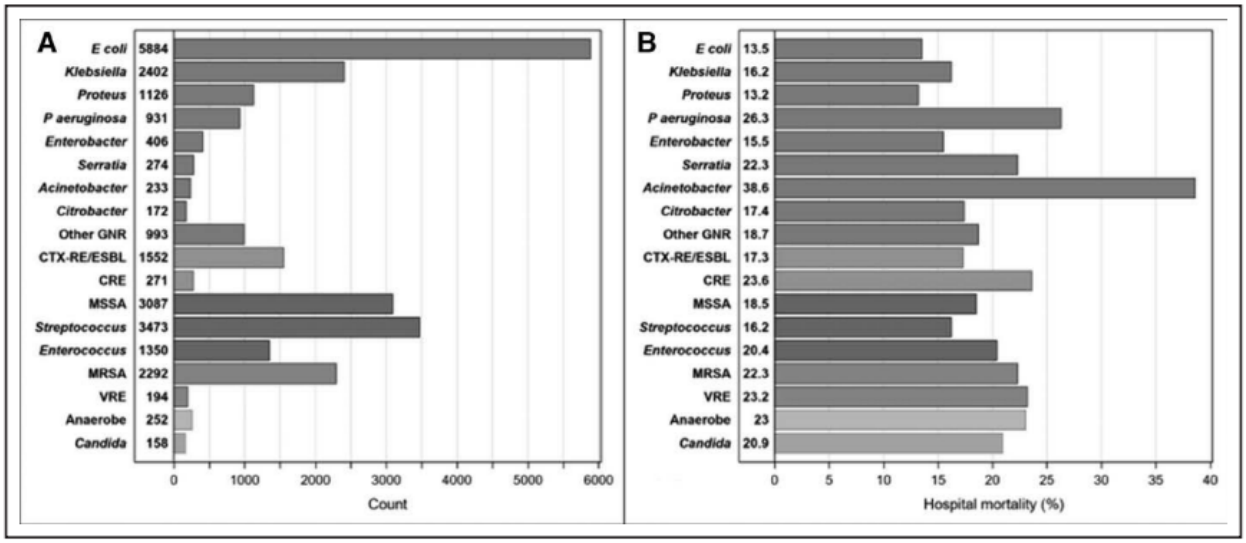
Within the nearly four-year period, 147,061 patients from 201 hospitals were included in the study. Of these, 21,167 (14%) had positive blood cultures and 20,326 (14%) had positive cultures from other sites. Blood culture positivity was 25% in patients with septic shock and 18% in patients without shock. Polymicrobial results were present in 7.6% of the cultures. Gram-negative bacilli made up 55%, gram-positive cocci 47%, anaerobes 1.2%, and *Candida* species 0.7%.

The median age was 67 years, of which 54% were male, 35% were mechanically ventilated, 39% required vasopressors, and length of stay averaged 7 to 8 days. Mortality was 17% in blood culture-positive sepsis, 17% in blood culture-negative sepsis, and 13% in patients with positive cultures from sites other than blood. Common comorbidities for culture-positive sepsis included diabetes (41.1%), renal disease (29%), congestive heart failure (28.4%), chronic obstructive pulmonary disease (22.3%), neurologic disorders (16.5%), liver disease (13.5%),

and cancer (11.5%). Admission to the intensive care unit occurred in 75.8% of culture-positive sepsis and 74.3% of culture-negative sepsis.

The most common source of culture-positive sepsis was genitourinary (33.1%), followed by pulmonary (29.9%), skin/soft-tissue (15.4), and intra-abdominal (8.6%). Empiric antibiotic choices included vancomycin (79.4%), cephalosporins (76.3%), penicillins (60.6%), carbapenems (29.6%), and fluoroquinolones (23.3%). The most common combination of antibiotics was vancomycin and piperacillin-tazobactam, which was prescribed in 13% of patients.

The most identified organism was *E coli*, followed by Streptococcus, MSSA, Klebsiella, and MRSA. ESBLs were isolated in 7.3% and carbapenem resistance was isolated in 1.3% of the culture-positive sepsis cases. Mortality was highest in those infected with Acinetobacter (38.6%), followed by P aeruginosa, MSSA, and MRSA. Patients infected with Proteus, Klebsiella, E coli, and Streptococcus had a lower risk of in-hospital mortality.



Comment: In patients hospitalized with community-onset sepsis, the prevalence of blood culture-positive sepsis was 14%. Among positive blood culture sepsis, resistant organisms were infrequent. Compared with culture-negative sepsis, blood culture-positive sepsis and nonblood culture-positive sepsis were associated with lower in-hospital mortality. These findings were similar to a prior study that demonstrated a higher mortality in culture-negative severe sepsis. [Chest. 2016;150(6):1251-1259] However, a recent meta-analysis of 10 studies found no significant difference in all-cause mortality, need for mechanical ventilation, renal replacement therapy, or intensive care unit length of stay between patients with culture-positive and culture-negative sepsis. [Cureus. 2023; 15: e35416] However, this meta-analysis was not limited to community-acquired sepsis. Another study mirrored the 14% blood-culture positivity rate of a prior study of 173,690 patients, with pulmonary and genitourinary infections being the most common. [JAMA. 2017; 318:1241-1249] The Premier database does not allow researchers to control for timing of antibiotic administration relative to cultures if both occur on the same day. Thus, some patients who received antibiotics prior to obtaining the blood cultures might be misclassified to the blood culture-negative group, which might have an impact on outcomes.

In the end efforts should be made to maximize the yield of blood cultures, ensuring they are drawn prior to the administration of antibiotics and that adequate blood volume is cultured. As pathogen identification appears to improve outcomes, diagnostic efforts should not hinge solely on blood cultures alone, but extravascular sites should also be cultured if available.

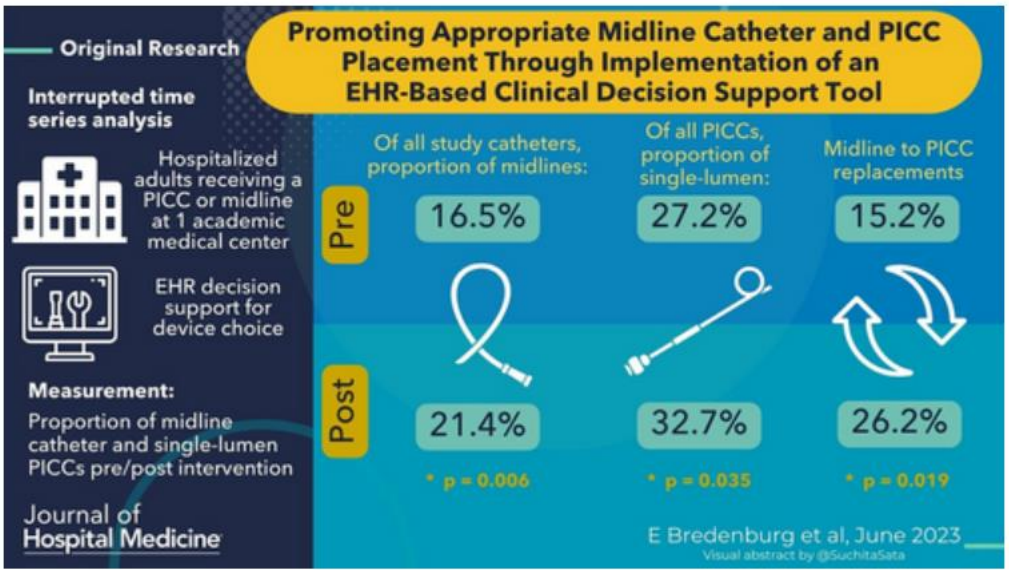
Promoting appropriate midline catheter and PICC placement through implementation of an EHR-based clinical decision support tool: An interrupted time-series analysis J Hosp Med 2023;18:283-490

https://doi.org/10.1002/jhm.13093

Evidence shows that both midline catheters (peripheral intravenous devices) and single-lumen peripherally inserted central catheters (PICCs) have lower rates of complications (e.g., central line–associated bloodstream infection and venous thromboembolism [VTE]) than multi-lumen PICCs. Despite the known risks of PICCs, interhospital variability in their use is substantial.

U.S. researchers performed an observational trial during 3 years at a single academic medical center to examine the effects of an embedded electronic health record (EHR) order, which guided providers to select the appropriate catheter based on indication and expected duration of use. [A clinical decision tool was developed using MAGIC recommendations and embedded with the EHR (Epic® Systems) on November 19, 2017. The intervention replaced a previous EHR-based order set that simply allowed a provider to order any vascular access device without guidance. The new order set prompted ordering providers to select the reason for device placement as well as the expected duration of catheter use and then guided the provider toward the most appropriate type of vascular access device based on the inputted data. Once implemented, the order set was the only way providers could order PICC and midline devices at the facility] Approximately 2300 catheters were placed in the 11-month preintervention period and nearly 6500 were placed in the 25-month postintervention period.

The proportions of catheter types changed significantly from preintervention to postintervention periods: Use of midline catheters increased from 14% to 24%, use of single-lumen PICCs increased from 25% to 28%, and use of multi-lumen PICCs decreased from 59% to 47%. Results were consistent across multiple service specialties (e.g., internal medicine, surgery, intensive care), but oncology use didn't change. Line placement rates — for all PICCs plus midlines — and complication rates were unchanged.



Comment: This study shows that a fairly simple intervention can lead to more appropriate use of midline and single-lumen PICCs, although its findings might not apply to oncology patients who often require central access for multiple infusions. The 2022 SHEA/IDSA guidelines now introduce a critical step in preventing CLABSI: pausing to determine whether a central venous catheter is appropriate or necessary before insertion. [Infect Control Hosp Epidemiol. 2022; 43:553-569] Whether these findings will be reproducible outside these settings is unknown. Their intervention was implemented in the Epic® System. They did not detect a difference in rates of CLABSI and VTE as they were underpowered for these outcomes related to PICCs and midlines. In a recent study, patients who used midline experienced fewer CRBSI than those who use PICCs. However, the use of midline catheter was associated with greater risk of superficial vein thrombosis. [OFID 2023; 10, February 2023, ofad024] As midline catheters are not considered CVC, their infection rates are not routinely reported as part of the CLABSI metrics. The investigators in this study did not assess rates of peripheral bloodstream infections, such as might result from midlines which are considered peripheral lines; instead, they elected to focus on CLABSI alone since CLABSIs are publicly reported and may impact hospital reimbursement. In a recent article reviewed in ID Watch, the investigators found there were ~4 times as many non CLABSI healthcare onset (HO) BSIs as CLABSI cases. The CDC has proposed reporting all cause HO bacteremia and fungemia (BSIs) which has now been endorsed by NQF/Batelle. See next review.

Evaluation of hospital-onset bloodstream infections compared to central line–associated bloodstream infections at an acute, tertiary care hospital Am J Infect Control 2023; 51: 1120–1123

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While central venous catheters (CVPs) may be the primary culprit in the cause of hospital-onset BSIs (HOBSI), there is little research on those caused by peripheral and midline venous catheters. Therefore, using HOBSI as a benchmark may be a more sensitive indicator of preventable BSIs, which may further minimize the occurrence and the detrimental effects

associated with them. The objective of this study was to assess the potential impact of a change to HOBSI surveillance by comparing the incidence of BSI using the National Health care and Safety Network (NHSN) LabID (Laboratory Identified) and BSI definitions compared to CLABSI.

The investigators conducted a retrospective analysis of all positive blood cultures (n = 763) among patients admitted to a regional academic acute tertiary care facility with 1,000 beds including adult and pediatric patients, between July 2018 and June 2019. Cultures were identified using electronic medical records. The facility peripheral line policy requires peripheral line dressing changes be performed at least every 7 days or whenever they become loose, wet, soiled, or when inspection of the site is necessary. Routine changing of peripheral venous catheters is not required unless clinically indicated. Daily CHG bathing is performed for all patients in ICUs and for all other patients with central venous catheters.

They defined cases using the LabID and BSI criteria established by NHSN. There is no definition for HOBSI yet published by NHSN, so they chose to use NHSN LabID and BSI definitions and labeled them HOBSI-1 and HOBSI-2, respectively.

National Health care and Safety Network (NHSN) criteria and case definitions used to classify bloodstream infections (BSIs)[4]

LabID criteria (also referred to as HOBSI-1)	• Positive blood culture in a patient with *any* intravenous line for > 3 days when the patient has been on an inpatient unit for > 2 days and the patient has no other positive blood cultures during days 1-2 of admission • Patients with only one blood culture positive for a common commensal will not be considered
BSI criteria (also referred to as HOBSI-2)	• Positive blood culture in a patient with *any* intravenous line for > 2 days when the patient has been on an inpatient unit for > 2 days and the patient has no other positive blood cultures during days 1-2 of admission • Patients with only one blood culture positive for a common commensal will not be considered • Patients with blood cultures positive for mucosal barrier injury (MBI) organism that also meet MBI LCBI criteria will not be considered • Patients whose BSI is deemed secondary to another infection will not be considered

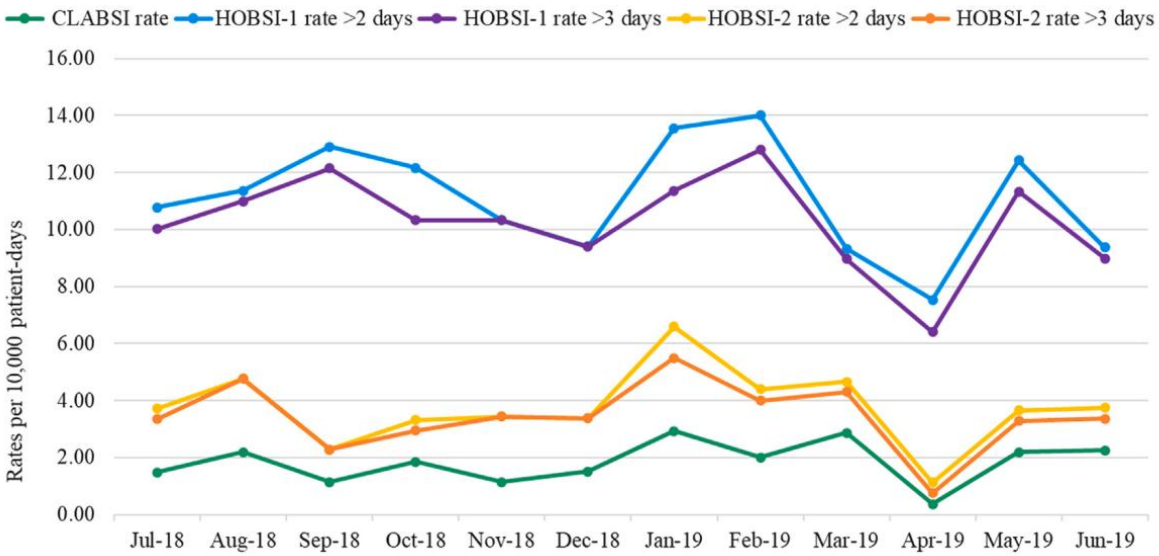
CLABSI criteria	• LCBI 1
	• Patient of any age has a recognized bacterial or fungal pathogen, not included on the NHSN common commensal list:
	  • Identified from one or more blood specimens obtained by a culture OR
	  • Identified to the genus or species level by non-culture based microbiologic testing (NCT)* methods
	• Organism(s) identified in blood is not related to an infection at another site
	• LCBI 2
	  • Patient of any age has at least one of the following signs or symptoms: fever (> 38.0 °C), chills, or hypotension AND
	  • Organism(s) identified in blood is not related to an infection at another site AND
	  • The same NHSN common commensal is identified by a culture of two or more blood specimens collected on separate occasions

They chose the LabID definition to measure how many BSIs are acquired within the hospital in patients who have central and peripheral venous catheters, including arterial lines and midlines. They chose the BSI definition to determine whether those BSIs could be attributed to another infection, and if so, they were not included in the HOBSI-2 rates. They calculated HOBSI rates based on a line being present for both > 2 and > 3 days since the LabID criteria include the presence of a line for > 3 days and the BSI criteria include the presence of a line for > 2 days. Their facility did not currently collect line days for peripheral venous catheters, as is done for CVPs, so as an alternative, patient days were used to calculate the HOBSI rates. Since CLABSI rates are calculated using line days, they recalculated the CLABSI rate using patient days to allow for better comparison to the HOBSI rates.[calculated the incidence rates (IRs) per 10,000 patient days for both definitions and compared them to the CLABSI rate per 10,000 patient days for the same period] All patients who had multiple BSIs were managed using the NHSN repeat infection timeframe definition where no new infections of the same type can be reported within 14 days from the original infection.

The average IR of HOBSI-1 using the NHSN LabID definition was 10.25 per 10,000 patient days. After excluding all BSIs that were secondary to other infections using the NHSN BSI definition (HOBSI-2), they found an average IR of 3.77 per 10,000 patient days. Most

commonly, the BSIs that did not meet HOBSI-2 criteria were deemed secondary to pneumonia or intra-abdominal infections. The average IR of CLABSI for the same period was 1.84 per 10,000 patient days. Even after accounting for secondary infections, the incidence of HOBSI was still double that of CLABSI (IR ratio = 2.05, 95% confidence interval = [1.5, 2.8]). For comparison, IR of CLABSI is 0.575 per 1000-line days.

Of the 121 BSIs that met HOBSI-2, using NHSN BSI criteria of having an intravenous line for > 2 days, 49% of them had multiple lines at time of infection. Of the 121 BSIs that met HOBSI-2, 48% of them had only peripheral venous catheters present. After excluding BSIs secondary to another infection (HOBSI-2), the organisms more commonly associated with HOBSI were S aureus (19%) and coagulase-negative staphylococcus (14%).



Comment: After excluding secondary BSIs, the HOBSI rate is still double that of the CLABSI rate. HOBSI surveillance is a more sensitive indicator of BSI than CLABSI. HOBSI may prove to be a better benchmark by increasing the surveillance of peripheral venous catheters including midlines and using NHSN definitions that exclude secondary infections, to identify, classify, and prevent BSIs. Future studies should examine HOBSI prevention measures and how their implementation affects HOBSI incidence.

Editor's Choice

Are contact precautions "essential" for the prevention of healthcare-associated methicillin-resistant Staphylococcus aureus? Clin Infect Dis published online September 21, 2023

doi.org/10.1093/cid/ciad571

In a recent publication Strategies to Prevent Methicillin-resistant Staphylococcus aureus Transmission and Infection in Acute-care Hospitals: 2022 Update (SHEA/IDSA/APIC Compendium) [Infect Control Hosp Epidemiol 2023; 44:1039-1067] the authors state contact precautions (CP) continue to be recommended as an essential practice. This has become a controversial topic. Recently, several studies have sought to study the impact of discontinuing contact precautions for MRSA-colonized and MRSA-infected patients. Many of these studies have demonstrated that discontinuing contact precautions did not lead to an increase in HAIs [Am J Infect Control 2020; 48:1466–1473; Infect Control Hosp Epidemiol 2022; 43:1595–1602]. The Compendium panel recognized that because of the large cost of performing cluster randomized trials, there are no trials at present that evaluate contact precautions versus no contact precautions for MRSA. Many of the studies demonstrating success have also had several horizontal strategies in place, such as CHG bathing. The 2022 Update suggest facilities that chooses or have already chosen to modify the use of CP for some or all of these patients should conduct a MRSA-specific risk assessment to evaluate the facility for transmission risks and to assess the effectiveness of other MRSA risk mitigation strategies (e.g., hand hygiene, cleaning and disinfection of the environment, CHG bathing, single occupancy patient rooms etc.), and establish a process for ongoing monitoring, oversight, and risk assessment. (Quality of evidence: MODERATE)

The authors in this Viewpoint article "commend the authors for this carefully crafted guidance, which will help acute care hospitals as they continue efforts to prevent MRSA infections. However, we are concerned that the inclusion of contact precautions (CP) for all MRSA colonized or MRSA-infected patients as an "essential practice" (to be adopted by all acute care facilities) is not supported by current evidence and could have unintended adverse consequences." In this Viewpoint, they explain why the practice of CP for MRSA should instead be considered an "additional approach," reserved for specific settings (e.g., outbreaks or evidence of ongoing transmission despite application of essential practices). I will provide some of the studies discussed in this Viewpoint to support their recommendation followed by my own perspective in the Comment section.

