ID WATCH
by Ed Septimus, MD

## Editor's Choice




1

## Quorum-sensing regulation of phenazine production heightens Pseudomonas aeruginosa resistance to ciprofloxacin

Antimicrob Agents Chemother 0:e00118-24
doi.org/10.1128/aac.00118-24

Quorum sensing (QS) refers to the ability of bacterial pathogens such as P aeruginosa to regulate their gene expression based on cellular density. One such cell–cell signaling system — the Pseudomonas quinolone signal (PQS) system — responds directly to quinolone selection pressure.

The investigators in this study used QS receptor gene knockout bacteria to show that the PQS system is a key component in the development of quinolone resistance under sublethal ciprofloxacin selection pressure. When treated with sub-lethal ciprofloxacin for 20 days, the MIC of P. aeruginosa increased significantly. Phenazine biosynthesis was upregulated with the emergence of quinolone resistance (including pyocyanin, a phenazine pigment virulence factor produced by P. aeruginosa). A pyocyanin-deficient strain exhibited attenuated quinolone resistance under selection pressure that was restored with exogenous pyocyanin. Pyocyanin-driven quinolone resistance was not driven by the classic mechanisms

of efflux or reactive oxygen species mutagenesis, but rather by reduced carbon metabolism. The activation of carbon metabolism by pyruvate attenuated the development of quinolone resistance under ciprofloxacin selection.

## Dr. Septimus's Annotations

MDR-P. aeruginosa or DTR-P. aeruginosa generally is the result of an interplay of multiple resistance mechanisms, including decreased expression of outer membrane porins (OprD), increased production of or amino acid substitutions within Pseudomonas derived cephalosporinase (PDC) enzymes (commonly referred to as pseudomonal AmpC enzymes), upregulation of efflux pumps (e.g., MexAB-OprM), mutations in penicillin-binding protein targets, and the presence of expanded-spectrum β-lactamases (e.g., blaOXA-10). Carbapenemase production is an uncommon cause of carbapenem resistance in P. aeruginosa isolates in the US, [Antimicrob Agents Chemother 2022; 66(5): e0018922] but is identified in upwards of 20% of carbapenem resistant P. aeruginosa in other regions of the world, most commonly due to the presence of blaVIM enzymes.[Lancet Microbe. 2023; 4 3e159–e170]

This study demonstrates another mechanism for bacterial survival under antibiotic selection pressure through QS-mediated pathway that influences carbon metabolism, including the PRS system. Of interest azithromycin has been shown to downregulate the QS network in P aeruginosa. Therapy with azithromycin has been used in patients with cystic fibrosis infected with MTR-P. QS targeting may be a useful adjunctive strategy to preserve the activity of antibiotics.

### BOTTOM LINE

**The study demonstrated that PQS-regulated pyocyanin affects resistance by altering carbon metabolism and that exogenous pyruvate can hinder resistance evolution, providing new avenues to exploring resistance evolution and the application of compounds that might impair the development of resistance.**

2

## Assessing Clinician Utilization of Next-Generation Antibiotics Against Resistant Gram-Negative Infections in U.S. Hospitals: A Retrospective Cohort Study

Ann Intern Med published online April 19, 2024
doi:10.7326/M23-2309

The retrospective cohort study looked at use of antibiotics in adults at 619 US hospitals between 2016 and 2021. The goal was to assess use of gram-negative antibiotics newly approved between 2014 and 2019 (ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, plazomicin, eravacycline, imipenem-relebactam-cilastatin, and cefiderocol) and identify factors associated with their use (versus traditional generic agents) in patients with gram-negative resistant infections.

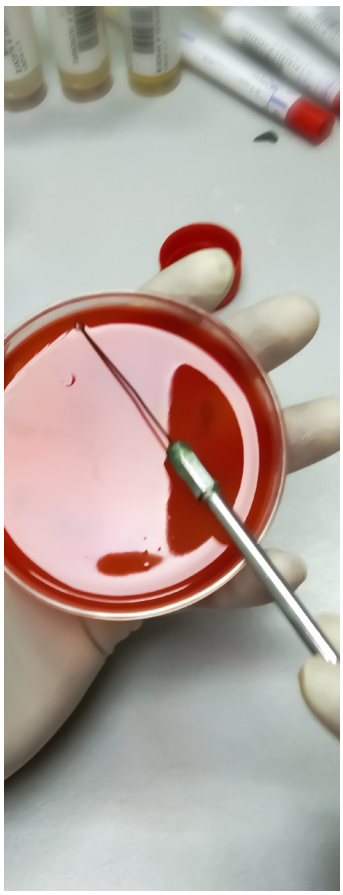
The study found that ceftolozane-tazobactam and ceftazidime-avibactam, which were approved in 2014 and 2015, respectively, were the most commonly used new drugs; subsequently approved gram-negative antibiotics saw a slow uptake. Of the 362,142 studied gram-negative infection hospitalizations, 0.7% were caused by pathogens with difficult-to-treat resistance (DTR). In 41.5% of those cases, patients received only older antibiotics; 79.3% of that subgroup received antibiotics categorized as "reserve," such as polymyxins, aminoglycosides, and tigecycline. Throughout the study period, use of older "reserve" antibiotics for gram-negative infections (aminoglycosides, polymyxins, and tigecycline) slowly declined, while use of the first two of the newer agents (ceftolozane-tazobactam and ceftazidime-avibactam) generally increased. By contrast, use of meropenem-vaborbactam, eravacycline, imipenem-cilastatin-relebactam, and cefiderocol was

minimal (and plazomicin was not used at all). Among patients with DTR infections, 59% received newer agents and 41% received "reserve" agents; utilization of the new agents specifically for DTR bacteremia was 72%. Use also varied geographically (61% in the Midwest and 34% in the West) and was less likely in smaller hospitals and those with low incidence of DTRs.

Patients with bacteremia or a chronic disease were more likely to get new antibiotics. Acute liver failure and infection with Acinetobacter baumannii complex and other nonpseudomonal nonfermenter pathogens were associated with lower likelihood of getting a new drug. The new antibiotics were used more when susceptibility testing was available.

## Dr. Septimus's Annotations

Antibiotic development is difficult that can take 10 to 15 years and cost an estimated $1 billion. Fewer than 1.5% of antibiotic candidates reach the market, and, even if this occurs, financial success is uncertain. With antimicrobial resistance (AMR) estimated to cause 1.2 million deaths globally per year, we need to ensure that new antibiotics are not only being developed but also correctly used. Their findings have implications for both prescribing clinicians hoping to optimize management of DTR infections and healthcare executives trying to control healthcare costs since the newer drugs are six times more expensive than the older ones disincentivizes hospitals from using these drugs. They also noted that another barrier to use may be that the newer antibiotics have limited evidence against the resistant infections that physicians are commonly seeing. Without robust clinical trial evidence, expert guidance can be helpful. Starting in 2020, IDSA has published a guidance document on AMR updated regularly. The authors in this paper call for continued innovation in programs to incentivize drug discovery, as well as wider timely availability of susceptibility testing and more evidence demonstrating new drugs' effectiveness in resistant infections. Improvements in rapid diagnostic testing and susceptibly testing are also imperative.



### BOTTOM LINE

**Continued efforts to raise awareness, invest in pathogen-specific trials, regularly updated antimicrobial resistance guidance, and rapid susceptibility testing will be key to appropriate and optimal use of these new antibiotics. The need for new antibiotics remains critical. As I explain to healthcare executives, the most expensive antibiotic is one that does not work.**

3

## Characterization of Acinetobacter baumannii-calcoaceticus complex(ABC) isolates and microbiological outcome for patients treated with sulbactam-durlobactam in a phase 3 trial (ATTACK)

Antimicrob Agents Chemother published online April 3, 2024.
doi.org/10.1128/aac.01698-23

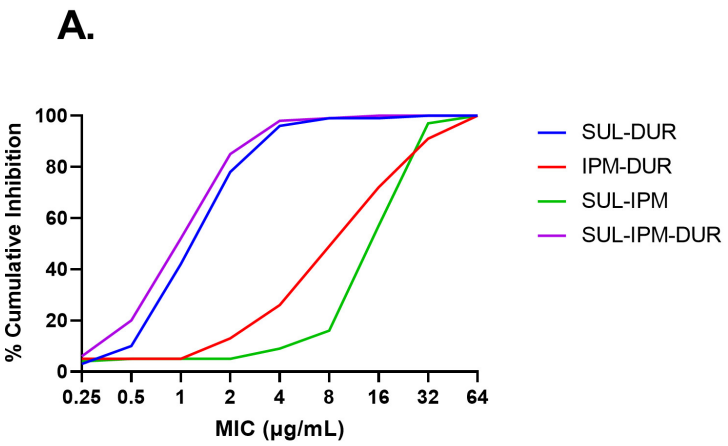
Management of carbapenem-resistant Acinetobacter baumannii (CRAB) is a priority in the antimicrobial drug pipeline. The beta-lactam–beta-lactamase inhibitor combination sulbactam-durlobactam (sul-dur) was FDA-approved in 2023 for treating CRAB based on favorable results in the ATTACK trial, in which imipenem plus either sul-dur or colistin

was assessed. [Lancet Infect Dis 2023; 23:1072–1084] In multiple surveillance studies, the MIC90 of SUL-DUR against ABC ranged from 2 to 4 µg/mL. [Antimicrob Agents Chemother 2022; 66:e00781-22] This report describes the characterization of the baseline CRAB isolates from patients enrolled in ATTACK, including an analysis of the correlation of microbiological outcomes with SUL-DUR MIC values and the molecular drivers of SUL-DUR resistance.

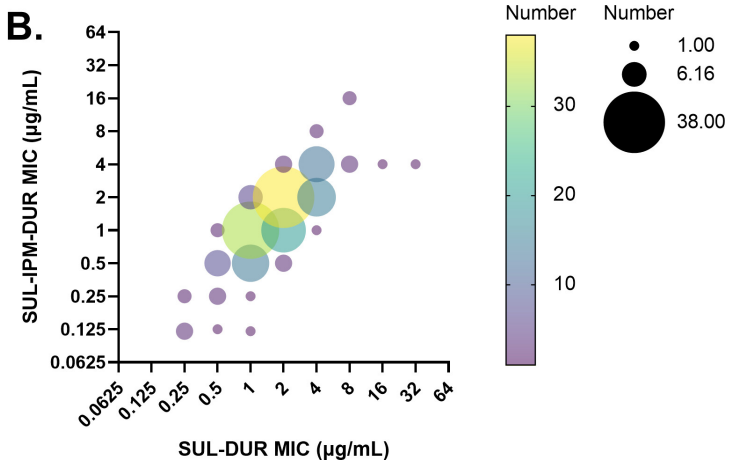
Among 175 isolates, 96% were carbapenem resistant, 95% were sulbactam resistant, and 5% were resistant to sul-dur (MIC >4 mg/L). Although imipenem did not have an appreciable impact on sul-dur MIC for sul-dur–susceptible isolates in vitro, 5 of the 8 sul-dur nonsusceptible isolates showed at least a two-fold decrease in sul-dur MIC with imipenem. Overall, microbiologic eradication at test of cure was achieved in 72% of patients. Three of four patients with sul-dur MICs 8–16 mg/L who received sul-dur experienced clinical cure, two achieved microbiologic cure, and all four survived up to 28 days. Mutations in the active site of PBP3 were found among isolates with pre-existing sul-dur nonsusceptibility.

**Comparison of sulbactam-durlobactam versus imipenem-sulbactam-durlobactam MIC values for 175 baseline ABC isolates from ATTACK**

(a) Cumulative percent inhibition by MIC




(B) Bubble graph comparing MIC values of SUL-IPM-DUR to SUL-DUR. MIC values were determined as follows: SUL-DUR = titration of sulbactam in the presence of 4 µg/mL durlobactam; IPM-DUR = titration of imipenem in the presence of 4 µg/mL durlobactam; SUL-IPM = titration of a 1:1 ratio of sulbactam:imipenem; SUL-IPM-DUR = titration of a 1:1 ratio of sulbactam:imipenem in the presence of 4 µg/mL durlobactam.




## Dr. Septimus's Annotations

Characteristic of the Acinetobacter isolates from patients enrolled in ATTACK demonstrated higher rates of antibiotic resistance compared to results described in recent surveillance studies. Acinetobacter isolates from a 6-year global surveillance study were significantly more susceptible to comparator antibiotics than those isolated from patients enrolled in the ATTACK phase 3 trial. [Antimicrob Agents Chemother 2022; 66: e00781-22] Of particular interest was the difference in carbapenem susceptibility: approximately 50% of Acinetobacter isolates from the global surveillance study were carbapenem-non-susceptible whereas 96% of Acinetobacter isolates from m-MITT patients in ATTACK were carbapenem-non-susceptible. Durlobactam is a potent inhibitor of Ambler class A, C, and D serine β-lactamases, but it does not inhibit class B metallo-β-lactamases (MBLs). Microbiological eradication rates did not correlate to the SUL-DUR MIC for MIC values of ≤4 µg/mL, i.e., higher rates of eradication were observed in patients infected with CRAB isolates with a SUL-DUR MIC of 4 µg/mL than was seen with patients whose CRAB isolates had a SUL-DUR MIC of 0.5 µg/mL. This is likely due to the relatively small patient numbers at the lower MICs. Of note, favorable clinical and microbiological outcomes were observed for four patients with SUL-DUR non-susceptible baseline CRAB isolates (MIC = 8–16 µg/mL) who received SUL-DUR therapy, which supports the intermediate susceptibility breakpoint for SUL-DUR of 8 µg/mL which was recently FDA approved. While ATTACK was a global study, it is possible that different clones of ABC from underrepresented parts of the globe could influence outcomes.

BOTTOM LINE

**The microbiological data presented here provide further support for the use of SUL-DUR for the treatment of hospital-acquired and VAP caused by CRAB.**

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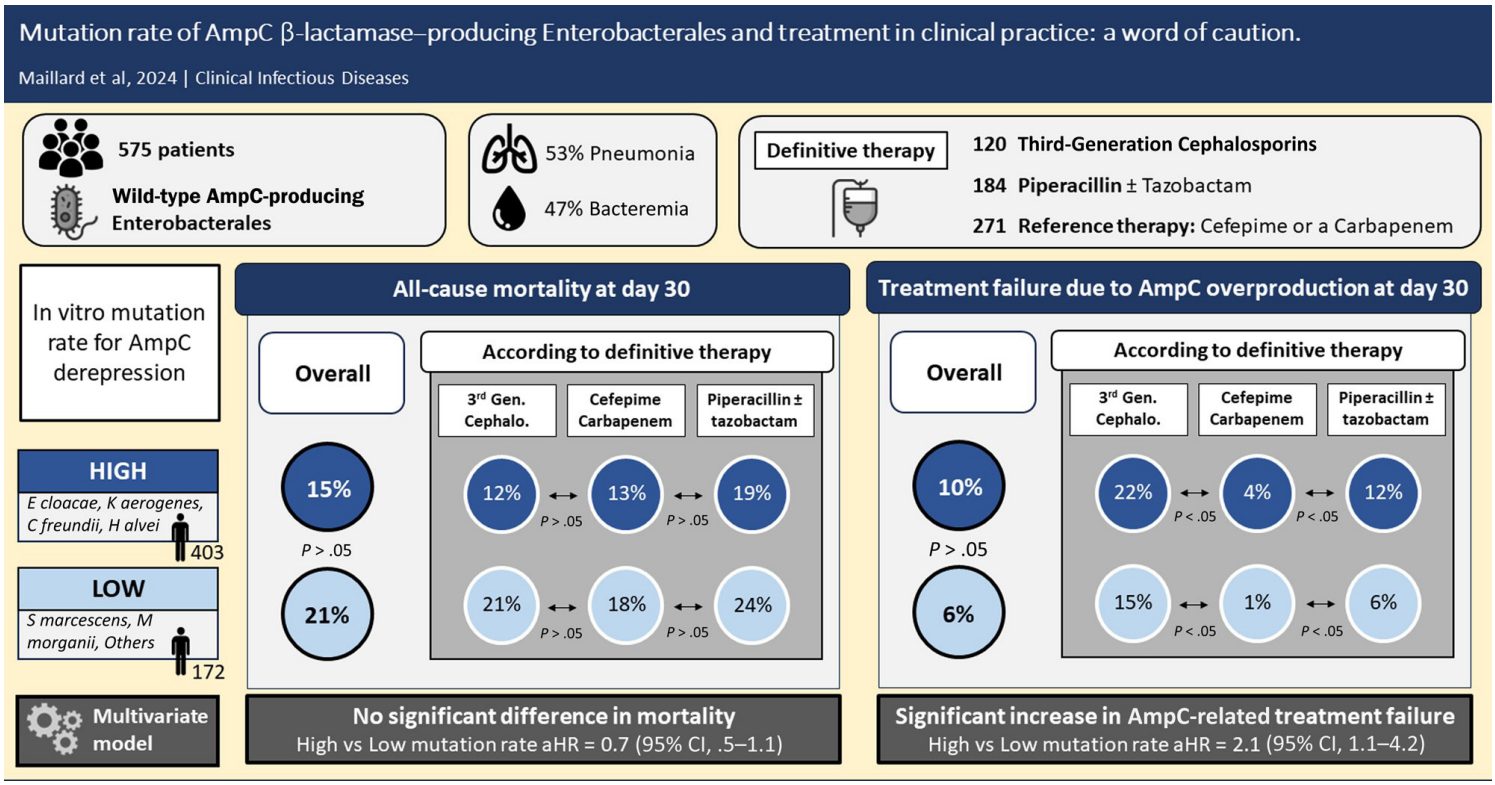
## Mutation rate of ampc-β-lactamase-producing Enterobacterales and treatment in clinical practice: A word of caution

Clin Infect Dis published online March 25, 2024
doi.org/10.1093/cid/ciae160

Certain bacteria produce wild-type AmpC β-lactamases at low levels, making these organisms susceptible to third generation cephalosporins (3GCs) and piperacillin with or without tazobactam. However, among other bacterial species — particularly Enterobacter cloacae, Klebsiella aerogenes, and Citrobacter freundii — such therapy can induce AmpC derepression, leading to increased β-lactamase production and clinical treatment failure. IDSA recommends avoiding the use of 3GCs and piperacillin for these organisms, but not for other AmpC-producing pathogens (such as Serratia marcescens, M. morganii, and Providencia species) that have not been associated with AmpC derepression. [Clin Infect Dis 2022;74:2089-2114]

Investigators conducted a retrospective cohort study involving 575 adult patients with hospital-acquired blood stream infections or pneumonia caused by wild-type AmpC-β-lactamase–producing Enterobacterales that were susceptible to 3GCs, piperacillin, cefepime, and carbapenems. Among the 403 infections with organisms associated with AmpC derepression, treatment failure was more common with 3GCs (22%) or piperacillin with or without tazobactam (12%) than with cefepime or carbapenems (4%). However, among 172 infections caused by organisms not associated with AmpC derepression, treatment failure was also more likely with 3GCs (15%) and piperacillin with or without tazobactam (6%) compared to cefepime or carbapenems (1%).



## Dr. Septimus's Annotations

In the literature, the optimal treatment for AmpC-producing Enterobacterales remains controversial, and the retrospective design of this study with a limited sample size means their results should be interpreted with caution. This study was probably underpowered to show a difference in mortality. They were also unable to collect data on antibiotic dosing, drug monitoring, and infusion regimens, which could be important for the emergence of AmpC derepression. The study demonstrated even in patients infected with species with a low in vitro mutation rate, non-reference therapy remained associated with more clinical failure/recurrence due to AmpC overproduction. From an antimicrobial stewardship point of view, the source, the severity of infection, and source control should be considered and balanced with the risk of using broader-spectrum antibiotics.

### BOTTOM LINE

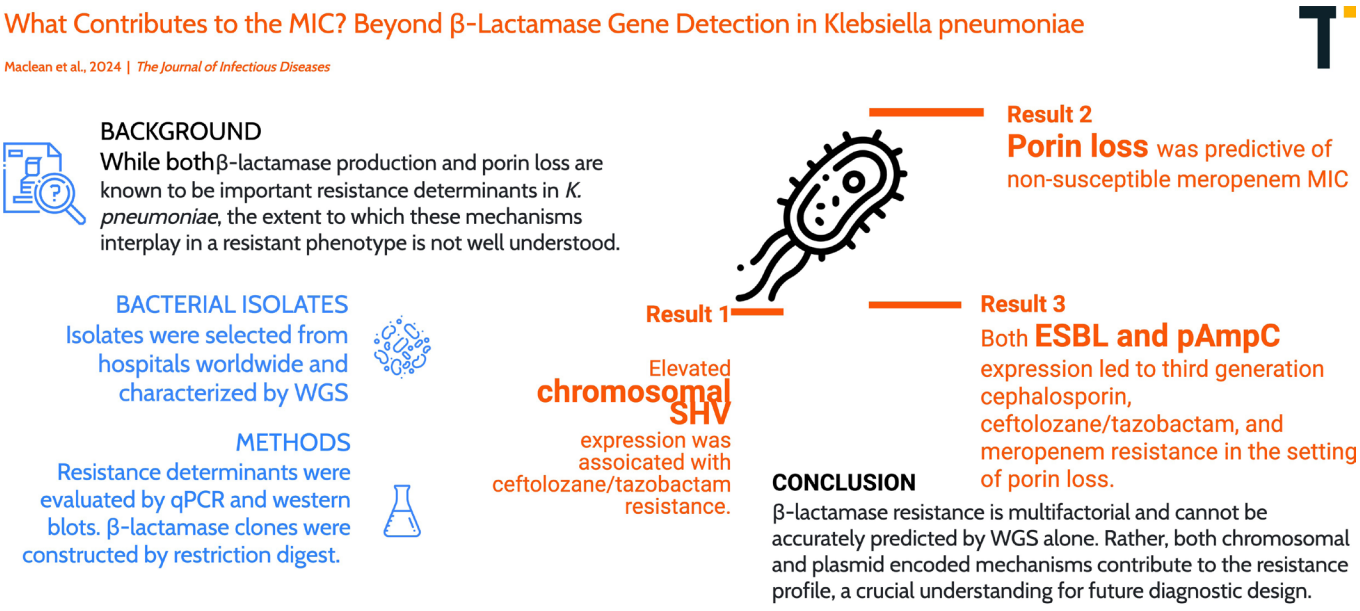
**This study suggests that cefepime and carbapenems may be the drugs of choice for all AmpC-beta-lactamase producing Enterobacterales regardless of species. See next review**

5

## What Contributes to the MIC? Beyond β-Lactamase Gene Detection in Klebsiella pneumoniae

J Infect Dis published online April 24, 2024
DOI: 10.1093/infdis/jiae204

The purpose of this study was to determine the extent to which b-lactamases and outer membrane porins affected β-lactam resistance. MICs to β-lactams and inhibitor combinations were determined by agar dilution or E-test. Outer membrane porin production was evaluated by western blot of outer membrane fractions. b-lactamase carriage was determined by whole genome sequencing and expression evaluated by RT-qPCR.



