# ID WATCH

by Ed Septimus, MD

## Editor's Choice




1

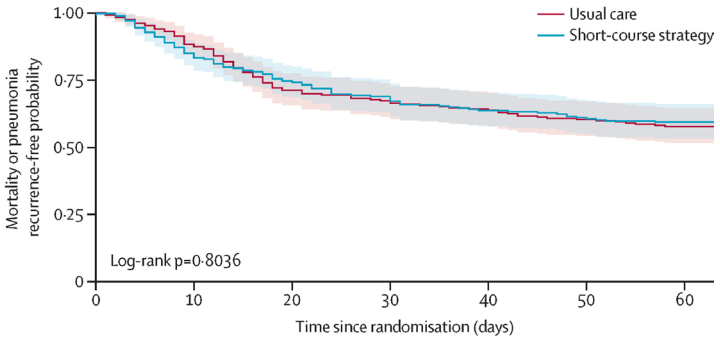
## Individualised, short-course antibiotic treatment versus usual long-course treatment for ventilator-associated pneumonia (REGARD-VAP): a multicentre, individually randomised, open-label, non-inferiority trial

Lancet Respir Med 2024; 12: 399–408
doi.org/10.1016/S2213-2600(23)00418-6

This trial was an individually randomized, open-label, hierarchical non-inferiority–superiority trial in 39 intensive care units in six hospitals in Nepal, Singapore, and Thailand. They enrolled adults (age ≥18 years) who met the US CDC National Healthcare Safety Network criteria for VAP, had been mechanically ventilated for 48 hours or longer, and were administered culture-directed antibiotics. In culture-negative cases, empirical antibiotic choices were made depending on local hospital antibiograms reported by the respective microbiology laboratories or prevailing local guidelines. Participants were assessed until fever resolution for 48 h and hemodynamic stability, then randomly assigned (1:1) to

individualized short-course treatment (≤7 days) or usual care (≥8 days, with precise durations determined by the primary clinicians). Independent assessors for recurrent pneumonia and participants were masked to treatment allocation, but clinicians were not. The primary outcome was a 60-day composite endpoint of death or pneumonia recurrence. The non-inferiority margin was prespecified at 12% and had to be met by analyses based on both intention-to-treat (all study participants who were randomized) and per-protocol populations (all randomized study participants who fulfilled the eligibility criteria, met fitness criteria for antibiotic discontinuation, and who received antibiotics for the duration specified by their allocation group).

**Unadjusted Kaplan-Meier Survival Estimates by Intervention in the Intention-to-Treat Population**




Day 0 refers to the day of randomisation, and day 60 refers to the last day of follow-up. All participants were followed up for 60 days; there were no participants lost to follow-up.

461 patients were enrolled and randomly assigned to the short course treatment group (n=232) or the usual care group (n=229). The median age was 64 with VAP. Patients in the short-course group were assessed daily for antibiotic discontinuation based on hemodynamic stability (i.e., no vasopressors) and absence of fever for 48 hours. When these criteria were met, antibiotics were discontinued as early as day 3 for patients with culture-negative VAP and as early as day 5 for patients with positive cultures. One third of patients had culture-negative VAP. More than half of positive cultures were gram-negative bacilli; 34% showed carbapenem resistance, and 18% were resistant to third-generation cephalosporins. Median duration of antibiotics was 6 days for the short-course group and 14 days for the usual-care group. Mortality, duration of mechanical ventilation, and ICU length of stay were similar between groups. Antibiotics were restarted within 5 days in one third of short-course patients, but diagnoses of recurrent pneumonia did not differ (≈18% in each group). Results were similar in the per-protocol population. The non-inferiority of short-course antibiotic treatment was met in the analyses. In the per-protocol population, antibiotic side-effects occurred in 86 (38%) of 224 in the usual care group and 17 (8%) of 211 in the short-course group (risk difference −31% [95% CI −37 to −25%; p<0·0001]). Among patients with VAP associated with carbapenem-resistant Gram-negative bacilli and Gram-negative non-fermenting bacilli, the individualized short-course strategy was also similar to usual care, with no major differences in the primary outcome.

## Dr. Septimus's Annotations

This is the first randomized controlled trial of antibiotic treatment duration for VAP conducted in hospitals across low-income, middle income, and high-income settings, with patients predominantly enrolled from low-income and middle-income countries. As most of you know diagnosing VAP can be challenging and subjective. This study supports stopping antibiotics sooner if the patient is quickly improving. For most patients, duration of 7-8 makes sense. The current major international guidelines, including the Infectious Disease Society of America (IDSA), and the European Society of Clinical Microbiology and Infectious Diseases, recommend 7–8 days of antibiotic treatment for VAP. [Eur Respir J 2017; 50: 1700582; Clin Infect Dis 2016; 63: e61–111] This recommendation is mainly based on several recent randomized trials. [JAMA 2003; 290: 2588–98; PLoS One 2012; 7: e41290]

They found a high proportion of VAP associated with carbapenem-resistant Gram-negative bacilli and high antibiotic consumption. These VAP episodes were mostly treated with combinations of colistin or polymyxin B, beta-lactams (including carbapenems), and aminoglycosides, which were frequently associated with acute kidney injury. These patterns of antibiotic prescription reflected the epidemiology of bacteria causing VAP and the limited access to newer-generation antibiotics (e.g., novel β-lactam–β-lactamase inhibitors or cefiderocol) in many

regions where the study was conducted. Although the trial intervention to reduce antibiotic treatment duration was ultimately aimed at reducing overall antimicrobial resistance and side effects, they did not obtain unit-level antimicrobial resistance colonization (i.e., stool or sputum samples) or infection data from other ICU patients during the study. However, they did show antibiotic side-effects occurred more frequently in the usual care group. One third of patients had culture-negative VAP which I would have excluded from analysis.

BOTTOM LINE

**In this study of adults with VAP, individualized shortened antibiotic duration guided by clinical response was non-inferior to longer treatment durations in terms of 60-day mortality and pneumonia recurrence, and associated with substantially reduced antibiotic use and side-effects.**

2

## Evaluation of the HANDOC score and the 2023 ISCVID and ESC Duke clinical criteria for the diagnosis of infective endocarditis among patients with streptococcal bacteremia

Clin Infect Dis published online June 6. 2024
doi.org/10.1093/cid/ciae315

This retrospective study included adult patients with streptococcal bacteremia hospitalized at Lausanne University Hospital. Episodes were classified as IE by the Endocarditis Team. A HANDOC score >2 classified patients as high-risk for IE. Cases were classified as rejected, possible, or definite IE according to the three versions of the Duke clinical criteria (2015 Duke-ESC,[European heart journal 2015; 36: 3075-128] 2023 Duke-ISCVID,[ Clin Infect Dis,2023 77: 518–526] and 2023 Duke-ESC[Eur Heart J 2023;44:3948-4042]. Additionally, cases were characterized as high-risk (>2 points) or low-risk (≤2 points) for IE using the HANDOC score;[Clin Infect Dis 2018; 66: 693-8] HANDOC stands for Heart murmur or valve disease; Aetiology with Streptococcus mutans, S. bovis, S. sanguinis, or S. anginosus; Number of positive blood cultures two or greater; Duration of symptoms seven days or longer; Only one species growing in blood cultures; and Community-acquired infection.

**Performance of the two versions of the HANDOC score in identifying patients at high-risk for infective endocarditis and the three versions of the Duke clinical criteria for the diagnosis of infective endocarditis among 707 episodes from the bacteremia cohort with the reference standard being the diagnosis of Endocarditis Team**

| | Sensitivity % (95% CI) | Specificity % (95% CI) | PPV % (95% CI) | NPV % (95% CI) | Accuracy % (95% CI) |
|---|---|---|---|---|---|
| HANDOC score >2 points (all streptococci) | 91 (85-95) | 83 (80-86) | 58 (53-62) | 97 (96-98) | 85 (82-87) |
| HANDOC score >2 points (non-beta-hemolytic streptococci; n=607) | 95 (90-98) | 82 (78-85) | 61 (56-65) | 98 (96-99) | 85 (82-88) |
| 2015 Duke-ESC | 65 (57-72) | 100 (98-100) | 97 (92-99) | 92 (90-93) | 93 (91-94) |
| 2023 Duke-ISCVID | 81 (74-86) | 99 (98-100) | 95 (90-97) | 95 (94-97) | 95 (94-97) |
| 2023 Duke-ESC | 73 (65-79) | 99 (98-100) | 95 (90-98) | 93 (92-95) | 94 (92-95) |

*ESC: European Society of Cardiology; ISCVID: Internation Society of Cardiovascular Infectious Diseases*

Among 851 episodes with streptococcal bacteremia, IE was diagnosed in 171 episodes (20%). Among 607 episodes with non-beta-hemolytic streptococci, 213 (35%) had HANDOC scores >2 points; 132 (22%) had IE. The sensitivity of the HANDOC score to identify episodes at high-risk for IE was 95% (90-98%), the specificity 82% (78-85%), and the NPV 98% (96-99%). 2015 Duke-ESC, 2023 Duke-ISCVID, and 2023 Duke-ESC clinical criteria classified 114 (13%), 145 (17%), and 126

(15%) episodes as definite IE, respectively. Sensitivity for the 2015 Duke-ESC, 2023 Duke-ISCVID, and 2023 Duke-ESC clinical criteria was calculated at 65% (57-72%), 81% (74-86%), and 73% (65-79%), respectively, with specificity at 100% (98-100%), 99% (98- 100%), and 99% (98-100%), respectively.

### BOTTOM LINE

**The HANDOC score showed an excellent NPV to identify episodes at high-risk for IE. Among the different versions of the Duke criteria, the 2023 Duke-ISCVID version fared better for the diagnosis of IE among streptococcal bacteremia.**

## Antimicrobial Stewardship Programs in Neonates: A Meta-Analysis

Pediatrics 2024;153(6):e2023065091
doi.org/10.1542/peds.2023-065091

The goal of this article was to review the components of neonatal antimicrobial stewardship programs (ASP) and their effects on clinical outcomes, cost-effectiveness, and antimicrobial resistance. They selected randomized and nonrandomized trials and observational and quality improvement studies evaluating the impact of ASP with a cutoff date of May 22, 2023. The data sources for these studies included PubMed, Medline, Embase, Cochrane CENTRAL, Web of Science, and SCOPUS. Details of the ASP components and clinical outcomes were extracted into a predefined form.

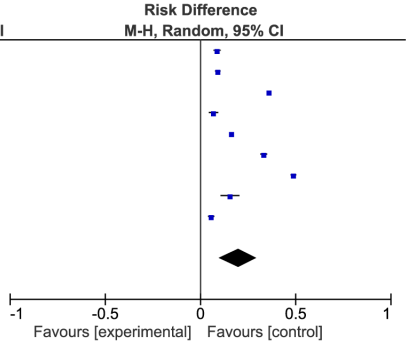
Of the 4048 studies retrieved, 70 studies (44 cohort and 26 observational studies) of >350,000 neonates met the inclusion criteria. Moderate-certainty evidence reveals a significant reduction in antimicrobial initiation in NICU (pooled risk difference [RD] 19%; 95% confidence interval [CI] 14% to 24%) and combined NICU and postnatal ward settings (pooled RD 8%; 95% CI 6% to 10%), duration of antimicrobial agents therapy[DOT] (pooled RD 20%; 95% CI 10% to 30%), length of therapy[LOT] (pooled RD 1.82 days; 95% CI 1.09 to 2.56 days), and use of antimicrobial agents >5 days (pooled RD 9%; 95% CI 3% to 15%). Low-certainty evidence reveals a reduction in economic burden and drug resistance without an increase in sepsis-related mortality or the reinitiation of antimicrobial agents. Studies had heterogeneity with significant variations in ASP interventions, population settings, and outcome definitions. The studies were classified as moderate- to low-certainty evidence.