First, they discuss that most trials are observational and involve more than one intervention. They go into detail discussing the VA study which is the largest observational study to date which is discussed in the Compendium. [N Engl J Med 2011; 364:1419–30]. The VA MRSA prevention bundle did not only use CP for those known by clinical cultures to be colonized or infected with MRSA. In fact, most VA hospitals were already using CP for this indication but added active surveillance. The VA bundle included screening of all hospital admissions for MRSA and, in addition to CP for all carriers, they also focused on hand hygiene and provided funding for a "MRSA Prevention coordinator" which generally meant was an additional infection preventionist (IP). In general, these practices increased awareness on infection prevention culture across the VA system. This bundle represented a combination of one "vertical"

intervention (vertical interventions being those focused on a single pathogen, in this case MRSA) and several “horizontal” interventions (horizontal interventions being those that impact all potential pathogens like hand hygiene). Later VA studies revealed that reductions in both hospital-onset Gram negative bacteremia and candidemia began at the same time as the VA MRSA Prevention Initiative and resulted in reductions of similar magnitude as that of MRSA (43% for Gram negative bacteremia, 77% for candidemia) [Clin Infect Dis 2016;63:642-650; Clin Infect Dis 2019;73:689-696]. These findings suggest the importance of the addition of horizontal interventions and raising awareness. This raises the question of what, if any, reduction was due to active screening and CP alone. Viewpoint did not include the recent VA study. [Clin Infect Dis published online June 30, 2023] (see next review) which found that facility removal of MRSA prevention practices [active surveillance and/or CP) was associated with higher rates of MRSA HAIs in ICUs and non-ICUs.

Other studies they referenced were the STAR*ICU cluster randomized trial in 18 ICUs, which found that MRSA screening (with CP for all carriers, and gloves while awaiting test results) did not reduce MRSA infection or transmission although the use of barrier precautions by providers was less than what was expected.[New Engl J Med 2011;364:1407-1418] The REDUCE MRSA trial was a cluster randomized trial which found that universal decolonization (CHG and mupirocin) was superior to MRSA screening and CP at reducing MRSA clinical cultures and all-cause bloodstream infections [N Engl J Med 2013;368:2255-2265]. The MOSAR trial was a cluster randomized trial, which found no additional decrease in MRSA associated when adding screening-guided CP after an initial hand hygiene and CHG bathing intervention which did demonstrate a reduction in MRSA acquisition [Lancet Infect Dis 2014;14:31-39]. The one study that demonstrated benefit from expansion of CP was the cluster RCT that examined the effectiveness of universal use of gowns and gloves in all ICU patients (the “Benefits of Universal Gown and Glove” (BUGG) study) [JAMA 2013; 310:1571-80]. The primary endpoint in this study revealed no difference in MRSA or VRE acquisition or infection in the intervention arm, but a pre-planned secondary analysis limited to MRSA found a statistically significantly greater reduction in MRSA acquisition events in the intervention units.

The Viewpoint went on to discuss potential harm of CP. They reference studies on patient satisfaction and anxiety [Am J Infect Control 2009; 37:85-93]. Prior studies have also demonstrated that isolated patients have fewer contacts with clinicians compared with control patients and are half as likely to be examined by attending physicians on rounds [Am J Infect Control 2003; 31:354-6]. In another study the investigators observed longer lengths of stay, higher hospital costs, and higher rates of 30-day readmissions among patients isolated for MRSA compared to non-isolated patients in a propensity-matched cohort study [J Gen Intern Med. 2017**;** 32:262-268].

The Viewpoint concludes that CP be moved from essential practices to additional approaches.

Comment: First by way of disclosure, I was on the Expert Panel for the Compendium and part of the discussion around CP for MRSA. In the end I think the Compendium got it right. The Compendium states “although CP remain an essential practice, considerations have been provided for hospitals that have strong horizontal prevention measures and neither ongoing MRSA outbreaks nor high or increasing rates of MRSA infection or hospital-onset MRSA-positive cultures and that choose to modify the use of CP for some, or all MRSA colonized or MRSA-infected patients.” Facilities should first conduct a MRSA-specific risk assessment to evaluate the facility for transmission risks and to assess the effectiveness of other MRSA risk

mitigation strategies (e.g., hand hygiene, CHG bathing, cleaning and disinfection of the environment, single occupancy patient rooms), and establish a process for ongoing monitoring, oversight, and risk assessment. It also identifies and prioritizes high-risk populations for which you may wish to maintain contact precautions such as ICU, NICU, burn units, and transplant patients.

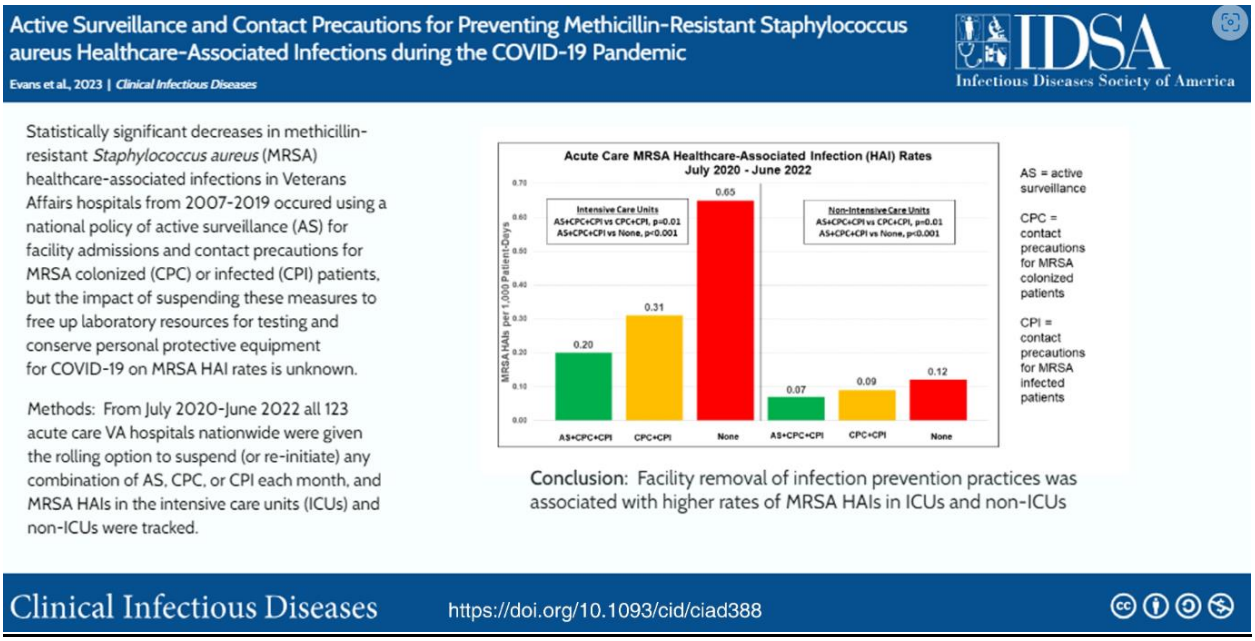
The pandemic resulted in extraordinary challenges for infection prevention in hospitals. Increased HAIs were observed throughout 2020 and 2021 including hospital onset MRSA BSI. [Infect Control Hosp Epidemiol 2022; 43:12–25] This was probably due to increased patient volumes, increased patient acuity levels, and staffing challenges. Burnout and turnover were widely reported. This will impact facilities for years to come. I think the key given the turnover of IPs and nurses combined with staffing challenges and variation in IP practices [and my own direct observations], most US facilities are probably not at the point where they can say that mitigation strategies are hardwired and actually done with a high level of reliability and sustainability. On the other hand, there are some sites where they have robust and stable programs and low rates of MRSA where they can modify CP with the understanding, they must establish a process to monitor and snap back when rates go up or clusters are seen. If we moved CP to additional approaches now before we see stability in terms of IP and nurse staffing and HAI rates, I am afraid hospitals will drop CP without doing a thorough assessment suggested by the Compendium which may result in patient harm. I agree with an earlier publication pre-pandemic: "Higher quality research on the benefits and harms of CP in the control of endemic MRSA and VRE is needed. Until more definitive data are available, the use of CP for endemic MRSA or VRE in acute care hospitals should be guided by local needs and resources." [Infect Control Hosp Epidemiol 2015; 36:1163-72] The recent VA experience is a wakeup call that if we relax MRSA prevention practices including CP, we can see higher rates of MRSA HAIs in ICUs and non-ICUs. See next review Bottom line before we move CP to additional practices, we need more real-world experience post Covid-19.

Active Surveillance and Contact Precautions for Preventing Methicillin-Resistant *Staphylococcus aureus* Healthcare-Associated Infections During the COVID-19 Pandemic Clin Infect Dis published online June 30, 2023

doi.org/10.1093/cid/ciad388

This was a prospective cohort analysis from July 2020 through June 2022. Local facility MRSA infection control policy at each of the 123 VA acute care facilities was assessed monthly using an online electronic questionnaire with follow-up ensuring a 100% response rate. Facilities were asked if they had (a) stopped active admission surveillance (AS) and contact precautions (CP), (b) stopped AS but continued CP, (c) continued admission surveillance but stopped CP contact, or (d) continued admission surveillance and CP. If contact precautions were continued or stopped, it was asked whether the practice was done only for MRSA colonized or infected patients or both. All 123 acute care VA hospitals nationwide were given the rolling option to suspend (or re-initiate) any combination of active surveillance (AS), contact precautions for MRSA colonized (CPC), or MRSA infected (CPI) each month, and MRSA HAIs in intensive care units (ICUs) and non-ICUs were tracked.

There were 917,591 admissions, 5,225,174 patient-days, and 568 MRSA HAIs. In July 2020, only 20% of facilities continued all 3 MRSA infection control measures, but by June 2022 this had increased to 57%. In July 2020, 15% of facilities discontinued all three infection control measures, but this decreased to 0 by May 2022. The MRSA HAI rate/1000 patient-days in ICUs was 0.20 (95% confidence interval [CI], .15–.26) for facilities practicing "AS + CPC + CPI" compared to 0.65 (95% CI, .41–.98; $P < .001$) for those not practicing any of these strategies, and in non-ICUs was 0.07 (95% CI, .05–.08) and 0.12 (95% CI, .08–.19; $P = .01$) for the respective policies. During the pandemic (July 2020– June 2022), the rates were 0.25 ± 0.12 in the ICUs and 0.08 ± 0.03 in the non-ICUs. Monthly pre-pandemic rates were not different than pandemic rates for non-ICU MRSA HAIs ($P = .38$) however were significantly increased in the ICUs ($P < .05$). They also showed that the continuation or re-instatement of active surveillance for MRSA colonization upon admission and contact precautions for colonized or infected patients was significantly associated with a lower incidence of MRSA HAIs compared to policies with fewer interventions. During both periods, MRSA HAI rates were higher in the ICUs than in the non-ICUs ($P < .05$) The most common MRSA HAIs were BSIs (32%), pneumonias (26%), soft-tissue infections (14%), and urinary tract infections (10%). Overall, 33% of MRSA BSIs were device associated (DA), and 67% were non-device associated (NDA), 19% of pneumonias were DA and 81% NDA, and 53% of urinary tract infections were DA and 47% NDA. Accounting for monthly Covid-19 facility admissions using a negative binomial regression model did not change the relationships between facility policy and MRSA HAI rates. There was no significant difference in monthly facility urinary catheter-associated infection rates, a non-equivalent dependent variable, in the policy categories in either ICUs or non-ICUs.



Comment: With the decline in the prevalence of MRSA HAIs in recent years, several investigators have suggested that contact precautions may not be needed for the prevention of MRSA HAIs; however, NHSN data show that hospital-onset MRSA bacteremia increased 14% from 2020 to 2021 during the pandemic suggesting that infection control strategies, which may have changed during the pandemic, may explain the rise in MRSA infections [Am J Infect Control 2021; 49:784–91] This prospective analysis of MRSA infection control policy and MRSA

HAI rates over 2 years during the pandemic at VA facilities showed that the continuation or re-instatement of active surveillance for MRSA colonization upon admission and contact precautions for colonized or infected patients was significantly associated with a lower incidence of MRSA HAIs compared to policies with fewer interventions. There was no way of confirming compliance with contact precautions in the facilities during this analysis. Unfortunately, the requirement for VA facilities to collect MRSA surveillance on admission, unit to unit transfer, and discharge was relaxed in 2016. They also could not account for patients who may have developed a MRSA infection after discharge.

Editor's Choice

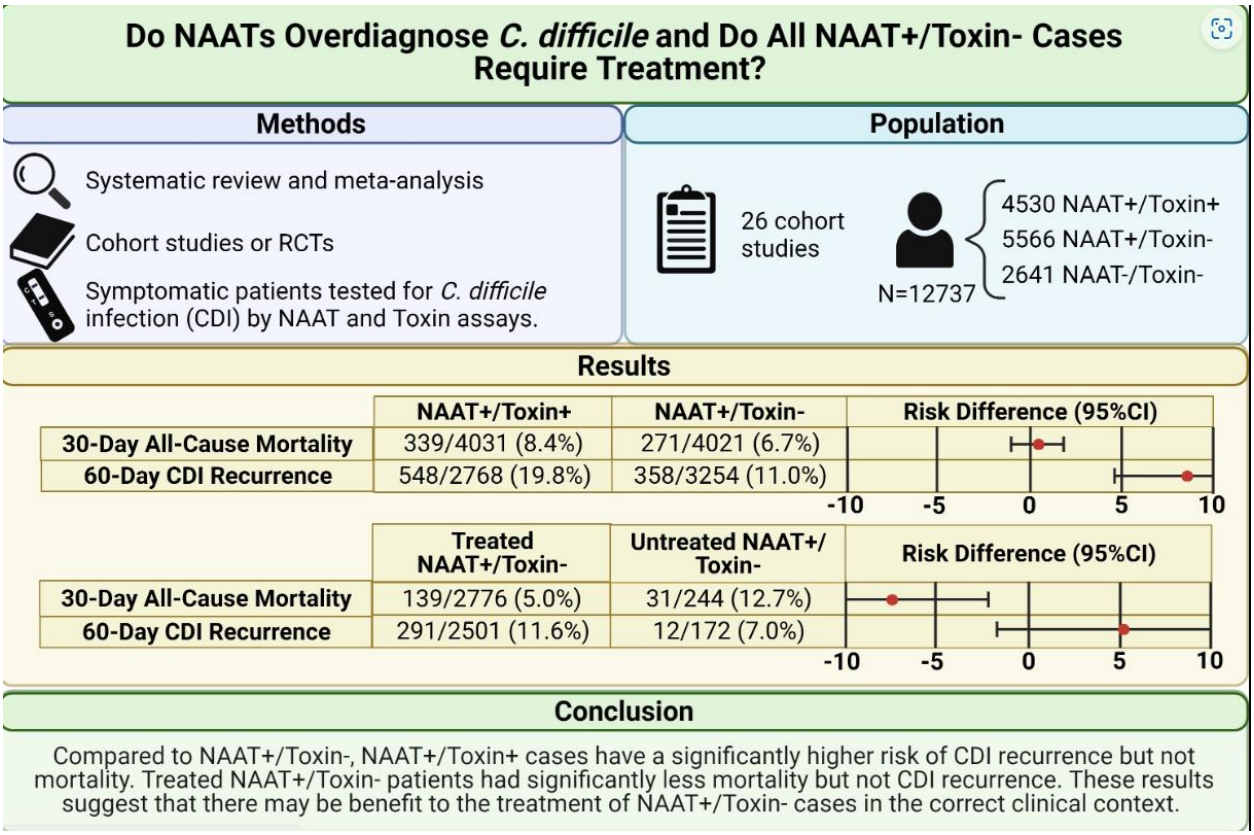
Clinical Outcomes and Management of NAAT Positive/Toxin-Negative *Clostridioides difficile* Infection: A Systematic Review and Meta-Analysis Clin Infect Dis published online August 30, 2023

DOI: 10.1093/cid/ciad523

The authors searched EMBASE and MEDLINE from inception to April 1, 2023, for articles comparing CDI outcomes among symptomatic patients tested by NAAT and Toxin tests. The risk differences (RD) of all-cause mortality and CDI recurrence were computed by random effects meta-analysis between patients who were NAAT+/Toxin+ and NAAT+/Toxin-, as well as between patients who were NAAT+/Toxin- and treated or untreated. Studies were included in the review if they reported on adult patients tested for CDI by both NAAT and a toxin EIA or when a GDH and toxin EIA assay was used with a reflex NAAT in discordant cases. At least one of the following clinical outcomes had to be reported for inclusion: all-cause mortality, CDI-related mortality (attributable or contributing, as defined by the study authors), or CDI recurrence. Included articles had to report these outcomes with ≥30 patients per group and for at least one of the following comparisons: patients who were NAAT+/Toxin- treated versus not treated for CDI; or patients who were NAAT+/Toxin- versus those who were NAAT+/Toxin+ or NAAT-/Toxin-. Articles were excluded if they were limited to pediatric or asymptomatic patients. Gray literature and conference abstracts were excluded. They conducted sensitivity analyses limited to studies specifically requiring diarrhea as an inclusion criterion and studies using the IDSA-SHEA guideline-recommended definition of diarrhea (≥3 unformed stool in 24h).[tracking of clinically significant diarrhea and laxative use at time of C. difficile testing ordering] They performed a subgroup analysis of patients diagnosed by the GDH/Toxin EIA with reflex NAAT algorithm.

Twenty-six observational studies comprising 12,737 patients were included. 30-Day all-cause mortality was not significantly different between those who were NAAT+/Toxin+ (8.4%) and NAAT+/Toxin- (6.7%) (RD=0.41%, 95%Confidence interval [95%CI] =-0.67, 1.49). Recurrence at 60 days was significantly higher among patients who were NAAT+/Toxin+ (19.8%) versus NAAT+/Toxin- (11.0%) (RD=7.65%, 95%CI=4.60, 10.71). Among treated compared to untreated NAAT+/Toxin- cases, the all-cause 30-day mortalities were 5.0% and 12.7%, respectively (RD=-

7.45%, 95%CI=-12.29, -2.60), but 60-day recurrence was not significantly different (11.6% versus 7.0%, respectively; RD=5.25%, 95%CI -1.71, 12.22).