Plasmid-encoded b-lactamases were important for cefotaxime and ceftazidime resistance. Elevated expression of chromosomal SHV was important for ceftolozane/tazobactam resistance. Loss of outer membrane porins was predictive of meropenem resistance. ESBLs and plasmid-encoded AmpCs (pAmpCs) in addition to porin loss were sufficient to confer resistance to the third generation cephalosporins, piperacillin/tazobactam, ceftolozane/tazobactam, and meropenem. pAmpCs (CMY-2 and DHA) alone conferred resistance to piperacillin/tazobactam.

## Dr. Septimus's Annotations

The contribution of ESBLs to the β-lactam MICs in K. pneumoniae is well known. However, there is limited data available regarding the impact of pAmpCs on β-lactam MICs, despite research indicating their ability to hydrolyze a wide variety of β-lactam antibiotics [Microb Drug Resist 2015; 21:7-16]. Additionally, the contribution of outer membrane porins to the resistance profile of K. pneumoniae isolates expressing ESBLs or pAmpCs against the newer β-lactam/β-lactamase inhibitor combinations are unknown. In addition to plasmid-encoded enzymes and/or porin production, K. pneumoniae harbors a chromosomally encoded broad-spectrum b-lactamase, SHV-1, conferring intrinsic resistance to penicillins. [Antimicrob Agents Chemother 2001; 45:2856-61] This β-lactamase may be problematic for ceftolozane/tazobactam which has been shown to hydrolyze tazobactam [Clin Infect Dis 2016; 63:234-41].

**"The data presented in this study indicate that piperacillin/tazobactam and ceftolozane/tazobactam resistance only occurs in ESBL producing isolates when outer membrane porins are lost."**

The results of this work highlight the complexity of β-lactam resistance in gram-negative bacteria. In order to use existing or newly available antibiotics appropriately, we need to be aware that the susceptibility profile presented by the organism is based on the combination of resistant mechanisms. It is clear from this study that gene identification alone cannot determine the impact on the susceptibility profile of an organism. There was a significant increase in blaCTX-M-15 expression among cefepime non-susceptible clinical isolates, suggesting that CTX-M-15 contributes to cefepime resistance. Although clinical isolates often carry blaOXA-1 in addition to CTX-M-15, the Kp 23 clone producing CTX-M-15 alone had a cefepime MIC above the resistant breakpoint. Against ceftolozane/tazobactam, factors important for resistant MICs included pAmpC production, regardless of porin status, ESBL production in the setting of porin loss, and elevated expression of the chromosomal SHV. Against piperacillin/tazobactam, resistance patterns were variable in the clinical isolates with no one mechanism clearly contributing to the MIC. However, piperacillin/tazobactam MICs for the clones deficient in porin production but producing an ESBL resulted in a resistant phenotype. The data presented in this study indicate that piperacillin/tazobactam and ceftolozane/tazobactam resistance only occurs in ESBL producing isolates when outer membrane porins are lost. SHV β-lactamases are encoded on the chromosome of virtually all K. pneumoniae. While this enzyme is known to confer resistance to penicillins and aminopenicillins, the contribution of broad-spectrum chromosomal SHVs to other β-lactam MICs is not well established. In this analysis, there was a significant increase in RNA expression of blaSHV among isolates that were non-susceptible to ceftolozane/tazobactam, regardless of whether the SHV was a broad spectrum or an ESBL. In both the clinical isolates and clones, porin loss was predictive of resistant MICs to meropenem. Carbapenem resistance, notably, occurs in isolates lacking carbapenemases, typically in the setting of an ESBL or pAmpC and porin loss.

### BOTTOM LINE

**It's complicated! The analyses carried out in the current study expand our understanding of pAmpC and ESBL-mediated resistance. Their study underscores the need to identify pAmpCs in clinical isolates. Finally, these data highlight the need for development of diagnostic tools capable of rapidly identifying both the production of β-lactamases and porins in order to tailor antibiotic therapy in a timely manner.**

# Carbapenem use in extended-spectrum cephalosporin-resistant Enterobacterales infections in US hospitals and influence of IDSA guidance: a retrospective cohort study

Lancet Infect Dis published online April 25, 2024
doi.org/10.1016/S1473-3099(24)00149-X

Managing non-severe infections caused by ESBL producing Enterobacterales challenges carbapenem stewardship. The authors aimed to understand the real-world management of extended-spectrum cephalosporin-resistant (ECR) Enterobacterales infections in US hospitals and factors influencing preference for carbapenems over alternative treatments. This was a retrospective cohort study that included adults (aged ≥18 years) admitted to hospital with ECR Enterobacterales infections in the PINC AI database (Premier). Antibiotic regimens were assessed during empirical and targeted treatment periods and by infection severity and site. The likelihood of receiving targeted carbapenems over time and before or after initial release of the IDSA guidance in 2020, was established with generalized estimating equations controlling for patient, hospital, and temporal confounders.

Between January 1, 2018, and December 31, 2021, 30,041 inpatient encounters with ECR Enterobacterales infections were identified at 168 US hospitals, of which 16,006 (53.3%) encounters were in women and 14,035 (46.7%) were in men, with a mean age of 67·3 years (SD 15·1). Although few patients received carbapenems empirically (5324 [17.7%] of 30,041), many did so as targeted treatment (17,518 [58.3%] of 30,041), including subgroups of patients without septic shock (3031 [45.6%] of 6651) and patients with urinary tract infections without septic shock (1845 [46.8%] of 3943) in whom specific narrower-spectrum alternatives were active. Transitions from non-carbapenem to carbapenem antibiotics occurred most often on the day that the ECR phenotype was reported, regardless of illness severity. Carbapenems were the predominant choice to treat ECR Enterobacterales infections over time (adjusted odds ratio 1.00 [95% CI 1.00–1.00]), with no additional immediate change (1.07 [0.95–1.20]) or sustained change (0.99 [0.98–1.00]) after IDSA guidance release.

## Dr. Septimus's Annotations

The use of carbapenems is now considered the drug of choice (DOC) for severe ESBL-producing Enterobacterales infections based on the large multicenter MERINO trial published in 2018 which was unable to show non-inferiority of piperacillin–tazobactam to meropenem in patients with bacteremia caused ECR E coli and K pneumoniae.[JAMA 2018; 320: 984–94] However, the optimal management of non-severe presentations is controversial. The IDSA released their first guidance document in 2020. [Clin Infect Dis 2021; 72: e169–83] The initial version of this expert guidance advocated for liberal use of carbapenems as first line therapy for complicated cystitis and all infections outside of the urinary tract due to ESBL-producing Enterobacterales, primarily based on the MERINO trial. This guidance was followed by a formal guideline published by the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) in 2021. [Clin Microbiol Infect 2022; 28: 521–47] Unlike IDSA guidance, the ESCMID guideline recommended limiting carbapenem use exclusively for severe presentations of ECR Enterobacterales infections (which includes ESBL-producing Enterobacterales), specifically septic shock or bloodstream infection. Notably, both societies recognized the opportunity to transition to trimethoprim–sulfamethoxazole or a fluoroquinolone once the patient is clinically stable if isolate is susceptible. Further, a 2023 update to the IDSA guidance highlights stewardship and no longer recommends carbapenems as first-line treatment for complicated UTIs and pyelonephritis due to ESBL-producing

**"This study explored treatment of all ECR Enterobacterales infections, whereas IDSA guidance specifically targets ESBL-producing pathogens."**

Enterobacterales unless toxicities, resistance, or critical illness preclude the use of trimethoprim–sulfamethoxazole or fluoroquinolones.[Clin Infect Dis 2023; published online July 18, 2023] This study explored treatment of all ECR Enterobacterales infections, whereas IDSA guidance specifically targets ESBL-producing pathogens. They selected the ECR Enterobacterales definition for two reasons: first, testing for the presence of an ESBL gene or production of an ESBL enzyme is not routinely available across hospital laboratories, including those reporting data in PINC AI; and second, the landmark MERINO trial was done in a population with ECR pathogens, with only a subset confirmed to have ESBL carriage or production.

In the current study, carbapenems were used infrequently as empirical therapy, even in patients with septic shock. Importantly, carbapenems were the preferred choice to target ECR Enterobacterales even in patients with less severe infections, such as those with UTI and without septic shock. These findings highlight an actionable stewardship gap between prevailing real-world use of carbapenems in US hospitals and updated and recent practice recommendations from both the US and European infectious disease societies. One other consideration is the is the use of piperacillin/tazobactam (P/T) for less severe infections. In the MERENO trial subset analysis demonstrated if the organism had an MIC to P/T ≤8 outcomes were similar to carbapenems. CLSI updated breakpoints against Enterobacterales have been lowered to ≤8 for P/T to be considered susceptible. Currently susceptibility to P/Z is reported as resistant regardless of P/T MICs if the organism may be an ESBL producer in some laboratories. Should this be changed? Finally translating this updated guidance to clinical practice has proven to be challenging. Targeted prescriber education regarding the use of carbapenem-sparing alternative therapies should be discussed with prescribers for treatment of infections in patients with non-severe presentations.

**BOTTOM LINE**

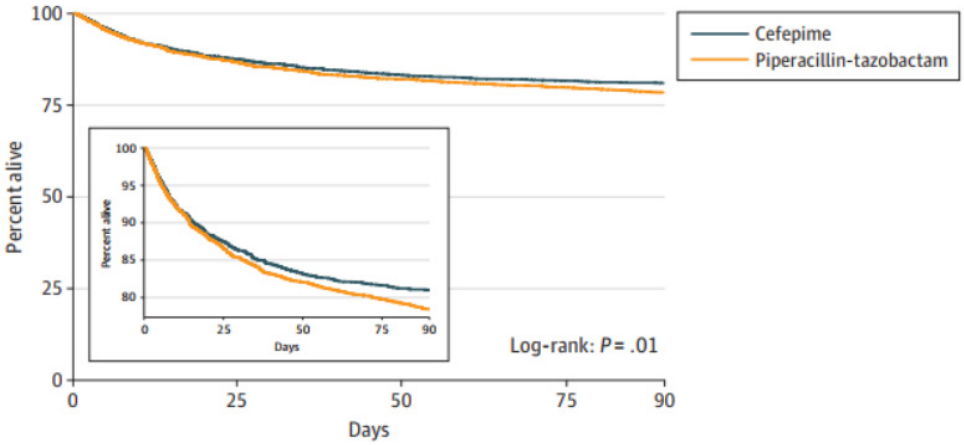
**These findings highlight several opportunities to improve carbapenem stewardship, including for patients with mild disease manifestations and with pathogens for which other narrower-spectrum agents retain in-vitro activity.**

## Mortality of Patients With Sepsis Administered Piperacillin-Tazobactam vs Cefepime

JAMA Intern Med published online May 13, 2024
doi:10.1001/jamainternmed.2024.0581

The investigators studied the use of piperacillin-tazobactam compared with cefepime in 90-day mortality in patients treated empirically for sepsis, using instrumental variable analysis of a 15-month piperacillin-tazobactam shortage. Using electronic health records, the investigators analyzed adults with suspected sepsis who were treated with either regimen in the ED of the University of Michigan from July 2014 through December 2018. Patients with indications for antianaerobic antibiotic therapy within 24 hours of presentation were excluded. The primary outcome was 90-day mortality. Secondary outcomes included organ failure-free, ventilator-free, and vasopressor-free days.

Among the 7,569 patients (55% men; median age, 63 years) with sepsis who met study eligibility, 4,523 were treated with vancomycin and piperacillin-tazobactam and 3,046 received vancomycin and cefepime. Of the piperacillin-tazobactam–treated patients, 97% were admitted outside the shortage period and 3% within. There were no significant differences between the treatment groups in terms of age, comorbidities, organ failure assessment scores, or time to antibiotic administration. In an instrumental variable analysis that controlled for unobserved differences in patient characteristics, 90-day mortality in patients treated with piperacillin-tazobactam was 22.5%, compared with 17.5% in those treated with cefepime, for an absolute increase in 90-day mortality of 5% (95% confidence interval [CI], 1.9% to 8.1%). Piperacillin-tazobactam was also associated with 2.1 fewer organ failure-free days (95% CI, 1.4 to 2,7), 1.1 fewer ventilator-free days (95% CI, 0.57 to 1.62), and 1.5 fewer vasopressor-free days (95% CI, 1.01 to 2.01). Additional analysis found that metronidazole, another anti-anaerobic antibiotic that was used in sepsis patients during the piperacillin-tazobactam shortage, was also associated with increased 90-day mortality.




## Dr. Septimus's Annotations

A combination of vancomycin and piperacillin-tazobactam is the most frequently prescribed empirical regimen for sepsis. Multiple observational studies have suggested that among critically ill patients, combination therapy with piperacillin-tazobactam and vancomycin is associated with increased mortality compared with cefepime and vancomycin. [Eur Respir J. 2023;61(5):2300413; Eur Respir J. 2023;61(2):2200910] However, a recent pragmatic randomized clinical trial (ACORN) found among adults hospitalized with acute infections, acute kidney or death was not significantly different between those treated with piperacillin-tazobactam or cefepime. [JAMA. 2023; 330:1557-1567] The ACORN study, however, was limited by analyzing only short-term outcomes (14 days) and only 54% of the ACORN cohort had sepsis and only 8% were admitted to an ICU. [Reviewed in ID Watch November 2023] Since this study was a retrospective cohort study relying on electronic medical records, it may be vulnerable to unobserved confounding.

### BOTTOM LINE

**Clinicians should be aware of the potential risks associated with antianaerobic treatment and consider alternatives when treating patients with sepsis without a clear indication for antianaerobic antibiotic therapy. Future studies are needed to investigate the mechanisms by which anaerobe depletion worsens clinical outcomes including impact on the microbiome.**

8

## Comparison of Daily versus Admission and Discharge Surveillance Cultures for Multidrug-Resistant Organism Detection in an Intensive Care Unit

J Infect Dis March 28, 2024
DOI: 10.1093/infdis/jiae162

Daily rectal or fecal swab samples and clinical data were collected over 12 months from patients in one 25-bed IC- in Chicago, IL and tested for the following multidrug-resistant organisms (MDROs): vancomycin-resistant enterococci (VRE); third- generation cephalosporin-resistant Enterobacterales, including extended-spectrum β-lactamase-producing Enterobacterales (ESBL); and carbapenem-resistant Enterobacterales (CRE). MDRO detection by (1) admission /discharge surveillance cultures or (2) clinical cultures were compared to daily surveillance cultures. Samples underwent 16S rRNA gene sequencing to measure the relative abundance of operational taxonomic units (OTUs) corresponding to each MDRO.

Compared with daily surveillance cultures, admission/discharge cultures detected 91% of prevalent MDRO colonization and 63% of incident MDRO colonization among medical ICU patients. Only a minority (7%) of MDRO carriers were identified by clinical cultures. Higher relative abundance of MDRO-associated OTUs and specific antibiotic exposures were independently associated with higher probability of MDRO detection by culture.

Daily surveillance cultures did improved MDRO detection, but it was not perfect; longitudinal surveillance for VRE, CR Klebsiella or Enterobacter species and ESBL-producing E.coli yielded a negative culture result after a positive result on 26% of ICU days. They found that higher OTU relative abundance and specific antibiotic exposures were associated with MDRO culture positivity among known carriers. Studies have demonstrated antibiotic exposure can influence the concentration of MDROs in patient samples. [Am J Infect Control 2012; 40:474-476; N Engl J Med 2000; 343:1925- 32]

### Dr. Septimus's Annotations

The investigators admit "additional analyses are needed to understand whether the benefit of daily culture screening outweighs the cost of performing such activities, including increased financial expense and burden on infection preventionist or nursing staff. Until proven benefit, resources may be better utilized for universal infection control interventions (i.e. hand hygiene, environmental disinfection, routine chlorhexidine bathing, etc.) to reduce spread of MDROs in the acute care setting."

**BOTTOM LINE**

**Accurate and timely identification of MDRO-colonized patients is important for implementation of targeted infection prevention interventions. Future research should focus on improving surveillance approaches to better inform prevention strategies.**

## 9 Rapid diagnostic tests and antimicrobial stewardship programs for the management of bloodstream infection: what is their relative contribution to improving clinical outcomes? A systematic review and network meta-analysis.

Clin Infect Dis published online April 28,2024
DOI: 10.1093/cid/ciae234

Investigators performed a systematic review and network meta-analysis of studies of patients with bloodstream infection(BSIs) to compare the clinical impact of rapid diagnostic tests(RDT) versus conventional blood cultures, with and without antimicrobial stewardship programs(ASP). Eighty-eight studies published through November 2023 and involving 25,682 patient encounters (10 randomized controlled trials, 78 quasi-experimental studies) were included. The primary outcomes were mortality, length of stay (LOS), and time to optimal therapy.

Forty-two studies (48%) reported information about time to optimal therapy, 71 (81%) reported information about LOS, and 76 (86%) reported information about mortality. In a network meta-analysis, a significant reduction in mortality was associated with RDT plus ASP versus blood cultures alone (odds ratio [OR], 0.72; 95% CI, 0.59 to 0.87) and with RDT

plus ASP versus blood cultures plus ASP (OR, 0.78; 95% CI, 0.63 to 0.96). There was no survival benefit associated with RDT alone compared with blood cultures alone or compared with blood cultures plus AST.

LOS was lower with RDT plus ASP versus blood cultures alone (OR, 0.91; 95% CI, 0.84 to 0.98), but there was no difference in LOS for any other comparisons. Time to optimal therapy was shorter with RDT plus ASP compared with blood cultures alone (−29 hours; 95% CI, −35 to −23 hours), with blood cultures plus ASP (−18 hours; 95% CI, −27 to −10 hours), and with RDT alone (−12 hours; 95% CI, −20 to −3 hours).

## Dr. Septimus's Annotations

This review and meta-analysis confirmed what was expected according to previous evidence showing a decreased mortality associated with the use of RDT in combination with ASP compared to BC alone [Clin Microbiol Infect 2018; 24: 944-55]. Importantly, this review also showed a survival benefit associated with RDT vs conventional systems when both are integrated in ASP. The key is using ASP to intervene in a timely manner when results of RDT are available.

Limitations include the high level of heterogeneity among studies, different definitions of LOS and time to optimal therapy, and risk for confounding. They concluded that their analysis suggests how the implementation of RDT+ASP probably confers a survival benefit even in institutions already implementing conventional culture results through effective ASP, overall supporting the recommendation of the IDSA to use RDT within ASP for the management of BSIs. [Clin Infect Dis 2016; 62: e51-77]

**BOTTOM LINE**

**This review demonstrated RDT in conjunction with ASP can reduce mortality for patients with BSIs compared to conventional blood culture systems, even in settings already using ASP.**

## Cefazolin as a predictor of urinary cephalosporin activity in indicated Enterobacterales

J Clin Microbiol published online March 8, 2024
10.1128/jcm.00788-21

Cefazolin susceptibility has been used as a proxy for uncomplicated urinary tract infections (uUTIs) caused by E coli, K pneumoniae, and Proteus mirabilis. As a result, the Clinical Laboratory Standards Institute (CLSI) implemented a urine-specific, cefazolin breakpoint and updated the M100 in 2014 to recommend cefazolin as a surrogate to predict the susceptibility of seven oral cephalosporins: cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef for treatment of uUTIs. Surrogate testing for oral cephalosporins is necessary, as individual CLSI breakpoints have not been established for some of the drugs, such as cephalexin, and access to individual cephalosporins is limited on commercial susceptibility platforms. This review focused on cefazolin antimicrobial susceptibility results as a surrogate for predicting oral cephalosporin activity in uUTIs.