**Forest plot of pairwise meta-analysis between pre-ASP and post-ASP group (using random effects model): Proportion of DOT**

A

| Study or Subgroup | Pre-ASP Events | Pre-ASP Total | Post-ASP Events | Post-ASP Total | Weight | Risk Difference M-H, Random, 95% CI |
|---|---|---|---|---|---|---|
| Berardi 2021 | 1694 | 5608 | 1240 | 5767 | 11.1% | 0.09 [0.07, 0.10] |
| Cantey 2016 | 5405 | 15749 | 2596 | 10293 | 11.1% | 0.09 [0.08, 0.10] |
| Feng 2023 | 25927 | 33628 | 8763 | 21322 | 11.2% | 0.36 [0.35, 0.37] |
| Gustavsson 2020 | 2402 | 4498 | 1753 | 3762 | 11.1% | 0.07 [0.05, 0.09] |
| Lu 2019 | 39803 | 73275 | 23098 | 60753 | 11.2% | 0.16 [0.16, 0.17] |
| Maalouf 2023 | 2770 | 3611 | 9623 | 22131 | 11.1% | 0.33 [0.32, 0.35] |
| Malviya 2022 | 7115 | 9461 | 3273 | 12397 | 11.1% | 0.49 [0.48, 0.50] |
| McCarthy 2018 | 572 | 1000 | 316 | 758 | 10.9% | 0.16 [0.11, 0.20] |
| Thampi 2019 | 4147 | 10498 | 3083 | 9093 | 11.1% | 0.06 [0.04, 0.07] |
| **Total (95% CI)** | | **157328** | | **146276** | **100.0%** | **0.20 [0.10, 0.30]** |
| Total events | 89835 | | 53745 | | | |

Heterogeneity: Tau² = 0.02; Chi² = 5415.35, df = 8 (*P* <.00001); I² = 100%
Test for overall effect: Z = 3.99 (*P* <.0001)

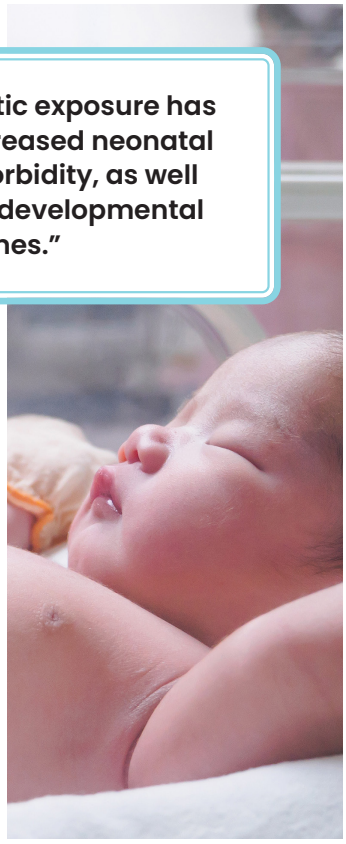



## Dr. Septimus's Annotations

Neonatal sepsis is a major contributor to morbidity and mortality worldwide. [Arch Dis Child. 2021; 106:745–752] Empirical treatment with broad-spectrum antibiotics is a common practice for neonates to either prevent infection or

reduce the progression to fulminant sepsis. Excessive antibiotic exposure has been linked to increased neonatal mortality and morbidity, as well as adverse neurodevelopmental outcomes. [JAMA Pediatr.2016;170:1181–1187; J Infection. 2022; 85:213–300] In 2009 the Neonatal Research Network published that prolonged, early antibiotic exposure is associated with necrotizing enterocolitis (NEC) and death in extremely preterm infants. [Pediatrics. 2009; 123:58–66] This current meta-analysis reviewed seventy articles and over 350,000 neonates. This meta-analysis showed that neonatal ASP interventions are in fact associated with reduction in the initiation and duration of antimicrobial use, without an increase in adverse events.

**"Excessive antibiotic exposure has been linked to increased neonatal mortality and morbidity, as well as adverse neurodevelopmental outcomes."**



Process measures were used to measure the success of neonatal ASP. Days of therapy [DOT] per 1000 patient-days, calendar days of therapy [LOT], antimicrobial usage rate, and antimicrobial spectrum index are all used, but it is unclear which, if any, of those measures is the best one. The best measure is the one that predicts patient outcomes, such as late-onset sepsis, NEC, prolonged length of stay, colonization or infection with drug-resistant organisms, or death. Uncertainty remains as to which metric best predicts these outcomes. We also need more patient-level outcomes for neonatal ASP. The authors also point out that very few manuscripts include economic impact or antimicrobial resistance as outcomes. However, this meta-analysis confirms that neonatal ASPs can reduce unnecessary antibiotic consumption. Now, we need to show that effective neonatal antimicrobial stewardship will improve meaningful, patient-level outcomes.

**BOTTOM LINE**

**ASP interventions in neonates are associated with either limiting initiation or decreasing duration of antimicrobial exposure, both in the NICU and postnatal settings, without increasing adverse events. Future studies are needed to evaluate the development of drug resistance and economic burden.**

## 4 Molecular Epidemiology of Clostridioides difficile Colonization in Families with Infants

OFID published online June 10,2024
DOI: 10.1093/ofid/ofae299

Families of healthy infants were recruited at the baby's 4-month well child visit and were followed longitudinally until the baby was approximately 9 months old. Stool samples or rectal swabs were collected from the infants and their parents every 2 weeks. Families were instructed to mail a soiled infant diaper via the United States Postal Service to a research microbiology laboratory every two weeks until the child was approximately 8-9 months of age, resulting in a total of 8 study time points over 4 months. Simultaneous adult rectal specimens were collected using commercial diaper wipes that were sent in the same mailer as the diapers but in separate sealed plastic bags. C. difficile isolates were strain-typed by fluorescent PCR ribotyping and by core genome multilocus sequence typing, and the number of families in whom the same strain was cultivated from >1 family member.

Samples were collected from 33 infants (three sets of twins), 30 mothers, and 19 fathers. C difficile was isolated in at least one member in 28 of 30 families, though no parent or infant was diagnosed as having C difficile infection (CDI). A total of 225 organisms were cultivated from the samples, and 191 were recovered and strain typed.

C difficile strains were shared in 17 of the 28 families harboring C difficile, with three families found to share two separate strains. The infant and at least one adult family member were implicated in 17 of 20 instances of strain sharing, and, in at least 13 of these, the strain was detected in the infant first. Excretion of shared strains was persistent.

## Dr. Septimus's Annotations

With infants known to asymptomatically excrete C difficile throughout the first 2 years of life, the investigators wanted to measure the frequency in which C difficile excreted by infants can be identified in a parent, which could help determine the role infants might play in the spread of the disease in the community. C. difficile strain-sharing was frequent in healthy families caring for an infant, increasing the likelihood that asymptomatically excreting babies and their families represent a reservoir of the organism in the community. Although they were unable to demonstrate the directionality of C difficile transmission with certainty, the investigators say the data from this study support adding asymptomatically excreting infants and their families to the list of potential sources of community-associated CDI.

**BOTTOM LINE**

**The findings of the current study represent an important step in defining the epidemiological role of infants in CA-CDI in adults.**

5

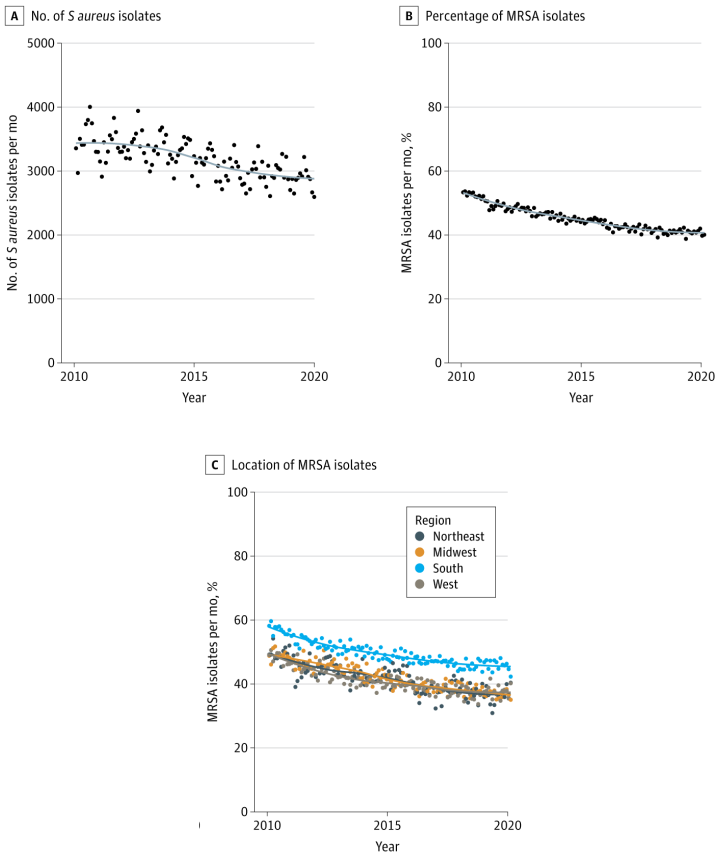
## Antimicrobial Resistance Patterns of Outpatient Staphylococcus aureus Isolates

JAMA Network Open. 2024;7(6): e2417199
doi:10.1001/jamanetworkopen.2024.17199

This was a cross-sectional study using data from Veterans Health Administration clinics collected from adult outpatients with S aureus infection in 48 states and Washington, DC, from January 1, 2010, to December 31, 2019. Data were analyzed from January to November 2023. The objective was to characterize the spatiotemporal trends of resistance to non–β-lactam antibiotics among community-onset S aureus infections, including regional variation in resistance rates and geographical heterogeneity in multidrug resistance. Spatiotemporal variation of S aureus resistance to these 4 classes of non–β-lactam antibiotics, stratified by MRSA and MSSA, and subdivided by regions of the US (Northeast, Midwest, South, and West). Trend tests and bivariate mapping were used to determine significant changes in resistant proportions over time and identify counties where rates of resistance to multiple non–β-lactams were high.

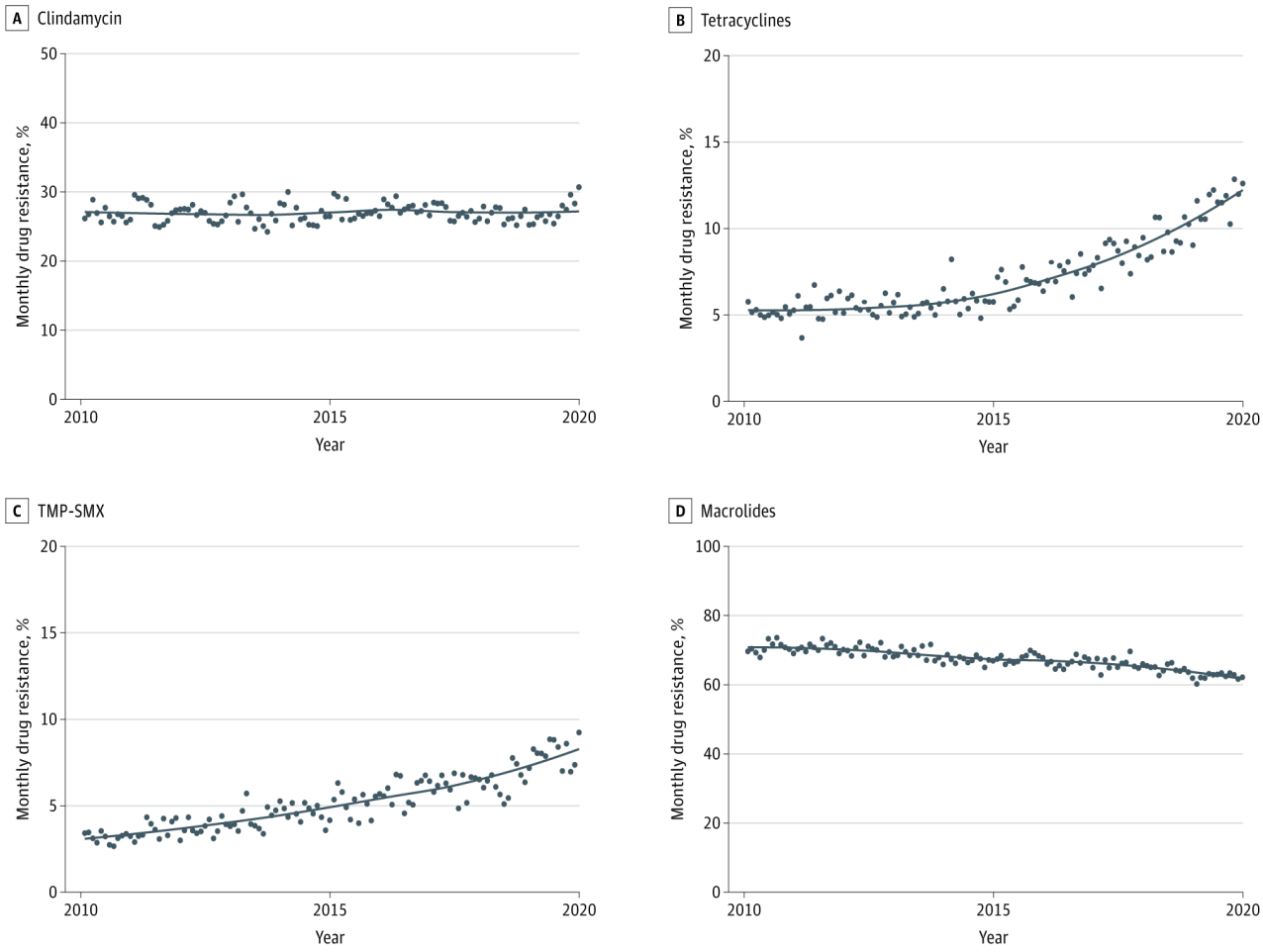
A total of 382,149 S aureus isolates from 268,214 unique outpatients (mean age, 63.4 years; 252,910 males [94%]) were analyzed. There was a decrease in the proportion of MRSA nationwide, from 53.6% in 2010 to 38.8% in 2019. Among MRSA isolates, they documented a significant increase in tetracycline resistance (from 3.6% in 2010 to 12.8% in 2019; P for trend < .001) and TMP-SMX resistance (from 2.6% in 2010 to 9.2% in 2019; P for trend < .001),

**Patterns of Staphylococcus aureus Isolates From 2010 to 2019**



modest and not significant increases in clindamycin resistance (from 24.2% in 2010 to 30.6% in 2019; P for trend = .34), and a significant decrease in macrolide resistance (from 73.5% in 2010 to 60.2% in 2019; P for trend < .001). Among MSSA isolates, significant upward trends in clindamycin, tetracyclines, and TMP-SMX resistance were observed. Regional stratification over time showed that the Northeast had slightly higher rates of clindamycin resistance but lower rates of tetracycline resistance, while the South had notably higher rates of resistance to tetracyclines and TMP-SMX, particularly among MRSA isolates. Bivariate mapping at the county scale did not indicate clear regional patterns of shared high levels of resistance to the 4 classes of antimicrobials studied.