Comment: By way of background**,** hospitals in the US typically apply the NHSN LabID event definitions to CDI. This reporting focuses on positive laboratory tests in relation to hospital admission and does not consider the presence or timing of onset of symptoms. Healthcare facility–onset CDI is defined as having a positive NAAT or toxin (based on the result of the last test performed if a multistep algorithm is done) ≥4 days after healthcare facility admission, with the day of admission counted as day 1. An event may be identified as 'recurrent' when there is a previous event at the same facility in the previous 56 days. The NHSN is updating the healthcare facility-onset CDI surveillance definition to incorporate antibiotic treatment in addition to test results (i.e., healthcare facility onset, treated CDI [HT-CDI]). This has now been endorsed by NQF/Batelle. Meaning if someone tests positive by NAAT and is toxin negative and is treated this will now be captured by this new measure. [>75% of patients are treated for CDI despite having a negative toxin EIA following a positive NAAT] See below

This systematic review and meta-analysis found similar all-cause mortality between patients who were NAAT+/Toxin+ and NAAT+/Toxin-. However, combined with the finding that treated patients who were NAAT+/Toxin- had significantly lower all-cause mortality than untreated patients, suggests that withholding therapy from all patients who were NAAT+ solely based on the toxin being negative may not be justified and that therapy should be considered using clinical judgment. However, these results differ from a recent study comparing exclusive reporting of NAAT results versus exclusive reporting of a toxin EIA surrogate (PCR cycle threshold cut-off; CT-Toxin).[J Clin Microbiol. 2022 2022;60(6): e02187-21 45] Exclusive CT-Toxin reporting resulted in a six-fold decrease in the number of patients treated for CDI but no

statistically significant increase in all-cause mortality among NAAT+/CT-Toxin- patients. Another recent multicenter time-series study reported that two-step testing was associated with a decrease in HO-CDI incidence, a similar level decrease in utilization rates for oral vancomycin and fidaxomicin, and no significant level change in emergent colectomy rates, however, mortality alone was not reported.[Clin Infect Dis. 2023:ciad334 published online June 6, 2023] While colectomy is a proxy for severe disease, there are numerous reasons why patients with severe CDI may not require a colectomy. In another study, Polage et al found among hospitalized adults with suspected CDI, virtually all CDI-related complications and deaths occurred in patients with positive toxin immunoassay test result. Patients with a positive molecular test result and a negative toxin immunoassay test result had outcomes that were comparable to patients without *C difficile* by either method. [JAMA Intern Med. 2015; 175:1792-1801]

Certainly, many patients who are NAAT+ are colonized and not infected and it continues to be important to ensure testing is performed for patients presenting with defined clinical criteria, such as those presented in the IDSA-SHEA guidelines [Clin Infect Dis. 2018 2018;66(7):e1-e48] Furthermore, EIA toxin assays have different sensitivities. Earlier EIA assays had lower sensitivity than more recent assays which adds another confounder to their review. An example, in the Polage study they detected toxin in 29.6% (48 of 162) of Tox-/PCR+ patients by the historical cell cytotoxin assay. It is possible that some toxin-negative patients have mild or early infection because clinical toxin tests can miss toxin at low concentrations. However, the relative lack of adverse events in this subgroup suggests that these patients are also at lower risk of complications than clinical toxin immunoassay–positive patients and that routine treatment may not be unnecessary. In addition, we need to keep in mind that some patients who are NAAT+/Toxin- may have another non-CDI causes of diarrhea (*e.g.,* inflammatory bowel disease flare-up or other gastrointestinal conditions). [most nosocomial diarrhea is noninfectious] Like any diagnostic test, the pretest probability of disease becomes important to consider. [PLoS One. 2018;13(12): e0207128]

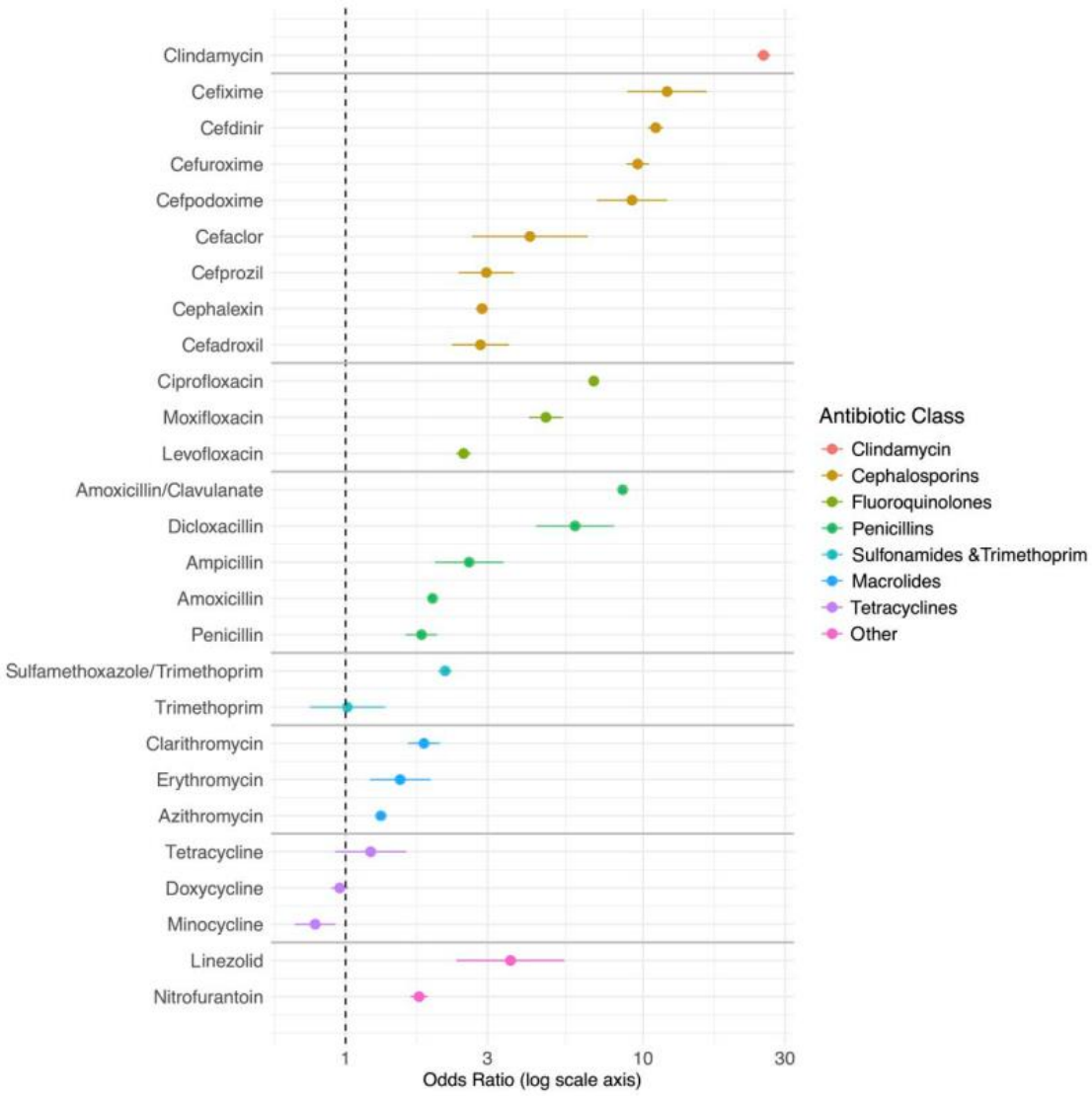
The Compendium on “Strategies to prevent Clostridioides difficile infections in acute-care hospitals: 2022 Update” [Infect Control Hosp Epidemiol 2023; 44, 527–549] states at minimum, C. difficile testing should be avoided in patients without clinically significant diarrhea, in those who have been tested in the prior 7 days, and in children aged <1 year. Additional action may be taken to reduce testing in individuals with diarrhea from a more likely etiology such as recent laxative use or initiation of enteral tube feeding. “Data from the CDC (not yet published) suggest that >75% of patients are treated for CDI despite having a negative toxin EIA following a positive NAAT even though data suggest that treatment may not be necessary” which led to the new recently endorsed measure. This is an antimicrobial stewardship issue since unnecessary treatment can lead to increased resistance. [most potential CDI is still treated with PO Vancomycin which also can lead to dysbiosis] Some organizations who use the two-step-PCR +reflex to toxin have added a statement that “PCR+ toxin negative patients generally represent colonization and treatment is rarely indicated.” This discourages unnecessary treatment while allowing for clinical judgment. The authors in this review conclude: “While our results also suggest a potential benefit for treatment of patients presenting with a clinical suspicion of CDI who are NAAT+, regardless of toxin status, the data are limited and observational. Overall, these results provide the clinical equipoise needed for multicentre, prospective, and ideally randomized studies of CDI testing and treatment algorithms.” Can we identify the clinical parameters in NAAT+, toxin- patients that would benefit from treatment?

Comparison of Different Antibiotics and the Risk for Community-Associated *Clostridioides difficile* Infection: A Case–Control Study OFID published online August 5, 2023

doi.org/10.1093/ofid/ofad413

The investigators conducted a matched case–control study using a large database of insurance claims capturing longitudinal health care encounters and medications. [Merative MarketScan Research Databases including the Commercial, Medicare, and Multi-State Medicaid databases. The Commercial and Medicare databases covered the years 2001–2021, and the Medicaid database covered 2014–2018] Case patients with community-associated CDI were matched to 5 control patients by age, sex, and enrollment period. Antibiotics prescribed within 30 days before the CDI diagnosis along with other risk factors, including comorbidities, health care exposures, and gastric acid suppression were considered. 27 individual antibiotic types were selected for which ≥50 case and control observations had exposure within 30 days before index. Conditional logistic regression and a Bayesian analysis were used to compare risk across individual antibiotics. A sensitivity analysis of antibiotic exposure windows between 30 and 180 days was conducted.

They identified 159,404 cases and 797,020 controls. The 5 most prescribed antibiotics among cases were clindamycin, amoxicillin/clavulanate, ciprofloxacin, cephalexin, and cefdinir. Among control patients, the most common antibiotics were amoxicillin, azithromycin, amoxicillin/clavulanate, ciprofloxacin, and cephalexin. Antibiotics with the greatest risk for CDI included clindamycin and later generation cephalosporins, and those with the lowest risk were the tetracyclines minocycline and doxycycline. They were able to differentiate and order individual antibiotics in terms of their relative level of associated risk for CDI. Risk estimates varied considerably with different exposure windows considered.

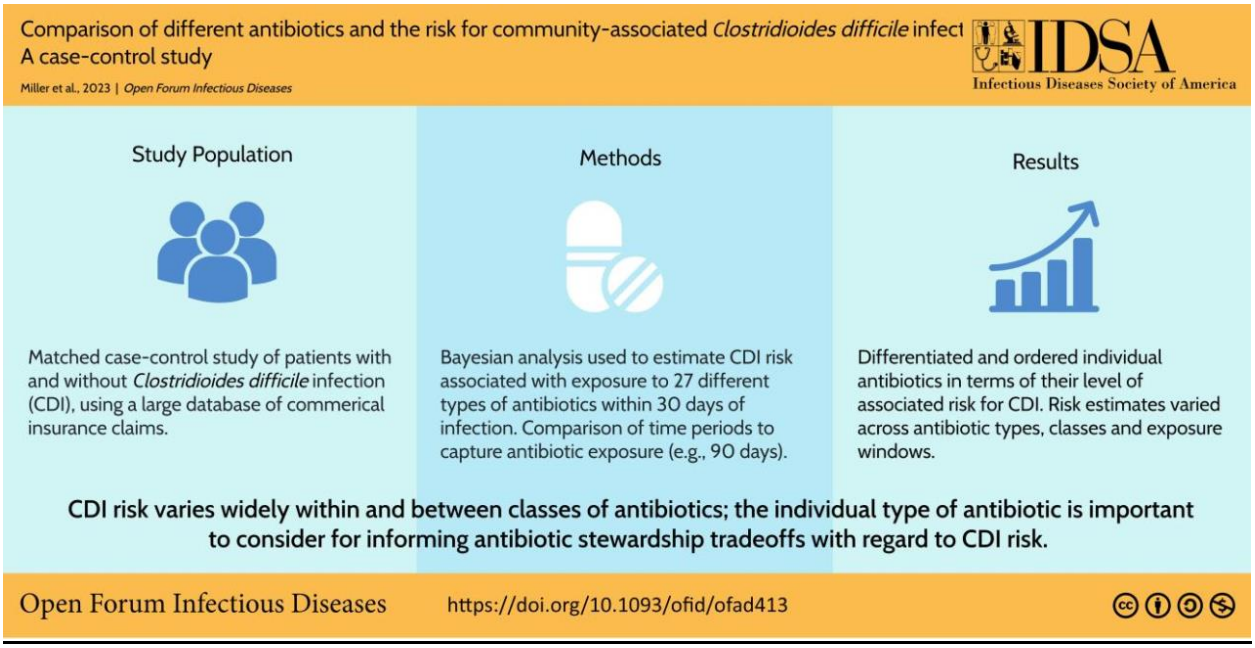


Comment: Their results are consistent with prior investigations. They found that clindamycin is deserving of its high-CDI-risk reputation. Also consistent with other reports, they found that tetracyclines are associated with the lowest levels of risk. They found considerable variation of risk across antibiotic classes and across individual antibiotics within classes. These findings may have important implications for clinical prescribing decisions and illustrate some of the potential tradeoffs when choosing between different antibiotics in terms of CDI-related risk. They demonstrated that the risk associated with first-generation cephalosporins is substantially lower than later-generation cephalosporins. Amoxicillin/clavulanate was similar in risk to later-generation cephalosporins and was associated with substantially more risk than amoxicillin without clavulanate. While much interest has been focused on the risks of CDI associated with fluroquinolones, they found that the risks associated with fluroquinolones were in between the risks associated with first- and later-generation cephalosporins. They also considered how risk

estimates for different antibiotics may change depending on the period used to capture antibiotic exposure. Existing literature has been largely inconsistent when considering different exposure windows; 30- to 90-day windows are commonly used, but longer windows have also been considered. Their findings raise important questions about the comparability of results across different studies and settings. They found that for most antibiotics, the risk estimates varied by a large degree when different exposure windows were considered. Comparing the 30-day vs 90-day exposure window results in quite a dramatic shift for many antibiotics. Examples: Clindamycin went from an odds ratio of 25.39 to 17.19, cefixime went from 12.04 to 5.01, and amoxicillin/clavulanate went from 8.53 to 5.06.

In addition, their results demonstrate that crude class-based risk models may be too broad to capture distinctions between antibiotics in a given class. In fact, they found that the variability within some classes in terms of associated risk level may exceed the variation between classes. Thus, attempts to define risk models in terms of simple high- vs low risk classes may obscure important and meaningful differences within a class. The duration of antibiotic exposure and time since last exposure, along with multiplicative interactions or comparisons of combination vs sequential antibiotic exposures when patients received multiple antibiotics, may also be modeled. They found the effect for 2 antibiotics increased when restricting the analysis to adults.

This study has some limitations. First, they relied on administrative claims data to identify health care visits and diagnoses of CDI. They did not have lab data or clinic notes to conclusively identify CDI or the timing of symptom onset. Second, they also could not identify stewardship practices at individual institutions and if they had changed over the study period. They also had to rely on outpatient claims submitted for reimbursement to identify antibiotic exposure. Lastly, they did not have access to antibiotics associated with inpatient stays.



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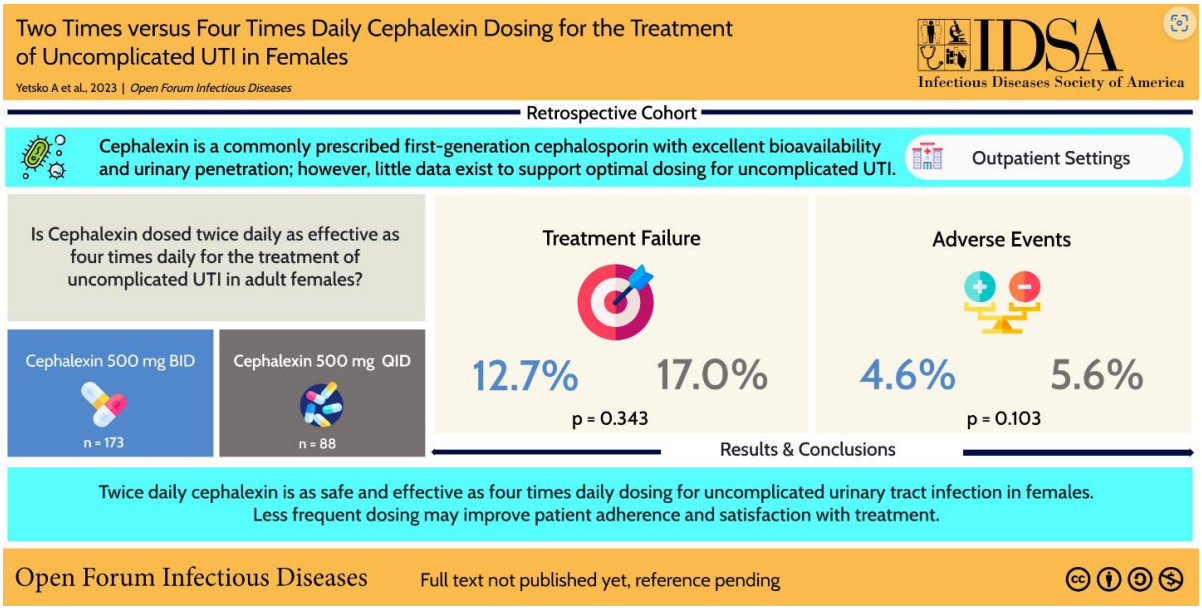
Two times versus four times daily cephalexin dosing for the treatment of uncomplicated urinary tract infections in females OFID published online August 11, 2023

DOI: 10.1093/ofid/ofad430

This is a retrospective, multicenter, cohort study which included adult female patients who received 5-7 days of cephalexin for symptomatic uUTI[cystitis] with a cefazolin-susceptible urine culture. The primary objective was to compare uUTI treatment failure (e.g., continued or recurrent symptoms within 30 days) between patients treated with cephalexin 500 mg twice daily (BID Group) versus 500 mg four times daily (QID Group) in the outpatient setting. Secondary outcomes included time to treatment failure, reported adverse events within 7 days of treatment, and occurrence of C. difficile within 30 days of treatment.

A total of 261 patients were included (BID Group, n= 173; QID Group, n= 88). Baseline characteristics were similar between groups. E coli was the most isolated pathogen (85.4%). There was no difference in treatment failure observed between groups (BID Group 12.7% vs QID Group 17%, p=0.343), including failure while on therapy (BID Group 2.3% vs QID Group 5.7%, p=0.438) or recurrence within 30 days (BID Group 10.4% vs QID Group 11.3%, p=0.438). No differences in reported adverse events (BID Group 4.6% vs QID Group 5.6%, p=0.103) were observed between groups.



Comment: Multiple studies have shown that less frequent dosing leads to improved compliance. This study provides evidence that cephalexin BID is as effective as QID for cystitis. If the patient did not have contact with the healthcare system within 30 days of completing therapy, they were assumed to have treatment success and no adverse events, so some adverse outcomes may have been missed. As with all retrospective EHR analyses, there is a reliance on accurate documentation within the electronic medical record. See next review.

Outcomes of high-dose oral beta-lactam definitive therapy compared to fluoroquinolone or trimethoprim-sulfamethoxazole oral therapy for bacteremia secondary to a urinary tract infection Antimicrobial Stewardship & Healthcare Epidemiology 2023, 3, e148, 1–6

doi:10.1017/ash.2023.435

Adult patients admitted between February 1, 2020, and October 1, 2022, with gram-negative bacteremia from a urinary source were evaluated. Patients receiving active empiric intravenous (IV) antibiotics and transitioned to appropriately dosed oral cephalexin, amoxicillin, fluoroquinolone (FQ), or trimethoprim/sulfamethoxazole (TMP/SMX) were included. Patients receiving less than 72 hours of oral therapy, diagnosed with renal abscess, lobar nephronia, or expired during admission were excluded. Standard oral therapy was defined as FQ or TMP/SMX. Oral FQ and TMP/SMX have bioavailability equivalent to IV. The primary outcome compared the composite of recurrent bacteremia or mortality within 30 days of therapy between groups. Specifically, this study was designed to evaluate the outcomes of utilizing high-dose cephalexin 1 g three times daily or amoxicillin 1 g three times daily as definitive oral therapy for Enterobacterales bacteremia from a urinary source compared to optimally dosed alternative therapy with FQ and TMP/SMX. Secondary outcomes compared recurrent UTI, ED or hospital readmission, and C difficile within 30 days. Adults 18 years or older with matching urine and blood cultures with E coli, K pneumoniae or oxyctoca, or Proteus mirabilis who received an empiric antibiotic regimen active against the isolated pathogen and then transitioned to appropriately dosed oral therapy.