Cefazolin itself is administered via the parenteral route and is not available in an oral formulation. Therefore, three cefazolin breakpoints were included in the CLSI M100-S24: 1) systemic IV breakpoints for infections other than uUTIs, 2) uUTI IV breakpoints, and 3) uUTI oral cephalosporin surrogate breakpoints. The current CLSI (M100-S33) MIC breakpoint for cefazolin surrogacy testing for treating uncomplicated urinary tract infections is ≤16 µg/mL for susceptible and ≥32 µg/mL for resistant. A susceptible breakpoint of ≤16 µg/mL was selected for two reasons: 1) peak urine concentrations for standard oral cephalosporin dosing regimens are well above this MIC, and 2) this cutoff demonstrated sufficient

agreement with the seven additional cephalosporins to support its use as a surrogate breakpoint. Isolates testing resistant to cefazolin may still be susceptible to cefdinir, cefpodoxime, and cefuroxime, and these antibiotics may be tested individually. A single-center study reported that one-third of the cefazolin-resistant Enterobacterales tested were susceptible to a third-generation cephalosporin (cefpodoxime/cefdinir) or cefixime. This study also demonstrated that cefpodoxime and cefdinir could be used to predict susceptibility to each other for E. coli; however, cefixime susceptibility was not reliably predicted or predictive among the other third-generation cephalosporins. At this time, the CLSI does not provide guidance for the use of susceptibility results of one third-generation cephalosporin to predict the susceptibility results of other third-generation cephalosporins, and the data to do this are largely lacking. The cephalosporin breakpoints for the Enterobacterales vary between the breakpoint setting institutions, including the FDA, CLSI, and EUCAST. See below

| Organization | Indication | Disk diffusion Disk content: 30 µg | | | MIC method | | | Corresponding comments |
|---|---|---|---|---|---|---|---|---|
| | | S | I | R | S | I | R | |
| CLSI (10) | Cefazolin as a surrogate for predicting the activity of oral cephalosporins in uncomplicated UTIs | ≥15 | N/A | ≤14 | ≤16 µg/mL | N/A | ≥32 µg/mL | • For uncomplicated UTIs due to *E.coli, K. pneumoniae*, and *P. mirabilis*<br>• Predicts results for the following oral agents: cefaclor, cefdinir, cefpodoxime, cefprozil, cefuroxime, cephalexin, and loracarbef<br>• Isolates resistant to cefazolin may still be susceptible to the individual drugs, which can be tested directly if necessary |
| | Parenteral cefazolin for uncomplicated UTIs | ≥15 | N/A | ≤14 | ≤16 µg/mL | N/A | ≥32 µg/mL | • For uncomplicated UTIs due to *E.coli, K. pneumoniae*, and *P. mirabilis*<br>• Breakpoints based on a cefazolin dosage regimen of 1 g administered every 12 h |
| | Parenteral cefazolin for infections other than uncomplicated UTIs | ≥23 | 20–22 | ≤19 | ≤2 µg/mL | 4 µg/mL | ≥8 µg/mL | • Cefazolin for infections other than uncomplicated UTIs due to *E.coli, K. pneumoniae*, and *P. mirabilis*<br>• Breakpoints based on a cefazolin dosage regimen of 2 g administered every 8 h |
| FDA (17) | The FDA recognizes CLSI cefazolin breakpoints for infections other than uncomplicated UTIs as of 10/14/21 | ≥23 | 20–22 | ≤19 | ≤2 µg/mL | 4 µg/mL | ≥8 µg/mL | • The FDA does not recognize separate susceptibility interpretive criteria for Enterobacteriaceae for therapy of uncomplicated UTI |
| EUCAST (16) | EUCAST (infections originating from the urinary tract) | ≥50 | 20-49 | <20 | ≤0.001 mg/L | 0.002–4mg/L | >4 mg/L | • For *E. coli* and *Klebsiella* spp. (except *K. aerogenes*) |

In 2020, the CLSI added a caret symbol (^) to the intermediate (I) susceptibility category to denote antibiotics that are concentrated in the urine and are likely to be successful in treating uUTIs . The ^ notation can be found next to the MIC or zone size diameter values within the intermediate column of the M100. For the Enterobacterales, the majority of antibiotics with an intermediate category contain the ^ designation. The I^ does not reflect a change in breakpoints; instead, it offers a more precise definition of the intermediate category, indicating that an antibiotic may still be considered for treatment of an uUTI given the higher urine concentration of the agent. Beta-lactam antibiotics, including cephalosporins, can be utilized as they achieve adequate concentrations in the urine.

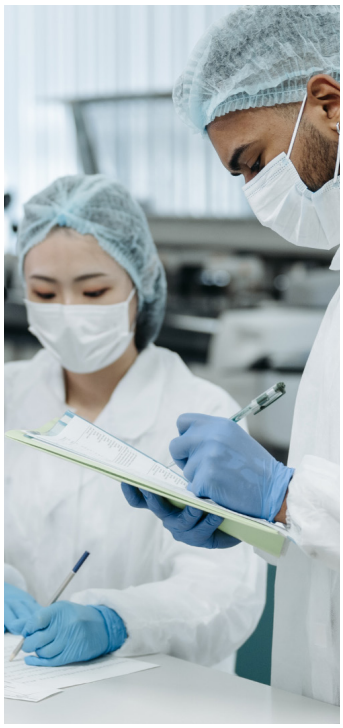
Within the class of cephalosporins, the pharmacokinetic characteristics can vary. See below

| Drug (generation) | Dose (mg) | $C_{max}$ (mg/L) (dose) | Protein binding (%) | Half-life (h) | Bio-availability (%) | Cumulative % of dose recovered in urine |
|---|---|---|---|---|---|---|
| Cephalexin (1st) (26–28) | 500–1,000 q6h | 15–20 (500 mg)<br>32–39 (1,000 mg) | 10–20 | 0.5–1.3 | >90 | 80–100 |
| Cefadroxil (1st) (27, 29) | 500 q12h | 16–18 (500 mg) | 20 | 1.2 | >70 | 80 |
| Cefaclor (2nd) (26, 30, 31) | 250–500 q8h | 6–10 (250 mg)<br>13–17 (500 mg) | 50 | 0.6 | 52–95 | 60–80 |
| Cefprozil (2nd) (26, 30, 32, 33) | 500 q12h | 8–11.5 (500 mg) | 36–45 | 1–1.3 | 71–95 | 60–70 |
| Cefuroxime (2nd) (26, 34, 35) | 500 q12h | 5.6–7 (500 mg) | 33–50 | 1.2–1.5 | 30–52 | 50 |
| Loracarbef (2nd) (26, 35, 36) | 200–400 q12-24h | 14–19.2 (400 mg) | 25 | 1–1.2 | 90 | 85–98 |
| Cefdinir (3rd) (37, 38) | 300 q12h or 600 q24h | 1.6 (300 mg)<br>2.3–2.9 (600 mg) | 60–70 | 1.5–1.7 | 16–25 | 12–18 |
| Cefpodoxime (3rd) (39–41) | 200–400 q12h | 2.1–2.6 (200 mg)<br>3.7–4.5 (400 mg) | 20–30 | 2.2–2.8 | 50 | 24–40 |
| Cefixime (3rd) (35, 42–44) | 200 q12h or 400 q24h | 2–3 (200 mg)<br>3.7–4.9 (400 mg) | 60–70 | 3–4 | 40–50 | 16–21 |

While beta-lactams often get lumped into a "low bioavailability" category relative to other classes of antibiotics (i.e., fluoroquinolones), it is not necessarily true for all cephalosporins. For example, cephalexin is an oral cephalosporin that is almost completely absorbed, resulting in high oral bioavailability. In the setting of UTIs, antibiotics that achieve sufficient concentrations in the urine are highly desirable as the primary goal of treatment is to eradicate the bacteria at the site of infection. This should be distinguished from infections that have progressed into more extensive disease such as bacteremic UTI or pyelonephritis where antibiotic exposures must be sufficient in the bloodstream or penetrate the tissue of the kidneys for adequate eradication. The use of cefazolin testing as a surrogate for oral cephalosporin susceptibility is not recommended for other species of Enterobacterales.

## Dr. Septimus's Annotations

Clinical laboratories face significant operational hurdles associated with the implementation of oral cephalosporin surrogate breakpoints, including validation of disease-specific breakpoints and the associated complexity of reporting. Clinical laboratories should collaborate with their antimicrobial stewardship and information technology teams and as well as clinical stakeholders to establish clear and concise breakpoint reporting and education. Beta-lactam antibiotics are not typically favored for treatment of uUTIs largely based on higher relapse and failure rates against comparative agents[FQ or TMP/SMX] particularly with short treatment duration; however, emerging resistance to trimethoprim–sulfamethoxazole and fluoroquinolones along with fluoroquinolone toxicity suggest oral cephalosporins should be considered an alternative for the treatment of uUTIs. Despite limited clinical outcome data evaluating the efficacy of the oral cephalosporins for uUTIs, these drugs reach high concentrations in the urine, suggesting that oral cephalosporins are probably an adequate and safe treatment option for uUTIs if given for the appropriate duration.



**BOTTOM LINE**

**Emerging resistance to trimethoprim–sulfamethoxazole and fluoroquinolones along with fluoroquinolone toxicity may nudge providers toward oral cephalosporins for the treatment of uUTIs.**

11

## Propensity Score-Weighted Analysis of Postoperative Infection in Patients With and Without Preoperative Urine Culture

JAMA Network Open. 2024;7(3): e240900
doi:10.1001/jamanetworkopen.2024.0900

The investigators asked is the practice of preoperative urine culture associated with reduced risk of postoperative urinary tract infection or surgical site infection. To examine this question, they performed a cohort study analyzing surgical procedures performed from January 1, 2017, to December 31, 2019, at any of 112 Veterans Affairs (VA) medical centers. The cohort comprised VA enrollees who underwent major elective noncardiac, nonurological operations. Machine learning and inverse probability of treatment weighting (IPTW) were used to balance the characteristics between those who did and did not undergo a urine culture. Data analyses were performed between January 2023 and January 2024. The two main outcomes were UTI and SSI occurring within 30 days after surgery. Weighted logistic regression was used to estimate odds ratios (ORs) for postoperative infection based on treatment status.

A total of 250,389 VA enrollees who underwent 288,858 surgical procedures were included, with 88.9% (256,753) of surgical procedures received by males and 48.9% (141,340) received by patients 65 years or older. Baseline characteristics were well balanced among treatment groups after applying IPTW weights. Preoperative urine culture was performed for 10.5% of surgical procedures (30,384 of 288,858). The IPTW analysis found that preoperative urine culture was not associated with SSI (adjusted OR [AOR], 0.99; 95% CI, 0.90-1.10) or postoperative UTI (AOR, 1.18; 95% CI, 0.98-1.40). In analyses limited to orthopedic surgery and neurosurgery as a proxy for prosthetic implants, the adjusted risks for UTI and SSI were also not associated with preoperative urine culture performance.

**Table 2. Risk of Urinary Tract Infection (UTI) and Surgical Site Infection (SSI) Associated With Preoperative Urine Culture Performed in Surgical Patients**

| Balanced study population | Independent factor | Postoperative outcome | AOR (95% CI) |
|---|---|---|---|
| All eligible surgical procedures | 30-d Preoperative urine culture performed vs not performed | SSI | 0.99 (0.90-1.10) |
| | | UTI | 1.18 (0.98-1.40) |
| Orthopedic and neurosurgery | 30-d Preoperative urine culture performed vs not performed | SSI | 0.93 (0.76-1.12) |
| | | UTI | 1.27 (0.97-1.65) |

## Dr. Septimus's Annotations

Although recent guidelines recommend against performance of preoperative urine culture before nongenitourinary surgery, many clinicians still order preoperative urine cultures and prescribe antibiotics for treatment of asymptomatic bacteriuria in an effort to reduce SSIs. The 2019 IDSA clinical practice guidelines recommend against testing for and treating ASB in all patients undergoing nonurological surgical procedures. [Clin Infect Dis. 2019;68:e83-e110] Prior studies have shown that up to 25% of nonurological surgical procedures are preceded by a screening urine culture, and the rate is almost 50% among certain surgical specialties.[JAMA Surg. 2019;154(3):241-248] This practice is also more frequent prior to implant-related procedures. A recent study demonstrated that after a urine culture is ordered and found to be positive for possible infection, antibiotic treatment often follows, even if the patient is entirely asymptomatic. [Mayo Clin Proc Innov Qual Outcomes. 2020;4:126-131] Previous studies on cardiac, vascular, and orthopedic surgical procedures reported that preoperative ASB was not associated with lower postoperative risk of infection, even when accounting for antibiotics. The unintended consequences [AR, ADE, CDI] of unnecessary urine culture are well-described in the literature. [Clin Orthop Relat Res. 2013; 471:3822-3829] When ASB is identified, almost 75% of patients still get antibiotics. [Clin Infect Dis. 2017;65:910-917] Randomized clinical trials of antibiotic treatment vs no treatment of ASB primarily in nonsurgical populations have found more harm than benefit. [Cochrane Database Syst Rev. 2015;4(4):CD009534] The main limitation of this study is its potential inability to control for unobserved and unobservable confounders. As with most VA studies the absolute number of females evaluated in the study was small compared with males, making subgroup analysis by sex not feasible. In the neurosurgery and orthopedic surgery cohort, patient outcomes were not obtained beyond 30 days although CDC definitions allows 90 days of follow-up for infections after procedures with implants.

### BOTTOM LINE

**Testing for ASB was not associated with reduced risk of SSI or UTI among the surgical specialties evaluated in this study. The results support elimination of screening urine cultures and associated antibiotic treatment on patients with ABU prior to surgery, even when using prosthetic implants.**

12

## Performance of Urinalysis Parameters in Predicting Urinary Tract Infection: Does One Size Fit all?

Clin Infect Dis published online April 26, 2024
DOI: 10.1093/cid/ciae230

The extensive use of urinalysis (UA) in patients without suspicion of UTI leads to identification of UA parameters like pyuria or presence of nitrite, which in turn trigger urine cultures and inappropriate antimicrobial use. A recent survey of academic and community hospitals reported almost 50% of hospital laboratories used reflex urine culture approaches (also referred to as UA with reflex to culture). [Infect Control Hosp Epidemiol 2019. 40:228-231] Performance of UA parameters in predicting UTI has not been systematically investigated or validated. UTI was defined as bacterial growth of >105 CFU/ml in the urine of patients with any genitourinary signs or symptoms or presence of at least two of the following without other cause: fever, rigors, hypotension, nausea or vomiting, delirium, or new urologic obstruction or trauma causing bleeding. This study included adult patients if

1. They were hospitalized or seen in the ED and
2. received UA and urine culture order within 24 hours of each other.

They evaluated the performance of relevant UA parameters (pyuria, nitrite, leukocyte esterase, bacteria) in predicting UTI by assessing sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). They also combined 18 different UA criteria and used area under receiver operating curves (AUROC) to identify the five best-performing models. They further assessed the NPV of pyuria, leukocyte esterase and nitrite across different groups: male vs. female, and age <65 or ≥65. They also performed sub analyses for (A) outcome of UTI as defined by IDSA, (B) growth of E coli in urine culture, (C) clean catch collection methods.

**"In this cohort study of 3392 patients who received urine tests for suspicion of UTI, all UA parameters, alone or in combination, had poor positive predictive value for the diagnosis of UTI."**

In this cohort study of 3392 patients who received urine tests for suspicion of UTI, all UA parameters, alone or in combination, had poor positive predictive value for the diagnosis of UTI. However, absence of urinalysis parameters (e.g., pyuria) had a high NPV for ruling out UTI. Additionally, both NPV and PPV of all UA parameters were low in older women, likely due to contamination or colonization. Most importantly, combined urinalysis parameters (pyuria or nitrite) performed better than pyuria alone for ruling out UTI, especially in men and in patients younger than 65 years of age. If hospital laboratories leveraged combined UA criteria (1+ leukocyte esterase or nitrite OR pyuria≥10 WBCS/hpf or nitrite) for their NPV, almost half of unnecessary urine culture orders can be avoided.

### Dr. Septimus's Annotations

The results of this study demonstrate that abnormal UAs are poor at predicting UTIs as defined by culture and clinical criteria. An inherent limitation was the retrospective design. They did not include pediatric, catheterized, or outpatient clinic populations. In the absence of patient-specific antibiotic use data, they could not exclude patients who received prior antibiotics.

BOTTOM LINE

**Obtaining reflex urine cultures should be limited to patients with signs and symptoms of a UTI. If this practice was implemented, we could reduce unnecessary urine cultures which in turn would reduce unnecessary antimicrobial therapy.**

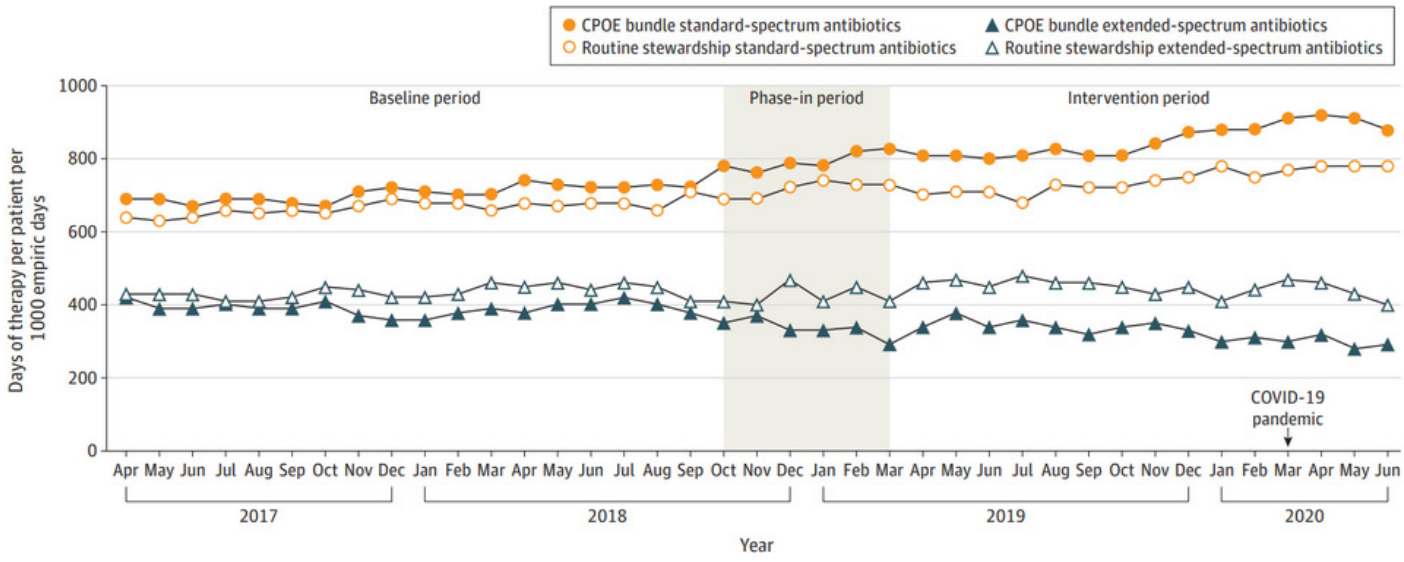
13

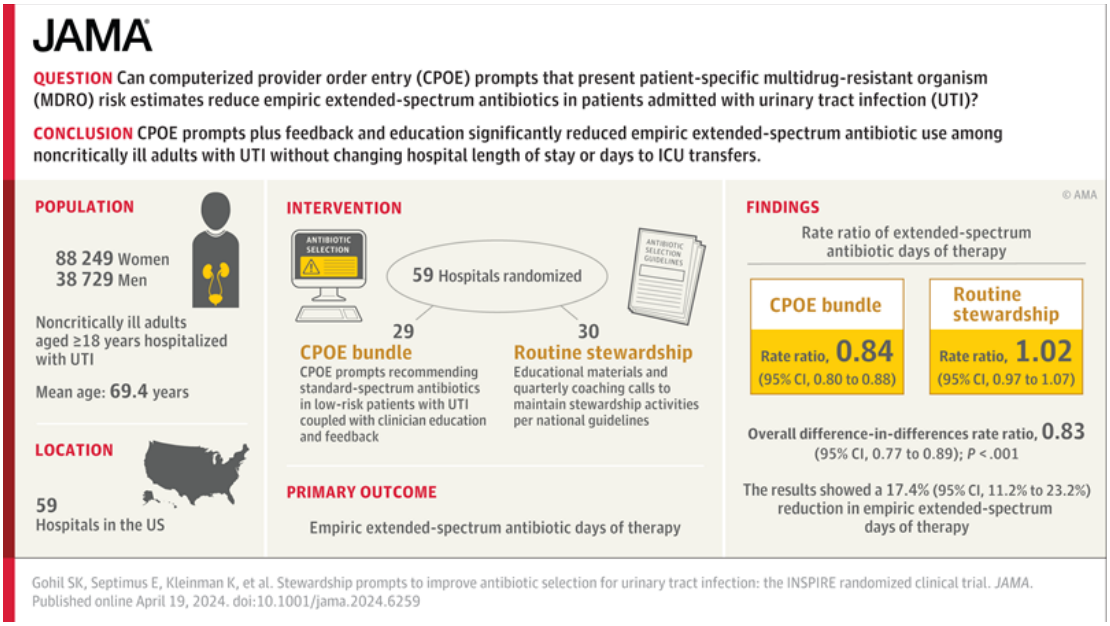
## Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection The INSPIRE Randomized Clinical Trial

JAMA published online April 19, 2024
doi:10.1001/jama.2024.6259

The purpose of this trial was to evaluate whether computerized provider order entry (CPOE) prompts providing patient- and pathogen-specific MDRO risk estimates could reduce use of empiric extended-spectrum antibiotics for treatment of UTI. This was a cluster-randomized trial in 59 US community hospitals comparing the effect of a CPOE stewardship bundle (education, feedback, and real-time and risk-based CPOE prompts; 29 hospitals) vs routine stewardship (n = 30 hospitals) on antibiotic selection during the first 3 hospital days (empiric period) in noncritically ill adults (>18 years) hospitalized with UTI with an 18-month baseline (April 1, 2017–September 30, 2018) and 15-month intervention period (April 1, 2019–June 30, 2020). CPOE prompts recommending empiric standard-spectrum antibiotics in patients ordered to receive extended-spectrum antibiotics who have low estimated absolute risk (<10%) of MDRO UTI, coupled with feedback and education. The primary outcome was empiric (first 3 days of hospitalization) extended-spectrum antibiotic days of therapy (DOT). Secondary outcomes included empiric vancomycin and antipseudomonal DOT. Safety outcomes included days to ICU transfer and hospital length of stay (LOS).