**Prevalence Among Methicillin-Resistant Staphylococcus aureus (MRSA) Isolates of Resistance to Clindamycin, Tetracycline, Trimethoprim-Sulfamethoxazole (TMP-SMX), and Macrolides From 2010 to 2019**




## Dr. Septimus's Annotations

In this cross-sectional study of 382,149 S aureus isolates, significant increases in resistance to tetracyclines and trimethoprim-sulfamethoxazole were observed over a 10-year period. There was a decrease in the proportion of MRSA nationwide, from 53.6% in 2010 to 38.8% in 2019. This shift has been identified in hospitals as well. Rates of MRSA were highest in the South over the duration of the study period. Prior work has suggested that the combination of sociodemographic factors (e.g., crowding, poverty), climate factors (e.g., heat, humidity), and antibiotic prescribing patterns have contributed to consistently higher rates of antimicrobial resistance in the South. [Clin Infect Dis. 2017; 64:597-604] The Veterans Health Administration clinics are a nationwide integrated provider of health care in the US. The

population it serves tends to be older and male and is not necessarily representative of the larger US patient population. Only infections among outpatients were considered in this analysis of antimicrobial resistance among community S aureus infections; different rates of resistance to non–β-lactam agents might be observed among inpatients with infections.

**BOTTOM LINE**

**In this study of outpatient S aureus isolates, MRSA became less common over the 10-year period, and MRSA isolates were increasingly resistant to tetracyclines and trimethoprim-sulfamethoxazole.**

6

## Cow's Milk Containing Avian Influenza A(H5N1) Virus — Heat Inactivation and Infectivity in Mice

N Engl J Med published online May 24, 2024
DOI: 10.1056/NEJMc2405495

The Texas A&M Veterinary Medical Diagnostic Laboratory obtained cow's milk samples from an affected herd in New Mexico, from which eight HPAI A(H5N1) viruses were isolated. They compared the genetic origin of these HPAI A(H5N1) milk virus isolates with the sequences publicly available at the time of our analysis. The cow viruses form a single clade encompassing many smaller clades of viruses isolated from cats, raccoons, chickens, and wild birds. The phylogeny is consistent with a single introduction into cows. The viruses isolated in this study fall within the clade of publicly available cow virus sequences, including that from a human isolate, A/Texas/37/2024. They identified a reassortment event for NP and PB2 segments that occurred immediately before the introduction of HPAI A(H5N1) viruses into cows.

Next, they tested heat inactivation of four HPAI A(H5N1) virus–positive milk samples. Undiluted milk samples were incubated in a PCR thermocycler at 63°C for 5, 10, 20, or 30 minutes or at 72°C for 5, 10, 15, 20, or 30 seconds. Control samples were left untreated. Heat treatment at 63°C reduced the virus titers below the detection limit of the TCID 50 (50% tissue-culture infectious dose) assay (1.5 log10/ml). Heat treatment at 72°C was performed, with the default settings of the PCR thermocycler (i.e., preheated lid at 105°C) or with a metal lid (heated to 72°C) covering the PCR block. After heat treatment, samples were inoculated into embryonated chicken eggs or Madin–Darby canine kidney (MDCK) cells for virus detection. Under these conditions, heat treatment for 15 or 20 seconds reduced virus titers by more than 4.5 log units but did not completely inactivate the virus. The stability of HPAI A(H5N1) virus in cow's milk stored at 4°C is another important question. For a milk sample, they detected a decline of only two log units over 5 weeks. They concluded that HPAI A(H5N1) virus may therefore remain infectious for several weeks in raw milk kept at 4°C.

Next they assessed the risk that HPAI A(H5N1)– positive milk poses to animals and humans, by orally inoculating BALB/cJ mice with 50 µl (3×106 pfu). The animals showed signs of illness starting on day 1. All the animals survived until day 4, when they were euthanized to determine virus titers in multiple organs. They detected high virus titers in the respiratory organs (which suggests that infection may have occurred through the pharynx) and moderate virus titers in several other organs, findings consistent with the systemic infections typically caused by HPAI H5 viruses in mammals. Detection of virus in the mammary glands of two mice was consistent with the high virus load in the milk of lactating cows, even though these mice were not lactating.

### Dr. Septimus's Annotations

Their data indicate that HPAI A(H5N1) virus in untreated milk can infect susceptible animals that consume it. Therefore, HPAI H5–positive milk poses a risk when consumed untreated. As reported in June's ID Watch, 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. Therefore, the FDA still strongly advised against consuming raw, unpasteurized dairy products. H5N1 avian flu has been reported in 94 dairy herds across 12 states since late March. See next review

**BOTTOM LINE**

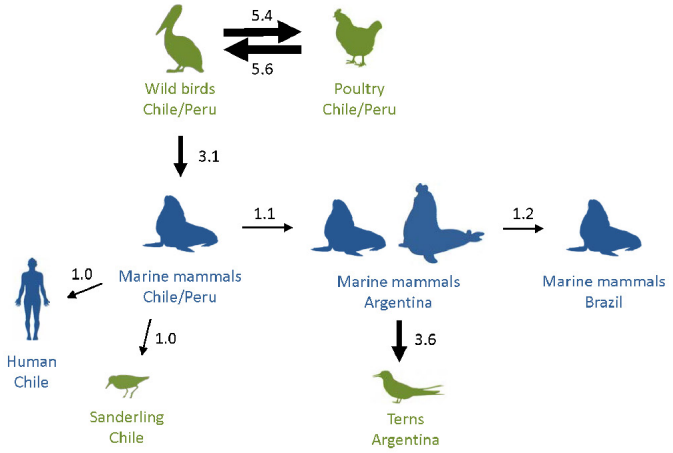
**Heat inactivation under the laboratory conditions used here reduces HPAI H5 virus titers by more than 4.5 log units. However, laboratory experiments do not exactly replicate commercial pasteurization processes.**

7

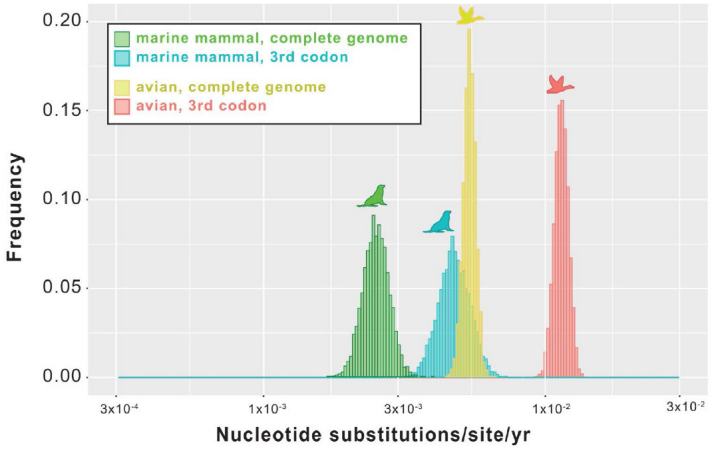
## Massive outbreak of Influenza A H5N1 in elephant seals at Península Valdés, Argentina: increased evidence for mammal-to-mammal transmission

bioRxiv posted online June 1, 2024
doi.org/10.1101/2024.05.31.596774

H5N1 high pathogenicity avian influenza (HPAI) viruses of the clade 2.3.4.4b have killed thousands of marine mammals in South America since 2022. In October 2023, following outbreaks in sea lions in Argentina, they recorded unprecedented mass mortality (~17,000) in southern elephant seals (Mirounga leonina) at Península Valdés. Seal pups were disproportionately affected. Frequent interactions with sea lions and scavenging by seagulls were observed. Deaths of terns(birds) concurred with seals but peaked weeks later. HPAI H5N1 was confirmed in seals and terns.




Genomic characterization showed viruses from pinnipeds(seals) and terns in Argentina form a distinct clade with marine mammal viruses from Peru, Chile and Brazil. These mammal-clade viruses share an identical set of mammalian adaptation mutations which are notably also found in the terns. The combined ecological and phylogenetic data support mammal-to-mammal transmission and occasional mammal-to-bird spillover.




### Dr. Septimus's Annotations

The emergence of H5N1 high pathogenicity avian influenza (HPAI) viruses from clade 2.3.4.4b in 2020 triggered numerous outbreaks in wildlife worldwide. [Waterbirds 46, 2023] In 2021–2022, these H5N1 HPAI 2.3.4.4b viruses spread to North America, further impacting wildlife, especially waterbirds and birds of prey and reassorting with endemic strains. [Virology 2023; 587:109860] The virus then spread to South America in 2022. The investigators claim this is the first multinational transmission of H5N1 viruses in mammals observed globally. The implication that H5N1 viruses are becoming more evolutionary flexible and adapting to mammals in new ways could have global consequences for wildlife, humans, and/or livestock. The worry now is that as H5N1 continues to infect mammals and evolve, it may pick up the mutations needed to spread efficiently among people, setting off another pandemic. This article has not been peered reviewed.

BOTTOM LINE

**From a public health perspective, mammal-to-mammal transmission could be a critical stepping-stone in the evolutionary pathway for these viruses to become capable of human-to-human transmission and thus potentially be the next pandemic.**

8

## Multicountry spread of influenza A(H1N1)pdm09 viruses with reduced oseltamivir inhibition, May 2023–February 2024

Emerg Infect Dis. 2024 published online June 12, 2024
doi.org/10.3201/eid3007.240480

Oseltamivir, an NA (neuraminidase) inhibitor, is the drug most prescribed for influenza. The NA amino acid substitution H275Y, acquired spontaneously or after drug exposure, confers resistance to oseltamivir. Monitoring oseltamivir susceptibility is a priority for the WHO Global Influenza Surveillance and Response System (WHO-GISRS). In addition to H275Y, many NA substitutions in N1 subtype viruses are suspected of reducing oseltamivir susceptibility. The CDC monitors antiviral susceptibility of viruses submitted to the national surveillance system and those collected in other countries. Nearly all influenza-positive samples undergo next-generation sequencing. They analyzed NA sequences of submitted viruses for substitutions previously associated with reduced susceptibility, tested the viruses in an NA inhibition assay, and compared IC50s with a reference IC50 to determine inhibition levels. [Antiviral Res. 2016;128:28–35]

From May 2023–February 2024, the CDC analyzed 2,039 pH1N1 viruses from the US (n = 1,274) and 38 other countries (n = 765). Four had the H275Y substitution, indicating low frequency of oseltamivir resistance. Analysis revealed NA substitution I223V in 18 and S247N in 15 viruses; those substitutions confer mildly elevated oseltamivir IC50 (<10-fold). They also detected 17 viruses carrying both substitutions, I223V + S247N. As expected, single mutants exhibited normal inhibition by oseltamivir and other NA inhibitors in NA inhibition assay. The 6 viruses with I223V + S247N displayed 13- to 16-fold reduced inhibition for oseltamivir and normal inhibition (<4-fold) for other NA inhibitors. Both single and dual mutants remained susceptible to the CEN (cap-dependent endonuclease) inhibitor baloxavir.

**Influenza A(H1N1)pdm09 viruses with amino acid substitutions in neuraminidase that may affect inhibition by oseltamivir***

| NA substitution† | No. viruses with NA substitution | Viruses collected from countries (no. in each) |
|---|---|---|
| H275Y | 4 | Argentina (1),‡ Panama (1), USA (2) |
| I223V | 18 | Abu Dhabi (5), Bangladesh (5), Bahrain (2), Canada (1), Costa Rica (1), USA (4) |
| S247N | 15 | Abu Dhabi (2), Bhutan (3), Brazil (1), Canada (1), Hong Kong (1), Oman (1), USA (6) |
| I223V + S247N§ | 17 | Bangladesh (11), Hong Kong (1), Maldives (1), Niger (3), USA (1) |

**Next-generation sequencing–based virologic surveillance conducted at the Centers for Disease Control and Prevention, May 2023–February 2024.*

*†According to a subtype-specific NA amino acid numbering system.*

*‡This virus also contains NA-S247N. Virus was not recovered in cell culture.*

*§Combination of I223V + S247N was not reported previously.*

Dr. Septimus's Annotations

The investigators report the emergence and intercontinental spread of pH1N1 viruses displaying reduced susceptibility to oseltamivir resulting from acquisition of NA-I223V + S247N mutations. The dual mutants that we tested retained susceptibility to other approved influenza antiviral drugs, including baloxavir. Analysis of available sequence data revealed that dual mutants have been in global circulation since May 2023; overall detection frequency was low (0.67%, 101/15,003).