194 patients were included (beta-lactam, n = 75 vs standard therapy, n =119). E coli was the most common pathogen isolated. Patients in both groups were treated for a median of 11 days, with 4 days IV and 7 days oral therapy. There was no difference in the primary outcome between groups (beta-lactam 1.3% vs standard therapy 1.7%, OR 1.27 [95% CI 0.11–14.2]). No patients experienced C. difficile in either group (p = 1.0). Infectious disease consultation was independently associated with standard therapy prescribing (OR 4.4 [95% CI 2.24–8.26]). Susceptibilities of the isolated pathogens to first-generation cephalosporins and fluoroquinolones were over 90% in both groups, but aminopenicillins were <60% in both groups. Hospital length of stay was the same in both groups (median 5 days; [IQR] 4–6 days; p = 0.330).

Supplementary Table 1: Bioavailability of Oral Antibiotics

Penicillins	Bioavailability	Protein binding	Urinary excretion
Amoxicillin	70-80% [9, 10]	17-20% [9]	60% [21]
Amoxicillin/clavulanate	70-80% [9, 10]	18-25% [9]	25-40% [22]
Cephalosporins			
Cephalexin	95% [11]	10-19% [9]	90% [9]
Cefadroxil	90% [12]	20% [12]	90% [12]
Cefuroxime	30-52% (increased with food) [13]	33-50% [13]	66-100% [13]
Cefpodoxime	29-53% (increased with food) [9]	18-30 [9]	29-33% [23]
Cefdinir	21-25% [14]	60-70% [14]	12-18% [14]
Fluoroquinolones			
Ciprofloxacin	70% [15]	20-40% [15]	35-70% [24]
Levofloxacin	99% [16]	24-38% [16]	87% [25]
Other			
Sulfamethoxazole/trimethoprim	100% [9]	SMX: 70% [9] TMP: 44% [9]	SMX: 84.5% [26] TMP: 66.8% [26]

Comment: Previous studies evaluating oral beta-lactam therapy for UTI demonstrated increased rates of recurrent infection compared to alternative treatment. [Expert Opin Pharmacother 2019; 20:903–907] Sutton and colleagues evaluated 4089 patients with bacteremia from a urinary source; 955 patients received an oral beta-lactam and 3134 patients received either a FQ or TMP/SMX. [JAMA Netw Open 2020;3(10):e2020166] The primary outcome of 30- day mortality or recurrent bacteremia occurred in 4.4% of patients in the beta-lactam cohort compared to 3% of patients in the FQ or TMP/SMX cohort (95% CI 0.87–1.95). In the past, highly bioavailable options included FQ or TMP/ SMX while less bioavailable oral antibiotics were beta-lactams. In addition, cefazolin is the only antibiotic tested to determine susceptibility to 1GCs. MICs to oral 1GC are generally higher than to cefazolin which has led

some to prescribe 3rd and 4th GC oral cephalosporin for PO step down. The investigators in this study optimized dosing of beta-lactams after bacteremia had cleared, recommending high-dose amoxicillin 1000 mg three times (<60% were susceptible) and cephalexin 1000 mg three times daily for susceptible isolates. This study provides important insight into the efficacy of standard dosing of amoxicillin and cephalexin dosed 1 g three times daily in the treatment of bacteremic UTI and address the limitations of previously published retrospective studies which included a variety of beta-lactam agents and dosing strategies without indicating the appropriateness of dosing based on renal function. While the serum half-life of cephalexin is approximately one hour, cephalexin achieves high concentrations within the urine with an estimated concentration more than 500 times the MIC breakpoint after a single 500 mg oral dose and concentrations exceeding the breakpoint at 8–12 hours post-dose.(see above) As most patients will have received multiple days of IV antibiotics targeting bacteremia which should have cleared bacteremia, cephalexin dosed three times daily is optimally aimed to treat the source of infection, the urine. This study was a retrospective cohort of limited size. As with all retrospective analyses, this may have selection bias. Lastly, as recent studies have demonstrated treatment durations of less than 14 days was safe and efficacious for the treatment of uncomplicated gram-negative bacteremia.

Clinician Testing and Treatment Thresholds for Management of Urinary Tract Infection OFID published online August 31, 2023

doi.org/10.1093/ofid/ofad455

In a survey, US primary care clinicians answered questions about a low-risk scenario for UTI. The case described a 65-year-old man with foul-smelling urine, trace blood upon dipstick, and no pain or dysuria. Clinicians were asked whether they would obtain a urine culture and treat if the culture were positive. They were also asked to provide a risk estimate for each outcome.

Of 551 respondents who completed the survey, 61% would order a urine culture and 71% would treat following a positive culture. The threshold (that 50% would test) occurred when the estimated chance of a UTI was 19%; for treating, the threshold occurred at an estimated UTI chance of 42%. Among physicians, longer duration of time in practice made testing and treatment more likely (range, 58%–66% [testing]; 64%–82% [treatment]). NPs and PAs were more likely than physicians to test (82%) and treat (90%).

Comment: Across a population of primary care clinicians in 8 US states, they found that clinicians on average would test with a 19% chance of UTI and treat with a 42% chance of UTI. Variation in thresholds was noted by type of clinician, years in practice, and geographic location. For this hypothetical case, IDSA guidelines do not recommend a urine culture or antibiotics if the culture is positive. The authors conclude that better clinician understanding of the initial likelihood of UTI and consideration for decision thresholds for testing and treatment is key for improving antibiotic overuse. Study after study continues to show opportunities to improve both urinary diagnostic and antimicrobial stewardship.

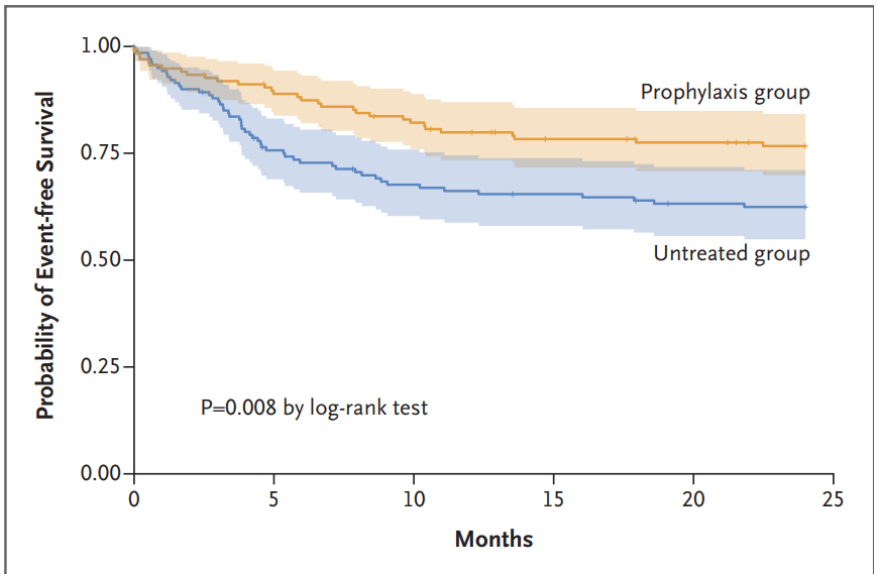
Antibiotic Prophylaxis in Infants with Grade III, IV, or V Vesicoureteral Reflux N Engl J Med 2023;389:987-97

DOI: 10.1056/NEJMoa2300161

This was a randomized, open-label trial performed in 39 European centers, we randomly assigned infants 1 to 5 months of age with grade III, IV, or V vesicoureteral reflux and no previous UTIs to receive continuous antibiotic prophylaxis (prophylaxis group) or no treatment (untreated group) for 24 months. The primary outcome was the occurrence of the first UTI during the trial period. Secondary outcomes included new kidney scarring and the estimated GFR at 24 months. Infants with previous UTI, posterior urethral valves, neurogenic bladder, or ureteropelvic-junction or ureterovesical-junction obstruction were excluded.

A total of 292 participants underwent randomization (146 per group). Approximately 75% of the participants were male; the median age was 3 months, and 235 participants (80.5%) had grade IV or V vesicoureteral reflux. In the intention-to-treat analysis, a first UTI occurred in 31 participants (21.2%) in the prophylaxis group and in 52 participants (35.6%) in the untreated group (hazard ratio, 0.55; 95% confidence interval [CI], 0.35 to 0.86; P=0.008); the number needed to treat for 2 years to prevent one UTI was 7 children (95% CI, 4 to 29). Among untreated participants, 64.4% had no UTI during the trial. The incidence of new kidney scars and the estimated GFR at 24 months did not differ substantially between the two groups. Pseudomonas species, other non–Escherichia coli organisms, and antibiotic resistance were more common in UTI isolates obtained from participants in the prophylaxis group than in isolates obtained from those in the untreated group. Serious adverse events were similar in the two groups.

Urinary Tract Infection (UTI)–free Survival during the 24-Month Trial.



Comments: Double-blind, placebo-controlled trials such as the Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR) trial and the Prevention of Recurrent Urinary Tract Infection in Children with Vesicoureteric Reflux and Normal Renal Tracts (PRIVENT) trial showed that continuous antibiotic prophylaxis significantly reduced the risk of UTI among children with vesicoureteral reflux.[N Engl J Med 2014;370:2367-76; N Engl J Med 2009;361:1748-59] However, other randomized trials showed either no beneficial effect or a beneficial effect that was limited to female patients. [Pediatrics 2008;121(6):e1489-e1494; Pediatr Nephrol 2015;30:479-86] Systemic reviews and meta-analyses have also yielded mixed results. In the current trial infants with grade III, IV, or V vesicoureteral reflux and no previous UTIs, continuous antibiotic prophylaxis provided a small but significant benefit in preventing a first UTI despite an increased occurrence of non–E. coli organisms and antibiotic resistance. This trial was not blinded or placebo-controlled, and four different antibiotic options were used for continuous antibiotic prophylaxis. Little was reported about protocol adherence. The entry criterion of no prior UTI limits the comparability of the trial with other trials that mostly involved patients with a history of UTI. The American Urological Association, the European Association of Urology–European Society for Pediatric Urology, and the Swedish and the Italian Societies for Pediatric Nephrology all recommend a more selective approach for using continuous antibiotic prophylaxis, based on a combination of factors that include patient age and sex, severity of vesicoureteral reflux, and the presence of bladder or bowel dysfunction or renal scarring. Nonetheless, the results of this trial demonstrated that continuous antibiotic prophylaxis significantly reduced the risk of UTI, but at the expense of increased antimicrobial resistance.

Current Pyuria Cutoffs Promote Inappropriate Urinary Tract Infection Diagnosis in Older Women Clin Infect Dis 2023; 76:2070–6

doi.org/10.1093/cid/ciad099

Women ≥65 years with ≥2 new-onset lower urinary tract symptoms (LUTS)[(dysuria, frequency, urgency, or suprapubic pain] and 1 uropathogen ≥10^4 colony-forming units (CFU)/mL were included in the UTI group. Controls were asymptomatic and classified as ASB (1 uropathogen ≥10^5 CFU/mL), negative culture, or mixed flora. Patients with an indwelling catheter or antimicrobial pretreatment were excluded. Although cutoff values for “significant” pyuria vary in the literature and depend on quantification methods, commonly accepted cutoffs include 10 leukocytes/μL and 5–10 leukocytes per high-power field (hpf). These cutoff values are largely derived from studies involving nonpregnant premenopausal women, in whom ASB is uncommon. The objective of this study was to determine sensitivity and specificity of automated microscopy and urine flowcytometry for diagnosing UTI in older women, with the ultimate goal to derive optimal cutoff values for pyuria for UTI in this population, taking ASB into account. Leukocyte medians were compared and sensitivity–specificity pairs were derived from a receiver operating characteristic curve.

They included 164 participants. UTI patients had higher median urinary leukocytes compared with control patients (microscopy: 900 vs 26 leukocytes/μL; flowcytometry: 1575 vs 23 leukocytes/μL; $P < .001$). In other words, UTI patients had significantly more WBCs on

automated microscopy — almost 900 cells/μL (≈180 cells/HPF). However, the degree of pyuria among controls was considerably higher than anticipated: Median WBC cells/μL ranged from negligible in controls with insignificant culture results to almost 300 (60 cells/HPF) in those in whom ASB was diagnosed. Area under the curve was 0.93 for both methods. At a cutoff of 264 leukocytes/μL, sensitivity and specificity of microscopy were 88% (positive and negative likelihood ratio: 7.2 and 0.1, respectively). The commonly used cutoff of 10 leukocytes/μL had a poor specificity (36%) and a sensitivity of 100%.

Comment: Current pyuria cutoffs appear too low and may promote inappropriate UTI diagnosis in older women. Prior studies have demonstrated 20% of community-dwelling and 50% of institutionalized older women have asymptomatic bacteriuria (ASB), defined as the presence of 1 or more uropathogens with 10^5 colony-forming units (CFU)/ mL or higher in the absence of signs or symptoms attributable to UTI [Clin Infect Dis 2019; 68:1611–5], leading to inappropriate antimicrobial treatment, leading to unnecessary side effects, drug interactions, C difficile infection, and the selection of antimicrobial-resistant pathogens. [Arch Intern Med 2011; 171:438–43] Distinguishing ASB from UTI is further complicated by the fact that over 90% of older women with ASB have concomitant pyuria. [Ann Intern Med 1989; 110:404–5] Consequently, the positive-predictive value of the presence of pyuria for UTI is low in older women. Results may not be generalizable to institutionalized older people with high frailty and/or advanced dementia. See next review

The take home message is not that patients with UTIs have substantial pyuria, but rather older women with ASB have far more white cells in their urine than expected.

Are Antibiotics Helpful for Older Adults with Delirium and Pyuria or Bacteriuria?

N Engl J Med Evidence 2023;2(9) August 22, 2023

DOI: 10.1056/EVIDtt2300119

Delirium is common, affecting 30 to 50% of hospitalized older adults. [N Engl J Med 2017; 377:1456-1466] A urinalysis is frequently performed as part of a comprehensive evaluation for delirium because lower UTIs occur commonly in older adults. If bacteriuria (>100,000 colony-forming units per 1 ml) or pyuria (>10 leukocytes per high-power field) [see review above] is present, many clinicians prescribe antibiotics even without clear lower urinary tract symptoms. In a recent study of 150 older adults admitted to the hospital with delirium, 86% received antibiotics for a suspected UTI, despite the absence of localizing urinary tract symptoms. [BMC Geriatr 2022; 22:916] Studies have shown that bacteriuria and pyuria are commonly identified in healthy older adults, and in that setting, these findings have not been associated with the development of infection. [J Am Geriatr Soc 2013; 61:62-66]

The American Geriatrics Society recommends against treatment of asymptomatic bacteriuria, and the IDSA recommends careful observation rather than antimicrobial treatment for older adults with bacteriuria and delirium without systemic or local symptoms. [Clin Infect Dis 2019; 68:1611-1615] These recommendations are rated as “very-low-quality evidence” since the results of these trial are based observational studies. Retrospective and prospective cohort studies have found that antibiotic treatment for asymptomatic pyuria or bacteriuria in hospitalized older adults with delirium does not lead to improved outcomes. Instead, treatment has been associated with longer duration of hospitalization, worse functional recovery, and no

difference in resolution of delirium 7 days later. [Arch Gerontol Geriatr 2017;72:127-134] The authors point out that nonrandomized studies are prone to selection bias, particularly confounding by indication related to the decision to prescribe antibiotics to patients who are at higher risk of adverse outcomes.

They conclude there is a dearth of high-quality evidence in this area which may have contributed to marked practice variation across medical specialties and settings. However, despite the absence of evidence that antimicrobial treatment is beneficial, a survey of 296 Canadian physicians presented with hypothetical cases found that 60% would still treat pyuria or bacteriuria in the presence of confusion. [CJEM 2022;24:61-67]

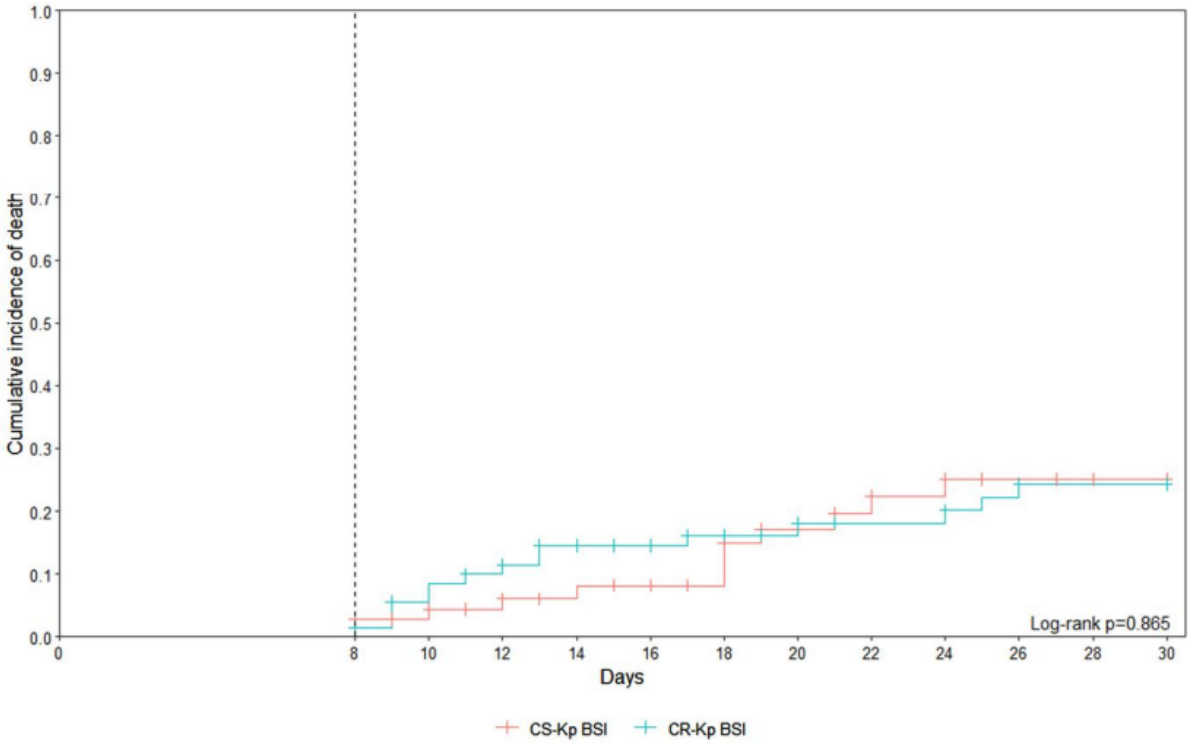
Comment: In the end, the authors recommend that a RCT randomized is needed to evaluate the effectiveness of antibiotics in older adults who present with delirium and pyuria or bacteriuria. The question is can we wait since it is well known the harms of antibiotics including GI symptoms, hyperkalemia, QT prolongation, and C difficile infection. More broadly, antibiotic overuse drives antimicrobial resistance, which is a growing threat to public health. Pending such a trial [which may never be done] I believe the IDSA approach makes the most sense.