Among 127,403 adult patients (71,991 baseline and 55,412 intervention period) admitted with UTI in 59 hospitals, the mean (SD) age was 69.4 (17.9) years, 30.5% were male, and the median Elixhauser Comorbidity Index count was 4 (IQR, 2-5). Compared with routine stewardship, the group using CPOE prompts had a 17.4% (95% CI, 11.2%-23.2%) reduction in empiric extended-spectrum DOT (rate ratio, 0.83 [95% CI, 0.77-0.89]; P < .001). The safety outcomes of mean days to ICU transfer (6.6 vs 7.0 days) and hospital LOS (6.3 vs 6.5 days) did not differ significantly between the routine and intervention groups, respectively.






## Dr. Septimus's Annotations

The antibiotic stewardship intervention used in this study resulted in a 17.4% reduction in empiric extended-spectrum antibiotic use for noncritically ill patients hospitalized for UTI. Excessive antibiotic use for community-onset UTI and the high propensity for recurrent UTI have likely contributed to a national rise in the prevalence of gram-negative MDROs. In this trial, the overall frequency of patients with UTI who had urine cultures positive for Pseudomonas was 3.4% or less and for ESBL was 8.0% or less, confirming that most patients do not require empiric extended-spectrum antibiotics. In fact, among those estimated to be at low risk for MDRO by the study algorithm, less than 6% actually grew an MDRO. Positive urine cultures were included regardless of colony count and asymptomatic bacteriuria could not be distinguished from true UTI.

### BOTTOM LINE

**Real-time CPOE recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated infections can safely reduce empiric extended-spectrum antibiotic use in patients hospitalized for UTI.**

## 14 FDA Approves Pivmecillinam

The FDA approved the oral antibiotic pivmecillinam for treating uncomplicated urinary tract infections (uUTIs) in women. Pivmecillinam has a unique mechanism of action but is not a new antibiotic. In fact, it has been used outside of the US to treat uUTIs for more than 40 years and is recommended as a first-line treatment in several countries. The approval is for treatment of uUTIs caused by susceptible isolates of E coli, Proteus mirabilis, and S saprophyticus. This is the first antibiotic approved by the FDA for uUTIs in more than two decades.

The FDA said approval was based on results from three randomized controlled trials that compared pivmecillinam to placebo, to another antibiotic, and to an anti-inflammatory. The primary measure of efficacy in each trial was a composite response of clinical cure (resolution of symptoms) and microbiologic response (reduction of the bacteria culture at trial entry).

In the trial comparing pivmecillinam to placebo, 62% of 137 participants who received the antibiotic achieved composite response, compared to 10% of 134 who received placebo. Compared with another antibiotic, 72% of 127 subjects who received pivmecillinam achieved composite response versus 76% of 132 who received the comparator drug. Composite response was achieved in 66% of 105 participants who received pivmecillinam compared with 22% of the 119 who took ibuprofen. The most common side effects of pivmecillinam included nausea and diarrhea.

Dr. Septimus's Annotations

Pivmecillinam is an orally active prodrug of mecillinam, an extended-spectrum penicillin antibiotic. Pivmecillinam is the pivaloyloxymethyl ester of mecillinam. The mode of action is also unique among the β-lactam antimicrobials, as mecillinam has a high specificity for the penicillin-binding protein-2. The bioavailability for pivmecillinam is high, and pharmacokinetic studies have shown the urine mecillinam concentration to exceed 200 mg/L. [Clin. Microbiol. Infect. 2004; 10:54–61] Its use has increased significantly in recent years, because of the rise in resistance to other commonly used antimicrobials for UTIs, and its clinical effect against (ESBL producing E. coli. [Antimicrob. Chemother. 2018; 73:2503–2509]

**BOTTOM LINE**

**In light of increased resistance to FQs and TMP-SMX Pivmecillinam is a welcomed addition for the treatment of UTIs but must be used responsibly.**

15

## Clarithromycin for early anti-inflammatory responses in community-acquired pneumonia in Greece (ACCESS): a randomised, double-blind, placebo-controlled trial

Lancet Respir Med 2024; 12: 294–304
doi.org/10.1016/ S2213-2600(23)00412-5

The ACCESS trial was a phase 3 prospective, double-blind, randomized controlled trial, in which adults in hospital with community-acquired pneumonia (CAP) who had systemic inflammatory response syndrome, Sequential Organ Failure Assessment (SOFA) score of 2 or more, and procalcitonin 0.25 ng/mL or more were enrolled in 18 internal medicine departments. Patients were randomly assigned (1:1) by computer generated block randomization to standard of care medication (including intravenous administration of a third-generation cephalosporin or intravenous administration of β-lactam plus β-lactamase inhibitor combination) plus either oral placebo or oral clarithromycin 500 mg twice daily for 7 days. Investigators, staff, and patients were masked to group allocation. The primary composite endpoint required that patients fulfilled both of the following conditions after 72 hours (i.e., day 4 of treatment): (1) decrease in respiratory symptom severity score of 50% or more as an indicator of early clinical response and (2) decrease in SOFA score of at least 30% or favorable procalcitonin kinetics (defined as ≥80% decrease from baseline or procalcitonin <0.25 ng/mL), or both, as an indicator of response. Blood was sampled on visit 1 and follow-up visits for cytokine measurements and isolation of peripheral blood mononuclear cells (PBMCs) for cytokine stimulation.

Patients were enrolled between Jan 25, 2021, and April 11, 2023, and 278 individuals were randomly allocated to receive standard of care in combination with either clarithromycin (n=139) or placebo (n=139). 134 patients in the clarithromycin group (five withdrew consent) and 133 patients in the placebo group (six withdrew consent) were included in the analysis of the primary endpoint. The primary endpoint was met in 91 (68%) patients in the clarithromycin group and 51 (38%) patients in the placebo group (difference 29·6% [95% CI 17·7–40·3]; odds ratio [OR]

3·40 [95% CI 2·06–5·63]; p<0·0001). Patients who received dual antibiotics also were significantly less likely to develop sepsis (13% vs. 24%; NNT, 10), significantly more likely to be discharged and alive at 3 months (79% vs. 62%; NNT, 6), and somewhat less likely to be readmitted within 90 days (8% vs. 15%; NNT, 14; P=0.09).

## Dr. Septimus's Annotations

Guidelines recommend treating patients who are hospitalized for community-acquired pneumonia (CAP) with a β-lactam antimicrobial plus a macrolide antibiotic (i.e., azithromycin or clarithromycin. [ Am J Respir Crit Care Med 2019; 200: e45] However, this recommendation is based predominantly on observational studies showing that the combined regimen is associated with higher survival than monotherapy. The general presumption has been that macrolides have an anti-inflammatory effect. The investigators in this study observed that at day 4, the peripheral blood mononuclear cells of patients in the clarithromycin group produced more TNF-α and less interleukin-10 in response to lipopolysaccharide stimulation than patients in the placebo group. Although it is observational and might be an epiphenomenon unrelated to the affected by clarithromycin, this finding would seem to be counterintuitive to a primary anti-inflammatory action and, as the investigators conclude, fits better with potential interference in immune downregulation. If impairment in early downregulation of pro-inflammatory responses is beneficial, this has fundamental implications for our understanding of the pathobiology of severe sepsis. The contribution of clarithromycin treatment towards reversal of immunoparalysis has also been shown in a previous randomized controlled trial. Patients with VAP were randomly assigned to 3 days of intravenous adjunctive treatment with clarithromycin (n=100) or placebo (n=100). At the end of treatment, the production of IL-6 by circulating PBMCs was increased and the TNFα:IL-10 ratio was increased. [Antimicrob Agents Chemother 2012; 56: 3819–25]

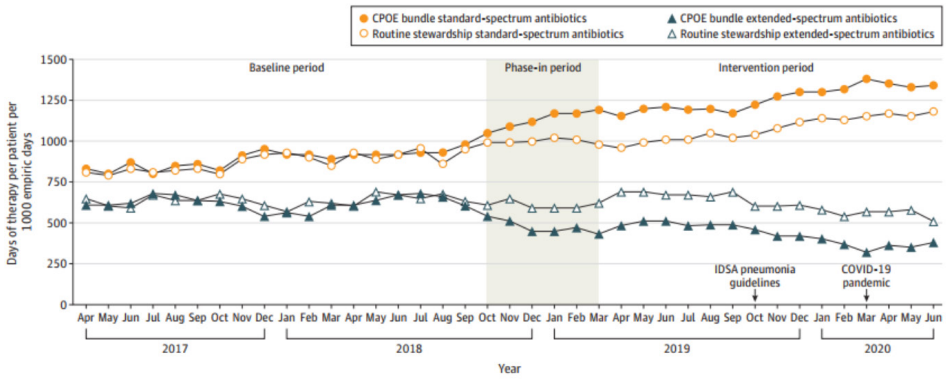
**BOTTOM LINE**

**This RCT supports the benefit of macrolide plus a β-lactam for treatment in patients hospitalized with CAP.**

## Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial

JAMA published online April 19, 2024
doi:10.1001/jama.2024.6248

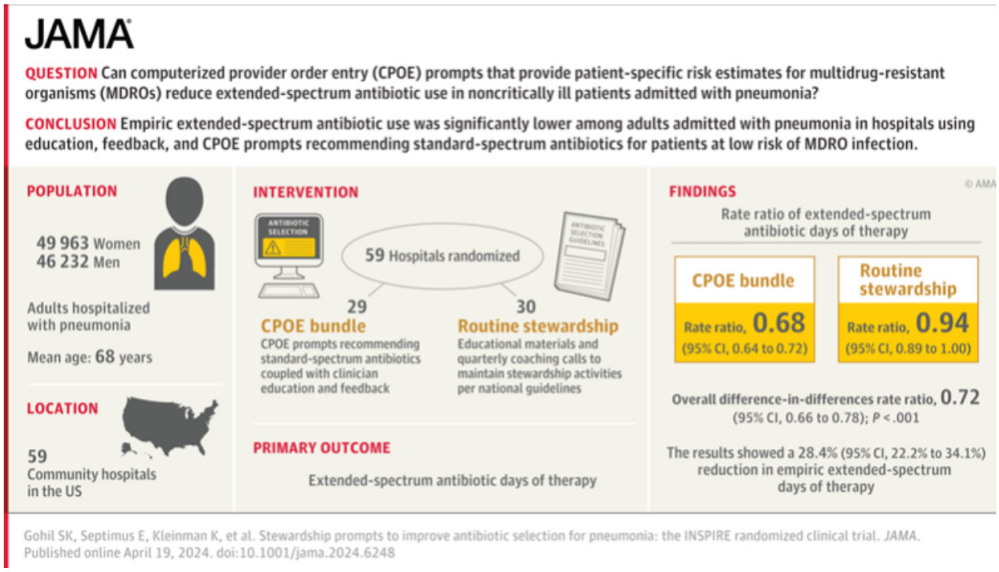
The purpose of this study was to evaluate whether computerized provider order entry (CPOE) prompts providing patient- and pathogen-specific MDRO infection risk estimates could reduce empiric extended-spectrum antibiotics for non–critically ill patients admitted with pneumonia.




This was a cluster-randomized trial in 59 US community hospitals comparing the effect of a CPOE stewardship bundle (education, feedback, and real-time MDRO risk-based CPOE prompts; n = 29 hospitals) vs routine stewardship (n = 30 hospitals) on antibiotic selection during the first 3 hospital days (empiric period) in non–critically ill adults (>18 years) hospitalized with pneumonia (CAP). There was an 18-month baseline period

from April 1, 2017, to September 30, 2018, and a 15-month intervention period from April 1, 2019, to June 30, 2020. CPOE prompts recommending standard-spectrum antibiotics in patients ordered to receive extended-spectrum antibiotics during the first 3 days who have low estimated absolute risk (<10%) of MDRO pneumonia, coupled with feedback and education. Safety outcomes included days to ICU transfer, escalation of antimicrobial therapy, and hospital length of stay (LOS).

Among 59 hospitals with 96,451 (51,671 in the baseline period and 44,780 in the intervention period) adult patients admitted with pneumonia, the mean (SD) age of patients was 68.1 (17.0) years, 48.1% were men, and the median (IQR) Elixhauser comorbidity count was 4 (2-6). Compared with routine stewardship, the group using CPOE prompts had a 28.4% reduction in empiric extended-spectrum days of therapy (DOT) (rate ratio, 0.72 [95% CI, 0.66-0.78]; P < .001). Safety outcomes of mean days to ICU transfer (6.5 vs 7.1 days) hospital length of stay (6.8 vs 7.1 days) or escalation of antimicrobial therapy did not differ significantly between the routine and CPOE intervention groups.




## Dr. Septimus's Annotations

Empiric extended-spectrum antibiotic use was significantly lower among adults admitted with pneumonia to non-ICU settings in hospitals using education, feedback, and real-time CPOE prompts recommending standard-spectrum antibiotics for patients at low risk of MDRO infection, compared with routine stewardship practices. The CPOE bundle did not include appropriate diagnostic criteria for accurate diagnosis of pneumonia. In addition, most patients classified as CAP did not have a respiratory culture. it was not possible to separate the effect of the prompt itself from the effects of education and feedback, although the rapid reduction in extended-spectrum antibiotic use suggests that the prompt played a prominent role because education and feedback campaigns generally not been that effective. The use of AI hopefully will accelerate the ability for EHR vendors to develop models to predict the risk of MDROs associated with suspected infection.

### BOTTOM LINE

**Real-time electronic health record–generated recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated infections can substantially and safely reduce empiric extended-spectrum antibiotic use in patients hospitalized for pneumonia.**

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# ECDC SURVEILLANCE REPORT Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals 2022–2023

Stockholm, May 2024

European Centre for Disease Prevention and Control

This report contains data from the third ECDC point-prevalence survey (PPS), which included 1,332 acute care hospitals in 28 European Union/European Economic Area (EU/EEA) countries and three western Balkan countries (Kosovo, Montenegro, and Serbia). The prevalence of patients with at least one HAI in the EU/EEA sample was 7.1% (country range: 3.1–13.8%). When extrapolated to the average daily number of occupied beds per country, the weighted HAI prevalence was 6.3% (cumulative 95% confidence interval [CI]: 5.3–7.4%). Correcting for results of national validation studies, the adjusted prevalence of patients with at least one HAI was estimated at 8.0% (95% confidence interval: 6.6–9.6%). After adjustment for the one non-participating EU/EEA country (Denmark), this corresponded to an estimated total of 93,305 (95% CI: 76 427–111,899) patients with at least one HAI on any given day, 4.3 million (95% CI: 3.1–5.8 million) patients with at least one HAI and 4.8 million (95% CI: 3.1–5.8 million) HAIs (infection episodes) per year in the period 2022 to 2023 in acute care hospitals in the EU/EEA.

Of a total of 22,806 reported HAIs in the EU/EEA, the most frequently reported types of HAI were respiratory tract infections (29.3% of the total, including pneumonia 19.0%, COVID-19 7.0% and other lower respiratory tract infections 3.3%), urinary tract infections (19.2%), surgical site infections (16.1%), bloodstream infections (11.9%) and gastro-intestinal infections (9.5%), with C. difficile infections accounting for 62.1% of the latter and 5.9% of all HAIs. ICU patients, hematology/bone marrow transplant patients, and burn patients were at the highest risk of acquiring HAI.

**Major recommendations from the findings of the ECDC PPS 2022–2023 include:**

| | |
|---|---|
| 1. | An urgent need to harmonize diagnostic stewardship and improve access to microbiological diagnostic testing in EU/EEA hospitals. |
| 2. | Increasing IPC nurse staffing levels to (ideally) one IPC nurse per 100 occupied beds. |
| 3. | Installing AHR [hand hygiene] dispensers at the point-of-care. |
| 4. | Increasing the percentage of single rooms to improve isolation capacity. |
| 5. | Implement multimodal strategies for IPC. |
| 6. | Ensure the implementation of preventive measures for COVID-19 and other respiratory viral infections. |
| 7. | Increasing post-prescription review of antimicrobial treatment, de-escalating, and switching from intravenous to oral when possible. |
| 8. | Reduce the unnecessarily prolonged surgical prophylaxis and the use of antimicrobials for medical prophylaxis when not indicated. |
| 9. | Ensure training, dedicated skilled personnel and time for antimicrobial stewardship interventions. |

More concerningly, among microbiologically documented HAIs, 32% of microorganisms detected were resistant to antimicrobials. The survey also found that 35.5% of patients received an antimicrobial during their hospital stay, compared with 32.9% in the ECDC's previous PPS in 2016-2017. The estimated number of patients receiving an antimicrobial on any given day was 390,957. A total of 16,948 microorganisms were reported in 13,875 (60.8%) HAIs. The microorganisms most frequently isolated from HAIs were, in decreasing order, E coli (12.7%), Klebsiella spp. (11.7%), Enterococcus spp. (10.0%), SARS-CoV-2 (9.5%), S. aureus (9.0%), C. difficile (8.0%), P. aeruginosa (7.9%), coagulase-negative staphylococci (5.8%), Candida spp. (4.7%), Proteus spp. (3.2%), Acinetobacter spp. (3.2%) and Enterobacter spp. (3.0%). The PPS protocol required the reporting of antimicrobial susceptibility testing (AST) data only on specific bug-drug combinations. Selected AST data were available on the day of the survey for 90.4% of microorganisms selected for AST reporting in the PPS protocol. Methicillin resistance was reported in 23.7% of S. aureus isolates with known AST results. Vancomycin

resistance was reported in 15.6% of isolated enterococci. Third-generation cephalosporin resistance was reported in 34.7% of all Enterobacterales and was the highest in K. pneumoniae with 58.1%. Carbapenem resistance was reported in 29.7% of P. aeruginosa isolates and 82.9% of Acinetobacter baumannii isolates. The combined index of these first-level antimicrobial resistance (AMR) markers (composite index of AMR) showed that in microbiologically documented HAIs, 32.0% of microorganisms were resistant to antimicrobials (mean of countries: 29.6%, median of countries: 21.8%). The second-level AMR markers showed that carbapenem resistance was reported in 9.3% of all included Enterobacterales (mean of countries: 9.5%, median of countries 3.4%) and was the highest (25.1%) in K. pneumoniae.

Dr. Septimus's *Annotations*

In the US, despite improvements, HAIs continue to affect about one out of every 31 hospitalized patients, leading to substantial morbidity, mortality, and excess healthcare expenditures. Pneumonia, GI infections (most of which were due to C difficile), and SSIs were the most common health care–associated infections in the US. [N Engl J Med.2018; 379:1732-1744] Unfortunately, there are persistent gaps between what is recommended and what is practiced. In fact, it is estimated that over 50% of HAIs may be preventable with proper infection prevention and patient safety interventions. [Infect Control Hosp Epidemiol 2018; 39: 1277–1295]

The ECDC report highlights prolonged antimicrobial prophylaxis and frequent use of broad-spectrum antibiotics as priority targets for future antimicrobial stewardship efforts. The report also recommends increased infection prevention staffing levels, improved hand hygiene, isolation for patients with certain microorganisms, and implementation of preventive measures for viral respiratory infections to help reduce HAIs.

**BOTTOM LINE**

**New data today from the ECDC highlights the continuing challenge that HAIs and antibiotic resistance pose for European hospitals.**

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## WHO bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance.

May 17, 2024

World Health Organization

The updates are the first since the WHO released its initial Bacterial Priority Pathogens List (BPPL) in 2017. The updated list, which covers 24 pathogens and 15 "drug-bug" combinations, focuses on the bacterial phenotypes that WHO experts say result in the "highest, most significant health burden" and for which there is the greatest unmet need. The combinations were assessed using eight criteria: mortality, incidence, non-fatal health burden, trend of resistance, transmissibility, preventability in healthcare settings and the community, treatability, and the number of antibiotics in the pipeline that address them.

At the top are the critical priority pathogens, which are those that present the highest threat to public health due to limited treatment options, high morbidity and mortality, and ability to share resistance mechanisms. This group is focused on gram-negative bacterial pathogens primarily found in hospitals, such as carbapenem-resistant Acinetobacter baumannii and carbapenem-resistant Enterobacterales (CRE). Among the notable changes in the critical priority group is the addition of third-generation cephalosporin-resistant Enterobacterales (3GCRE), which have been associated with high rates of treatment failure and increased healthcare costs in low- and middle-income countries (LMICs) and

vulnerable populations. Another notable change is carbapenem-resistant P aeruginosa moving from critical to high priority, a group that includes pathogens that are difficult to treat, cause substantial disease burden, and are becoming increasingly resistant.