**BOTTOM LINE**

**This study highlights the need to closely monitor evolution of dual mutants because additional changes may further affect susceptibility to antiviral drugs or provide a competitive advantage over circulating wild-type viruses.**

9

## Impact of Intrapartum Azithromycin on the Carriage and Antibiotic Resistance of Escherichia coli and Klebsiella pneumoniae in Mothers and their Newborns: a sub-study of a Randomized Double-Blind Trial Conducted in The Gambia and Burkina Faso

Clin Infect Dis published online May 16, 2024
DOI: 10.1093/cid/ciae280

Recent double-blinded randomized trials, PregnAnZI-2 and A-PLUS, explored the use of azithromycin to decrease neonatal sepsis and mortality across nine African and Asian countries [JAMA 2023; 329: 716-24; N Engl J Med. 2023; 388: 1161–1170]. Although no reduction in neonatal sepsis and mortality was observed, a significant impact in reducing maternal infections including puerperal sepsis, was noted. The PregnAnZI-2 trial, conducted in West Africa, also reported a reduction in neonatal infections and a lower rate of prescribed antibiotics during the neonatal period. Data on the effect of intrapartum azithromycin on carriage and antibiotic resistance of gram-negative bacteria causing neonatal sepsis, E. coli and K. pneumoniae, are limited. The investigators stated it is important to evaluate the impact of the intervention on these two gram-negative bacteria due to their role in neonatal sepsis and their rising rates of multidrug resistance which severely limits treatment options. This current study aimed to determine the effect of intrapartum azithromycin on the prevalence of carriage and antibiotic resistance of E. coli and K. pneumoniae among mother-infant pairs from Gambia and Burkina Faso. The phase 3 PregnAnZI-2 trial recruited and randomized 12,000 women in Gambia and Burkina Faso to received either oral azithromycin or placebo during labor. A sub-group of 250 mother/infant pairs per country participated in a carriage sub-study to determine the impact of intrapartum azithromycin on the prevalence of carriage and antibiotic resistance of E coli and K pneumoniae. Biological samples were collected pre-intervention until 4 months post-intervention. A maternal nasopharyngeal (NPS) and rectovaginal swab (RVS) were collected during labor before the intervention. Within 4 hours after birth, an NPS and a Rectal Swab (RS) were collected from newborns. Additional samples were collected during household visits: from mothers; NPS at day-6, breast milk (BM) at day-6, 28 and month-4 and from infants; NPS and RS at day-6, 28 and month-4. For The Gambia, the last two sample collection timepoints were affected by the state of emergency declared in March 2020 due to the Covid-19 pandemic.

Overall, 500 mother-infant pairs participated in this sub-study, 250 from The Gambia, 250 from Burkina Faso (122 in azithromycin and 128 in placebo arm per country). The proportion of samples collected was >98% at day-0 and 6, 92% at day-28, and 79% at month-4. In study women for pre-intervention RVS, prevalence of E. coli carriage was similar in azithromycin and placebo arms (68.9% and 67.6% respectively). The prevalence of carriage of azithromycin-resistant isolates was low and ranged between 2.7% and 4.5%. For post-intervention samples, there were no differences between arms in the prevalence of carriage of E. coli or azithromycin-resistant E. coli in BM at any timepoint.

Prevalence of E. coli carriage in infants' RS samples was lower in azithromycin arm compared to placebo at days 6 (63.0% vs. 75.2%, PR, 0.84; CI, 0.75-0.95, p=0.006) and 28 (52.7% vs. 70.4%, 0.75; 0.64-0.87, p<0.001). Prevalence of azithromycin resistant E. coli in the azithromycin arm was significantly higher at days 6 (13.4% vs. 3.6%, 3.75; 1.83-7.69, p<0.001) and 28 (16.4% vs. 9.6%, 1.71; 1.05-2.79, p=0.036). The frequency of azithromycin resistance among E. coli isolated from RS was higher in the azithromycin arm at day-6 and 28. For pre-intervention RVS and post-intervention BM, there were no differences between arms in the prevalence of E. coli resistant to ampicillin, trimethoprim-sulfamethoxazole, gentamicin, and ciprofloxacin. For pre-intervention RVS, there was higher prevalence of ESBL carriage (2.0% vs. 0% p=0.027) in azithromycin arm compared to placebo. There was no resistance to meropenem and cefoxitin resistance was low. For infants' RS, prevalence of carriage of E. coli resistant to ampicillin at days 6 (46.2% vs. 58.4%, 0.80; 0.67-0.94, p=0.009) and 28 (44.1% vs. 59.6%, 0.74; 0.62-0.89, p=0.001) was lower in the azithromycin arm. Prevalence of carriage of E. coli resistant to trimethoprim-sulfamethoxazole was lower in the azithromycin arm at days 6 (45.4% vs. 57.6%, 0.79; 0.66-0.94, p=0.009) and 28 (42.3% vs. 57.1%, 0.74; 0.61-0.89, p=0.002). Prevalence of carriage of E. coli resistant to cefoxitin was lower at day-28 (0% vs. 2.9%, p=0.016) in the azithromycin arm. Prevalence of E. coli resistant to gentamicin, ciprofloxacin and ESBL carriage was similar between arms. No meropenem-resistant E. coli was detected.

The prevalence of K. pneumoniae carriage was similar between arms for all samples and timepoints. Prevalence of azithromycin-resistant isolates before and after the intervention was low and similar between arms (0.4% vs. 1.6%). Prevalence of K. pneumoniae carriage in infants in RS was higher in the azithromycin arm at days 6 (49.6% vs. 37.2%, 1.33; 1.08-1.64, p=0.006) and 28 (53.6% vs. 32.9%, 1.63; 1.31-2.03, p<0.001). For azithromycin-resistant K. pneumoniae in RS, study arms were different at day-28 (7.3% vs. 2.1%, 3.49; 1.30-9.37, p=0.012) in azithromycin arm vs. placebo. For NPS, no differences between arms were found for prevalence of K. pneumoniae carriage nor azithromycin resistance.

For pre-intervention maternal RVS and post-intervention BM there were no differences between arms in the prevalence of K. pneumoniae resistant to trimethoprim-sulfamethoxazole, gentamicin, ciprofloxacin, and ESBL carriage. For pre-intervention maternal RVS, prevalence of K. pneumoniae resistant to cefoxitin was higher in the azithromycin arm (2.0% vs. 0%, p=0.027). No resistance to meropenem was detected. For maternal NPS, resistance to all antibiotics was either absent or low. In infants RS, resistance to trimethoprim-sulfamethoxazole (23.2% vs. 8.8%, 2.65; 1.65- 4.26, p<0.001), gentamicin (10.5% vs. 5.0%, 2.09; 1.07-4.10, p=0.034), ciprofloxacin (15.5% vs. 5.8%, 2.65; 1.46-4.80, p=0.001), and ESBL carriage (9.5% vs. 3.3%, 2.86; 1.30-6.33, p=0.007) at day-28 was higher in the azithromycin arm. Resistance to cefoxitin was low with no resistance to meropenem. In NPS, resistance to all tested antibiotics was either low or absent.

## Dr. Septimus's Annotations

Clinical trials have shown that prophylactic intrapartum azithromycin decreases maternal and neonatal infections. However, it is important to evaluate the effect of this intervention on bacterial colonization and antimicrobial resistance. Although this trial found that intrapartum azithromycin did not achieve the primary outcome of reducing neonatal sepsis and mortality, it did reduce neonatal and maternal infections.

While little impact was found on the samples collected from the mothers, E coli carriage in infant rectal samples was lower in the intervention than placebo arm at days 6 (63.0% vs 75.2%; prevalence ratio [PR], 0.84; 95% CI, 0.75 to 0.95) and 28 (52.7% vs 70.4%; PR, 0.75; 95% CI, 0.64 to 0.87) postintervention. But the prevalence of azithromycin-resistant E coli was higher in the azithromycin arm at days 6 (13.4% vs 3.6%; PR, 3.75; 95% CI, 1.83 to 7.69) and 28 (16.4% vs 9.6%; PR, 1.71; 95% CI, 1.05 to 2.79). For K pneumoniae, carriage in infant rectal samples was higher in the intervention than placebo arm at days 6 (49.6% vs 37.2%; PR, 1.33; 95% CI, 1.08 to 1.64) and 28 (53.6% vs 32.9%; PR, 1.63; 95% CI, 1.31 to 2.03), and the prevalence of azithromycin-resistant K pneumoniae was higher in the azithromycin arm at day 28 (7.3% vs 2.1%; PR, 3.49; 95% CI, 1.30 to 9.37). They could not ascertain the mechanisms of resistance involved.

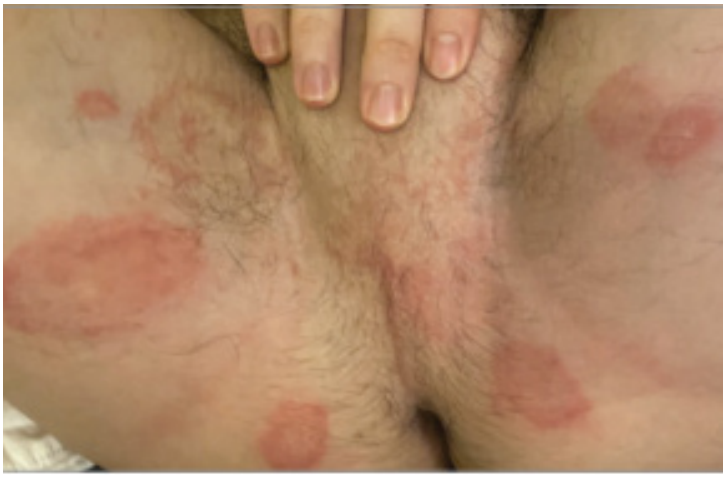
BOTTOM LINE

**Intrapartum azithromycin decreases carriage of E. coli and increases carriage of K. pneumoniae in the gut of neonates. The intervention also increases carriage of azithromycin-resistant E. coli and K. pneumoniae isolates, a potential threat to the spread of such resistance to the community and NICU.**

10

## Potential Sexual Transmission of Tinea Pubogenitalis From TMVII

JAMA Derm published online June 5, 2024
doi:10.1001/jamadermatol.2024.1430



Tinea genitalis has increasingly been reported in Europe attributed to the emerging dermatophyte, T mentagrophytes internal transcribed spacer (ITS) genotype VII (TMVII), which may spread via sexual contact. The authors describe a patient with TMVII resulting in tinea genitalis, glutealis, and corporis to highlight risk factors, diagnosis, and treatment.

A male in his 30s was referred with a scaly, erythematous eruption in the inguinal region, genitalia, legs, arms, and back. He traveled to Europe (England and Greece) and within the US (California) prior to developing skin lesions. He reported multiple male sexual partners while traveling, none with a similar infection, and visited a sauna 2 months prior to developing skin lesions. He reported shaving and waxing the pubic region and denied pet exposure. He did not have HIV or immunocompromising conditions. Prior to referral, a skin biopsy from the right thigh demonstrated dermatophytosis, and he was treated with 150-mg fluconazole weekly for 4 weeks with no response. On referral, a fungal culture grew an isolate conventionally identified as T interdigitale. Sequencing of the ITS region of the ribosomal gene at the Wadsworth Center, New York State Department of Health, confirmed TMVII (GenBank No. PP564912). He was treated with 6 weeks of terbinafine, 250 mg, daily with improvement. Due to persistent infection, he was transitioned to itraconazole, 200 mg daily, with further improvement.

### Dr. Septimus's Annotations

Tinea genitalis/pubogenitalis is a rare manifestation of dermatophytosis affecting the genitals and pubic region. In the last decade, male genital dermatophytosis has been increasingly reported in India, corresponding to the emergence of Trichophyton indotineae. [Mycoses. 2016;59(10):606-614] Dermatophytosis due to TMVII may result in tinea genitalis/pubogenitalis, corporis, faciei, and barbae, which may be abscess forming and scarring. [Sex Transm Infect. 2015; 91:493-496] Despite being zoophilic, few pet exposures are documented. Early case reports of TMVII infection occurred among patients who had contact with commercial sex workers in Southeast Asia. Recent evidence highlights TMVII is now circulating locally in Europe, where infection may be acquired in fitness clubs, or during sexual intercourse, including among men who have sex with men as highlighted in a case series of TMVII infection in France. [ Emerg Infect Dis. 2023; 29:1411-1414] Routine culture cannot distinguish T mentagrophytes from the closely related T interdigitale. Sequencing of the ITS region identifies species and genotypes yet may not be widely available. Clues to diagnosis include tinea genitalis, which may be inflammatory or abscess forming, and recent sexual intercourse. In vitro susceptibility data for TMVII is unreported. This patient's isolate had a terbinafine minimal inhibitory concentration value of 0.0039 µg/mL or less

and fluconazole minimal inhibitory concentration value of 32 µg/mL. Current evidence suggests responsiveness to terbinafine, yet some patients may require itraconazole. Prolonged treatment duration may be necessary. When TMVII is suspected or diagnosed, sexual partners should be evaluated, and the patient screened for other sexually transmitted infections. ID Watch in June 2023 reported the first reported US cases of Tinea caused by T indotineae.[ MMWR 2023; 72:536-7] see next review

**BOTTOM LINE**

**This is the first case of sexually transmitted fungal infection caused by Trichophyton Mentagrophytes Type VII reported in the US. Prolonged treatment duration with terbinafine is necessary.**

11

## Clinical Course, Antifungal Susceptibility, and Genomic Sequencing of Trichophyton indotineae

JAMA Derm May 15, 2024
doi:10.1001/jamadermatol.2024.1126

This was a retrospective cohort study of patients with T indotineae infections in New York City spanned May 2022 to May 2023. Patients with confirmed T indotineae infections were recruited from 6 New York City medical centers.