Mortality in KPC-producing *Klebsiella pneumoniae* bloodstream infections: a changing landscape J Antimicrob Chemother published online August 22, 2023

doi.org/10.1093/jac/dkad262

Bloodstream infection (BSI) caused by carbapenem-resistant *Klebsiella pneumoniae* (CR-KP) has historically been associated with higher mortality than BSI caused by carbapenem-susceptible *K. pneumoniae* (CS-KP). As this difference could not be explained by comorbidities, illness severity, time to antibiotic initiation, or pathogen virulence, the shortcomings of polymyxin-based regimens were deemed responsible. What effect does carbapenem resistance have on mortality from *K. pneumoniae* BSI in the era of novel β-lactam/β-lactamase inhibitor (BL/BLI) combinations?

This retrospective, multicenter study involved 427 hospital patients (median age, 67) between January and August 2020, 75% of participants had CS-KP and 25% had CR-KP, yielding a crude 30-day mortality of 21% and 34%, respectively (p=0.027). The most common treatment for CR-KP BSI was ceftazidime/avibactam (CAZ/AVI; 80/107, 75%). In multivariate analysis, Pitt bacteremia score and age-adjusted Charlson comorbidity index were associated with mortality, but presence of CR-KP was not. In propensity-score–matched analysis, mortality did not differ significantly between patients appropriately treated with CAZ/AVI for CR-KP BSI and those appropriately treated with other agents (mainly meropenem monotherapy or piperacillin/tazobactam monotherapy) for CS-KP BSI (hazard ratio, 1.07; p = 0.866).



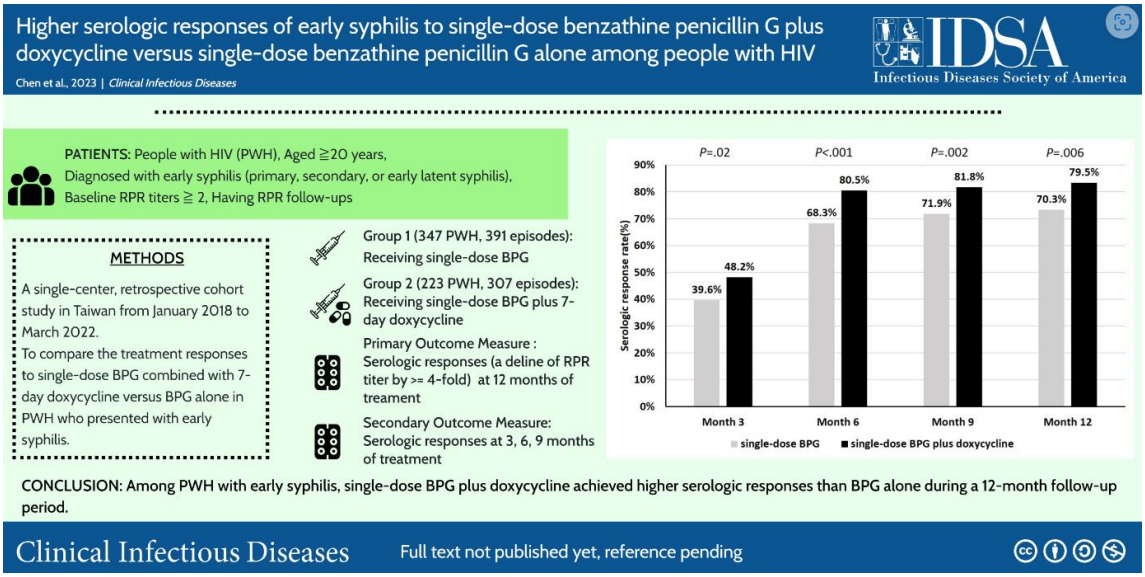
Comments: During the last decade, several studies have demonstrated that BL/BLI antibiotics are better tolerated, and have better outcomes compared to polymyxin-based therapies for carbapenem-resistant gram-negative infections. This study builds upon data that focuses on BSIs caused by CR-KP and shows that use of a newer BL/BLI like CAZ/AVI restores survival in patients with CR-KP to levels expected for treating CS-KP. While this study focused on CAZ/AVI I think similar results would be seen with other new BL/BLIs active against CR-KP such as imipenem/relebactam and meropenem/vaborbactam. This study and others support abandoning polymyxins for treatment of CREs.

Higher serologic responses of early syphilis to single-dose benzathine penicillin G plus doxycycline versus single-dose benzathine penicillin G alone among people with HIV Clin Infect Dis published online August 27, 2023

DOI: 10.1093/cid/ciad508

Standard treatment for early syphilis with benzathine penicillin G (BPG) yields lower response rates in people with HIV (PWH) than in those without. Investigators in Taiwan conducted a retrospective review of serologic outcomes following treatment for early syphilis in PWH who received either BPG alone (single dose) or BPG plus doxycycline (the latter given for 7 days) for presumed chlamydial coinfection and administered at the physician's discretion.

PWH with 307 episodes of early syphilis received single-dose BPG plus doxycycline and 347 PWH with 391 episodes received BPG alone. Patients were almost exclusively men, were receiving antiretroviral therapy, and had a median CD4 count of 600 cells/mm^3 and undetectable viral load. Serologic response (defined as a fourfold decline in rapid plasma reagin [RPR] at month 12) was achieved in 79.5% of 223 patients receiving BPG plus doxycycline versus 70.3% of 347 patients receiving BPG alone (p=0.006). Factors associated with 12-month serologic response were RPR titer (per 1-log2 increase, adjusted odds ratio [AOR], 1.25; 95% CI, 1.15–1.35) and receipt of BPG plus doxycycline (AOR, 1.71; 95% CI, 1.20–2.46). In the subgroup analyses, BPG plus doxycycline was consistently associated with a better serologic response than BPG alone at month 12.



Comments: Previous studies failed to demonstrate an improvement in serologic responses of early syphilis to enhanced therapy. In a randomized trial comparing treatment with single-dose BPG versus single-dose BPG plus a 10-day course of amoxicillin and probenecid in participants with and those without HIV, enhanced therapy did not show better serologic responses at 12 months of treatment (83% vs 82%) and clinical outcomes. [N Engl J Med 1997; 337:307-1412]. Other studies comparing serologic responses to single-dose versus three-dose BPG among PWH drew conflicting conclusions. The additional benefit of BPG/Doxy for sexually transmitted co-infections among PWH with early syphilis had not been investigated before. The STIs treatment guidelines recommend that individuals treated for gonococcal infection should also

receive therapy for chlamydial infection since 20-42% of individuals infected with N. gonorrhoeae are co-infected with C. trachomatis. In light of a high prevalence of chlamydial co-infection among PWH with early syphilis (17% to 29%). [Cent Eur J Public Health 2019; 27:285-91], doxycycline-based combination therapy for early syphilis may prevent complications and onward transmission of chlamydial infection.

Management of syphilis can be challenging and RPR is an indirect gauge of disease activity. The investigators speculate that doxycycline has good brain penetration which could help eradicate pathogens from CNS, a common site for occult infection in PWH. The retrospective design and potential for the potential for between groups limit the strength of the evidence. Patients were almost exclusively men, were receiving antiretroviral therapy, and had a median CD4 count of 600 cells/mm^3 and undetectable viral load so these results may not be generalizable to other patients with PWH who have lower CD4 counts and detectable viral loads.

Editor's Choice

Treatment Failure and Adverse Events After Amoxicillin-Clavulanate vs Amoxicillin for Pediatric Acute Sinusitis JAMA. 2023; 330:1064-1073.

doi:10.1001/jama.2023.15503

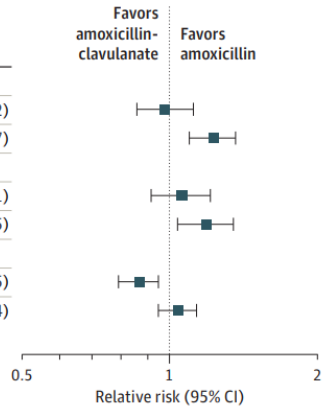
The investigators asked the question, for pediatric acute sinusitis, is amoxicillin-clavulanate associated with different rates of treatment failure or adverse events compared with amoxicillin? They report that the effectiveness and safety of amoxicillin-clavulanate vs amoxicillin for the treatment of new diagnoses of acute bacterial sinusitis in children has not been studied since the first introduction of conjugate pneumococcal vaccines in 2000. Since that time, the routine use of this vaccine and increasing antibiotic resistance rates may have shifted the microbiology of acute bacterial sinusitis, with reports of reductions in the contributions of S pneumoniae and increases in the rates of β-lactamase– producing H influenzae. Cohort entry was defined as an outpatient encounter with an ICD-10 code for acute sinusitis and a same day prescription dispensation for either amoxicillin or amoxicillin-clavulanate, a definition with a positive predictive value of 92% (95% CI, 87%-97%) for new diagnoses of acute bacterial sinusitis. Patients were excluded if they were 18 years or older at cohort entry, lacked at least 365 days of continuous enrollment in their insurance plan prior to their qualifying encounter; or had chronic sinus disease, a same-day additional infectious disease diagnosis, or an acute sinusitis diagnosis or oral antibiotic dispensation in the 30 days prior to their qualifying encounter. The primary outcome was treatment failure, an aggregate outcome assessed 1 to 14 days after cohort entry. Treatment failure was defined as the first occurrence of any of the following individual outcomes: (1) a new antibiotic dispensation, different from the index antibiotic, in the absence of an outpatient encounter (e.g., a prescription called in after an unbilled phone encounter); (2) a new antibiotic dispensation, different from the index antibiotic, with a same-day outpatient encounter for acute sinusitis; (3) an emergency department encounter for acute sinusitis; (4) an inpatient encounter for acute sinusitis; or (5) an inpatient encounter for a complication of sinusitis. Secondary analyses included the 5 component treatment failure outcomes individually, and an aggregate of the emergency department and inpatient encounters, termed serious treatment failure. They assessed adverse events, including GI

symptoms, hypersensitivity and skin reactions, acute kidney injury, yeast infections, and C difficile infections.

The cohort included 320,141 patients. After propensity score matching, there were 198,942 patients (99,471 patients per group), including 100,340 (50.4%) who were female, 101,726 (51.1%) adolescents aged 12 to 17 years, 52,149 (26.2%) children aged 6 to 11 years, and 45, 067 (22.7%) children aged 0 to 5 years. Treatment failure occurred in 1.7% overall; 0.01% had serious failure (an emergency department or inpatient encounter). There was no difference in the risk of treatment failure between the amoxicillin-clavulanate and amoxicillin groups (relative risk [RR], 0.98 [95% CI, 0.92-1.05]). The risk of GI symptoms (RR, 1.15 [95% CI, 1.05-1.25]) and yeast infections (RR, 1.33 [95% CI, 1.16-1.54]) was higher with amoxicillin-clavulanate. After patients were stratified by age, the risk of treatment failure after amoxicillin-clavulanate was an RR of 0.98 (95% CI, 0.86-1.12) for ages 0 to 5 years; RR was 1.06 (95% CI, 0.92-1.21) for 6 to 11 years; and RR was 0.87 (95% CI, 0.79-0.95) for 12 to 17 years. The age-stratified risk of adverse events after amoxicillin-clavulanate was an RR of 1.23 (95% CI, 1.10-1.37) for ages 0 to 5 years; RR was 1.19 (95% CI, 1.04-1.35) for 6 to 11 years; and RR was 1.04 (95% CI, 0.95-1.14) for 12 to 17 years.

Figure 4. Treatment Failure and Adverse Outcomes Stratified by Age After Propensity Score Matching

Outcome	No. of events (%)		Difference, % (95% CI)	Relative risk (95% CI)
	Amoxicillin-clavulanate[a]	Amoxicillin[a]		
Ages 0-5 y, n = 22 573[b]				
Treatment failure	448 (2.0)	455 (2.0)	-0.03 (-0.29 to 0.22)	0.98 (0.86 to 1.12)
Adverse events	759 (3.4)	622 (2.8)	0.61 (0.29 to 0.92)	1.23 (1.10 to 1.37)
Ages 6-11 y, n = 25 975[b]				
Treatment failure	458 (1.8)	432 (1.7)	0.10 (-0.12 to 0.32)	1.06 (0.92 to 1.21)
Adverse events	512 (2.0)	433 (1.7)	0.30 (0.07 to 0.53)	1.19 (1.04 to 1.35)
Ages 12-17 y, n = 49 582[b]				
Treatment failure	805 (1.6)	926 (1.8)	-0.24 (-0.41 to -0.08)	0.87 (0.79 to 0.95)
Adverse events	937 (1.9)	903 (1.8)	0.07 (-0.10 to 0.24)	1.04 (0.95 to 1.14)



[a] Amoxicillin-clavulanate indicates the exposure group, and amoxicillin indicates the referral group.

[b] The sum of patients across strata does not equal the total number of patients in the primary analyses due to propensity score estimation and matching occurring after patients were stratified by age.

Comment: This study is the first to my knowledge to compare amoxicillin-clavulanate and amoxicillin for the treatment of acute sinusitis in children since the introduction of the pneumococcal conjugate vaccines. In this cohort study of over 320,000 children, treatment failure was rare (1.7% overall) and serious treatment failure was very rare (0.01%). There was no difference in treatment failure between groups while adverse events, specifically GI symptoms and yeast infections, were more frequent among patients treated with amoxicillin-clavulanate. In subgroup analyses, adolescents aged 12 to 17 years did have a lower risk of treatment failure with amoxicillin-clavulanate, but given the overall low risk of treatment failure, 417 additional patients would need to be treated with amoxicillin-clavulanate to prevent 1 additional treatment failure with amoxicillin.

This study cohort was only commercially insured. Rates of treatment failure based on utilization data might vary among commercially insured, uninsured, and Medicaid-insured patients due to differences in health care access and utilization. This study used medication dispensation but

could not evaluate medication adherence. There are several prescriber factors (age and sex of prescriber, practice size, type of clinician) that have been associated with prescribing broader antibiotics, which were not available in their data set. [Infect Control Hosp Epidemiol. 2018;39(3):307-315] They did not have microbiologic data and could not determine whether acute sinusitis diagnoses were due to viral or bacterial etiologies. Data on race, ethnicity, and socioeconomic status were not available.

The Infectious Diseases Society of America (IDSA) recommends amoxicillin-clavulanate, [Clin Infect Dis. 2012;54: e72-e112] while the American Academy of Pediatrics recommends amoxicillin with or without clavulanate [Red Book: 2021–2024 Report of the Committee on Infectious Diseases. 32nd ed. American Academy of Pediatrics; 2021] as first-line empirical antibiotic treatment for an initial diagnosis of acute sinusitis. Therefore, evaluating whether amoxicillin or amoxicillin-clavulanate is preferred as first line is of considerable clinical importance. Clavulanate extends additional antimicrobial spectrum through inhibition of bacterial β-lactamases, but the increase in coverage may come at the cost of increased adverse events and increasing antimicrobial resistance. [JAMA. 2017; 318:2325-2336]

Several months ago, ID Watch reviewed an article in Clin Infect Dis [DOI: 10.1093/cid/ciad385] reminding us that the PIDS/IDSA pediatric CAP guideline strongly recommends narrow spectrum antibiotic use for uncomplicated CAP as first-line therapy for healthy children without penicillin allergy, specifically amoxicillin for children treated in the outpatient setting and amoxicillin or ampicillin for children treated in the ED or inpatient setting. [Clin Infect Dis. 2011;53: e25-76]

In this study amoxicillin was safer than amoxicillin-clavulanate, with no differences in outcomes, and is less expensive. The investigators conclude "These findings may help inform decisions for empirical antibiotic selection in acute sinusitis." The PIDS/IDSA pediatric CAP guideline and the current study suggests that amoxicillin remains a viable alternative to broader spectrum antimicrobials for the treatment of sinusitis and uncomplicated CAP.

Statement Following the September 2023 FDA Meeting of the Nonprescription Drugs Advisory Committee (NDAC) to Evaluate New Data Concerning the Efficacy of Oral PE (phenylephrine) September 12, 2023

An advisory panel to the FDA declared Tuesday September 12th that an ingredient in widely used oral decongestants doesn't work. The FDA panel's unanimous vote clears the way for the agency to remove oral phenylephrine from its list of approved over-the-counter ingredients. That would mean that products containing the ingredient could not be sold in the U.S. The FDA said in an analysis before the panel's meeting that the oral phenylephrine formulations are safe but ineffective at standard or even higher doses. The agency said that three large recent industry-funded studies evaluating medicines with phenylephrine by manufacturers found that people who took medicines with phenylephrine fared no better than those who received a placebo. The agency also found that research from decades ago didn't meet current clinical trial design standards and included inconsistent results.

Comment: I am glad the FDA finally weighed in on phenylephrine since it has been known that phenylephrine was probably not effective. I am not sure what FDA so long. Instead of taking pills that contain phenylephrine to clear congestion, people can take pills containing pseudoephedrine, antihistamines, or nasal spray products. Sales of products containing pseudoephedrine are required to be behind the pharmacy counter because the ingredient can be used to make methamphetamine.

Human Papillomavirus Concordance Between Parents and Their Newborn Offspring: Results From the Finnish Family Human Papillomavirus Study J Infect Dis published online August 10, 2023

doi.org/10.1093/infdis/jiad330

The objective of this study was to determine whether HPV transmission from parents to their offspring occurs before or during birth. Altogether, 321 mothers, 134 fathers, and their 321 newborn offspring from the Finnish Family HPV study cohort were included. Parents' genital and oral brush samples and semen samples were collected for HPV testing at baseline (36 weeks of pregnancy). Oral, genital, and umbilical samples from the newborn and placenta samples were collected for HPV testing immediately after delivery. HPV risk for the newborn was calculated from the mother's and father's HPV status by using logistic regression analyses.

Concordances between mothers' and their newborns' HPV genotype at any site were statistically significant with HPV-6, -16, -18, -31, and -56; odds ratios (ORs) ranged from 3.41 (95% confidence interval [CI], 1.80–6.48) for HPV-16 to 634 (95% CI, 28.5–14 087) for HPV-31. Father–newborn HPV concordance was statistically significant with HPV-6 and HPV-31 (ORs, 4.89 [95% CI, 1.09–21.9] and 65.0 [95% CI, 2.92–1448], respectively).

Comment: To date, only 1 meta-analysis [Arch Gynecol Obstet 2018; 298:35–44] of type-specific intrauterine vertical transmission has been published, suggesting an intrauterine transmission rate of 4.9%, but the rate of transmission in selected studies varied between 0% and 46.7%. This study demonstrated a transmission rate of 37.0% (37/ 100) from mothers' any anatomic site to newborns' any anatomic site, and transmission rate of 35.1% (33/94) from mothers' genital site to newborns' any anatomic site. This study had a lower number of fathers (n = 134) than mothers (n = 321), due to fathers' unwillingness to participate in the study. In addition, parental samples were collected only at 36 weeks of pregnancy. Transcriptionally active HPV was not examined, and thus the state of HPV infection could not be verified. In addition, they did not have information on the type-specific HPV variant via sequencing, which would provide more proof of the transmission between family members and should be considered in future studies.

Despite some limitations, the genotype-specific HPV concordance between parents and their newborn is suggestive for vertical HPV transmission. However, transmission from the father to the newborn remains more uncertain. Alternative to direct father-to-newborn transmission, the transmission to the newborn might have been vertical from the mother as mother and father are expected to share same HPV genotypes through sexual transmission.

Interim Effectiveness Estimates of 2023 Southern Hemisphere Influenza Vaccines in Preventing Influenza-Associated Hospitalizations — REVELAC–i Network, March–July 2023 MMWR early release September 8, 2023

Since 2013, multiple countries have participated in the Network for the Evaluation of Vaccine Effectiveness in Latin America and the Caribbean–influenza (la Red para la Evaluación de Vacunas en Latino América y el Caribe—influenza [REVELAC-i]) to estimate and monitor vaccine effectiveness (VE) in preventing severe acute respiratory infection (SARI)–associated hospitalization. VE against influenza-associated hospitalization was estimated using a test-negative case-control study design to compare the odds of vaccination between hospitalized patients with a positive influenza test result (test-positive patients [case-patients]) and influenza test-negative hospitalized control patients. Patients meeting criteria for severe acute respiratory infection (SARI), defined as acute respiratory infection with a history of fever or documented temperature of ≥100.4°F [≥38°C] and cough, with onset during the preceding 10 days resulting in hospitalization, were identified through sentinel SARI surveillance using a standardized protocol. Respiratory specimens were collected and tested for influenza virus type and subtype by PCR in national reference laboratories.