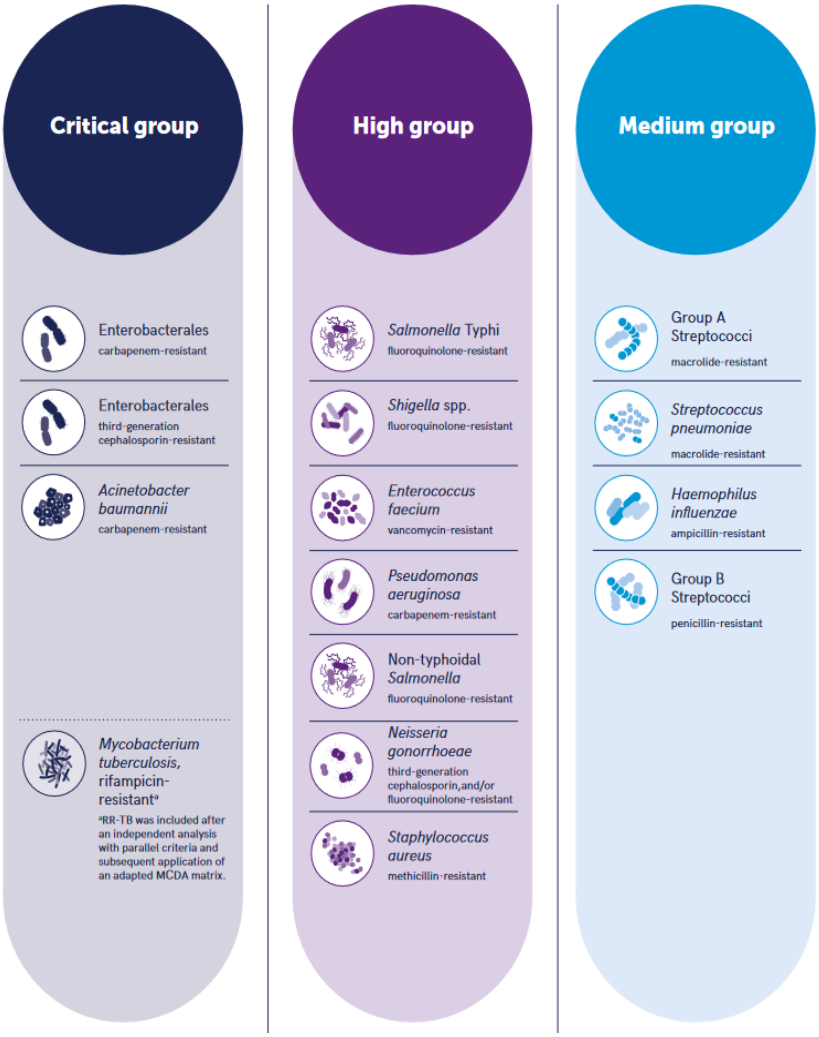
Also new in the high-priority pathogen group is fluoroquinolone-resistant Shigella, which is the second most common cause of diarrheal mortality in all age-groups globally. Previously listed in the medium-priority group. Other community pathogens that were previously listed as high priority but are given a higher ranking in the updated BPPL are fluoroquinolone-resistant Salmonella Typhi and fluoroquinolone-resistant non-typhoidal Salmonella.

Remaining in the high-priority group are methicillin-resistant S aureus, vancomycin-resistant Enterococcus faecium, and third-generation cephalosporin-resistant and/or fluoroquinolone-resistant N gonorrheae.

Also new in the critical-priority group is rifampicin-resistant tuberculosis (RR-TB), which was not included in the 2017 BPPL but was added to the 2024 list because it poses additional challenges to diagnosis, treatment, and clinical management.

Other new drug-bug combinations added to the 2024 BPPL are macrolide-resistant group A streptococci, penicillin-resistant group B streptococci, and macrolide-resistant S pneumoniae, which join ampicillin-resistant H influenzae in the medium-priority group.

Removals from the BPPL, based on evidence and expert consensus, include clarithromycin-resistant Heliobacter pylori, fluoroquinolone-resistant Campylobacter spp, penicillin-non-susceptible S pneumoniae, third-generation cephalosporin-resistant Providencia spp, and vancomycin-intermediate and -resistant S aureus.



Dr. Septimus's Annotations

The WHO BPPL acts as a guide for prioritizing R&D and investments in AMR, emphasizing the need for regionally tailored strategies to effectively combat resistance. It targets developers of antibacterial medicines, academic and public research institutions, research funders, and public–private partnerships investing in AMR R&D, as well as policy-makers responsible for developing and implementing AMR policies and programs.

**BOTTOM LINE**

**This report and the ECDC Surveillance Report Point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals (see above) emphasizes the continuing challenge that HAIs and antibiotic resistance.**

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## UK 5-year action plan for antimicrobial resistance 2024 to 2029

GOV.UK

The first 5-year national action plan for antimicrobial resistance, "Tackling antimicrobial resistance 2019 to 2024", was an important step towards achieving this vision. The work carried out across government led to progressive action towards reducing the negative impact of AMR in the UK and globally despite the pandemic. Successes of that plan included:

- further reductions in the use of antibiotics in food-producing animals
- the development of improved surveillance systems
- the piloting of new payment schemes for antibiotics on the NHS

This updated national action plan (NAP), "Confronting antimicrobial resistance 2024 to 2029", builds on the achievements and lessons of the first. It contains outcomes and commitments that will make progress towards the 20-year vision for AMR to be contained, controlled, and mitigated. To confront AMR, the 2024 to 2029 national action plan has 9 strategic outcomes organized under 4 themes. Action will be taken across all sectors (human health, animal health, agriculture, and the environment). The plan is divided into four themes outlined below.

**Theme 1 - Reducing the need for, and unintentional exposure to, antimicrobials**

1. Infection prevention and control and infection management - this outcome aims to reduce exposure to antimicrobials through a whole-systems approach to infection prevention and control (IPC), improved diagnostics and treatment in different settings (humans, animals, agriculture, and the environment).
2. Public engagement and education - this aims to empower and engage the public on the risk of exposure to antimicrobials.
3. Strengthened surveillance - this aims to improve understanding of AMR through capability to measure, predict and understand how resistant microorganisms spread across and between humans, animals, agriculture, and the environment.

**Theme 2 - Optimizing the use of antimicrobials**

4. Antimicrobial stewardship and disposal - this aims to improve the use of antimicrobials to preserve future effectiveness.
5. AMR workforce - this aims to raise awareness among the workforce in human health, animal health and agriculture to improve the optimal use of antimicrobials.

**Theme 3 - Investing in innovation, supply and access**

6. Innovation and influence - this calls on the life sciences sector to prioritize the development of new approaches to diagnose and treat infections, the development of vaccines to prevent infections as well as the development new antimicrobials.
7. Using information for action - this aims to enable decisions to be based on robust surveillance, scientific research, and data sets to provide the best information for decision making. This section also sets out the top research priorities from policy makers.
8. Health disparities and health inequalities - this aims to improve the information available to identify where the burden of AMR is greatest. This will help to target future interventions where they will have the greatest impact.

**Theme 4 - Being a good global partner**

9. AMR diplomacy - confronting AMR is a worldwide problem that requires global action. This outcome aims to fulfil the ambition to have sustained engagement via G7, G20 and other multilateral groups, technical networks, and bilateral relationships that will contribute to worldwide action on AMR.

The themes and outcomes of this plan hope to move the UK closer to achieving the vision to contain and control AMR by 2040. In taking a One Health approach across people, animals, food and the environment, this NAP aims to preserve the effectiveness of antimicrobials for future generations. The evidence gathered over the next 5 years, including through research, will help strengthen understanding of AMR as a fundamentally important issue and what works to address it.

## Dr. Septimus's Annotations

AMR is a significant threat. The emergence of infections is constant, while the pipeline for new antibiotics is limited. This NAP builds on progress made over the past 2 decades to strengthen our understanding of AMR, and of what works to mitigate it. It sets out an ambitious course of action, strengthening the existing UK commitment to prevent infections, optimize the use of antimicrobials, and invest in research and innovation to address AMR.

### BOTTOM LINE

**AMR remains a serious threat worldwide. We must work together, across the world, to address this threat. It is execution and accountability which hopefully will result in meaningful changes to reversse the current trajectory.**

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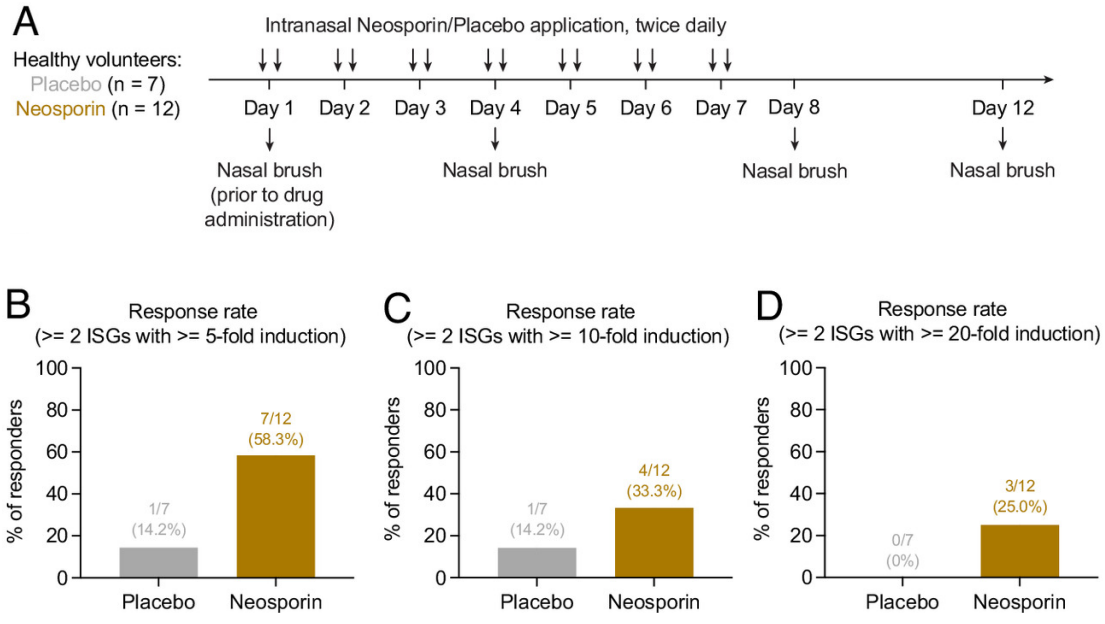
## Intranasal neomycin evokes broad- spectrum antiviral immunity in the upper respiratory tract

PNAS 2024; 121: e2319566121.
doi.org/10.1073/pnas.2319566121

In this study, the investigators found that intra-nasal delivery of neomycin induces the expression of interferon-stimulated genes (ISGs) in the nasal mucosa that is independent of the commensal microbiota. Prophylactic or therapeutic administration of neomycin provided significant protection against upper respiratory infection and lethal disease in a mouse model of Covid- 19. Furthermore, neomycin treatment protected Mx1 congenic mice from upper and lower respiratory infections with a highly virulent strain of influenza A virus. In Syrian hamsters, neomycin treatment potently mitigated contact transmission of SARS-CoV- 2. In healthy humans, intranasal application of neomycin- containing Neosporin ointment was well tolerated and effective at inducing ISG expression in the nose in a subset of participants. These findings suggest that neomycin has the potential to be utilized as a host- directed antiviral strategy for the prevention and treatment of respiratory viral infections.

**Neosporin application induces ISG expression in the nasal mucosa in healthy humans**




(A) Experimental schema. Healthy human participants were randomized at a 2:1 ratio into an experimental arm and a placebo arm to receive Neosporin (n = 12) or Vaseline (n = 7) treatment, respectively. Drug application was performed twice-daily for 7 d. Participants had a total of 4 in-person meetings. On days 1, 4, 8, and 12, a nasopharyngeal swab and a nasal brush collection were performed for viral testing and ISG assessment, respectively. (B–D) Response rate defined as a participant with at least 2 ISGs undergoing at least 5-, 10-, or 20-fold induction at any timepoint compared to day 0 measurements.

## Dr. Septimus's Annotations

Most therapeutic interventions for respiratory viral infections focus on mitigating disease progression once infections have been established. In contrast, therapeutics administered locally to the respiratory tract via an intranasal route aim to block/limit infection altogether before the virus has a chance to spread to the lower respiratory tract and cause severe or chronic diseases. Successful containment of viral infection in the upper respiratory tract also has important implications to reduce transmission. By reducing viral loads in the upper airway, topical medicines can limit the viral load being transmitted from infected donors to exposed recipients. [ Nat. Rev. Microbiol. 2021;19,528–545] The antiviral property of aminoglycoside antibiotics hinges on their ability to trigger the expression of ISGs in the genital and nasal mucosa. The investigators in this study found that intranasally administered neomycin does in fact induce marked ISG upregulation in the upper respiratory tract independent of the commensal microbiome. They provided evidence that stimulation of ISG responses in the upper airway by neomycin protects against SARS-CoV-2 infection in mice and contact transmission in hamsters. Next, they conducted a human study in which they demonstrated that intranasal application of over the counter (OTC) Neosporin also induced ISGs in the nose in a subset of healthy humans. The intranasal use of Neosporin poses minimal risks as Neosporin has already been extensively available OTC and has been used for nasal decolonization of bacteria. Unlike rIFNs and other complex biologics, neomycin is compositionally simple, easy to manufacture, cold chain requirement-free and can be readily distributed around the globe. Triple antibiotic ointment is also available OTC. Whether polymyxin B and bacitracin induce ISG expression in the upper airway directly/indirectly should be formally examined in animal models and humans in future studies.

**BOTTOM LINE**

**This study highlights an unexplored treatment modality that may evoke protective antiviral immunity in the upper airway with an inexpensive OTC product, Neomycin. This observation needs to be studied in randomized controlled human studies.**

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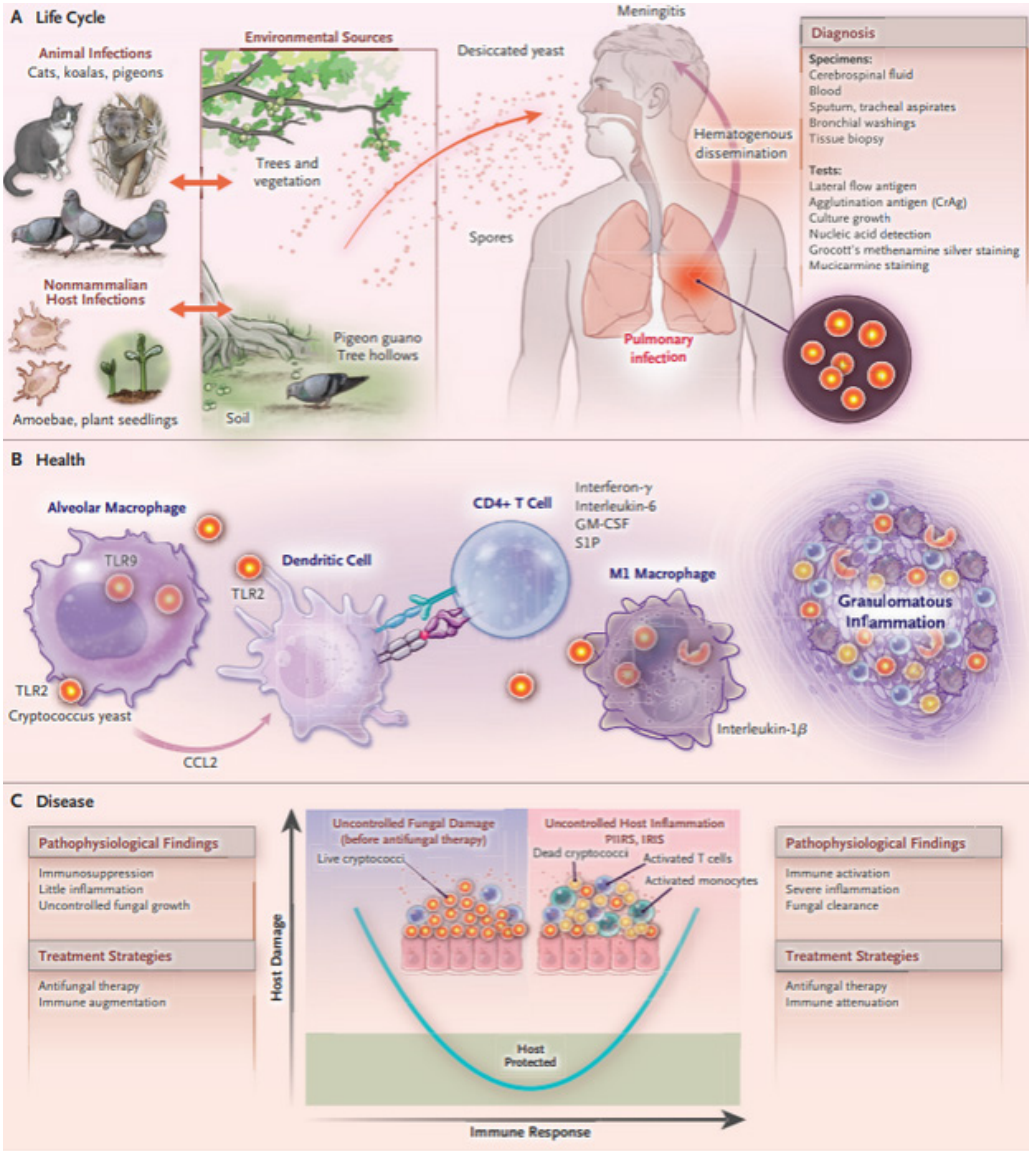
## Cryptococcal Disease in Diverse Hosts

N Engl J Med 2024; 390:1597-610
DOI: 10.1056/NEJMra2311057

**Key Points**

- Worldwide, cryptococcal meningitis kills up to 180,000 persons annually, is the most common cause of nonviral meningitis in the US and accounts for up to 68% of HIV-related cases of meningitis.
- Besides patients with immunosuppression due to human immunodeficiency virus (HIV) infection, chemotherapy, or immunotherapy, the cryptococcus fungus increasingly causes disease in apparently healthy persons, often without signs such as fevers, which results in diagnostic delays and poor outcomes.
- Despite HIV control in developing countries, expected reductions in the prevalence of cryptococcal disease remain elusive, and therapy is hampered by an inability to secure cost-effective drugs such as flucytosine. Prompt diagnosis, fungicidal therapy, and intracerebral pressure control are key for successful treatment of cryptococcal meningitis.
- Inflammatory syndromes such as the immune reconstitution and postinfectious inflammatory response syndromes are major causes of clinical deterioration and may necessitate the use of additional adjunctive therapeutic agents. See below.
- Ending Cryptococcal Meningitis Deaths by 2030 is a strategic framework that must be implemented worldwide to reduce deaths from cryptococcal meningitis, with a focus on screening, health care worker education, and shorter, more effective therapies.




**Other highlights**

- Approximately 20% of cryptococcal meningitis cases in the US occur in previously healthy persons without known immune deficits.
- Risk factors in persons without HIV infection include glucocorticoid treatment, sarcoidosis, and idiopathic CD4 lymphopenia.
- Pathogenic cryptococcus species have a strong predilection for the CNS, progressing from asymptomatic cryptococcal antigenemia to meningoencephalitis.
- Fever is seen in approximately half the patients with HIV-associated disease, but it is less common in persons who were previously healthy, which leads to delays in diagnosis.
- Visual symptoms can be associated with cranial nerve involvement (diplopia) or can be related to direct optic-nerve involvement or increased intracranial pressure.
- Elevated cell counts (with a predominance of lymphocytes) and total protein levels and low glucose levels in CSF are suggestive of cryptococcal meningitis in patients presenting with chronic, progressive neurologic symptoms.
- Imaging with CT or MRI, which is more sensitive than CT, is useful during the initial evaluation for identifying structural lesions, including hydrocephalus.

- Increased intracranial pressure is an important complication of cryptococcal meningitis, with approximately half of HIV-infected patients having pressures greater than 25 cm of water. High pressures are associated with headache, altered mental status, nausea, cranial-nerve deficits, and cognitive sequelae, with increased short-term mortality. Daily therapeutic lumbar punctures reduce intracranial pressures and are associated with reduced mortality.
- Isolated lung involvement is more common in transplant recipients and in patients who were previously healthy than in persons with AIDS. Rarely causing colonization, cryptococcosis can be manifested as nodules, hilar lymphadenopathy, or lung cavities.
- Inflammatory syndromes: Intracranial infections such as cryptococcal meningitis are particularly susceptible to these sequelae because of the subsequent swelling within the restricted confines of the skull.
    - Cryptococcal immune reconstitution inflammatory syndrome (IRIS) in HIV: The syndrome occurs 1 to 2 months after cryptococcal meningitis has been diagnosed, usually after the early initiation of ART (<4 weeks after diagnosis). Risk factors for cryptococcal IRIS include a high initial CSF fungal burden and low initial markers of inflammation, including blood CD4+ counts, CSF cells, and inflammatory markers such as interferon-γ, which are rapidly corrected after ART initiation. Based on this observation, ART is not recommended for at least 4-6 weeks after initiation of treatment for cryptococcal meningitis.
    - Similarly, in non-HIV–related cryptococcal meningitis, reductions in immunosuppression during conditioning for solid-organ transplantation or cancer chemotherapy may be accompanied by IRIS-like reconstitution syndromes.
    - For a substantial number of previously healthy persons who have not received immunosuppressive therapy, the release of fungal antigens after fungicidal therapy may precipitate PIIRS, a paradoxical postinfectious inflammatory syndrome. In a small study, patients with PIRS have responded to tapering does of steroids.