Among 11 patients with T indotineae (6 male and 5 female patients; median [range] age, 39 [10-65] years), 2 were pregnant; 1 had lymphoma; and the remainder were immunocompetent. Nine patients reported previous travel to Bangladesh. All had widespread lesions with variable scale and inflammation, topical antifungal monotherapy failure, and diagnostic delays (range, 3-42 months). Terbinafine treatment failed in 7 patients at standard doses (250 mg daily) for prolonged duration; these patients also had isolates with amino acid substitutions at positions 393 (L393S) or 397 (F397L) in squalene epoxidase that correlated with elevated terbinafine minimum inhibitory concentrations of 0.5 µg/mL or higher. Patients who were treated with fluconazole and griseofulvin improved in 2 of 4 and 2 of 5 instances, respectively, without correlation between outcomes and antifungal minimum inhibitory concentrations. Furthermore, 5 of 7 patients treated with itraconazole cleared or had improvement at the last follow-up, and 2 of 7 were lost to follow-up or stopped treatment. Based on whole-genome sequencing analysis, US isolates formed a cluster distinct from Indian isolates.

### Dr. Septimus's Annotations

The first 3 cases of T indotineae dermatophytosis in the US were reported in 2023. [MMWR 2023;72(19):536-537 reviewed ID Watch June 2023] The results of this case series suggest that disease severity, diagnostic delays, and lack of response to typically used doses and durations of antifungals for tinea were common in this primarily immunocompetent patient cohort with T indotineae, consistent with previous reports. Itraconazole was generally effective, and the acquisition of infection was likely in Bangladesh. Experts have also linked its emergence to inappropriate use of combination topical products containing antifungals and high-potency corticosteroids. [Am J Clin Dermatol published online March 18, 2024] Clinicians suspecting T indotineae infection should contact their local public health jurisdiction. Traditional diagnostic tools—such as clinical appearance, potassium hydroxide preparations, and fungal cultures—cannot distinguish T indotineae from other Trichophyton species or provide information on antifungal susceptibility. Only molecular testing, available in specialized laboratories capable of performing AFST, can do so.

**BOTTOM LINE**

**Clinicians should be aware of and become vigilant for T indotineae dermatophytosis, especially in instances of poor response to typical first-line topical antifungals (including combination anti-fungal corticosteroid topicals) and/or oral antifungal.**

12

## CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024

MMWR 73(2);1–8, 2024

CDC recommends that MSM (men who have sex with men) and TGW (transgender women) who have had a bacterial STI (syphilis, chlamydia, or gonorrhea) diagnosed in the past 12 months should receive counseling that doxy PEP can be used as postexposure prophylaxis to prevent these infections. Following shared decision-making with their provider, CDC recommends that providers offer persons in this group a prescription for doxy PEP to be self-administered within 72 hours after having oral, vaginal, or anal sex. The recommended dose of doxy PEP is 200 mg and should not exceed a maximum dose of 200 mg every 24 hours. Doxy PEP, when offered, should be implemented in the context of a comprehensive sexual health approach, including risk reduction counseling, STI screening and treatment, recommended vaccination and linkage to HIV PrEP, HIV care, or other services as appropriate. Persons who are prescribed doxy PEP should undergo bacterial STI testing at anatomic sites of exposure at baseline and every 3–6 months thereafter. Ongoing need for doxy PEP should be assessed every 3–6 months as well. HIV screening should be performed for HIV-negative MSM and TGW according to current recommendations.

**CDC recommendations for use of doxycycline as postexposure prophylaxis for bacterial sexually transmitted infections prevention**

| Recommendation* | Strength of recommendation and quality of evidence |
|---|---|
| Providers should counsel all gay, bisexual, and other men who have sex with men (MSM) and transgender women (TGW) with a history of at least one bacterial sexually transmitted infection (STI) (specifically, syphilis, chlamydia or gonorrhea) during the past 12 months about the benefits and harms of using doxycycline (any formulation) 200 mg once within 72 hours (not to exceed 200 mg per 24 hours) of oral, vaginal, or anal sex and should offer doxycycline postexposure prophylaxis (doxy PEP) through shared decision-making. Ongoing need for doxy PEP should be assessed every 3–6 months. | High-quality evidence supports this strong recommendation to counsel MSM and TGW and offer doxy PEP. |
| No recommendation can be given at this time on the use of doxy PEP for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons. | Evidence is insufficient to assess the balance of benefits and harms of the use of doxy PEP |

**Although not directly assessed in the trials included in these guidelines, doxy PEP could be discussed with MSM and TGW who have not had a bacterial STI diagnosed during the previous year but will be participating in sexual activities that are known to increase likelihood of exposure to STIs.*

### Dr. Septimus's Annotations

No vaccines and few chemoprophylaxis options exist for the prevention of bacterial STIs. These infections have increased in the US and disproportionately affect gay, bisexual, and MSM) and TGW. In several large randomized controlled trials, 200 mg of doxycycline taken within 72 hours after sex has been shown to reduce syphilis and chlamydia infections by >70% and gonococcal infections by approximately 50%.[Med J Aust 2024;220:381–6 10.5694/mja2.52258; Euro Surveill 2023;28:2300621] 10.2807/1560-7917.ES.2023.28.46.2300621] Although the pharmacokinetics of doxycycline and experience in treating bacterial STIs suggest that doxy PEP should be effective in other populations, clinical data to

support doxy PEP in other populations (i.e., cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons assigned female at birth) are limited. As a result, providers should use their clinical judgement and shared decision-making to inform use of doxy PEP with populations that are not part of CDC recommendations.

**BOTTOM LINE**

**Doxy PEP has demonstrated benefit in reducing syphilis, chlamydia, and gonorrhea in certain populations and represents an additional approach to addressing STI prevention in MSM and TGW at increased risk for these infections.**

13

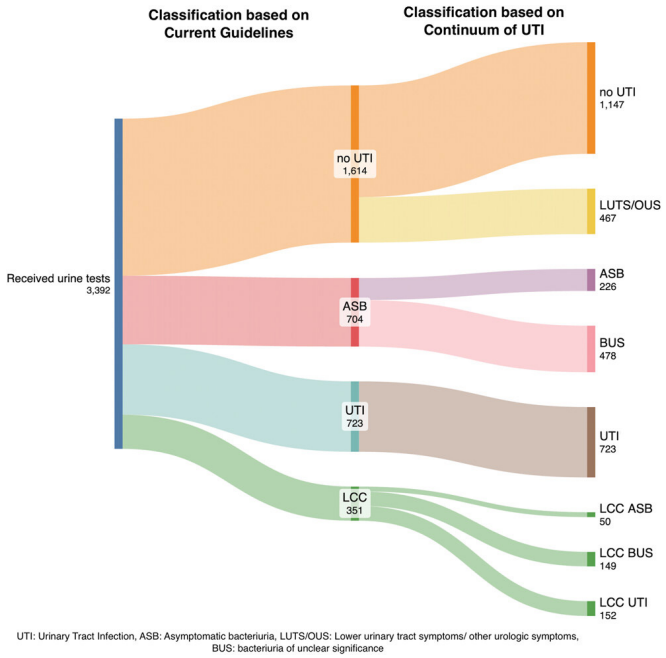
## Proposing the "Continuum of UTI" for a Nuanced Approach to Diagnosis and Management of Urinary Tract Infections

J Urol 2024; 211:690-698
doi.org/10.1097/JU.0000000000003874

This was a retrospective cohort study of a random sample of adult noncatheterized inpatient and emergency department encounters with paired urinalysis and urine cultures from 5 hospitals in 3 states between January 01, 2017, and December 31, 2019. Trained abstractors collected clinical (e.g., symptom) and demographic data. A focus group discussion with multidisciplinary experts was conducted to define the continuum of UTI, a 5-level classification scheme that includes 2 new categories: lower urinary tract symptoms/other urologic symptoms and bacteriuria of unclear significance. The newly defined continuum of UTI categories were compared to the current UTI classification scheme.

Of 220,531 encounters, 3392 randomly selected encounters were reviewed. Based on the current classification scheme, 32.1% (n [ 704) had ASB and 53% (n [ 1614) did not have a UTI. When applying the continuum of UTI categories, 68% of patients (n [478] with ASB were reclassified as bacteriuria of unclear significance and 29% of patients (n [ 467) with "no UTI" were reclassified to lower urinary tract symptoms/ other urologic symptoms.

**Comparison of UTI categories based on current Infectious Diseases Society of America guidelines and new "continuum of UTI" definition**




UTI: Urinary Tract Infection, ASB: Asymptomatic bacteriuria, LUTS/OUS: Lower urinary tract symptoms/ other urologic symptoms, BUS: bacteriuria of unclear significance

**Definitions Used for Different Clinical Presentations in Patients Who Receive Urine Tests**

| Culture results | Signs and symptoms per IDSA/AUA guidelines | Signs and symptoms per IDSA/AUA guidelines |
|---|---|---|
| Negative or mixed urine culture | | |
| No UTI | All patients | Without any lower or upper urinary tract symptoms |
| LUTS/OUS | NA | With upper or lower urinary symptoms, OR any urologic criteria |

*Abbreviations: ASB, asymptomatic bacteriuria; BUS, bacteriuria of unclear significance; IDSA, Infectious Diseases Society of America; LUTS/OUS, lower urinary tract symptoms/other urologic symptoms; NA, not applicable.*

**Definitions Used for Different Clinical Presentations in Patients Who Receive Urine Tests**

| Culture results | Signs and symptoms per IDSA/AUA guidelines | Signs and symptoms per IDSA/AUA guidelines |
|---|---|---|
| Positive urine culture>100,000 CFU/mL (>1000 CFU/mL in sensitivity analysis) | | |
| ASB | Without specific signs or symptoms of a urinary tract infection (may have clinical criteria) | Without specific signs or symptoms of a urinary tract infection or any clinical criteria |
| BUS | NA | 1 clinical criterion with or without other cause, OR cannot express symptoms (may have urologic criteria without clinical criteria) |
| UTI | Specific signs or symptoms of a urinary tract infection: lower or upper urinary tract symptoms, OR 2 clinical criteria without other cause (eg, fever + confusion), OR 1 clinical criterion + 1 urologic criterion (eg fever + hematuria) | Specific signs or symptoms of a urinary tract infection: lower or upper urinary tract symptoms, OR 2 clinical criteria without other cause, OR 1 clinical criterion + 1 urologic criterion |

## Dr. Septimus's Annotations

The IDSA guidelines recommend against antimicrobials in older adults with cognitive impairment and delirium in the absence of localized genitourinary symptoms or other systemic signs of infection. [Clin Infect Dis. 2019;68(10):1611-1615] This recommendation was supported by the recent article reviewed in May 2024 ID Watch. [ Bacteremia From a Presumed Urinary Source in Hospitalized Adults With Asymptomatic Bacteriuria [JAMA Network Open. 2024;7: e242283] However, many hospitalized patients, especially older adults, often present to the ED with nonspecific symptoms like fever, hypotension, and delirium in the setting of abnormal urine tests. Because of the diagnostic uncertainty in these cases, frontline clinicians consider these patients to be symptomatic and often treat them with antimicrobials for UTI. The JAMA Network Open paper reviewed in May makes it clear for patients who have either have altered mentation or have dementia and cannot attest to having specific signs or symptoms of UTI, clinicians should assess for SIRS, leukocytosis, and pyuria when deciding who may possibly benefit from empiric antibiotic treatment. If the patient with ASB does not have systemic signs of infection, they have a very low risk of bacteremia from a urinary source. The investigators in this article also discussed current UTI and ASB guidelines using 100,000 CFU/mL as the cutoff for diagnosing bacteriuria. A study in 2013 suggested that lower counts of E coli in midstream urine in symptomatic patients may be predictive of clinically significant bacteriuria/UTI, not contamination. [N Engl J Med. 2013;369(20):1883-1891]

This was a retrospective observational study, and they were limited in assessment of symptoms and signs of UTI by chart review. Their findings are primarily descriptive and should be interpreted with caution.