Based on data contributed by Argentina, Brazil, Chile, Paraguay, and Uruguay on 2,780 SARI patients hospitalized during March 27–July 9, 2023, the adjusted VE against SARI hospitalization associated with any influenza virus during the 2023 Southern Hemisphere season was 51.9% (95% Confidence Interval [CI] 39.2%–62.0%), including 55.2% (95% CI: 41.8%–65.5%) against the predominating A(H1N1)pdm09.

TABLE 2. Interim 2023 southern hemisphere seasonal influenza vaccine effectiveness against all influenza types A and B and against virus type A(H1N1)pdm09 — REVELAC-i Network, March–July 2023

Influenza type/Target group[§]	Influenza test-positive case-patients*		Influenza test-negative control patients		Vaccine effectiveness[†]	
	Total	Vaccinated no. (%)	Total	Vaccinated no. (%)	Unadjusted % (95% CI)	Adjusted[†] % (95% CI)
Influenza A and B						
Overall	900	138 (15.3)	1,880	526 (28.0)	53.3 (42.4 to 62.4)	51.9 (39.2 to 62.0)
Older adults	547	96 (17.6)	583	176 (30.2)	50.8 (34.1 to 63.3)	37.6 (13.1 to 55.2)
Children	214	19 (8.9)	1,048	286 (27.3)	74.0 (57.3 to 85.0)	70.2 (50.3 to 82.1)
Persons with preexisting conditions	139	23 (16.5)	249	64 (25.7)	42.7 (0.3 to 67.8)	38.0 (−10.8 to 65.3)
Influenza A/H1N1						
Overall	668	102 (15.3)	1,880	526 (28.0)	53.6 (41.2 to 63.6)	55.2 (41.8 to 65.5)
Older adults	422	70 (16.6)	583	176 (30.2)	54.0 (36.6 to 66.8)	42.7 (18.5 to 59.8)
Children	120	10 (8.3)	1,048	286 (27.3)	75.8 (52.9 to 88.9)	75.3 (52.1 to 87.3)
Persons with preexisting conditions	126	22 (17.5)	249	64 (25.7)	38.9 (−7.6 to 66.1)	43.0 (−6.7 to 69.5)
Influenza B						
Overall	85	10 (11.8)	1,880	526 (28.0)	65.7 (32.6 to 84.3)	46.2 (−7.9 to 73.2)

Comment: These early, interim estimates suggest that vaccination substantially reduced the risk for severe influenza illnesses, underscoring the benefits of influenza vaccination. Despite the encouraging influenza VE, fewer than 30% of persons identified through REVELAC-i were vaccinated against influenza before their illness onset. In anticipation of Northern Hemisphere influenza virus circulation, the WHO and CDC recommend that health authorities encourage health care providers to administer annual influenza vaccination to all eligible persons, particularly emphasizing the importance of vaccination for persons at increased risk for severe outcomes (e.g., very young children, persons with preexisting health conditions [including pregnant women], and older adults). Nearly 25% of the 1,194 otherwise eligible patients were missing PCR results for influenza and were excluded from analysis. Although the REVELAC-i protocol indicates PCR testing for all patients meeting SARI criteria, limited hospital resources for surveillance specimen collection during high-incidence periods might result in incomplete testing. Although statistical models accounted for important sources of confounding, the potential for unmeasured confounding associated with the likelihood of hospitalization or propensity for vaccination remains. See next review

Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2023–24 Influenza Season MMWR / August 25, 2023 / Vol. 72 / No. 2

The CDC's Advisory Committee on Immunization Practices (ACIP) has issued new guidelines for the prevention and control of seasonal influenza with vaccines for the 2023-2024 season.

Routine annual influenza vaccination is recommended for all patients 6 months of age and older who have no contraindications. Vaccination should ideally be completed by October though it should be offered throughout the season if influenza viruses continue to circulate. For the 2023–2024 season, all influenza vaccines are expected to be quadrivalent, containing hemagglutinin (HA) derived from 1 influenza A(H1N1)pdm09 virus, 1 influenza A(H3N2) virus, 1 influenza B/Victoria lineage virus, and 1 influenza B/Yamagata lineage virus.

Egg-based influenza vaccines:

- Will contain HA derived from an influenza A/Victoria/4897/2022 (H1N1)pdm09-like virus, an influenza A/Darwin/9/2021 (H3N2)-like virus, an influenza B/Austria/1359417/2021 (Victoria lineage)-like virus, and an influenza B/Phuket/3073/2013 (Yamagata lineage)-like virus.
- These include Afluria Quadrivalent, Fluarix Quadrivalent, FluLaval Quadrivalent, Fluzone Quadrivalent (all standard dose), Fluzone High-Dose Quadrivalent (high-dose formulation), Fluad Quadrivalent (standard dose with MF59 adjuvant), and FluMist Quadrivalent intranasal spray.

Cell culture-based inactivated or recombinant influenza vaccines:

- Will contain HA derived from an influenza A/Wisconsin/67/2022 (H1N1)pdm09-like virus, an influenza A/Darwin/6/2021 (H3N2)-like virus, an influenza B/Austria/1359417/2021 (Victoria lineage)-like virus, and an influenza B/Phuket/3073/2013 (Yamagata lineage)-like virus.
- These include Flucelvax Quadrivalent (standard dose cell culture-based) and Flublok Quadrivalent (recombinant).

Updates to the guidance for this upcoming influenza season include the following:

- influenza vaccine (egg-based or nonegg-based) that is otherwise appropriate for the recipient's age and health status.
    - It is no longer recommended that individuals who have had an allergic reaction to egg with symptoms other than urticaria should be vaccinated in a medical setting supervised by a health care provider who is able to recognize and manage severe allergic reactions if an egg-based vaccine is used.
    - Egg allergy alone does not require additional safety measures for influenza vaccination beyond those recommended for any recipient of any vaccine, regardless of severity of previous reaction to egg.
    - All vaccines should be administered in settings in which personnel and equipment needed for rapid recognition and treatment of acute hypersensitivity reactions are available.

Regarding simultaneous administration of influenza vaccine with the new RSV vaccine, data included in the prescribing information for GSK's Arexvy show no evidence for interference in the immune response to any of the antigens contained in both concomitantly administered vaccines. In this study (ClinicalTrials.gov Identifier: NCT04841577), participants 60 year of age and older received 1 dose of Arexvy and Fluarix Quadrivalent. The criteria for noninferiority of the immune responses in the control vs coadministration group were met, though RSV and influenza antibody titers were somewhat lower with coadministration; the clinical significance of this is unknown.

TABLE 1. Influenza vaccines — United States, 2023–24 influenza season*

Trade name (manufacturer)	Presentation	Age indication	µg HA (IIV4s and RIV4) or virus count (LAIV4) for each vaccine virus (per dose)	Route	Mercury (from thimerosal, if present) µg/0.5 mL
IIV4 (standard-dose, egg-based vaccines†)					
Afluria Quadrivalent	0.5-mL PFS§	≥3 yrs§	15 µg/0.5 mL	IM¶	—**
(Seqirus)	5.0-mL MDV§	≥6 mos§ (needle and syringe)	7.5 µg/0.25 mL	IM¶	24.5
		18 through 64 yrs (jet injector)	15 µg/0.5 mL		
Fluarix Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
FluLaval Quadrivalent (GlaxoSmithKline)	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
Fluzone Quadrivalent	0.5-mL PFS††	≥6 mos††	15 µg/0.5 mL	IM¶	—
(Sanofi Pasteur)	0.5-mL SDV††	≥6 mos††	15 µg/0.5 mL	IM¶	—
	5.0-mL MDV††	≥6 mos††	7.5 µg/0.25 mL	IM¶	25.0
			15 µg/0.5 mL		
ccIIV4 (standard-dose, cell culture–based vaccine)					
Flucelvax Quadrivalent	0.5-mL PFS	≥6 mos	15 µg/0.5 mL	IM¶	—
(Seqirus)	5.0-mL MDV	≥6 mos	15 µg/0.5 mL	IM¶	25.0
HD-IIV4 (high-dose, egg-based vaccine†)					
Fluzone High-Dose Quadrivalent (Sanofi Pasteur)	0.7-mL PFS	≥65 yrs	60 µg/0.7 mL	IM¶	—
aIIV4 (standard-dose, egg-based vaccine‡ with MF59 adjuvant)					
Fluad Quadrivalent (Seqirus)	0.5-mL PFS	≥65 yrs	15 µg/0.5 mL	IM¶	—
RIV4 (recombinant HA vaccine)					
Flublok Quadrivalent (Sanofi Pasteur)	0.5-mL PFS	≥18 yrs	45 µg/0.5 mL	IM¶	—
LAIV4 (egg-based vaccine†)					
FluMist Quadrivalent (AstraZeneca)	0.2-mL prefilled single-use intranasal sprayer	2 through 49 yrs	$10^{6.5–7.5}$ fluorescent focus units/0.2 mL	NAS	—

TABLE 2. Contraindications and precautions for the use of influenza vaccines — United States, 2023–24 influenza season*

Vaccine type	Contraindications	Precautions
Egg-based IIV4s	• History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine† or to a previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV)§	• Moderate or severe acute illness with or without fever • History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine
ccIIV4	• History of severe allergic reaction (e.g., anaphylaxis) to a previous dose of any ccIIV or any component of ccIIV4§	• Moderate or severe acute illness with or without fever • History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine • History of severe allergic reaction to a previous dose of any other influenza vaccine (i.e., any egg-based IIV, RIV, or LAIV)¶
RIV4	• History of severe allergic reaction (e.g., anaphylaxis) to a previous dose of any RIV or any component of RIV4§	• Moderate or severe acute illness with or without fever • History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine • History of severe allergic reaction to a previous dose of any other influenza vaccine (i.e., any egg-based IIV, ccIIV, or LAIV)¶
LAIV4	• History of severe allergic reaction (e.g., anaphylaxis) to any component of the vaccine† or to a previous dose of any influenza vaccine (i.e., any egg-based IIV, ccIIV, RIV, or LAIV)§ • Concomitant aspirin- or salicylate-containing therapy in children and adolescents§ • Children aged 2 through 4 years who have received a diagnosis of asthma or whose parents or caregivers report that a health care provider has told them during the preceding 12 months that their child had wheezing or asthma or whose medical record indicates a wheezing episode has occurred during the preceding 12 months • Children and adults who are immunocompromised due to any cause, including but not limited to immunosuppression caused by medications, congenital or acquired immunodeficiency states, HIV infection, anatomic asplenia, or functional asplenia (e.g., due to sickle cell anemia) • Close contacts and caregivers of severely immunosuppressed persons who require a protected environment • Pregnancy • Persons with active communication between the CSF and the oropharynx, nasopharynx, nose, or ear or any other cranial CSF leak • Persons with cochlear implants** • Receipt of influenza antiviral medication within the previous 48 hours for oseltamivir and zanamivir, previous 5 days for peramivir, and previous 17 days for baloxavir††	• Moderate or severe acute illness with or without fever • History of Guillain-Barré syndrome within 6 weeks of receipt of influenza vaccine • Asthma in persons aged ≥5 years • Other underlying medical conditions that might predispose to complications after wild-type influenza infection (e.g., chronic pulmonary, cardiovascular [except isolated hypertension], renal, hepatic, neurologic, hematologic, or metabolic disorders [including diabetes mellitus])

Comment: A few additional considerations:

1. For most persons who need only 1 dose of influenza vaccine for the season, vaccination should ideally be offered during September or October. However, vaccination should continue after October and throughout the influenza season as long as influenza viruses are circulating, and unexpired vaccine is available.

2. For pregnant persons in the third trimester, vaccination during July and August can be considered for pregnant persons who are in the third trimester during these months because vaccination has been associated in multiple studies with reduced risk for influenza illness in their infants during the first months after birth, when they are too young to receive influenza vaccine. For pregnant persons in the first or second trimester during July and August, waiting to vaccinate until September or October is preferable, unless there is concern that later vaccination might not be possible.

3. Specific data concerning the optimal timing of influenza vaccination of persons with Covid-19 illness are not available. For those who have moderate or severe Covid-19, vaccination should usually be deferred until they have recovered from the acute illness, consistent with “General Best Practice Guidelines for Immunization.” For those with mild or asymptomatic COVID-19, further deferral might be considered to avoid confusing COVID-19 symptoms with potential postvaccination reactions.

4. ACIP recommends that adults aged ≥65 years preferentially receive any one of the following higher dose or adjuvanted influenza vaccines: quadrivalent high-dose

inactivated influenza vaccine (HD-IIV4), quadrivalent recombinant influenza vaccine (RIV4), or quadrivalent adjuvanted inactivated influenza vaccine (aIIV4).

5. A history of Guillain-Barré syndrome (GBS) within 6 weeks of a previous dose of any type of influenza vaccine is considered a precaution for influenza vaccination. Persons who are not at higher risk for severe influenza complications and who are known to have experienced GBS within 6 weeks of a previous influenza vaccination typically should not be vaccinated. As an alternative to vaccination, providers might consider using influenza antiviral chemoprophylaxis for these persons.

Bottom line, this is the time to be vaccinated for influenza and Covid-19. For high-risk individuals RSV vaccine should also be considered in consultation with your physician.

COVID-19

CDC Covid-19 Hospitalizations from June 17 to September 16, 2023

CDC data shows the rate of Covid-19 hospitalizations per 100,000 population increasing from 0.29 to 0.85 — a 190 percent increase.

70 and older**:** Admissions rose more than 200 percent, from 1.44 to 4.35.

60 to 69 years old: Admissions increased about 220 percent, from 0.39 to 1.24.

50 to 59 years old: Admissions grew 180 percent, from 0.20 to 0.56.

40 to 49 years old: Admissions rose about 190 percent, from 0.12 to 0.35.

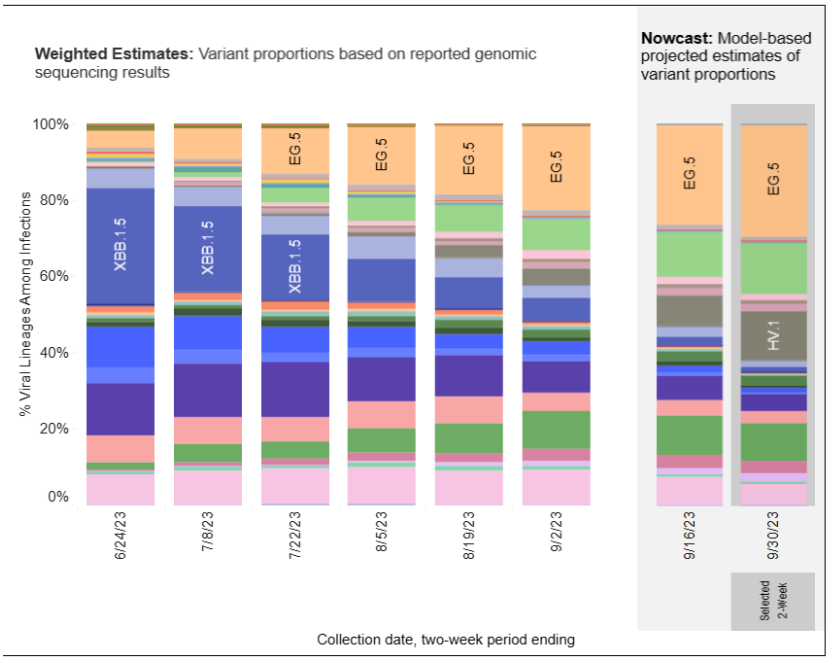
30 to 39 years old: Admissions grew 160 percent, from 0.11 to 0.29.

18 to 29 years old: Admissions increased nearly 200 percent, from 0.07 to 0.21.

17 and younger: Admissions rose 220 percent, from 0.05 to 0.16.

Comment: The data does not separate patients admitted for Covid versus patients admitted with Covid. Does not break down severity, ICU admissions, and deaths.

Covid-19 by the Numbers



USA

WHO label	Lineage #	%Total	95%PI
Omicron	EG.5	29.4%	26.4-32.6%
	FL.1.5.1	13.7%	10.8-17.1%
	HV.1	12.9%	10.5-15.6%
	XBB.1.16.6	10.1%	8.6-11.7%
	XBB.2.3	5.6%	4.7-6.5%
	XBB.1.16	4.3%	3.8-4.9%
	XBB.1.16.11	3.2%	2.6-3.9%
	XBB.1.16.1	3.0%	2.4-3.8%
	XBB.1.5.70	2.5%	1.9-3.4%
	XBB.1.16.15	2.0%	1.4-3.0%
	HF.1	1.8%	1.1-2.9%
	XBB	1.8%	1.5-2.1%
	GE.1	1.7%	1.3-2.2%
	XBB.1.5	1.1%	1.0-1.3%
	XBB.1.9.1	1.1%	0.9-1.3%
	EG.6.1	1.0%	0.7-1.4%
	GK.2	0.9%	0.7-1.3%
	XBB.1.5.72	0.8%	0.6-1.0%
	XBB.1.42.2	0.7%	0.4-1.1%
	XBB.1.9.2	0.5%	0.4-0.7%
	XBB.1.5.68	0.5%	0.3-0.8%
	XBB.1.5.10	0.4%	0.3-0.6%
	XBB.2.3.8	0.3%	0.2-0.4%
	CH.1.1	0.2%	0.1-0.3%
	XBB.1.5.59	0.2%	0.1-0.3%
	FD.1.1	0.2%	0.1-0.2%
	FE.1.1	0.1%	0.1-0.2%
	BA.2	0.1%	0.0-0.2%
	EU.1.1	0.0%	0.0-0.1%
	XBB.1.5.1	0.0%	0.0-0.0%
	BQ.1	0.0%	0.0-0.0%
	FD.2	0.0%	0.0-0.0%
	BA.5	0.0%	0.0-0.0%
Other	Other*	0.1%	0.0-0.1%

Comment: The CDC Tracker shows most indicators are trending down except deaths which tends to be a lagging indicator. Waste water surveillance measures in most areas are also trending down. EG.5 is up to 30%. FL.1.5.1 stands at 14%. HV.1 is up to 13%. So far, 21 countries have reported 198 sequences of the highly mutated BA.2.86 variant. BA.2.86 is still <1% in US.