### Dr. Septimus's Annotations

This review article concludes: "Focusing on preventing or reducing cryptococcal disease in HIV-infected and non–HIV-infected populations require further investment in the development of adjunctive therapies, new compounds, and a vaccine, as well as in continuing to educate health care providers in order to minimize diagnostic delays."

**BOTTOM LINE**

**This review along with the recent publication "Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHA care in cooperation with the ASM" published online February 9, 2024, in Lancet Infect Dis 2024 [reviewed in ID Watch April 2024] are excellent references.**

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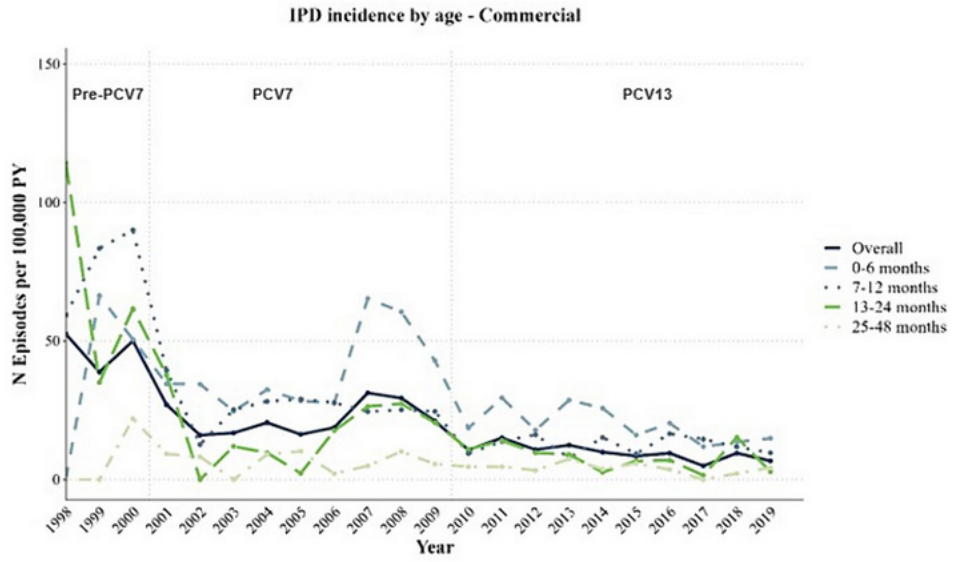
## Incidence of pneumococcal disease in children ≤48 months old in the United States: 1998–2019

Vaccine 2024; 42:2758-2769
doi.org/10.1016/j.vaccine.2024.03.013

The purpose of this study was to assess the incidence of pneumococcal disease (PD) over time by age group in young children with commercial or Medicaid coverage in the US. Episodes of invasive pneumococcal disease (IPD), all-cause pneumonia (ACP), and acute otitis media (AOM) were identified in the MarketScan® Commercial and Medicaid claims databases using diagnosis codes among children aged ≤ 48 months with confirmed date of birth (DOB), at any time during

the study period (1998–2019). DOB was assigned using diagnosis codes for birth or delivery using the child's or mother's medical claims to ensure accurate age determination. Annual incidence rates (IRs) were calculated as number of disease episodes/100,000 person-years (PY) for IPD and ACP and episodes/1,000 PY for AOM, for children aged 0–6, 7–12, 12–24, and 25–48 months.

Annual IPD IRs declined from 53 to 7 episodes/100,000 PY between 1998 and 2019 in commercial insured and 58 to 9 episodes/100,000 PY between 2001 and 2019 in Medicaid-insured children. Annual ACP IRs declined from 5,600 to 3,952 episodes/100,000 PY, and from 6,706 to 4,521 episodes/100,000 PY, respectively, over these periods. In both populations, children aged 0–6 months had the highest incidence of IPD and inpatient ACP. Annual AOM IRs declined from 1,177 to 738 episodes/1,000 PY (commercially-insured) and 633 to 624 episodes/1,000 PY (Medicaid-insured), over these periods. IRs were higher in rural vs. urban areas for all disease manifestations.




## Dr. Septimus's Annotations

In 2000, the first, 7-valent, pneumococcal conjugate vaccine (PCV7) was licensed in the US and recommended in the pediatric vaccine schedule by the Advisory Committee on Immunization Practices (ACIP). In 2010, a 13-valent PCV (PCV13), which includes 6 additional serotypes, replaced PCV7. In 2021, a 15-valent PCV (PCV15) and 20-valent PCV (PCV20) were introduced and approved for use in adults in the US. These vaccines include additional serotypes contributing to residual disease burden in the US. In 2022, PCV15 was approved for infants and children and in April 2023, PCV20 was approved for infants and children [MMWR Morb Mortal Wkly Rep. 2022; 71: 1174–81] This analysis of the burden of pneumococcal disease over a 22-year period in the post-PCV era is the first study to provide detailed data for a comprehensive set of PD manifestations by age group, insurance status, and sociodemographic characteristics in young children in the US over more than two decades. This study found there is still evidence of pneumococcal disease among young children with both commercial and Medicaid insurance coverage in the US. The annual IRs of overall IPD were higher in Medicaid-insured versus commercially-insured children, and in the youngest children (0–6 months of age) in both populations. There was a small spike in overall IPD, meningitis, bacteremia, and bacteremic pneumonia in both populations during the late PCV7 period (2007–2008), which has been previously attributed to serotype replacement, with IPD caused by non-vaccine serotypes. However, the incidence rates of IPD, ACP, and AOM decreased from the pre-PCV7 to the PCV13 periods in both commercially insured and Medicaid-insured children at most 48 months of age. As with any large claims database, miscoding of diagnoses may occur,

potentially leading to misclassification and measurement error, which could lead to over or under-estimates of disease. Pathogen-specific disease episodes caused by S. pneumoniae were identified using diagnosis codes; however, lab values for pathogen cultures were not available. Pneumococcal vaccination coverage rates were not assessed directly in the study population, which would have provided insights about higher rates of severe disease manifestations in Medicaid-insured children, and those living in rural areas.

**BOTTOM LINE**

**The incidence rates of IPD, ACP, and AOM decreased in children with commercial insurance and Medicaid coverage from 1998 to 2019 supporting the ACIP recommendation supporting pneumococcal vaccination in children.**

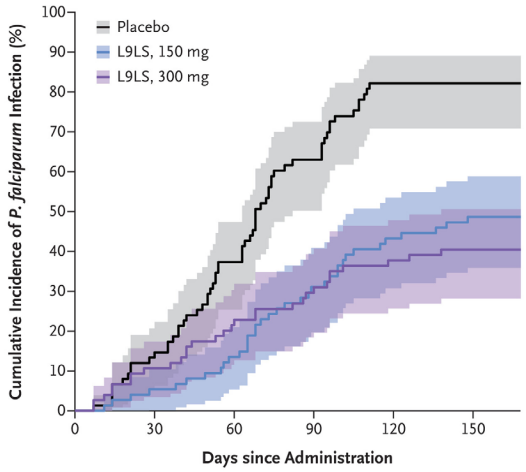
## Subcutaneous Administration of a Monoclonal Antibody to Prevent Malaria

N Engl J Med 2024; 390:1549-59.
DOI: 10.1056/NEJMoa2312775

The investigators conducted a phase 2 trial in Mali to assess the safety and efficacy of subcutaneous (SC) administration of L9LS in children 6 to 10 years of age over a 6-month malaria season. L9LS is a monoclonal antibody with an extended half-life that targets a highly conserved junctional PfCSP epitope. In part A of the trial, safety was assessed at three dose levels in adults, followed by assessment at two dose levels in children. In part B of the trial, children were randomly assigned, in a 1:1:1 ratio, to receive 150 mg of L9LS, 300 mg of L9LS, or placebo. The primary efficacy end point, assessed in a time-to-event analysis, was the first P. falciparum infection, as detected on blood smear performed at least every 2 weeks for 24 weeks. A secondary efficacy end point was the first episode of clinical malaria, as assessed in a time-to-event analysis.

No safety concerns were identified in the dose-escalation part of the trial (part A). In part B, 225 children underwent randomization, with 75 children assigned to each group. No safety concerns were identified in part B. P. falciparum infection occurred in 36 participants (48%) in the 150-mg group, in 30 (40%) in the 300-mg group, and in 61 (81%) in the placebo group. The efficacy of L9LS against P. falciparum infection, as compared with placebo, was 66% (adjusted confidence interval [95% CI], 45 to 79) with the 150-mg dose and 70% (adjusted 95% CI, 50 to 82) with the 300-mg dose (P<0.001 for both). Efficacy against clinical malaria was 67% (adjusted 95% CI, 39 to 82) with the 150-mg dose and 77% (adjusted 95% CI, 55 to 89) with the 300-mg dose (P<0.001 for both).

**Efficacy against *P. falciparum* Infection**




No. at Risk

| | | | | | | |
|---|---|---|---|---|---|---|
| Placebo | 75 | 65 | 47 | 27 | 13 | 13 |
| L9LS, 150 mg | 75 | 70 | 64 | 51 | 42 | 37 |
| L9LS, 300 mg | 75 | 66 | 58 | 52 | 46 | 40 |

### Dr. Septimus's Annotations

The investigators reported that a single subcutaneous dose of L9LS provided protective efficacy of up to 70% against P. falciparum infection and of up to 77% against clinical malaria in children 6 to 10 years of age over a 6-month malaria season, during which 81% of the participants in the placebo group became infected with P. falciparum and 59% had

clinical malaria. School-age children are a major reservoir of asymptomatic infection and transmission to mosquitoes. [Lancet Infect Dis 2021; 21:1568-78] Children were not eligible for the RTS, S/AS01 or R21/Matrix-M vaccines in this area. In 2021, the WHO recommended the RTS, S/AS01 vaccine for use in children ; four doses of the vaccine had 36% efficacy against malaria over a 4-year period among children 5 to 17 months of age. [Lancet 2015; 386:31-45] The WHO also recently endorsed the R21/Matrix-M vaccine for use in children. In locations where monthly seasonal malaria chemoprevention is the standard care during the 4-to-6-month malaria season, a three-dose regimen of the R21/Matrix-M vaccine had 75% efficacy over a 12-month period among children 5 to 36 months of age, and a booster after 12 months was necessary to maintain efficacy. [Lancet 2024;403: 533-44]

The results of this trial support the development of antimalarial monoclonal antibodies in other high-risk populations for whom the WHO recommends chemoprevention, including infants and young children, children with severe anemia after hospital discharge, and pregnant persons. [N Engl J Med 2020; 383:2242-54; Lancet Infect Dis 2018;18(4): e119-e132] Although malaria chemoprevention is safe and efficacious in children and pregnant persons, achieving a high level of compliance with regimens involving frequent administration is challenging. L9LS could complement or replace chemoprevention to improve coverage in these populations.

**BOTTOM LINE**

**This trial provides evidence to support the continued development of monoclonal antibodies as an additional tool to reduce malaria morbidity and mortality. Although the results in this trial are promising, further improvements in potency will be needed for monoclonal antibodies to have a broader effect in reducing the malaria burden.**

24

## Respiratory Syncytial Virus vs Influenza Virus Infection: Mortality and Morbidity Comparison Over 7 Epidemic Seasons in an Elderly Population

Infect Dis April 4, 2024
doi.org/10.1093/infdis/jiae171

This was a single-center retrospective study conducted in a university hospital during 7 epidemic seasons including 558 patients aged ≥75 years: 125 with RSV and 433 with influenza (median age, 84.8 years). The primary objective was to compare all-cause mortality at day 30. Secondary objectives were to compare clinical presentation and rates of consolidative pneumonia, hospitalization, and ICU admission.

Patients with RSV had more respiratory symptoms (wheezing, dyspnea) whereas patients with influenza had more general symptoms (fever, asthenia, myalgia). The following were higher in the RSV group: consolidative pneumonia (28.8% vs 17.2%, P = .004), hospitalization (83.2% vs 70%, P = .003), ICU admission (7.2% vs 3.0%, P = .034), and length of stay (median [IQR], 9 days [2–16] vs 5 days [0–12]; P = .002). Mortality rates on day 30 were comparable (9.6% vs 9.7%, P = .973).

Dr. Septimus's Annotations

This study included the largest cohort of patients infected with RSV aged >75 years documented in-depth

**Emergency Department Care and patients' Outcome**

| | Flu | RSV | *P* Value | Missing Data |
|---|---|---|---|---|
| Patients | 433 (77.6) | 125 (22.4) | | |
| Emergency department care | | | | |
| Lower tract respiratory infection[a] | 264 (61.5) | 104 (83.2) | <.001* | 4 |
| Consolidative pneumonia[b] | 74 (17.2) | 36 (28.8) | .004* | 3 |
| Antibiotic therapy | 155 (35.8) | 59 (47.2) | .021* | 0 |
| Oseltamivir | 293 (67.7) | 3 (2.4) | <.001* | 0 |
| Evolution | | | | |
| Hospitalization | 303 (70.0) | 104 (83.2) | .003* | 0 |
| ICU admission criteria | 33 (7.6) | 12 (9.6) | .474 | 0 |
| ICU admission | 13 (3.0) | 9 (7.2) | .034* | 0 |
| Hospital length of stay, d | 5 (0–12) | 9 (2–16) | .002* | 88 |

thus far. RSV shares a comparable mortality rate with influenza but is associated with higher rates of consolidative pneumonia, hospitalization, ICU admissions, and extended hospital stays.

**BOTTOM LINE**

**RSV is a serious infection in people >75 years of age. An effective vaccine is now available and should be considered in this age group. See next review.**

25

## Acute Cardiac Events in Hospitalized Older Adults With Respiratory Syncytial Virus Infection

JAMA Inten Med published online April 15, 2024
doi:10.1001/jamainternmed.2024.0212

We know that severe influenza in older adults can precipitate adverse cardiovascular (CV) events. [Ann Intern Med 2020; 173:605] To find out if this is also true for RSV infection, investigators performed a cross-sectional study of 6000 hospitalized adults (age, ≥50) who tested positive for RSV in 12 states during five RSV seasons. Mean age was 73, and 56% had known CV disease.

Overall, 23% of the 6000 patients experienced adverse CV events, most commonly acute heart failure or myocardial injury. These events occurred in 33% of patients with known CV disease but also in 9% of patients without known CV disease. Compared with patients who did not have acute adverse CV events, those with adverse CV events had 50% higher risk for intensive care unit admission and doubled risk for in-hospital death.

| | Bivariate models | | Multivariable models[a] | |
|---|---|---|---|---|
| Outcome and event | RR (95% CI) | *P* value | ARR (95% CI) | *P* value |
| **ICU admission** | | | | |
| ≥1 Acute cardiac event | 1.58 (1.24-2.03) | <.001 | 1.54 (1.23-1.93) | <.001 |
| Acute heart failure | 1.37 (1.04-1.81) | .02 | 1.25 (0.95-1.66) | .11 |
| Acute ischemic heart disease | 1.68 (1.41-2.01) | <.001 | 1.61 (1.41-1.85) | <.001 |
| Ventricular tachycardia | 1.84 (1.18-2.86) | .01 | 1.60 (1.18-2.17) | <.001 |
| Other acute heart disease[b] | 2.14 (1.71-2.66) | <.001 | 1.98 (1.71-2.30) | <.001 |
| **Invasive mechanical ventilation** | | | | |
| ≥1 Acute cardiac event | 2.00 (1.27-3.15) | <.001 | 2.00 (1.44-2.79) | <.001 |
| Acute heart failure | 1.56 (1.02-2.37) | .04 | 1.47 (1.08-2.00) | .01 |
| Acute ischemic heart disease | 2.58 (1.76-3.77) | <.001 | 2.28 (1.74-2.99) | <.001 |
| **In-hospital death** | | | | |
| ≥1 Acute cardiac event | 2.07 (1.60-2.66) | <.001 | 1.77 (1.36-2.31) | <.001 |
| Acute heart failure | 1.67 (1.32-2.11) | <.001 | 1.29 (1.01-1.65) | .03 |
| Acute ischemic heart disease | 2.05 (1.56-2.70) | <.001 | 1.86 (1.46-2.37) | <.001 |

### Dr. Septimus's Annotations

This study confirms for RSV a similar severity of CV adverse outcomes observed with other acute respiratory pathogens, such as influenza and SARS-CoV-2, that stem from infection-related metabolic and myocardial stress at the very least, but may also implicate other, more direct pathogen mediated effects. Older adults are particularly vulnerable due to greater prevalence of preexisting cardiopulmonary comorbidities and lower functional reserve. The CDC reported up to 10,000 deaths in adults older than 60 years, with the highest risk of severe RSV infections among patients living in long-term care facilities, as well as those with preexisting lung, heart, or kidney disease or immunosuppression. Recently there has been approval of two vaccines that are effective in preventing severe RSV infections in adults 60 years or older. [N Engl J Med 2023; 388:1465] Yet vaccine uptake has been very low— much lower compared with influenza vaccination—

in part due to the relative lack of knowledge of RSV as well as inconvenient access to vaccination. The current article focused on a broader older adult population, including those aged 50 to 59 years who are not currently recommended for vaccination. Preliminary data suggest similar immune response and safety of the RSV vaccine in these patients compared with those older than 60 years, and label expansion is under review.

**BOTTOM LINE**

**This article documents that older patients with acute RSV infections are at significant risk of adverse CV events associated with morbidity and mortality. RSV vaccines are safe and effective in preventing severe disease but underutilized.**

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## Highly Pathogenic Avian Influenza A(H5N1) Clade 2.3.4.4b Virus Infection in Domestic Dairy Cattle and Cats, United States, 2024

Emerg Infect Dis published online April 29, 2024
DOI: 10.3201/eid3007.240508

The investigators report highly pathogenic avian influenza A(H5N1) [HPAI] in dairy cattle and cats in Kansas and Texas which demonstrate the spread of clade 2.3.4.4b virus first isolated in the US in 2021. Infected cattle experience nonspecific symptoms such as reduced intake and rumination and a drop in milk production. In contrast fatal systemic influenza infection developed in domestic cats fed unpasteurized colostrum and milk from infected cows. Cow-to-cow transmission seems likely since infections were documented in cattle on Michigan, Idaho, and Ohio farms where avian influenza infected cows were transported.

Dr. Septimus's *Annotations*

The FDA has indicated that commercial pasteurized milk is safe, but the detection of virus in unpasteurized bovine milk may present a risk of potential cross-species transmission. The FDA has reported finding inactive fragments of the virus in about 20 percent of pasteurized-milk samples from around the country, however additional testing of retail dairy products from across the country has turned up no signs of live bird flu virus, strengthening the consensus that pasteurization is protecting consumers from the threat. FDA still strongly advised against consuming raw, unpasteurized dairy products. As of May 1st, the outbreak had spread to 36 herds in nine states, according to the Department of Agriculture. Initial reports from wastewater surveillance have detected H5N1, but unclear significance and if fragments or live virus. There have been only two cases of avian influenza in humans reported in the US since 2022. In its update, the USDA said it tested 30 samples of retail ground beef from states where dairy herds tested positive for H5N1. The samples underwent PCR testing, which can identify traces of the virus but not live virus, at the NVSL. All were negative. These results reaffirm that the meat supply appears to be safe.

Phylogenetic analysis using genome sequencing suggests that there was a reassortment event in late 2023 between the current highly pathogenic 2.3.4.4b clade in wild birds and a low-pathogenic wild bird strain, which produced the B3.13 genotype now circulating in dairy cows. [bioRxiv preprint posted May 1, 2024-see next review]

**BOTTOM LINE**

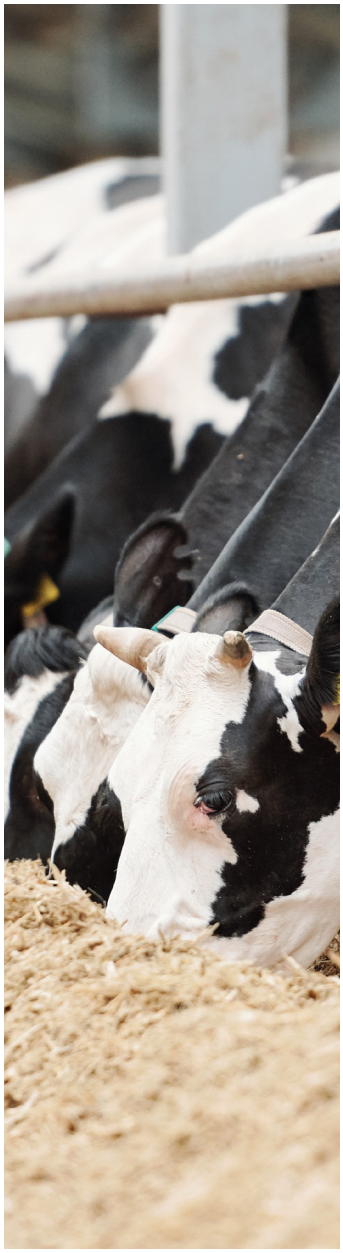
**Continued surveillance of highly pathogenic avian influenza is critical to prevent cross-species and mammal-to-mammal transmission. Avoid unpasteurized dairy products.**

27

## Emergence and interstate spread of highly pathogenic avian influenza A(H5N1) in dairy cattle

bioRxiv posted online May 1, 2024
doi.org/10.1101/2024.05.01.591751

Highly pathogenic avian influenza (HPAI) viruses can cross species barriers and have the potential to cause pandemics. In North America, HPAI A(H5N1) viruses related to the goose/Guangdong 2.3.4.4b hemagglutinin phylogenetic clade have infected wild birds, poultry, and mammals. The investigator's genomic analysis and epidemiological investigation demonstrated that a reassortment event in wild bird populations preceded a single wild bird-to-cattle transmission episode. The investigators collected samples containing virus from 26 dairy farms in eight states. Cows are not typically susceptible to this type of influenza, but H5N1 appears to have acquired mutations in late 2023 that allowed it to jump from wild birds to cattle in the Texas Panhandle. The movement of asymptomatic cattle has likely played a role in the spread of HPAI within the US dairy herd. Some molecular markers in virus populations were detected at low frequency that could lead to changes in transmission efficiency and phenotype after evolution in dairy cattle.