## BOTTOM LINE

**The authors in this study's approach led to the reclassification of bacteriuric patients with constitutional symptoms (e.g., fever) or those unable to provide symptom data (delirium) from ASB to BUS. Patients with BUS do not necessarily need antimicrobial treatment for bacteriuria but may benefit from additional evaluation or monitoring.**

# Preventing New Gram-negative Resistance Through Beta-lactam De-escalation in Hospitalized Patients With Sepsis: A Retrospective Cohort Study

Clin Infect Dis published online June 6, 2024 (*article suggested by Jamie Thomas*)
doi.org/10.1093/cid/ciae253

This is a retrospective cohort study enrolling patients with sepsis who were treated with at least 3 consecutive days of β-lactam (BL) antibiotics, the first 2 days of which were with a broad-spectrum BL defined as a spectrum score (SS) of ≥7. See below

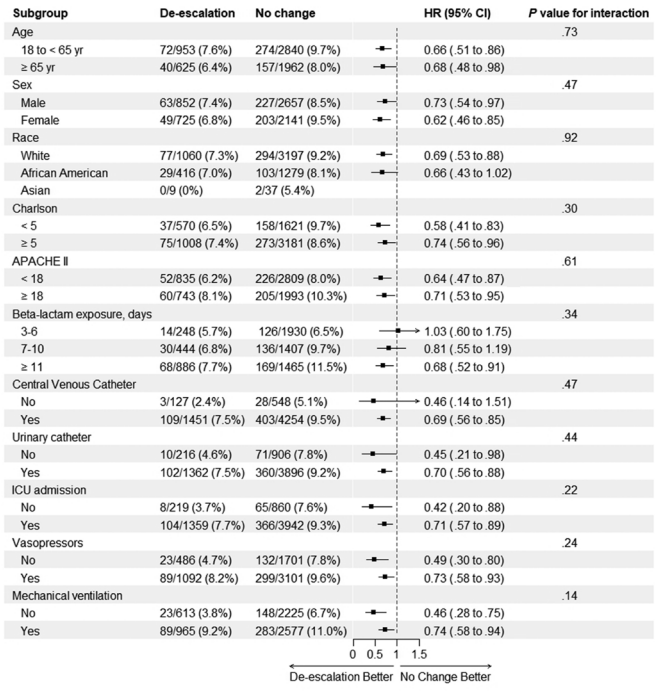
**Appendix 1: Modified Antibiotic Spectrum Index (ASI)**

| Antibiotic | MSSA | MRSA | *Enterococcus* | VRE | DRSP | *Moraxella, H. flu* | *E. coli, Klebsiella* | ESBL | CRE | *Citrobacter, Enterobacter, Serratia* | *Pseudomonas* | MDRO | Anaerobes | *B. fragilis* | Atypicals | Spectrum Score |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Oxacillin | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| Dicloxacillin | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1** |
| Amoxicillin | 0 | 0 | 1 | 0 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1.5** |
| Ampicillin | 0 | 0 | 1 | 0 | 0 | 0 | 0.5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **1.5** |
| Cephalexin | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **2** |
| Penicillin | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **2** |
| Aztreonam | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | **3** |
| Cefazolin | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **3** |
| Cefdinir | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | **3** |
| Ceftazidime | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 1 | 0 | 0 | **4** |
| Ceftriaxone | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | **5** |
| Amox/clav | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 0 | **6** |
| **Pivotal beta-lactam antibiotics** | | | | | | | | | | | | | | | | |
| **Amp/sulb** | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | **7** |
| **Cefepime** | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | **7** |
| **Ceftaroline** | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | **7** |
| **Ceftol/tazo** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | **8** |
| **Ceftaz/avi** | 0 | 0 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | 0 | **8** |
| **Pip/tazo** | 1 | 0 | 1 | 0 | 0 | 1 | 1 | 0 | 0 | 1 | 1 | 0 | 1 | 1 | 0 | **8** |
| **Ertapenem** | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 0 | **9** |
| **Meropenem** | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | **10** |
| **Mero/vabor** | 1 | 0 | 0 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 0 | **11** |
| **Imipenem** | 1 | 0 | 1 | 0 | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 0 | **11** |

MSSA = methicillin-sensitive *Staphylococcus aureus*, MRSA = methicillin-resistant *Staphylococcus aureus*, VRE = vancomycin-resistant *Enterococcus*, DRSP = Drug-resistant *Streptococcus pneumoniae*, H. flu = *Haemophilus influenzae*, ESBL = Extended spectrum beta-lactamase, CRE = Carbapenem-resistant Enterobacterale, MDRO = Multidrug-resistant organism, Amox/clav = amoxicillin/clavulanate; Amp/sulb = ampicillin/sulbactam; Ceftol/tazo = ceftolozane/tazobactam; Ceftaz/avi = ceftazidime/avibactam; Pip/tazo = piperacillin/tazobactam; Mero/vabor = Meropenem/vaborbactam

Patients were grouped into three categories: (1) de-escalation of beta-lactam spectrum score (BLSS), (2) no change in BLSS, or (3) escalation of BLSS. The primary outcome was the isolation of a new drug-resistant Gram-negative bacteria from a clinical culture within 60 days of cohort entry. Fine-Gray proportional hazards regression modeling while accounting for in-hospital death as a competing risk was performed.

644 patients of 7742 (8.3%) patients developed new gram-negative resistance. The mean time to resistance was 23.7 days yielding an incidence rate of 1.85 (95% confidence interval [CI]: 1.71–2.00) per 1000 patient-days. The lowest incidence rate was observed in the de-escalated group 1.42 (95% CI: 1.16–1.68) per 1000 patient-days. Statistically significant reductions in the development of new gram-negative resistance were associated with BL de-escalation compared to no-change (hazards ratio (HR) 0.59 [95% CI: .48–.73]).



## Dr. Septimus's Annotations

Antibiotic de-escalation is a fundamental stewardship approach that attempts to balance the need for early administration of broad-spectrum antibiotics in severely ill patients with a plan to reduce the risk of subsequent antibiotic resistance by narrowing the spectrum of antibiotics and/or discontinuing antibiotics as soon as possible if appropriate. This practice is recommended by several clinical practice guidelines. [Intensive Care Med 2020; 46:245–65; Clin Infect Dis 2016; 62:e51–77] Shorter duration of antibiotics have proven to be as effective as longer duration for common infections. Observational studies have suggested shorter durations of antibiotic therapy has been associated with a decreased risk of resistance development. [BMC Infect Dis 2014; 14:13; Annal Intensive Care 2017; 7:72] Whether antibiotic de-escalation reduces the risk of subsequent antibiotic resistance is uncertain. This study sought to determine if BL antibiotic de-escalation is associated with decreased risk of new Gram-negative resistance in hospitalized patients with sepsis. This study in fact suggests that de-escalation is associated with a reduced risk of developing new resistance in clinically relevant cultures within 60 days of BL initiation compared to no change in BL spectrum. Designation of de-escalation, escalation, or no change was based on a patient's entire BL exposure profile following initiation of broad-spectrum therapy and not based only on the early, initial phase of treatment as commonly reported (e.g., comparing BLSS on day 2 vs day 4). They also found the magnitude and significance of antibiotic de-escalation on reducing the risk of gram-negative resistance was enhanced the longer patients are exposed to BLs. The average time to resistance development in our study was 23.7 days (standard deviation 15.0 days). This supports their previous work, which found an association between each additional day of exposure to antipseudomonal BLs and the development of new resistance, a relationship that proved to be linear with each additional day of exposure up to >21 days [Pharmacotherapy 2019; 39:261–70]. This finding also suggests that de-escalation may not be associated with a reduced risk of gram-negative resistance when shorter courses of BL therapy are administered.

**"This study... suggests that de-escalation is associated with a reduced risk of developing new resistance in clinically relevant cultures within 60 days of BL initiation..."**

The time frame for this study is 2010– 2017 and may not represent the change in antibiotic utilization patterns that occurred during and after Covid-19 pandemic. Their data set did not include any possible antibiotic exposures or any relevant microbiologic data from hospitals outside our system that the patients may have encountered during the study period. Lastly their reliance on ICD-9-CM and ICD-10-CM codes and the retrospective nature of their design may lead to misclassification bias and confounding.

### BOTTOM LINE

**De-escalation was associated with a reduced risk of new gram-negative resistance compared to no change in BL spectrum in patients hospitalized with sepsis. Clinicians should increase their efforts to de-escalate broad-spectrum BL therapy and limit exposure by treating common infections for the proper duration.**

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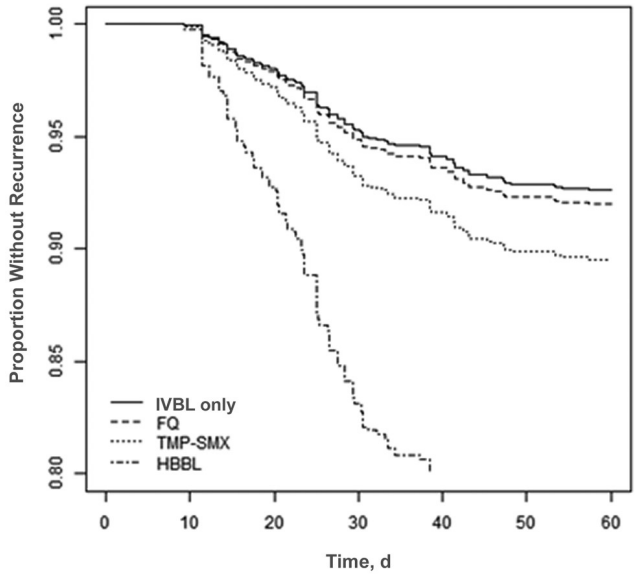
## Real-World Effectiveness of Intravenous and Oral Antibiotic Stepdown Strategies for Gram-Negative Complicated Urinary Tract Infection With Bacteremia

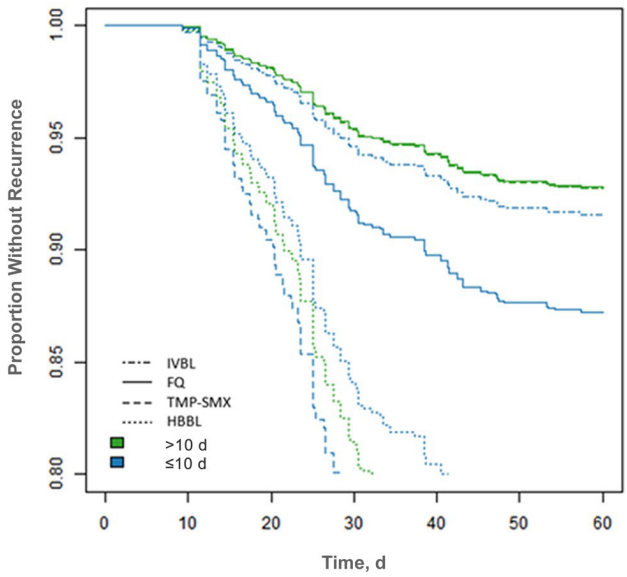
OFID published online April 4, 2024
doi.org/10.1093/ofid/ofae193

This is a multicenter observational cohort study. They simulated a 4-arm registry trial using a causal inference method to compare effectiveness of the following regimens for GN-BSI/cUTI: complete course of an intravenous β-lactam

(IVBL) or oral stepdown therapy within 7 days using fluoroquinolones (FQs), trimethoprim-sulfamethoxazole (TMP-SMX), or high bioavailability β-lactams (HBBLs) (amoxicillin, amoxicillin-clavulanate, and cephalexin). Oral antibiotic dosing and duration was per prescriber choice. However, the investigators prespecified a descriptive analysis of patients who received bacteremia dosing per Delphi expert consensus recommendations [Open Forum Infect Dis 2021; 8:ofab434] (with appropriate adjustments for renal impairment; all taken orally): ciprofloxacin (750 mg every 12 hours), levofloxacin (750 mg every 24 hours), TMP-SMX (5 mg/kg every 12 hours; e.g., approximately 2 double-strength tablets every 12 hours for a 70-kg patient), amoxicillin (1000 mg every 8 hours), amoxicillin/clavulanic acid (875– 1000 mg every 8 hours), and cephalexin (1000 mg every 6 hours). Adults treated between January 2016 and December 2022 for E coli or Klebsiella species GN-BSI/cUTI were included. Male and female patients with cUTI, defined by the presence of structural or functional urologic abnormalities, were included in the initial screening cohort. [excluded in earlier study] Propensity weighting was used to balance characteristics between groups. The 60-day recurrence was compared using a multinomial Cox proportional hazards model with probability of treatment weighting.

Of 2571 patients screened, 759 (30%) were included. Characteristics were similar between groups. However, patients receiving definitive IVBLs had more comorbid conditions, urologic abnormalities, and ESBL–producing isolates than the oral stepdown groups. The median time to oral switch (interquartile range) was 3 (3–4) days, and the median total duration of antibiotic treatment was 14 (11–15) days. More patients treated with FQs received consensus-recommended dosing compared with those treated with TMP-SMX (69% vs 4%; P < .001) or HBBLs (69% vs 43%; P < .001). Compared with IVBLs, they did not observe a difference in effectiveness for FQs (adjusted hazard ratio, 1.09 [95% confidence interval, .49–2.43]) or TMP-SMX (1.44 [.54–3.87]), and the effectiveness of TMP-SMX/FQ appeared to be optimal at durations of >10 days. A 7-day course for GN-BSI from a UTI source are most effective when the patient either lacks structural or functional urologic abnormalities or has source control. HBBLs were associated with nearly 4-fold higher risk of recurrence (adjusted hazard ratio, 3.83 [95% confidence interval, 1.76–8.33]), which was not mitigated by longer treatment durations. Most HBBLs (67%) were not optimally dosed for bacteremia.