CDC Endorses Covid-19 Boosters for Everyone Aged 6 Months and Older

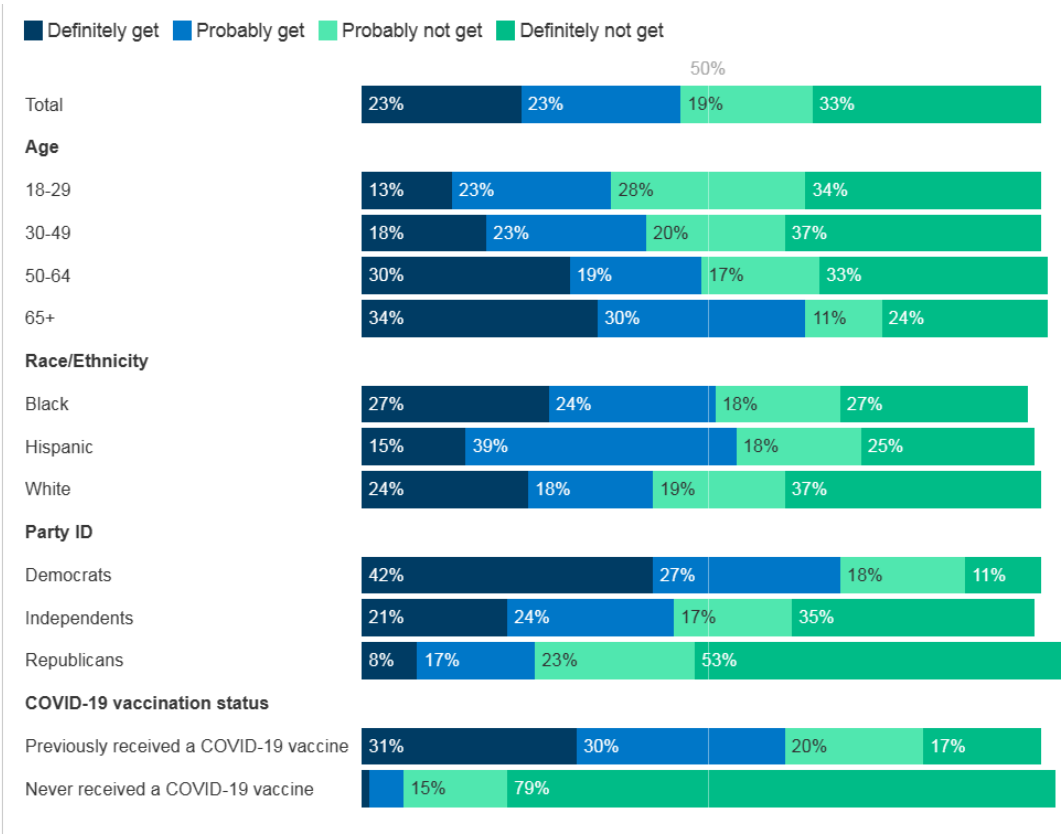
The CDC endorsed Covid-19 boosters for everyone six months old and above. The CDC on September 12th accepted the recommendation of its ACIP (Advisory Committee on Immunization Practices) to follow a universal booster strategy for the coming season. Everyone ages 5 and older should get a single dose of the updated Covid-19 vaccines, the CDC's committee said. Children ages six months to four-years-old should complete an initial

series including at least one new booster dose. Immunocompromised people should complete their initial series with at least one dose of the new vaccines and may get one or more additional doses,

Comment: The new boosters were designed to target the Omicron subvariant XBB.1.5 that dominated cases earlier this year. Moderna and Pfizer have said their boosters also produced strong immune responses against the newer circulating variants including EG. 5, the most common Omicron subvariant.

One of the committee's 15 voting members voted against the universal recommendation based on a lack of data among children. This physician favored a recommendation for ages 65 and older and other high-risk groups, with everyone else discussing it with their doctor. I think the UK recommendations are much better in defining recommendations by risk group. [see ID Watch September 2023] The US is now an outlier. Public officials in the UK, Sweden, Germany, Norway, Finland, and the WHO recommend booster dosing only for those at highest risk. Regarding vaccinating healthy young people, the WHO stated, "Although additional boosters are safe for this group, [we do] not routinely recommend them, given the comparatively low public health returns." Most people in the US now have immunity from vaccination and/or naturally infection. This "hybrid immunity" likely induces broad, long-lived protection against severe disease. At this point in the pandemic, it is hard to make a case for vaccinating everyone. This season is the first when vaccines will be available for Covid-19, flu and RSV. See KFF survey below

KFF COVID-19 Vaccine Monitor September 2023: Partisanship Remains Key Predictor Views Of COVID-19 Including Plans To Get Latest COVID-19 Vaccine



Comment: The KFF(Kaiser Family Foundation) survey reported nearly half of all adults in the US plan to get the newly recommended Covid-19 vaccine, according to results from a survey released earlier this week. The KFF Covid-19 Vaccine Monitor poll found that 23% of US adults say they will 'definitely' get the updated booster, 23% say they will 'probably' get it, while 19% say they will 'probably not' get it and 33% say they will 'definitely not' get it." Less than 20% received the bivalent booster last year. I hope this uptake will be better this fall, especially in the elderly and high-risk individuals.

Antibody neutralisation of emerging SARS-CoV-2 subvariants: EG.5.1 and XBC.1.6 Lancet Infect Dis published online September 11, 2023

doi.org/10.1016/ S1473-3099(23)00555-8

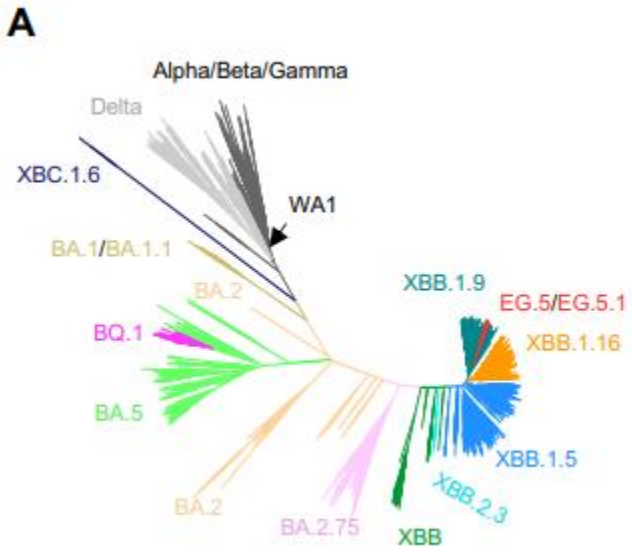
In the past 6 months, two emergent omicron subvariants, EG.5 and EG.5.1, have expanded rapidly worldwide, including in the US. EG.5 evolved from the omicron XBB.1.9 subvariant and harbors one additional Phe456Leu substitution in the receptor-binding domain (RBD) of the spike protein compared with the recently dominant subvariant XBB.1.5. Its immediate descendant, EG.5.1, contains one more mutation, Gln52His in the N-terminal domain (NTD) of the spike protein. Notably, both EG.5 and EG.5.1 subvariants have the Phe456Leu mutation, which could potentially evade some of the antibodies targeting the class-1 region of the RBD. Another emergent subvariant is XBC.1.6, a recombinant between the delta variant (B.1.617.2) and the omicron BA.2 subvariant, which has gained prevalence in Australia. XBC.1.6 has nine NTD mutations specific to the delta variant in addition to six more mutations compared with the spike protein of BA.2. They state that the local growth advantage of XBC.1.6 underscores the need to understand its antibody evasion properties.

The investigators evaluated the neutralization of EG.5.1 and XBC.1.6 by serum samples from three different clinical cohorts using a pseudovirus neutralization assay. The ancestral virus with an Asp614Gly mutation in the spike protein and subvariants XBB.2.3 and XBB.1.16 were included as comparators. The first cohort comprised individuals who received one of the BA.5 bivalent Covid-19 mRNA vaccines after receiving three doses of one of the original Covid-19 mRNA vaccines. The other two cohorts included individuals who had a BQ or XBB subvariant breakthrough infection after multiple vaccinations. In all three groups, the XBB subvariants (XBB.1.16, XBB.2.3, and EG.5.1) were substantially more resistant to serum neutralization than the ancestral virus, whereas XBC.1.6 showed greater sensitivity to serum neutralization than the XBB subvariants. In particular, in the two breakthrough cohorts, EG.5.1 showed a small (1·7-fold) but significant increase in resistance to serum neutralization compared with XBB.1.16, which is known to have an antibody neutralization profile similar to XBB.1.5.

These serum neutralization results were then used to generate antigenic maps to reflect the antigenic associations among the SARS-CoV-2 variants evaluated (appendix p 5). Moreover, although serum neutralization titers against EG.5.1 were modestly higher for individuals in the XBB breakthrough cohort than for individuals in the two other cohorts, they were overall low in all groups, perhaps due to the persistence of immunological imprinting.

They then tested antibody evasion properties of pseudotyped EG.5, EG.5.1, and XBC.1.6 using a panel of monoclonal antibodies that retained neutralizing activity against XBB.1.5 by targeting

several epitope clusters on the spike protein. D614G, XBB.1.5, XBB.1.16, XBB.2.3, and XBB.1.5 with Gln52His point mutation were included as comparators. XBB.1.5, XBB.1.16, and XBB.2.3 showed similar neutralization profiles, whereas EG.5 and EG.5.1 showed marked neutralization resistance to four of eight RBD class-1 monoclonal antibodies, undoubtedly mediated by the Phe456Leu mutation.



Comment: Their findings indicate that the recently surging subvariants EG.5 and EG.5.1 are only modestly (1·7-fold) more resistant to neutralization by serum antibodies than the previously dominant subvariant XBB.1.5, largely due to the Phe456Leu mutation in the viral spike knocking out the binding of some of the antibodies that target the class-1 region of the RBD. The good news is that these new subvariants will not be likely to substantially affect the efficacy of current Covid-19 vaccines. Although additional antibody resistance might confer a growth advantage to EG.5 and EG.5.1, spike mutations might enhance viral receptor binding affinity. Additionally, mutations elsewhere in the genome, such as the Ile5Thr mutation in ORF9b, could have a role in the growth advantage. By contrast, XBC.1.6 is more sensitive to antibody neutralization than XBB subvariants; therefore, it is less likely to compromise vaccine efficacy. The authors end by writing “As SARS-CoV-2 continues to spread and mutate, it is imperative that we remain vigilant in tracking its evolutionary trajectory as well as in understanding the functional consequences of its mutations.”

Procalcitonin-Guided Antibiotic Prescription in Patients With COVID-19 A Multicenter Observational Cohort Study Chest 2023; 164:596-605

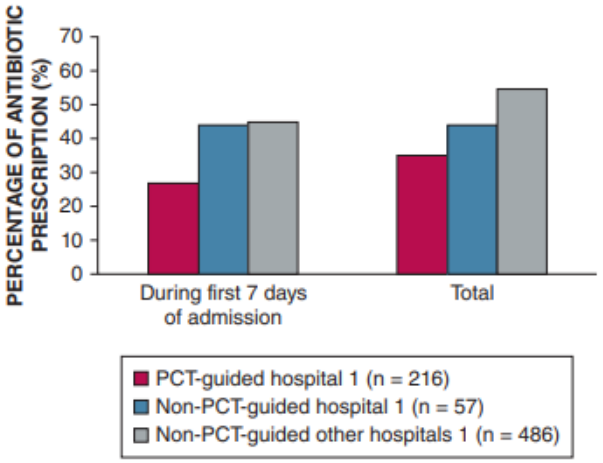
doi.org/10.1016/j.chest.2023.04.032

Despite the low rate of bacterial coinfection, antibiotics are still very commonly prescribed in community-onset patients admitted with COVID-19. The investigators asked does the use of a procalcitonin (PCT)-guided antibiotic protocol safely reduces the use of antibiotics in patients admitted with a Covid-19 infection?

This was a multicenter cohort, three groups of patients with Covid-19 were compared in terms of antibiotic consumption, namely one group treated based on a PCT-algorithm in one hospital (n =216)[prospective] and two control groups, consisting of patients from the same hospital (n = 57) and of patients from three similar hospitals (n = 486) without PCT measurements during the same period.[retrospective] Patients aged ≥ 18 years were eligible for inclusion if they presented at the ED with symptoms of a viral respiratory tract infection and the diagnosis Covid-19 was confirmed by means of a positive SARS-CoV-2 PCR on nasal and/or throat swabs and/or deep respiratory samples. Patients were only included if they were admitted to the hospital. All patients were admitted between October 2020 and July 2021. At PCT levels < 0.25 mg/L, antibiotics were discouraged; between PCT levels of 0.25 mg/L and 0.5 mg/L, antibiotics could be considered; and at PCT levels > 0.5 mg/L, antibiotics were recommended.

The primary end point was antibiotic administration in the first week of hospitalization. Secondary outcomes were the proportion of antibiotic administered during the total admission length of hospital stay, admission to the ICU, mechanical ventilation, noninvasive ventilation, 30-day all-cause mortality, 90- day all-cause mortality, and readmission within 30 days. Microbiological results, detected by blood cultures, sputum culture, urine culture, and/or other sites, were also recorded. They used a logistic regression model of variables for the adjusted models chosen based on a priori knowledge for being relevant patient characteristics and known risk factors for a worse outcome in patients with Covid-19.

The median age of all patients was 68 years (interquartile range [IQR], 57-78 years), and 475 participants (62.6%) were male. Significant differences in the baseline characteristics of the study groups were seen in median age, smoking status, COPD as comorbidity, diabetes as comorbidity, CRP levels at admission, WBC count at admission, and CURB-65 score at admission. In the PCT-guided group, the median PCT was 0.13 mg/L, and 103 participants (75.5%) had a PCT < 0.25 mg/L, 30 participants (13.9%) had a PCT between 0.25 and 0.50 mg/L, and 23 participants (10.6%) had a PCT > 0.50 mg/L. Antibiotic administration during the first 7 days was 26.8% in the PCT group, 43.9% in the non-PCT group in the same hospital, and 44.7% in the non-PCT group in other hospitals. Patients in the PCT group had lower odds of receiving antibiotics in the first 7 days of admission (OR, 0.33; 95% CI, 0.16-0.66 compared with the same hospital; OR, 0.42; 95% CI, 0.28-0.62 compared with the other hospitals). The proportion of patients receiving antibiotic prescription during the total admission was 35.2%, 43.9%, and 54.5%, respectively. The PCT group had lower odds of receiving antibiotics during the total admission only when compared with the other hospitals (OR, 0.23; 95% CI, 0.08-0.63). There were no significant differences in other secondary end points, except for readmission in the PCT group vs the other hospitals group, but the numbers were very low.



Comment: There have been a few retrospective studies which showed reduced antibiotic use in patients with Covid-19 who had PCT measured. [JAC Antimicrob Resist. 2021; 3: dlab133; Antibiotics (Basel). 2021; 10: 1119] This is the first partially prospective study on the use of PCT in patients admitted with Covid-19. The rate of bacterial coinfection in the group of patients with a PCT level > 0.50 mg/L was 10.6% in this study, but the antibiotic prescription rate was still 26.8%, but much lower than the other groups that did not use PCT. They did not have results of all microbiological cultures drawn in the other hospitals group during the total admission duration for all patients. The partly retrospective design may have introduced biases. The exact duration and dose of antibiotic therapy was not always available, especially in the patients from the COVID Predict database. This may have led to an overcalculation or undercalculation of antibiotic therapy in the other hospital group, causing information bias. The IDSA does not recommend using PCT to inform decisions on starting antibiotics with suspected Covid-19 pneumonia. This study, although limited by retrospective comparisons and possible residual confounders does suggest that a low PCT along with clinical judgment supports withholding unnecessary antibiotics. The strongest case for use of PCT is the high negative predictive value of a low PCT.

IDSA Updated Covid-19 on Testing

Recommendation 9: The IDSA panel suggests against routine SARS-CoV-2 NAAT of asymptomatic individuals without a known exposure to COVID-19 who are undergoing a medical or surgical procedure *(conditional recommendation, very low certainty evidence)*.

- **Remarks**:
  - NAAT is used to determine the presence of SARS-CoV-2 RNA, which may not represent infectious virus.
  - Detection of SARS-CoV-2 RNA in respiratory specimens without evidence of infectious virus has been reported widely.
  - The IDSA panel concluded that data were insufficient to establish SARS-CoV-2 infectiousness of a patient based on non-standardized instrument signal values, such as cycle threshold (Ct) values.

- Decisions on the timing of a procedure in a patient with prior SARS CoV-2 infection must balance the risk to the patient against the risks of delaying or avoiding the planned procedure, and should consider patient-related factors (e.g., vaccination status, symptomatic status, age), procedure-related factors (e.g., level of urgency, whether procedure generates aerosols), and procedural area infection control practices.
- Given limited evidence for poor outcomes in asymptomatic persons who undergo major surgery soon after testing positive for SARS-CoV-2 infection, testing may be considered during periods of high community transmission.
- Testing may also be considered before solid organ transplantation, hematopoietic stem cell transplantation or CAR-T cell therapy.
- This recommendation applies to settings where protective measures, such as PPE, are available and are used with adherence. Other factors to consider include the vaccination status of healthcare providers and patients, and whether patients will be roomed with other patients before or after the procedure. This recommendation is based on general exposure in the community as compared to a specific known exposure.

Recommendation 10: The IDSA panel suggests routinely repeating NAAT before medical or surgical procedures in patients with a recent history of COVID-19 *(conditional recommendation, very low certainty evidence)*.

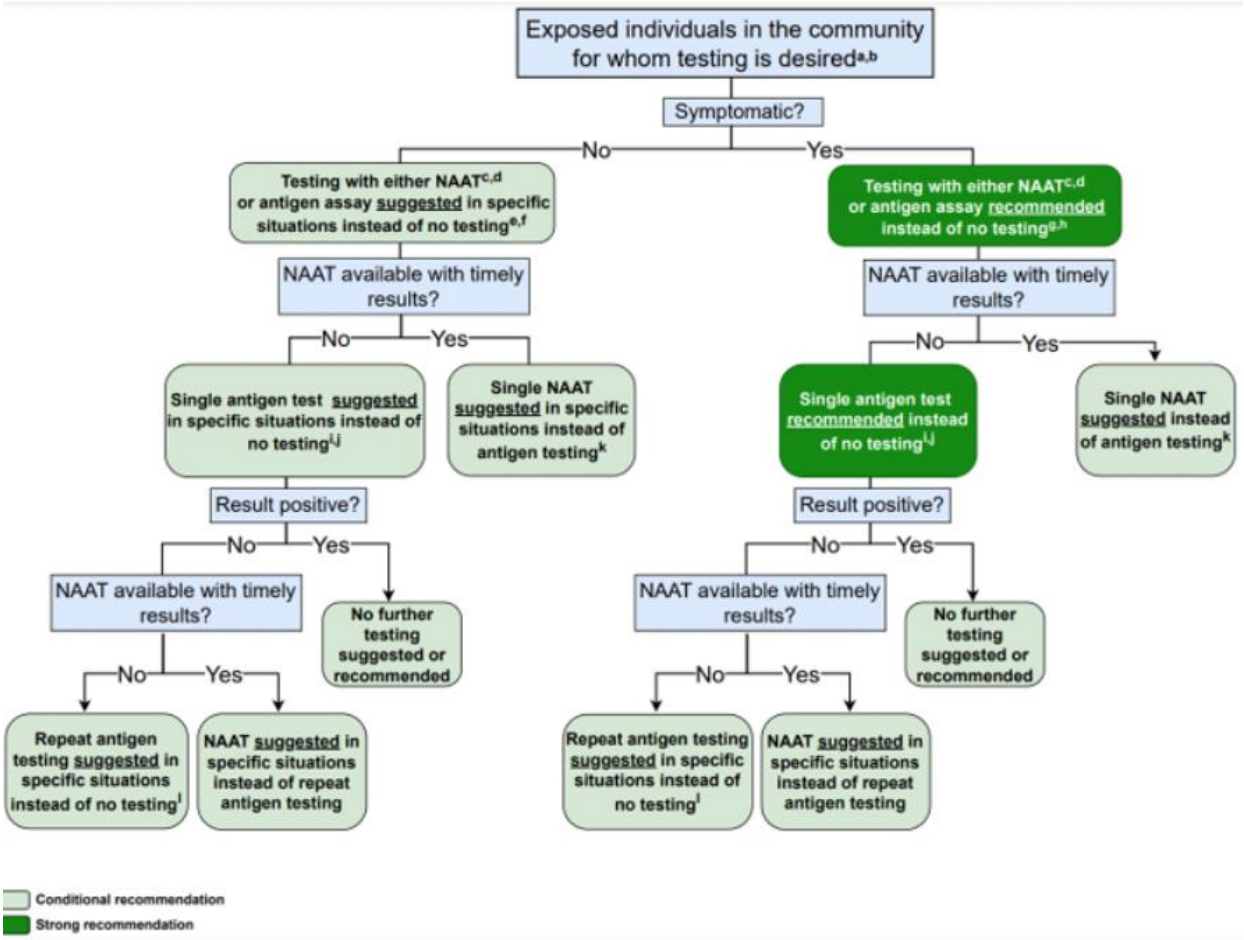
- **Remarks**:
  - NAAT is used to determine presence of SARS-CoV-2 RNA, which may not represent infectious virus.
  - Detection of SARS-CoV-2 RNA in respiratory specimens without evidence of infectious virus has been reported widely.
  - Conversely, the IDSA panel was unable to find definitive evidence demonstrating that a negative NAAT result following a positive result is proof that a patient is no longer infectious.
  - The IDSA panel concluded that data were insufficient to establish SARS-CoV-2 infectiousness of a patient based on Ct value results.
  - Decisions on the timing of a procedure in a patient with prior SARS CoV-2 infection must balance the risk to the patient against the risks of delaying or avoiding the planned procedure, and should consider patient-related factors (e.g., vaccination status, symptomatic status, age), procedure-related factors (e.g., level of urgency, whether procedure generates aerosols), and procedural area infection control practices.