### Dr. Septimus's Annotations

The study was posted online on May 1, 2024 and has not been peer reviewed. It is among the first to provide details of a Department of Agriculture investigation. The outbreak most likely began about four months before it was confirmed in late March and spread undetected through cows that had no visible symptoms. That timing is consistent with estimates from genetic analyses by other scientists. The virus has been detected in some dairy herds with no known links to affected farms, the investigators report, supporting the idea of transmission from cows without symptoms and suggesting there may be infected herds that have not yet been identified.

**BOTTOM LINE**

**I do not think we need to panic; however, continued transmission of H5N1 HPAI within dairy cattle increases the risk for infection and subsequent spread and the more chance there is that it could hit upon a combination of mutations that could increase its risk to humans.**

28

## Virome Sequencing Identifies H5N1 Avian Influenza in Wastewater from Nine Cities

medRxiv posted online May 10, 2024
doi.org/10.1101/2024.05.10.24307179

Since May of 2022, the Texas Epidemic Public Health Institute (TEPHI) has been using hybrid-capture sequencing to test weekly wastewater samples throughout Texas, detecting over 400 human and animal viruses to date, several of which (e.g. SARS-CoV-2, Influenza, and Mpox) correlate to clinical case data. Seasonal influenza serotypes H3N2 and

H1N1 are routinely detected in TEPHI wastewater samples, and levels have corresponded to clinical caseloads from May 2022 through the beginning of March 2024. Until that point, serotype H5N1 was never detected (0 out of 1,337 wastewater samples). However, in samples from March 4th through April 25th (most recent available data), H5N1 is detected in 9 of 10 cities, 19 (of 23) sites, and in 46 of 163 samples. The agnostic nature of this methodology means that these signals were observed without any change to routine protocols. The abundance of H5N1 sequences has not correlated with influenza-related hospitalizations, which have continued to decline during the spring. The article did not name the 10 cities.

All sequencing reads best match H5N1 genomes from birds and mammals (including the human case) collected since 2023 and are assigned to the 2.3.4.4b clade. A variant and SNP analysis found mutations consistent with either avian or cattle origin; mainly, the presence of glutamic acid, instead of a lysine, in position 627 of the PB2 gene supports a non-human source.

## Dr. Septimus's Annotations

This report demonstrates the widespread detection of H5N1 virus in wastewater from nine US cities during the spring of 2024. Although the exact cause of the signal is currently unknown, lack of clinical burden along with genomic information suggests avian or bovine origin. To date investigators have not seen any mutations with known links to human adaptation. To date CDC has monitored >260 people for H5N1 following symptoms after exposure to infected or potentially infected animals. At least 33 of them had flulike symptoms, but no additional human cases have been reported beyond an initial case in a Texas dairy worker who had conjunctivitis.

### BOTTOM LINE

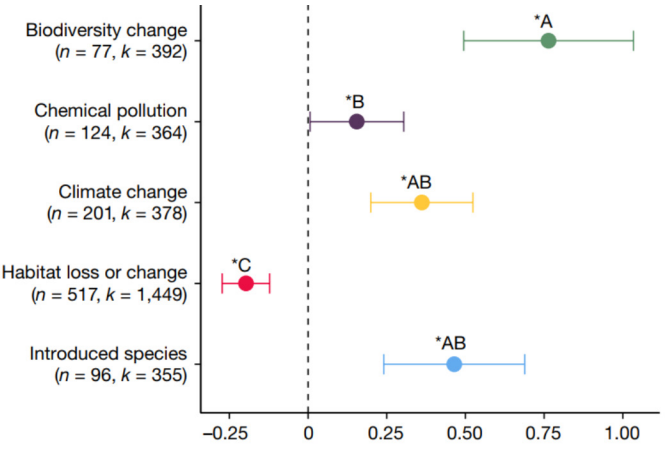
**This article along with the other two articles in this issue of ID Watch highlights the growing concern and spread of H5N1. The use of wastewater surveillance can provide early detection to support public health activities.**

## A meta-analysis on global change drivers and the risk of infectious disease.

Nature published online May 8, 2024
doi.org/10.1038/s41586-024-07380-6

Several large-scale, human-driven changes to the planet — including climate change, the loss of biodiversity and the spread of invasive species — are making infectious diseases more dangerous to people, animals, and plants. Studies have shown that infectious disease risk is modified by changes to biodiversity [Nature 2010; 468: 647–652], climate change [PLoS Biol.2020; 18: e3000938], chemical pollution [Ecol. Lett. 2019; 22:962–972] landscape transformations, [Biol. Rev. 2013; 88: 427–442] and species introductions. [Trends Ecol. Evol. 2017;32: 41–54] The authors collected a dataset from the literature that contains 2,938 observations of infectious disease responses to global change drivers across 1,497 host–parasite combinations, including plant, animal, and human hosts.

**The effects of five common global change drivers on infectious disease responses**



They found that biodiversity loss, chemical pollution, climate change and introduced species are associated with increases in disease-related end points or harm, whereas urbanization is associated with decreases in disease end points. Natural biodiversity gradients, deforestation and forest fragmentation are comparatively unimportant or idiosyncratic as drivers of disease. Overall, these results are consistent across human and non-human diseases. The movement of people, products and animals around the planet has resulted in pathogen introductions with massive health consequences for humans, domesticated plants and animals, and wildlife.

## Dr. Septimus's Annotations

The findings uncovered by this meta-analysis should help target disease management and surveillance efforts towards global change drivers that increase disease. Specifically, reducing greenhouse gas emissions, managing ecosystem health, and preventing biological invasions and biodiversity loss could help to reduce the burden of plant, animal, and human diseases, especially when coupled with improvements to social and economic determinants of health. Scientists have documented these effects before in more targeted studies that have focused on specific diseases and ecosystems. For instance, they have found that a warming climate may be helping malaria expand in Africa and that a decline in wildlife diversity may be boosting Lyme disease cases in North America. Some drivers are expected to worsen through time and are associated with increases in disease risk, such as climate change and biodiversity loss, and these drivers might therefore necessitate the greatest policy attention. However, global environmental change — habitat loss or change — appeared to reduce disease risk. This finding might appear to be at odds with previous studies, which had shown that deforestation can increase the risk of diseases ranging from malaria to Ebola. But the overall trend toward reduced risk was driven by increasing urbanization. We need more tests of interventions to remediate the highest priority drivers.

### BOTTOM LINE

**Leveraging the intersection among environmental, social, economic, and political domains will be necessary to effectively mitigate increases in disease associated with global change. Most of the studies included in this analysis examined just a single global change driver. However, in the real world, organisms are contending with many drivers simultaneously. The next step is to better understand the connections among them.**

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## Incidence of Influenza-Related Medical Encounters and the Associated Healthcare Resource Use and Complications Across Adult Age Groups in The United States During the 2015-2020 Influenza Seasons

Clin Infect Dis published online April 3, 2024
DOI: 10.1093/cid/ciae180

This study describes the incidence of influenza-related outpatient visits, ED visits, and hospitalizations, along with healthcare resource use and complications in the aging adult population. Individuals ≥18 years of age in the US were evaluated retrospectively in five seasonal cohorts (2015–2020 seasons) in strata of age with 5-year increments. Person-level electronic medical records linked to pharmacy and medical claims were used to ascertain patient characteristics and outcomes. Influenza-related medical encounters were identified based on ICD-10 diagnostic codes.

The incidence of influenza-related outpatient visits was highest among people aged 18–34 years and declined with increasing age. For ED visits, incidence tended to be elevated for people aged 18–34 years, relatively stable from 35 through 60, and increased rapidly after 60. Hospitalization incidence remained relatively stable until about 50 years of age and then increased with age. One in three patients was diagnosed with pneumonia after hospitalization, regardless of age. Across seasons, age groups, and clinical settings, on average, 40.8% of individuals were prescribed antivirals and 17.2% antibiotics.

Incidence of Influenza-Related Medical Encounters and the Associated Healthcare Resource Use and Complications Across Adult Age Groups in The United States During the 2015-2020 Influenza Seasons

McGovern et al., 2024 | *Clinical Infectious Diseases*

IDSA Infectious Diseases Society of America

**POPULATION AND METHODS**

Individuals ≥18 years of age in the United States were evaluated retrospectively in five seasonal cohorts (2015–2020 seasons) in strata of age with 5-year increments. Person-level electronic medical records linked to pharmacy and medical claims were used to ascertain patient characteristics and outcomes. Influenza-related medical encounters were identified based on diagnostic codes (ICD-10 codes J09*–J11*).

**RESULTS**

Influenza Incidence

Incidence of influenza-related outpatient visits was highest among people aged 18–34 years and declined with increasing age. For ER visits, incidence tended to be elevated for people aged 18–34 years, relatively stable from 35 through 60, and increased rapidly after 60. Hospitalization incidence remained relatively stable until about 50 years of age and then increased with age.

Complications and Prescriptions

One in three patients were diagnosed with pneumonia after hospitalization, regardless of age. Across seasons, age groups, and clinical settings, on average, 40.8% of individuals were prescribed antivirals and 17.2% antibiotics.

**CONCLUSION**

Incidence of influenza-related hospitalizations begins to increase around age 50 rather than the more common cut-point of 65, whereas incidence of outpatient visits was highest among younger adults. Influenza infections frequently led to antiviral and antibiotic prescriptions, underscoring the role influenza vaccination can play in combating antimicrobial resistance.

Clinical Infectious Diseases https://doi.org/10.1093/cid/ciae180

## Dr. Septimus's Annotations

The CDC estimates that during the 2015–2016 through the 2019–2020 influenza seasons, there were 24–41 million infections, 280,000–710,000 hospitalizations, and 23,000–52,000 deaths annually. [https://www.cdc.gov/flu/about/burden/past-seasons.html] The majority of influenza hospitalizations and deaths occur among adults ≥65 years of age, and the presence of certain medical conditions can increase the risk of severe outcomes following infection. [PLoS One 2019; 14: e0210353] Aging is also associated with the decline and dysregulation of the immune system, termed immunesenescence. [Immunology 2007; 120:435–446] This study aimed to evaluate the incidence of influenza-related outpatient visits, ED visits, and hospitalizations among adult age groups and to evaluate healthcare resource use and complications following influenza-related medical encounters across adult age groups. In this study, the incidence of influenza-related outpatient visits was highest among younger adults and decreased with age, while the incidence of influenza-related hospitalizations increased with age beginning around age 50. This retrospective study used routinely collected claims and EHR data, which can be subject to limitations, including data entry errors and missing data. Influenza outcomes were identified based on diagnostic codes, which may not include laboratory confirmation. This study captures the incidence of medically attended influenza, but it cannot capture the incidence of influenza among those who did not seek care. The dataset used in this analysis only included insured individuals and may not be representative of the uninsured population.

### BOTTOM LINE

**This analysis demonstrates that age-associated changes in influenza incidence and care setting occur gradually with increasing age, and the incidence of hospitalizations begins to increase around 50 years of age rather than the more common cut-point of 65. Strategies including vaccinations and antivirals to reduce the incidence and severity of influenza should consider the elevated risks among individuals 50–64 years old in addition to the current focus on individuals ≥65 years old.**

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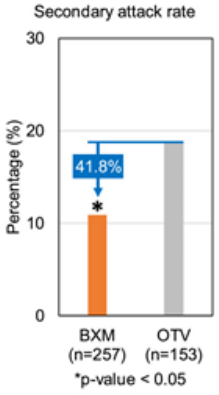
## Comparative Effectiveness of Baloxavir Marboxil and Oseltamivir Treatment in Reducing Household Transmission of Influenza: A Post Hoc Analysis of the BLOCKSTONE Trial

Influenza and Other Respiratory Viruses, 2024; 18: e13302
https://doi.org/10.1111/irv.13302

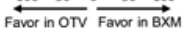
The aim of this study was to compare the effects of oseltamivir (OTV) and baloxavir marboxil (BXM) treatment of index cases on the secondary attack rate (SAR) of influenza within households. They performed a post hoc analysis of the BLOCKSTONE trial—a placebo-controlled, double-blinded post-exposure prophylaxis of BXM. Data were derived from the laboratory-confirmed index cases' household contacts who received placebo in the trial and from household members who did not participate in the trial but completed illness questionnaires. To assess the SAR of household members, multivariate analyses adjusted for factors including age, vaccination status, and household size were performed and compared between contacts of index cases treated with BXM or OTV.

In total, 185 index cases (116 treated with BXM and 69 treated with OTV) and 410 household contacts (201 from trial, 209 by questionnaire) were included. The Poisson regression modeling showed that the SAR in household contacts of index cases treated with BXM and OTV was 10.8% and 18.5%, respectively; the adjusted relative reduction in SAR was 41.8% (95% confidence interval: 1.0%–65.7%, p=0.0456) greater with BXM than OTV. Similar reductions were found in contacts from the trial and those included by the questionnaire. The relative reduction of adjusted SAR in female index cases (64.4%, 95% CI: 19.9%–84.2%) was much greater than that in male index cases (6.9%, 95% CI: −89.5%–54.2%). Furthermore, the relative reduction of adjusted SAR in index cases with A/ H1 infection (58.3%, 95% CI: 12.7%–80.1%) was greater than that with A/H3 infection (28.3%, 95% CI: −32.1%–61.0%).

**Secondary attack rate based on Poisson regression model**




| Category based on index case | Treatment | Number of household contacts | Number of infected cases | Unadjusted † SAR | Adjusted ‡ SAR | Adjusted ‡ Reduction rate (%) [95% CI] |
|---|---|---|---|---|---|---|
| Overall | BXM | 257 | 35 | 10.4% | 10.8% | 41.8 [1.0, 65.7] |
| | OTV | 153 | 37 | 18.5% | 18.5% | |
| Male | BXM | 142 | 24 | 13.0% | 14.1% | 6.9 [-89.5, 54.2] |
| | OTV | 78 | 18 | 17.8% | 15.2% | |
| Female | BXM | 115 | 11 | 7.2% | 7.4% | 64.4 [19.9, 84.2] |
| | OTV | 75 | 19 | 19.2% | 20.7% | |
| < 12 years | BXM | 142 | 19 | 10.3% | 10.3% | 45.8 [5.7, 68.8] |
| | OTV | 148 | 37 | 19.2% | 19.1% | |
| ≥ 12 years | BXM | 115 | 16 | 10.6% | 9.3% | |
| | OTV | 5 | 0 | 0.0% | 0.0% | |
| A/H1 | BXM | 105 | 12 | 8.1% | 7.6% | 58.3 [12.7, 80.1] |
| | OTV | 78 | 18 | 19.1% | 18.2% | |
| A/H3 | BXM | 147 | 23 | 12.9% | 13.6% | 28.3 [-32.1, 61.0] |
| | OTV | 75 | 19 | 17.9% | 19.0% | |




### Dr. Septimus's Annotations

This post hoc analysis of the BLOCKSTONE post-exposure prophylaxis trial found that the SAR for household contacts of BXM-treated index cases was significantly lower than that for household contacts of OTV-treated index cases. The adjusted SARs for household contacts of the index cases treated with BXM were consistently lower than OTV in both household contacts enrolled in the BLOCKSTONE trial and the subgroup with only questionnaire data. Their findings support the hypothesis that the more rapid decline in the infectious viral load with BXM than with OTV treatment [Internal Medicine 2020; 59:1509–1513] may be associated with greater reduction in the risk of household influenza

virus transmission. The use of BXM as a treatment for children with influenza does appears to reduce the risk of infection transmission in households, but the frequency of treatment-related emergence of BXM-resistant variants, especially in children aged 5 years or less with influenza A/H3 illness [Euro Surveillance 2019;12: 1900170] raises concerns. The BLOCKSTONE trial did not detect BXM-resistant variants in the household contacts receiving placebo who were exposed to BXM-treated index cases [New Engl J Med 2020; 383: 309–320]. This finding suggests that the risk of transmission of such variants is relatively low in the household setting but requires further study. This study has a few limitations. First, this was not a randomized trial. Second, the frequency of asymptomatic infections was not determined. Therefore, the frequency of household transmission may be underestimated. Next PCR testing was not performed during enrollment of household contacts, so some of them were likely already infected at enrollment. Lastly, the transmission risk profile of index cases did not include data on duration of infectious virus detectability or the possible effect of influenza vaccination within the preceding 6 months.

**BOTTOM LINE**

**This post hoc analysis found that the secondary influenza illness attack rate was lower in household contacts exposed to BXM-treated than OTV-treated index cases. The greater rapid reduction in infectious virus titers associated with BXM compared to OTV treatment may explain BXM's greater reduction in secondary household transmission than observed with OTV.**

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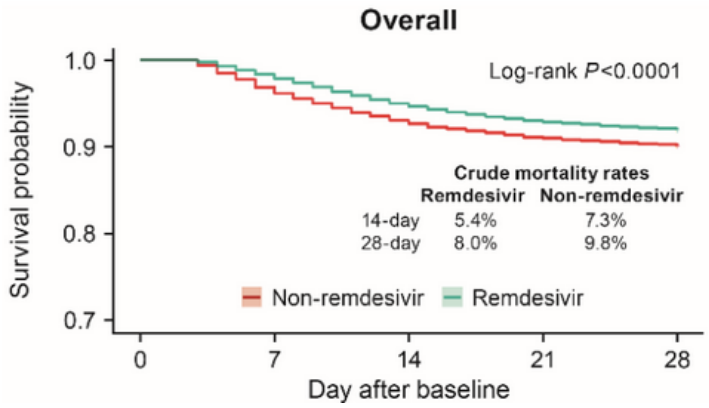
## Remdesivir is associated with reduced mortality in patients hospitalized for COVID-19 not requiring supplemental oxygen

OFID published online April 16, 2024
doi.org/10.1093/ofid/ofae202

Remdesivir has demonstrated benefit in some hospitalized patients with Covid-19 on supplemental oxygen and in non-hospitalized patients at room air. This comparative effectiveness trial compares inpatient mortality among patients hospitalized for Covid-19 not receiving supplemental oxygen at admission initiating remdesivir treatment in the first two days of admission vs. no remdesivir during the hospitalization across different variants of concern (VOC) periods.




The sample sizes for the non-remdesivir group are weighted since matching with replacement approach was used. Days after baseline refers to the time during which outcomes were assessed following the two-day period in which remdesivir treatment administration was identified (baseline).

They used a multicenter US hospital billing database to compare rates of in-hospital death among 58,188 patients on room air who received at least one dose of remdesivir within the first 2 days of hospital admission and 17,574 matched patients not given the drug. The drug is considered most effective when given early in infection when viral replication is most active. The study period, December 2020 to April 2022, spanned the predominance of the pre-Delta (e.g., Alpha, Beta), Delta, and Omicron SARS-CoV-2 VOC. Patients receiving remdesivir upon hospital admission were matched 1:1 to those not receiving remdesivir during hospitalization using propensity score (PS) matching.

In total, 5.4% of remdesivir-treated and 7.3% of non-remdesivir patients died within 14 days, and 8.0% and 9.8%, respectively, died by 28 days. Remdesivir therapy was tied to a statistically significant reduction in inpatient death relative to remdesivir nonreceipt (14-day adjusted hazard ratio [aHR], 0.75; 28-day aHR, 0.83), translating to a 25% and 17% reduction in risk of death for the two-time spans, respectively. During each VOC period, remdesivir therapy was linked to a significant decline in in-hospital death relative to remdesivir nonreceipt for both 14-day (pre-Delta aHR, 0.73; Delta aHR, 0.80; Omicron aHR, 0.73) and 28-day risk of death (aHRs, 0.83, 0.87, and 0.76, respectively).

## Dr. Septimus's Annotations

In this large, multicenter study, the data suggest that prompt remdesivir treatment on admission was associated with a statistically significant reduction in in-hospital mortality compared to not initiating remdesivir during the hospitalization among patients admitted for Covid-19 that did not require supplemental oxygen on admission.[wonder if Covid-19 was an incidental finding rather than reason for admission] These findings were consistent across VOC periods, indicating that remdesivir was effective regardless of VOC. The major remdesivir clinical trials (ACTT-1[N Engl J Med 2020; 383(19):1813-1826] and SOLIDARITY trials [Lancet 2022; 399:1941-1953) were not designed nor powered to detect significant differences in mortality between subgroups based on baseline supplemental oxygen requirement. Evidence from trials has also established the clinical benefits of remdesivir in outpatient settings within 5 days of symptoms who are at high risk to progress to more sever disease. A potential limitation of the present study is the potential for residual confounding due to imbalances in unmeasured variables between the treatment groups even after PS matching. The study cohort likely comprised of patients with heterogeneous time-since-symptom onset since this information is not available in this database, therefore patients were matched on presenting characteristics only.