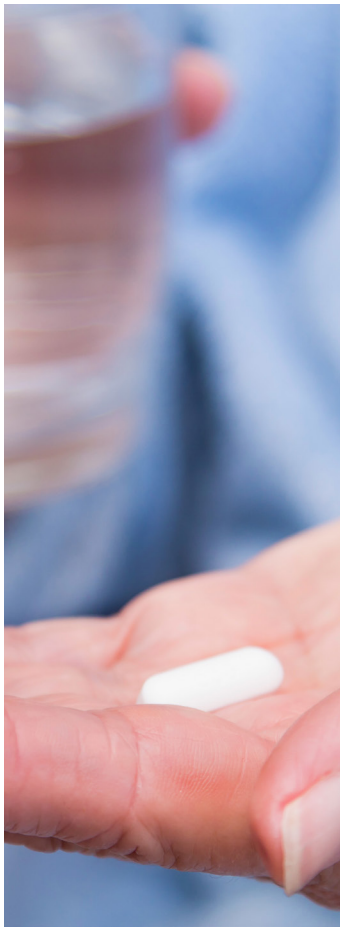



## Dr. Septimus's Annotations

This real-world study suggests that oral stepdown therapy with FQs or TMP-SMX have similar effectiveness as IVBLs. HBBLs were associated with higher recurrence rates adjusted for duration, but dosing was suboptimal. Further data are needed to define optimal dosing and duration to mitigate treatment failures. In March 2024, ID Watch reviewed a paper also in OFID entitled "Oral β-Lactams, Fluoroquinolones, or Trimethoprim-Sulfamethoxazole for Definitive Treatment

of Uncomplicated Escherichia coli or Klebsiella Species Bacteremia From a Urinary Tract Source." The prior study only included adults treated for uncomplicated E coli or Klebsiella species bacteremia of urinary tract origin who were transitioned to an oral regimen after ≤4 days of effective intravenous antibiotics. FQs and TMP-SMX had similar effectiveness. However, HBBLs were associated with higher recurrence rates but suboptimal dosing may have contributed to these results similar to the current paper [same authors]. Of note in the current publication, they observed no significant difference in recurrence risk for short versus long duration with FQ stepdown, but the recurrence risk for short-course TMP-SMX stepdown was much higher. These findings, particularly for TMP-SMX, raise the question of how best to optimize dosing and duration for effectiveness while limiting toxicity. Further studies are needed to clarify whether interventions such as higher dosing combined with shorter duration could optimize outcomes for TMP-SMX stepdown therapy. cUTI represents a heterogeneous group and their findings might apply differently to various subgroups. In addition, their ability to evaluate the effectiveness of HBBLs was limited by current susceptibility testing practices, including lack of granular MICs, use of surrogate intravenous antibiotics to infer susceptibility of oral agents, and lack of systemic susceptibility breakpoints for oral BLs.



**BOTTOM LINE**

**This study demonstrated that oral FQs and TMP-SMX are similar in effectiveness to IVBL therapy for GN-BSI/cUTI and should be considered for oral therapy transitions when the isolate is susceptible. TMP-SMX effectiveness might be optimized with total durations longer than 10 days, although further studies are needed. Conversely, HBBL stepdown therapy was associated with higher recurrence rates regardless of treatment duration.**

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## Impact of removing ESBL status labelling from culture reports on the use of carbapenems for non-bacteraemic patients diagnosed with ESBL-positive urinary tract infections

J Antimicrob Chemother published online May 2024
doi.org/10.1093/jac/dkae135

In this retrospective cohort study, across a network of 7 community hospitals, ESBL designation was suppressed after September 2022 from automated susceptibility system, still reporting resistant MICs and MICs of susceptible cefepime and piperacillin/tazobactam isolates in consideration for continued use based on 2023 IDSA guidelines of ESBL and simple cystitis if clinically improving.

Investigators found a significant decrease in the rate of carbapenem prescribing for initial definitive treatment of ESBL Enterobacterales UTI after susceptibilities released for at least 48 hours in non-bacteremic patients 6 months immediately pre- and post-removal (156/199 (78%) vs 93/153 (61%); P<0.01) which was a 40% decrease (P<0.01) in total days of therapy with carbapenem as initial definitive therapy. No significant difference in secondary endpoints of clinical cure rate, infection relapse, readmission, all cause in hospital mortality, length of stay or rate of guideline-compliant therapy.

### Dr. Septimus's Annotations

Removing ESBL status labels from microbiology lab results significantly reduced the rate of carbapenem prescribing and increased the rate of non-carbapenem agent use as initial definitive therapy for non-bacteremic hospitalized patients with ESBL-positive UTI, with no impact on clinical cure rates, infection relapse, readmission

or mortality. There was not a single agent that drove the overall increase in carbapenem-sparing treatment, but rather modest increases in the use of cefepime, piperacillin/tazobactam, trimethoprim/ sulfamethoxazole and levofloxacin prescribing contributed to the overall effect. Although cefepime and piperacillin/tazobactam use for complicated infections caused by ESBL-positive organisms is discouraged, they can be used for the treatment of uncomplicated UTIs (seen in about half of the cases here), and are currently recommended by the IDSA guidelines for uncomplicated cystitis if clinical improvement has occurred and the organism is susceptible with a low MIC. [Clin Infect Dis 2023; published online July 18, 2023] In a multicenter observational study comparing clinical outcomes of adults hospitalized with ESBL-producing pyelonephritis who were receiving piperacillin/tazobactam versus carbapenems the investigators demonstrated piperacillin/tazobactam was a reasonable alternative to carbapenems for the management of ESBL-producing pyelonephritis. [Clin Infect Dis 2020 Nov 5;71: e331-e337] In June 2024 ID Watch reviewed a paper in Lancet Infect Dis titled "Carbapenem use in extended-spectrum cephalosporin-resistant Enterobacterales infections in US hospitals and influence of IDSA guidance: a retrospective cohort study." This highlighted 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 including piperacillin/tazobactam. Taken together, these studies provide evidence that for non bacteremic UTIs due to ESBL-positive organism that narrower-spectrum agents which retain in-vitro activity can be used in place of carbapenems.

Limitations of this current study include challenges with lack of clear documentation delineating cystitis vs pyelonephritis in about ¼ of infections limiting understanding of appropriateness of therapy and comfort level with non-carbapenems prescribing. It is unclear how this stewardship tactic would affect infection prevention isolation practices.

**BOTTOM LINE**

**Removing ESBL status labels from urine culture reports in non-bacteremic patients and just reporting out MICs was shown to reduce use of carbapenems for targeted treatment of UTIs without significant impact in clinical outcomes.**

## Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis

The BLING III Randomized Clinical Trial.
published online June 12, 2024
doi:10.1001/jama.2024.9779

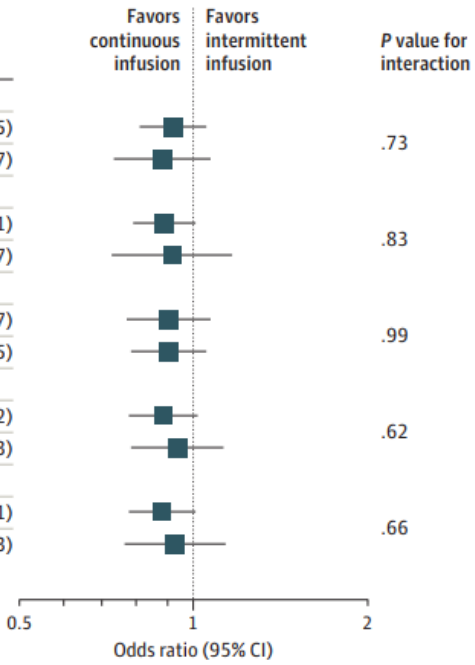
## Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock

ock A Systematic Review and Meta-Analysis
published online June 12, 2024
doi:10.1001/jama.2024.9803

The first article (*Continuous vs Intermittent β-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis*) is the β-Lactam Infusion Group (BLING) III trial which is a well-conducted, open-label, randomized trial in 104 ICUs in 7 countries. Patients received continuous infusions (with loading dose) of β-lactam antibiotics (piperacillin-tazobactam or meropenem) vs intermittent infusion with same antibiotics. The mean age was 59 years and 70% received vasopressors within the 24 hours prior to randomization. The respiratory tract was the most common source of sepsis, followed by intra-abdominal infections, with E coli, Klebsiella, Pseudomonas, and MRSA being the most prevalent causative pathogens. All-cause mortality within 90 days after randomization, the primary outcome of the study, occurred in 24.9% of those receiving continuous infusion of beta-lactam antibiotics and in 26.8% of those receiving intermittent infusions. The odds of dying within 90 days was 0.91 for the patients in the continuous group, reflecting a mortality reduction of 1.9%. While lacking statistical significance (P = .08), the investigators conclude that the confidence interval around the effect estimate includes the possibility of a clinically important benefit in the use of continuous infusions in this group of patients. Clinical cure was higher in the continuous compared with the intermittent infusion group 55.7% and 50.0%, respectively; absolute difference, 5.7% [95% CI, 2.4% to 9.1%]). Other secondary outcomes were not statistically different. Only piperacillin-tazobactam and meropenem were studied, and no data were provided for bacterial sensitivity to this empirical treatment.

**Figure 2. Subgroup Analysis of Mortality at Day 90**

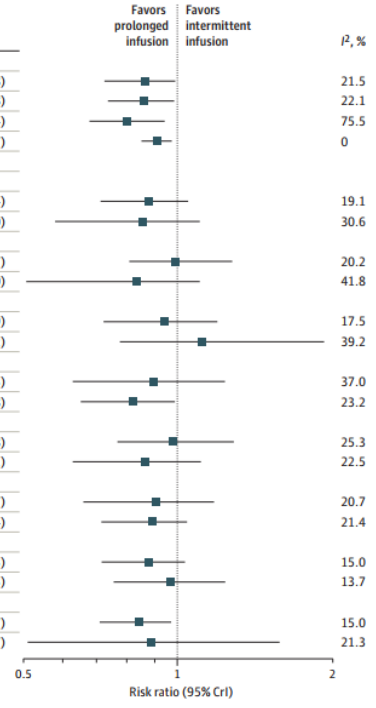
| | Group, No./total (%) | | | |
|---|---|---|---|---|
| | Continuous infusion | Intermittent infusion | Absolute difference, % (95% CI)[a] | Odds ratio (95% CI)[b] |
| Pulmonary infection | | | | |
| Yes | 593/2178 (27.2) | 647/2249 (28.8) | -1.7 (-5.2 to 1.9) | 0.92 (0.81 to 1.05) |
| No | 271/1296 (20.9) | 292/1258 (23.2) | -2.1 (-6.0 to 1.7) | 0.88 (0.73 to 1.07) |
| β-Lactam antibiotic | | | | |
| Piperacillin-tazobactam | 667/2749 (24.3) | 722/2746 (26.3) | -2.2 (-5.3 to 1.0) | 0.89 (0.79 to 1.01) |
| Meropenem | 183/696 (26.3) | 203/714 (28.4) | -1.7 (-7.0 to 3.7) | 0.92 (0.73 to 1.17) |
| Age, y | | | | |
| <65 | 348/1935 (18.0) | 375/1938 (19.3) | -1.5 (-4.5 to 1.6) | 0.91 (0.77 to 1.07) |
| ≥65 | 516/1539 (33.5) | 564/1569 (35.9) | -2.2 (-6.5 to 2.0) | 0.91 (0.78 to 1.05) |
| Sex | | | | |
| Male | 563/2290 (24.6) | 612/2279 (26.9) | -2.3 (-5.7 to 1.1) | 0.89 (0.78 to 1.02) |
| Female | 301/1184 (25.4) | 327/1228 (26.6) | -1.2 (-5.4 to 3.0) | 0.94 (0.78 to 1.13) |
| APACHE II score | | | | |
| <25 | 543/2599 (20.9) | 610/2661 (22.9) | -2.2 (-5.2 to 0.8) | 0.88 (0.77 to 1.01) |
| ≥25 | 320/872 (36.7) | 328/842 (39.0) | -1.7 (-7.1 to 3.7) | 0.93 (0.76 to 1.13) |