Recommendation 11: The IDSA panel suggests routinely repeating NAAT in patients with COVID-19 to guide release from isolation *(conditional recommendation, very low certainty evidence)*.

- **Remarks**:
  - NAAT is used to determine the presence of SARS-CoV-2 RNA, which may not represent infectious virus.

- Detection of SARS-CoV-2 RNA in respiratory specimens for prolonged periods without evidence of infectious virus has been reported widely. Predicating release from isolation on a negative SARS-CoV-2 NAAT may extend the duration of isolation unnecessarily.
- Conversely, the IDSA panel was unable to find definitive evidence demonstrating that a negative NAAT result following a positive result is proof that a patient is no longer infectious.
- The IDSA panel concluded that data were insufficient to establish SARS-CoV-2 infectiousness of a patient based on Ct value results.

Updated Algorithm



[a] No recommendation for or against antigen testing could be made for the specific populations of students in educational settings, employees at work, or individuals planning to attend a large social gathering (evidence gaps)
[b] No recommendation for or against home testing using NAAT could be made (evidence gap)
[c] Nucleic acid amplification test (NAAT) refers to rapid (i.e. ≤60 minutes in-laboratory turnaround time) or laboratory-based nucleic amplification test
[d] For NAAT, either rapid or standard laboratory-based testing is suggested (conditional recommendation)
[e] Individuals who have been exposed to someone known or suspected of having COVID-19 should be tested at least 5 days after the exposure. If symptoms develop before 5 days, they should get tested immediately.
[f] For asymptomatic individuals undergoing procedures or planned for hospital admission, no NAAT testing is suggested (conditional recommendations)
[g] For NAAT in symptomatic individuals, the IDSA panel suggests collecting either nasopharyngeal (NP) swab, , mid-turbinate (MT), combined anterior nasal (AN) plus oropharyngeal (OP) swab, saliva or mouth gargle specimens. Swabs of AN or OP alone are acceptable if collection of NP, AN/OP, or MT swabs; saliva; or mouth gargle is not feasible (conditional recommendation)
[h] For NAAT in symptomatic individuals, the IDSA panel suggests that AN and MT specimens can be either self-collected or collected by a healthcare provider (conditional recommendation)
[i] Either point-of-care or laboratory-based antigen testing is suggested (conditional recommendation)
[j] If the specimen is self-collected, either observed or unobserved collection is suggested (conditional recommendation)
[k] The IDSA panel suggests against using NAAT in patients with COVID-19 to guide discontinuation of isolation or prior to a procedure or surgery (conditional recommendations)
[l] For guidance on timing of repeat testing for a specific assay, please consult the respective assay package insert or the latest FDA guidance.

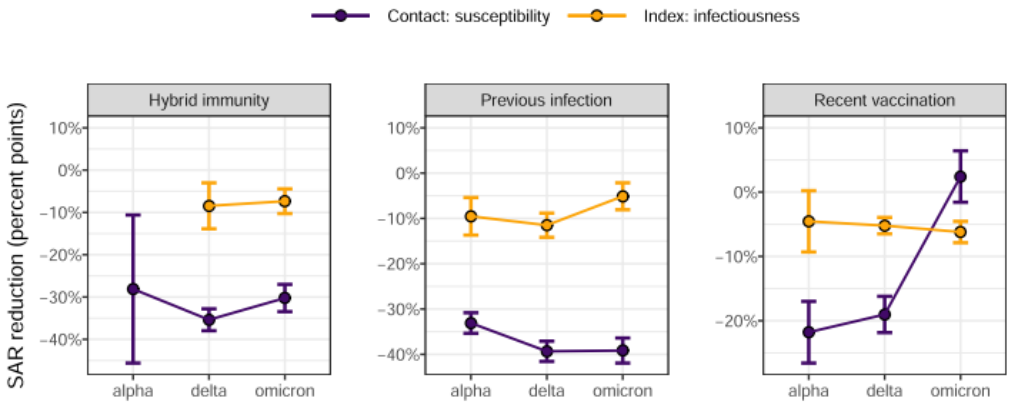
Effect of SARS-CoV-2 prior infection and mRNA vaccination on contagiousness and susceptibility to infection Nat Comm 2023; 14:5452

doi.org/10.1038/s41467-023-41109-9

The investigators asked the question, does immunity conferred by SARS-CoV-2 vaccines and/or natural infection reduces the transmission of the virus. To answer how the effect of immunity is shared between a reduction of infectiousness and an increased protection against infection, they examined >50,000 positive cases and >110,000 contacts from Geneva, Switzerland (June 2020 to March 2022). They assessed the association between secondary attack rate (i.e., proportion of new cases among contacts) and immunity from natural infection and/or vaccination, stratifying per four SARS-CoV-2 variants and adjusting for index cases and contacts' sociodemographic characteristics and the propensity of the contacts to be tested. They used a register dataset of 50,973 index cases having declared 111,674 contacts in the State of Geneva.

During the period of interest (01-06-2020 to 01-03-2022), 65,161 infections were recorded among persons living in Geneva and who declared at least one contact person. Index cases were at 73% adults between 18 and 64 years, 22% children and 4.6% adults older than 65 years. The proportion of children for the index cases tripled between the EU1 wave (11%) and the Delta wave (38%). Overall, children were overrepresented and adults >65 years underrepresented in their cohort when compared to the demographics of the Geneva state (18.5% of children and 16.5% of adults above 65 years in 2022 in Geneva. The vast majority of the index cases had symptoms (94%), among whom more than half had cough (58%). The majority of the contacts reported by the index were people sharing their home (63%), this percentage increasing up to 77% during the Omicron wave. Concerning the immunity status, the proportion of vaccinated index cases increased from around 2% during the alpha wave, up to 52% during the Omicron wave, of which 25% had their last dose more than 6 months before the infection. Contacts were less vaccinated (37% during omicron) and a higher proportion of them were previously infected (10%, compared to 2.9% for the index cases).

Among 111,674 contacts, 46,417 took a Covid-19 test during the 10 days following the date of the last contact with the index case, and 21,435 had a positive test result, a raw 19.2% secondary attack rate (SAR). The raw SAR was from 16% to 27% for each of the four VOCs, from 16.4% during the initial wild-type wave, 20.9% during the Alpha wave, 16.7% during the Delta wave, and 26.3% during the Omicron wave. Previous Covid-19 infection in the index case reduced the SAR by 10.5 adjusted percent points (pp) (95% confidence interval [CI], 7.0 to 14.0) during the wild-type wave, 8.6 pp during the Alpha wave (4.3 to 12.8), 11.3 pp during the Delta wave (8.6 to 14.0), and 4.3 pp during Omicron (1.3 to 7.3).



Comment: They showed that immunity protected contacts from infection, rather than reducing infectiousness of index cases. Natural infection conferred the strongest immunity. Hybrid immunity did not surpass recent infection. However, there was a reduction in infectiousness due to vaccination and/or natural infection. The other variables affecting the transmission of SARS-CoV-2 were the age of the contact person, the presence of symptoms - especially cough - for the index, the setting of the encounter between index and contact (e.g., home, work) and the tendency of the contact to get tested. These findings support the role of vaccine in reducing infectiousness and underscore the complementary role of interventions reducing SARS-CoV-2 propagation, such as mask use or indoor ventilation.

Nirmatrelvir/Ritonavir Use and Hospitalizations or Death in a Previously Uninfected Nonhospitalized High-Risk Population With COVID-19: A Matched Cohort Study J Infect Dis published online September 15, 2023

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The objective of this study was to determine the impact of nirmatrelvir/ritonavir (NMV/r) with hospitalization or death within 30 days as compared with untreated controls previously uninfected and nonhospitalized in the VA national Covid-19 Shared Data Resource database. They used a matched cohort design using inverse probability of treatment weight (IPTW). Individuals prescribed NMV/r within 3 days of Covid-19 diagnosis were compared with IPTW-based untreated controls. Variables for IPTW included age, race, sex, body mass index, geographic location, vaccination status, and multiple comorbidities. Additional analyses were conducted on NMV/r-treated and propensity score–matched untreated controls. Propensity score matching was done on age, race, sex, body mass index, multiple comorbidities, site of diagnosis, and vaccination status.

Among 7615 individuals prescribed NMV/r and 62,077 controls identified between January 1, 2022 and February 25, 2023, the risk of hospitalization/death was lower among NMV/r-treated persons vs untreated controls (243 vs 3468 events; absolute risk difference [ARD], -2.36 [95% CI, -2.57 to -2.14]). The difference was significant for those >60 and ≤60 years old (ARD, -3.86 [95% CI, -4.19 to -3.54] vs -0.27 [95% CI, -0.51 to -0.03]) and for persons asymptomatic and symptomatic (ARD, -7.09 [95% CI, -7.62 to -6.55] vs -1.46 [95% CI, -1.66 to -1.25]). Significant benefit was observed among individuals unvaccinated and vaccinated, with or without a booster dose.

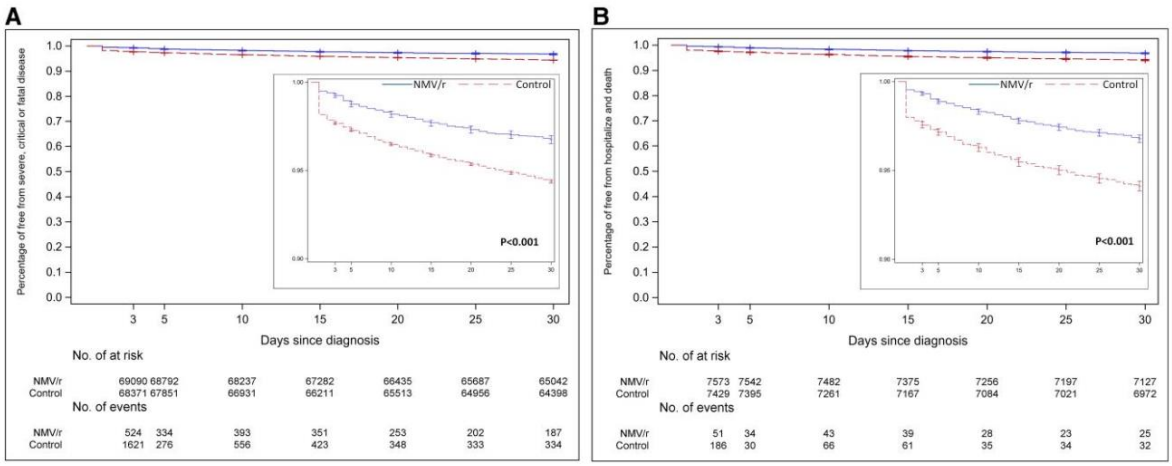

Figure 3. Kaplan-Meier curves depicting the proportion of individuals without hospitalization or death among those treated with and without nirmatrelvir/ritonavir. *A*, Inverse probability of treatment–weighted analysis. *B*, Propensity score–matched analysis. NMV/r, nirmatrelvir/ritonavir.

Comment: Emerging data has demonstrated the beneficial role of NMV/r in reducing hospitalization and death in early/mild symptomatic Covid-19 in persons at high risk of progression to more severe disease. This study provides additional evidence of the benefit of NMV/r in a population previously uninfected, at high risk, and nonhospitalized and clarifies its role in various demographic and clinical subgroups. In a previous study in the early Omicron variant–predominant era, this benefit seemed to be limited to the older population, with no significant benefit observed among those who were <65 years old. [N Engl J Med 2022; 387:790–8] This study observed a benefit among older and younger populations, though the magnitude of benefit was more pronounced in the older population. The study population in this study was older and with a higher burden of comorbidities than the general US population. Another important finding from this study was the benefit of NMV/r was observed among the unvaccinated, as well as those who had completed a primary series with or without a booster dose. Whether prior natural immunity with or without additional vaccine-induced immunity influences these outcomes is unknown since over 90% of the population has some form of immunity either due to natural infection and/or vaccination. Residual confounding is always a limitation of observational studies. Other limitations in this study include a predominantly male population that was exclusively veterans, which may not be generalizable to the overall US population. They also did not evaluate the association of supplemental oxygen use at baseline and other treatment modalities for Covid-19 (e.g., steroids, monoclonal antibodies, and remdesivir). Likewise, they did not examine the role of specific variants or sublineages.

Nirmatrelvir or Molnupiravir Use and Severe Outcomes From Omicron Infections
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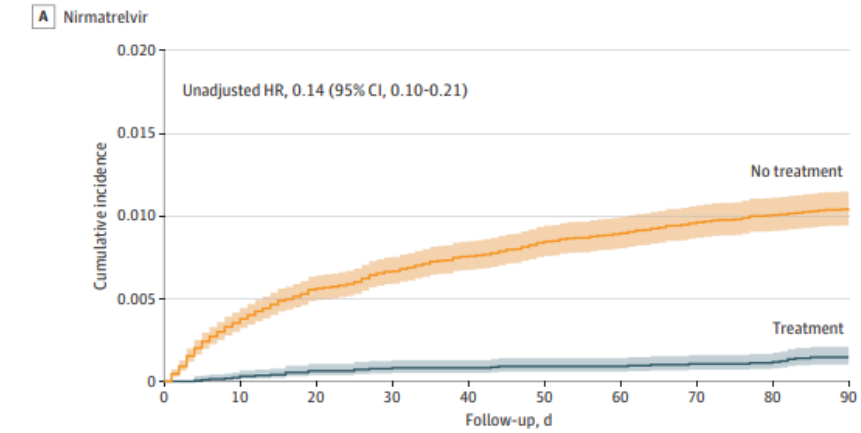
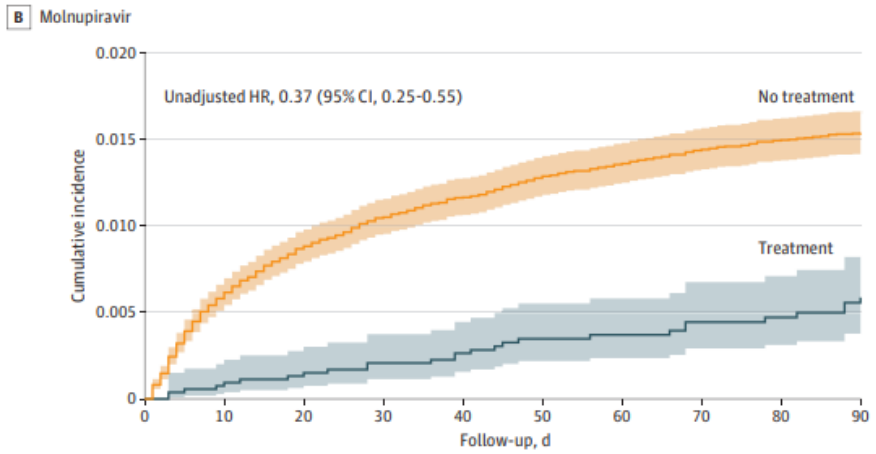
This was a cohort study of patients who received a diagnosis of Covid-19 at Cleveland Clinic from April 1, 2022, to February 20, 2023 (during which the Omicron variant evolved from BA.2 to BA.4/BA.5, then to BQ.1/BQ.1.1, and finally to XBB/XBB.1.5) and who were at high risk of progressing to severe disease, with follow-up through 90 days after diagnosis. The final date for follow-up data collection was February 27, 2023. The primary outcome was time to death. The secondary outcome was time to either hospitalization or death. The association of either nirmatrelvir or molnupiravir use with each outcome was measured by the hazard ratio (HR) adjusted for demographic factors, socioeconomic status, date of COVID-19 diagnosis, coexisting medical conditions, COVID-19 vaccination status, and previous SARS-CoV-2 infection.

There were 68,867 patients (29,386 [42.7%] aged ≥65 years; 26,755 [38.9%] male patients; 51, 452 [74.7%] non-Hispanic White patients). 30 of 22,594 patients treated with nirmatrelvir, 27 of 5311 patients treated with molnupiravir, and 588 of 40,962 patients who received no treatment died within 90 days of Omicron infection. The adjusted HRs of death were 0.16 (95% CI, 0.11-0.23) for nirmatrelvir and 0.23 (95% CI, 0.16-0.34) for molnupiravir. The adjusted HRs of hospitalization or death were 0.63 (95% CI, 0.59-0.68) for nirmatrelvir and 0.59 (95% CI, 0.53-0.66) for molnupiravir. The associations of both drugs with both outcomes were observed across subgroups defined by age, race and ethnicity, date of COVID-19 diagnosis, vaccination status, previous infection status, and coexisting conditions.

Figure 2. Cumulative Incidence of Death in Patients Infected With Omicron, by Treatment





Comment: In this study, both nirmatrelvir and molnupiravir use were found to be associated with reductions in mortality and hospitalization among patients infected with Omicron who were at high risk for progression to severe disease. The associations of both antiviral drugs with both outcomes were observed consistently across subgroups defined by age, race and ethnicity, date of Covid-19 diagnosis, vaccination status, previous infection status, and coexisting conditions. A recently completed open-label, randomized clinical trial did not find evidence that molnupiravir was associated with reduced frequency of Covid-19–associated hospitalizations or death among vaccinated adults in the UK. [Lancet. 2023; 401:281-293] However, the patients in that study were at much lower risk of progressing to severe Covid-19 than current study population. In the NIH Covid-19 treatment guidelines, nirmatrelvir was the preferred treatment for patients at high risk of progressing to severe Covid-19, with molnupiravir as an alternative therapy to be used only when the preferred therapy was not available, feasible to use, or clinically appropriate. The preference for nirmatrelvir over molnupiravir was the result of a greater reduction in the risk of progression to severe Covid-19 observed in the pivotal clinical trial on nirmatrelvir (89%) than that of molnupiravir (48%), but the data on mortality were very limited, with only 1 death observed in the molnupiravir group vs 9 observed in the placebo group through day 29, and with 0 deaths in the nirmatrelvir group vs 7 deaths in the placebo group through day 28. [N Engl J Med. 2022; 386:509-520] This current study had more patients and longer follow-up and demonstrated that both nirmatrelvir and molnupiravir were associated with reductions in mortality. This finding is particularly important because nirmatrelvir has substantial drug-drug interactions with concomitant medications.

As in any observational study, unmeasured confounders might impact results. Patients with no or mild symptoms were unlikely to seek therapy, and physicians tended to prioritize treatments for the patients at the highest risk of clinical progression when the treatment supply was limited. Nonetheless the findings in this study suggest that both nirmatrelvir and molnupiravir can be used to treat nonhospitalized patients who are at high risk of progressing to severe Covid-19.