### BOTTOM LINE

**Remdesivir initiation in patients hospitalized for Covid-19, not requiring supplemental oxygen at admission, was associated with a statistically significant reduction in inhospital mortality.**

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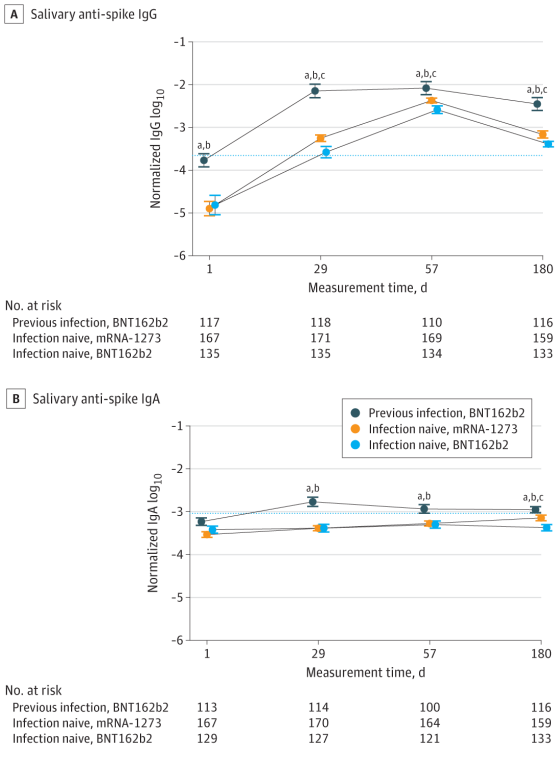
## Serum and Salivary IgG and IgA Response After COVID-19 Messenger RNA Vaccination

JAMA Network Open. 2024;7(4): e248051
doi:10.1001/jamanetworkopen.2024.8051

In this study, SARS-CoV-2–naive participants and those with previous infection were consecutively included in the CoviCompare P(Pfizer) and CoviCompare M(Moderna) mRNA vaccination trials and followed up to day 180 after vaccination with either the Pfizer vaccine or Moderna vaccine at the beginning of the Covid-19 vaccination campaign (from February 19 to June 8, 2021) in France. Data were analyzed from October 25, 2022, to July 13, 2023. An ultrasensitive digital enzyme-linked immunosorbent assay was used for the comparison of SARS-CoV-2 spike-specific serum and salivary IgG and IgA levels. Spike-specific secretory IgA level was also quantified at selected times.

Of 427 vaccinated individuals, a modest increase in spike-specific IgA levels in saliva of SARS-CoV-2–naive individuals having received the Moderna or Pfizer mRNA vaccines was observed using ultrasensitive digital enzyme-linked immunosorbent assay. This increase persisted after Moderna vaccination, and previously infected individuals demonstrated a stronger mucosal IgA response to vaccination.



Dr. Septimus's Annotations

The investigators compared individuals with previous SARS-CoV-2 infection and SARS-CoV-2– naive individuals included in 2 large vaccination trials for their saliva and serum IgA and IgG antibody responses. Importantly, they limited the study to individuals vaccinated at the beginning of the pandemic to select a substantial number of confirmed SARS-CoV-2–naive participants to be included in the study. The study suggest that mRNA vaccination was associated with mucosal immunity in individuals without prior SARS-CoV-2 infection, but at much lower levels than in previously infected individuals. The number of vaccine breakthrough cases reported in their study was too limited to address the association between SIgA levels and prevention of infection or transmission of SARS-CoV-2.

**BOTTOM LINE**

**The findings of this cohort study suggest that mRNA vaccination was associated with mucosal immunity in individuals with prior SARS-CoV-2 infection. Further studies are needed to determine the association between salivary IgA levels and prevention of infection or transmission.**

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## Infectious Diseases Society of America Guidelines on the Diagnosis of COVID-19: Serologic Testing

Clin Infect Dis published online March 15, 2024
DOI: 10.1093/cid/ciae121

**Recommendation 1**

The IDSA panel recommends against using serologic testing to diagnose SARS-CoV-2 infection during the first two weeks following symptom onset (*strong recommendation, low certainty of evidence*).

**Recommendation 2**

The IDSA panel recommends against using IgG antibodies to provide evidence of Covid-19 in symptomatic patients with a high clinical suspicion and repeatedly negative NAAT (*strong recommendation, very low certainty of evidence*)

**Recommendation 3**

To assist with the diagnosis of multisystem inflammatory syndrome in children (MIS-C), the IDSA panel recommends using both IgG antibody testing and NAAT to provide evidence of current or recent past COVID-19 (*strong recommendation, very low certainty of evidence*)

**Recommendation 4**

When evidence of previous SARS-CoV-2 infection is desired, the IDSA panel suggests testing for SARS-CoV-2 IgG, IgG/IgM, or total antibodies three to five weeks after symptom onset and against testing for SARS-CoV-2 IgM (*conditional recommendation, low certainty of evidence*). SARS-CoV-2 NAAT and antigen tests have superior performance characteristics for diagnosis of COVID-19, compared to serologic testing. There are very limited situations in which SARS-CoV-2 antibody testing might be useful, e.g., in helping to diagnose MIS-C.

**Recommendation 5**

When evidence of prior SARS-CoV-2 infection is desired, the IDSA panel suggests using serologic assays that target nucleocapsid protein rather than spike protein (*conditional recommendation, low certainty of evidence*).

**Recommendation 6**

In individuals with previous SARS-CoV-2 infection or vaccination, the IDSA panel suggests against routine serologic testing given no demonstrated benefit to improving patient outcomes (*conditional recommendation, very low certainty of evidence*). Serologic testing may be useful for diagnosing MIS-C in pediatric patients, especially when NAAT or antigen testing is negative, to provide evidence of recent COVID-19 (see Recommendation 3).

# COVID-19 OUTPATIENT TREATMENT GUIDELINES ROADMAP

COVID-19 Real-Time Learning Network
Brought to you by CDC and IDSA

*Last Updated: April 16, 2024*

This resource is intended to serve as a guide on available outpatient COVID-19 treatment options, with links to FDA prescribing information, FDA Emergency Use Authorization and guideline recommendations from national guideline-developing organizations, where available. **It is not intended to endorse or otherwise promote a specific clinical recommendation or course of action.** Additionally, it does not include other forms of guidance that may be available for specific subsets of populations. Finally, the guidelines referenced here may not consider local allocation and availability of scarce resources. Additional information on where to access these therapeutics can be found at the National Infusion Center Association[1] and HHS.[2]

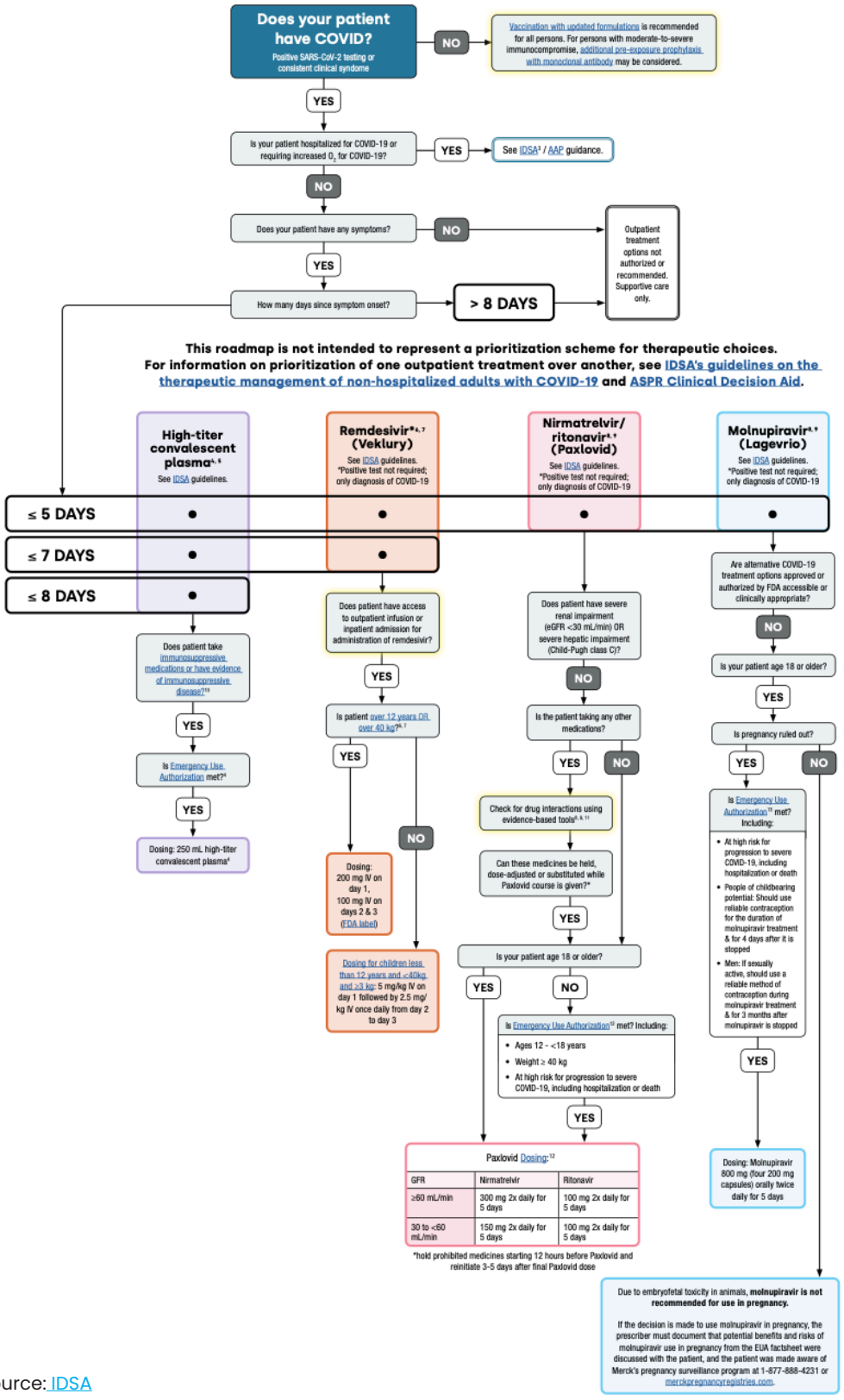
**Risk factors for severe COVID-19**

Included here are some medical conditions that may place patients at a higher risk for progression to severe COVID-19:

- Age 65 years and older
- BMI of more than 25 kg/m²
- Pregnancy
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppressing medications
- Cardiovascular disease or hypertension
- Chronic lung disease
- Sickle cell disease
- Neurodevelopmental disorders or conditions that confer medical complexity
- Medical technological dependence, e.g., tracheostomy

**When giving products under Emergency Use Authorization, providers must:**

1. Give patient fact sheet for patients.
2. Inform patient of alternatives to treatment.
3. Inform patient that this is an unapproved drug.




Source: IDSA

## Dr. Septimus's Annotations

This is a very nice summary of the latest outpatient Covid-19 treatment guideline. This can be posted in the ED, Urgent Care, and clinics as a reminder of current science.

## 35 COVID-19 by the Numbers

COVID-19 Update for the United States

**Early Indicators**

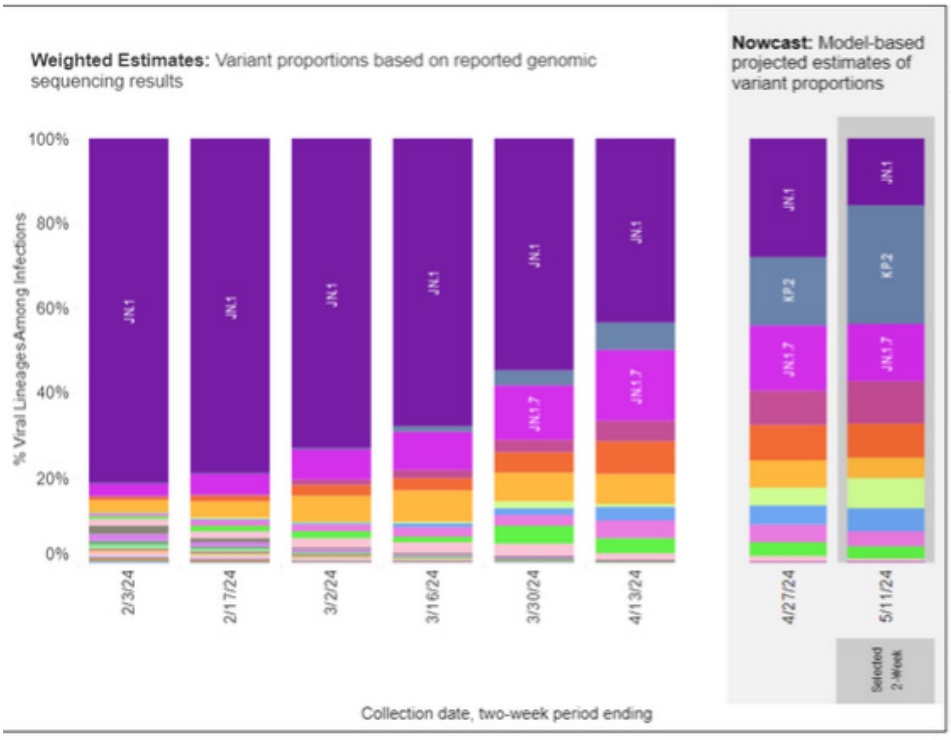
**Test Positivity**
% Test Positivity
3.2%
(May 5 to May 11, 2024)
Trend in % Test Positivity
**-0.1%** in most recent week
Mar 23, 2024 May 11, 202

**Emergency Department Visits**
% Diagnosed as COVID-19
0.3%
(May 5 to May 11, 2024)
Trend in % Emergency Department Visits
**-5.2%** in most recent week
Mar 23, 2024 May 11, 2024

**Severity Indicators**

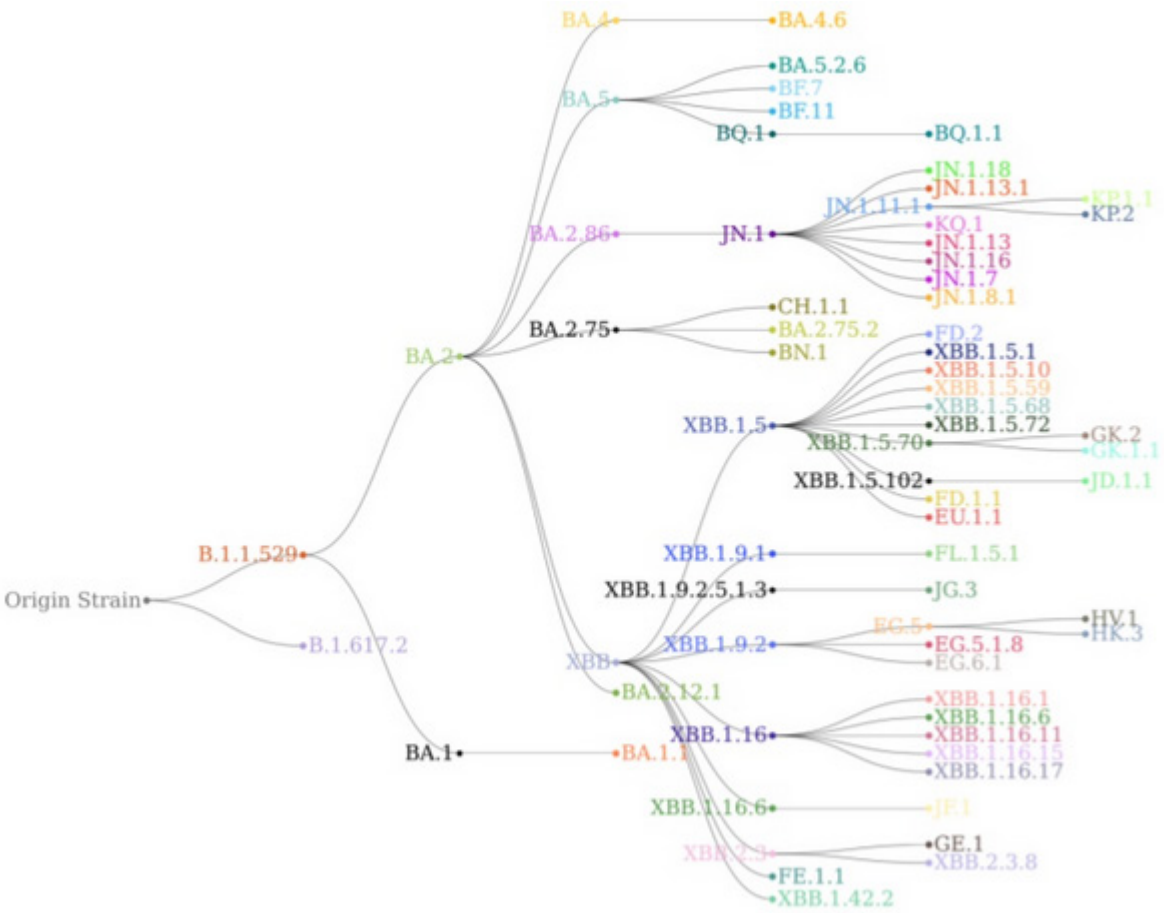
**Hospitalizations**
Hospitalization Rate per 100,000 population
1.2
(April 21 to April 27, 2024)
Trend in Hospitalization Rate
**+9.1%** from Apr 21 to Apr 27
Mar 9, 2024 Apr 27, 2024

**Deaths**
% of All Deaths in U.S. Due to COVID-19
0.6%
(May 5 to May 11, 2024)
Trend in % COVID-19 Deaths
**-14.3%** in most recent week
Mar 23, 2024 May 11, 2024




USA

| WHO label | Lineage # | %Total | 95%PI |
|---|---|---|---|
| Omicron | KP.2 | 28.2% | 20.5-37.3% |
| | JN.1 | 15.7% | 13.3-18.5% |
| | JN.1.7 | 13.3% | 10.5-16.8% |
| | JN.1.16 | 10.0% | 7.1-13.8% |
| | JN.1.13.1 | 8.0% | 5.2-11.9% |
| | KP.1.1 | 7.1% | 4.4-11.1% |
| | JN.1.11.1 | 5.4% | 3.0-9.3% |
| | JN.1.8.1 | 4.8% | 3.7-6.1% |
| | KQ.1 | 3.8% | 2.4-6.1% |
| | JN.1.18 | 2.6% | 1.9-3.6% |
| | JN.1.13 | 0.1% | 0.0-0.3% |
| | GE.1 | 0.0% | 0.0-0.1% |
| | BA.2.86 | 0.0% | 0.0-0.1% |
| | JG.3 | 0.0% | 0.0-0.0% |
| | XBB | 0.0% | 0.0-0.0% |
| | EG.5 | 0.0% | 0.0-0.0% |




## Dr. Septimus's Annotations

A new COVID-19 variant now makes up 28% of cases in the nation. Variant KP.2, nicknamed FLiRT, is the new dominant variant in the country, according to wastewater surveillance. From April 14 through April 27, two FLiRT variants accounted for roughly 30% of cases: KP.1.1 made up 7.5% of cases and KP.2 made up 28% of cases.

**BOTTOM LINE**

**FLiRT has overtaken JN.1 variants, which now accounts for 28% of Covid-19 cases. To date surveillance data does not demonstrate in cases. See next review**

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## Virological characteristics of the SARS-CoV-2 KP.2 variant

BioRxiv posted April 26, 2024
doi.org/10.1101/2024.04.24.590786

The JN.1 variant (BA.2.86.1.1), arising from BA.2.86(.1) with the S: L455S 35 substitution, exhibited increased fitness and outcompeted the previous dominant XBB lineage by the biggening of 2024. JN.1 has subsequently diversified, leading to the emergence of descendants with spike (S) protein substitutions such as 38 S: R346T and S: F456L. Particularly, the KP.2 (JN.1.11.1.2) variant, a descendant of JN.1 bearing both S: R346T and S:F456L, is rapidly spreading in multiple regions as of May 2024.

The investigators evaluated the virological properties of KP.2. KP.2 has three substitutions in the S protein including the two above and an additional one substitution in non-S protein compared with JN.1. They estimated the relative effective reproduction number (Ro) of KP.2 based on the genome surveillance data from the US, UK, and Canada where >30 sequences of KP.2 has been reported, using a Bayesian multinomial logistic model. The Ro of KP.2 is 1.22-, 1.32-, and 1.26-times higher than that of JN.1 in US, UK, and Canada, respectively. These results suggest that KP.2 has higher viral fitness and potentially can become the predominant lineage worldwide. Indeed, as of the beginning of May 2024, the estimated variant frequency of KP.2 has already reached 20% in UK and >25% in US.

The pseudovirus assay showed that the infectivity of KP.2 is significantly (10.5-fold) lower than that of JN.1. They then performed a neutralization assay using monovalent XBB.1.5 vaccine sera and breakthrough infection (BTI) sera with XBB.1.5, EG.5, HK.3 and JN.1 infections. In all cases, the 50% neutralization titer (NT50) against KP.2 was significantly lower than that against JN.1. Particularly, KP.2 shows the most significant resistance to the sera of monovalent XBB.1.5 vaccinee without infection (3.1-fold) as well as those who with infection (1.8-fold).

## Dr. Septimus's Annotations

Altogether, these results suggest that the increased immune resistance ability of KP.2 partially contributes to the higher Ro more than previous variants including JN.1. This paper has yet to be peer reviewed but suggests that the Covid vaccines currently recommended in the US may be less effective against KP.2 than against JN.1.

### BOTTOM LINE

**While cases in the US currently do not appear to be on the rise, we need to closely watch whether KP.2 will lead to a summer "wave."**