The second article (*Prolonged vs Intermittent Infusions of β-Lactam Antibiotics in Adults With Sepsis or Septic Shock*) is the latest meta-analysis of prolonged vs intermittent infusions of β-lactam antibiotics in critically ill adult patients with sepsis or septic shock including the BLING III trial. They included 18 RCTs of which 17 RCTs contributed to the primary outcome of all-cause 90-day mortality. Because of its size, the BLING III trial contributed 77.1% of patients included in this meta-analysis. The pooled estimated risk ratio (RR) for all-cause 90-day mortality for prolonged infusions of β-lactam antibiotics when compared with intermittent infusions was 0.86 with a 99.1% posterior probability that prolonged infusions reduced 90-day mortality. Prolonged infusions of β-lactam antibiotics were also associated with reduced risk of ICU mortality (RR, 0.84 [95% CrI, 0.70-0.97]) and increase in clinical cure (RR, 1.16 [95% CrI, 1.07-1.31]). No differences were seen in the predefined secondary outcomes of microbiological cure, adverse events, and duration of ICU stay between both groups. Prespecified subgroup analysis did not show a difference between continuous vs intermittent infusions for all-cause 90-day mortality between meropenem vs piperacillin-tazobactam, culture-positive vs culture-negative infection, kidney replacement therapy vs no kidney replacement therapy, lung infection vs other infections, sepsis vs septic shock, or male vs female. In contrast to previous reports highlighting the primary advantage of prolonged infusion over intermittent infusion in gram-negative bacterial infections,

A Primary outcome, subgroup analysis of primary outcome, and secondary outcomes

| Outcomes | No. of trials | No. of participants | Risk ratio (95% CrI) | $I^2$, % |
|---|---|---|---|---|
| Primary outcome: all-cause 90-d mortality | | | | |
| Vague priors | 17 | 9014 | 0.86 (0.72 to 0.98) | 21.5 |
| Semi-informative priors | 17 | 9014 | 0.86 (0.73 to 0.98) | 22.1 |
| Hartung-Knapp-Sidik-Jonkman[a] | 17 | 9014 | 0.80 (0.67 to 0.94) | 75.5 |
| DerSimonian-Laird[a] | 17 | 9014 | 0.91 (0.85 to 0.97) | 0 |
| Subgroup analysis of the primary outcome | | | | |
| Study β-lactam antibiotic | | | | |
| Meropenem | 10 | 2568 | 0.88 (0.71 to 1.04) | 19.1 |
| Piperacillin-tazobactam | 7 | 6009 | 0.86 (0.58 to 1.10) | 30.6 |
| Microbiologic infection | | | | |
| Culture-positive | 8 | 4060 | 0.99 (0.80 to 1.27) | 20.2 |
| Culture-negative | 7 | 4300 | 0.83 (0.51 to 1.10) | 41.8 |
| Gram infection | | | | |
| Negative | 7 | 2859 | 0.94 (0.72 to 1.19) | 17.5 |
| Positive | 6 | 1597 | 1.11 (0.77 to 1.92) | 39.2 |
| Kidney replacement therapy | | | | |
| Yes | 4 | 802 | 0.90 (0.62 to 1.23) | 37.0 |
| No | 13 | 7580 | 0.82 (0.65 to 0.98) | 23.2 |
| Infection | | | | |
| Lung | 8 | 5077 | 0.98 (0.76 to 1.28) | 25.3 |
| Other | 7 | 3088 | 0.86 (0.62 to 1.11) | 22.5 |
| Sepsis vs septic shock | | | | |
| Sepsis | 7 | 2565 | 0.91 (0.65 to 1.17) | 20.7 |
| Shock | 8 | 5782 | 0.89 (0.71 to 1.04) | 21.4 |
| Sex | | | | |
| Male | 10 | 5495 | 0.88 (0.71 to 1.03) | 15.0 |
| Female | 10 | 2923 | 0.97 (0.75 to 1.23) | 13.7 |
| Secondary outcomes | | | | |
| ICU mortality | 15 | 8967 | 0.84 (0.70 to 0.97) | 15.0 |
| Adverse events | 4 | 7761 | 0.89 (0.51 to 1.57) | 21.3 |



Dr. Septimus's Annotations

this current meta-analysis found no difference between gram-negative and gram-positive infections.

β-Lactam administration via prolonged (with an infusion time of 4 hours) or continuous infusion will lead to sustained concentrations throughout the dosing interval, longer time above MIC, and improved bacterial eradication. In sepsis, physiologic changes have pharmacokinetic pharmacodynamic impact, including increased cardiac output leading to increased drug clearance, and leaky capillaries leading to an increased volume of distribution. Both changes can result in lower antimicrobial plasma concentrations. Multiple meta-analyses have reported reduced short-term mortality with continuous infusion of β-lactam antibiotics. [Am J Respir Crit Care Med. 2016; 194:681-691; Lancet Infect Dis. 2012018; 18:1080] However, the MERCY trial published in 2023 found a nonsignificant 2% reduction in absolute 28-day mortality rate with continuous infusion of meropenem. [JAMA. 2023; 330:141-151]

The current BLING III trial was a well-conducted, open-label, randomized trial comparing patients receiving continuous infusions with patients receiving intermittent infusions (with loading dose) of β-lactam antibiotics (piperacillin-tazobactam or meropenem). All-cause mortality within 90 days after randomization, the primary outcome of the study, occurred in 24.9% of those receiving continuous infusion of β-lactam antibiotics and in 26.8% of those receiving intermittent infusions. Clinical cure was higher in the continuous compared with the intermittent infusion group (1930/3467 [55.7%] and 1744/3491 [50.0%], respectively; absolute difference, 5.7% [95% CI, 2.4% to 9.1%]). Other secondary outcomes were not statistically different. In the latest meta-analysis published alongside the BLING III trial, they compared prolonged vs intermittent infusions of β-lactam antibiotics in critically ill adult patients with sepsis or septic shock. The pooled estimated risk ratio (RR) for all-cause 90-day mortality for prolonged infusions of β-lactam antibiotics when compared with intermittent infusions was 0.86 (95% credible interval [CrI], 0.72- 0.98), with a 99.1% posterior probability that prolonged infusions reduced 90-day mortality. Similarly, prolonged infusions of β-lactam antibiotics were also associated with reduced risk of ICU mortality (RR, 0.84 [95% CrI, 0.70-0.97]) and increase in clinical cure (RR, 1.16 [95% CrI, 1.07-1.31]). No differences were seen in the predefined secondary outcomes of microbiological cure, adverse events, and duration of ICU stay between both groups.

**BOTTOM LINE**

**Although the BLING III trial did not reach statistical significance for mortality, clinical cure was higher in the continuous compared with the intermittent infusion. Despite the mixed result of the BLING III trial, I think the current evidence still favors prolonged infusions of β-lactam antibiotics (after loading dose) being associated with a reduced risk of death in critically ill adult patients with sepsis or septic shock compared with intermittent infusions.**

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## Counting the Cost of Daptomycin Versus Vancomycin in Hospitalized Patients: A Cost Minimization Analysis

OFID published online April 18, 2024
doi.org/10.1093/ofid/ofae217

Investigators conducted a multi-center, retrospective cost minimization study that involved 4 hospitals in the southeast US. All adult hospitalized patients who received at least 1 dose of intravenous (IV) vancomycin were included in the analysis. Each site contributed at least 50 patients, randomly selected. Patients who received vancomycin with an indication for treatment of a respiratory tract infection, central nervous system infection or surgical site infection prophylaxis were assigned the "vancomycin group". All others were included in the "daptomycin-eligible group". All associated costs for providing both daptomycin and vancomycin were determined and included: cost of drug, estimated cost of vancomycin serum concentration, creatine kinase measurement, drug preparation, drug administration, estimated time of pharmacist review, cost of adverse effects related to acute kidney injury (AKI).

A total of 239 patients received one dose of IV vancomycin; 144 of which were eligible to receive daptomycin; 95 were not. Among 239 patients, a total of 2369.72 grams of vancomycin was prescribed for 1147 days. Twenty-four patients developed AKI likely associated with vancomycin, with 5 patients experiencing a total of 20 ICU days and 4 patients requiring renal replacement therapy. Total treatment cost for 239 patients to receive vancomycin was $151,495. The total cost of treatment for 144 to receive daptomycin and 95 ineligible daptomycin patients to receive vancomycin was $114,373, resulting in an excess cost of $37,122. This equated to a potential cost savings of $155.32 per patient. Additionally, total pharmacist time was decreased from 120 hours to 45.44 hours.

Vancomycin remains a mainstay of therapy in many institutions for the treatment of serious gram-positive infections. While there is clinical evidence to support the change from trough-based dosing and monitoring to an AUC-based approach, there are logistical and financial challenges to widespread implementation of AUC-based monitoring, including time required, necessity for widespread training of clinicians responsible for dosing, and workflow impact of the switch on prescribers [Antimicrob Steward Healthc Epidemiol 2022; 2: e24.]. However, vancomycin resistance has been rare within MRSA over many decades despite ubiquitous use and overuse in many institutions. As facilities evaluate these changes to dosing but not resistance development, the future utility and use of vancomycin should be considered. If institutions switch to daptomycin therapy [or linezolid or ceftaroline] as the primary anti-MRSA workhorse, the development of resistance long term should be monitored closely.

**BOTTOM LINE**

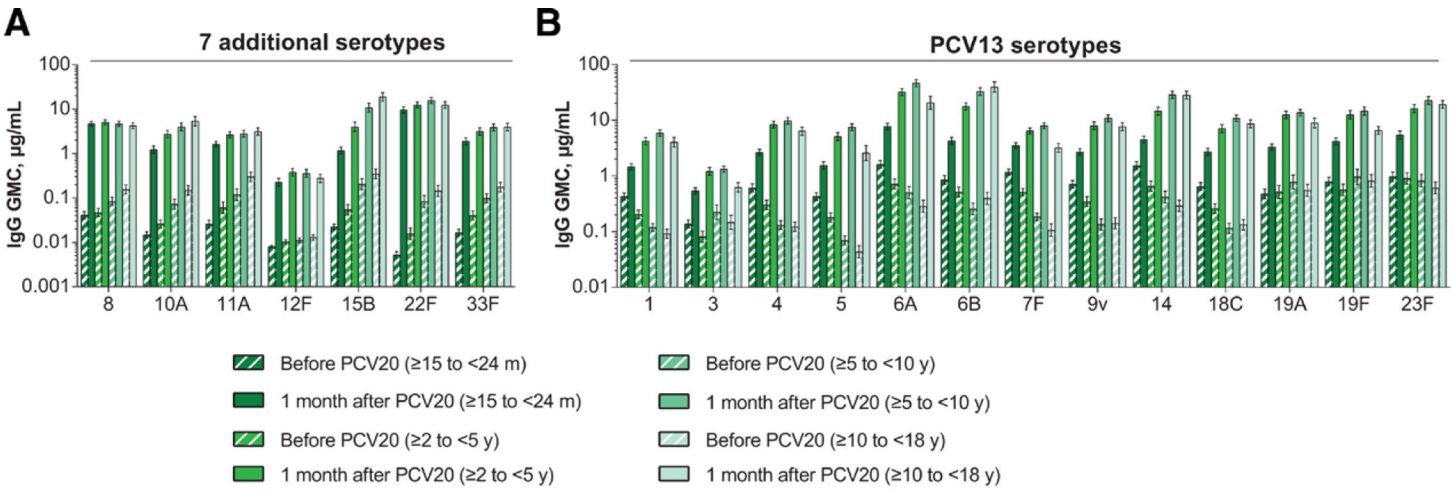
**Use of daptomycin in lieu of vancomycin may reduce cost and adverse effects compared to vancomycin. Daptomycin should not be used to treat MRSA pneumonia.**

20

## A Phase 3, Single-arm Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine in Healthy Children 15 Months Through <18 Year of Age

Pediatr Infect Dis J 2024;43:574–581
DOI: 10.1097/INF.0000000000004318

This was a phase 3 single armed study to assess the safety and immunogenicity of PCV20 in children. Children (≥15 months–<18 years of age) received 1 dose of PCV20. Children <5 years of age had ≥3 prior doses of PCV13; children ≥5 years were recruited regardless of previous PCV receipt. Serotype-specific IgG concentrations and opsonophagocytic activity (OPA) titers were measured before and 1 month after PCV20. Local reactions and systemic events, adverse events (AEs), serious AEs, and newly diagnosed chronic medical conditions were collected.



| IgG GMFRs from before to 1 month after PCV20 | | | | | | | |
|---|---|---|---|---|---|---|---|
| Serotype | 8 | 10A | 11A | 12F | 15B | 22F | 33F |
| ≥15 to <24 months | 113.4 | 83.2 | 62.7 | 27.9 | 52.1 | 1847.7 | 113.5 |
| ≥2 to <5 years | 107.0 | 106.7 | 43.6 | 36.6 | 73.3 | 796.2 | 78.3 |
| ≥5 to <10 years | 55.2 | 54.8 | 23.6 | 31.9 | 52.6 | 187.7 | 39.3 |
| ≥10 to <18 years | 27.3 | 35.9 | 10.5 | 21.4 | 53.8 | 86.2 | 22.4 |

| IgG GMFRs from before to 1 month after PCV20 | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Serotype | 1 | 3 | 4 | 5 | 6A | 6B | 7F | 9V | 14 | 18C | 19A | 19F | 23F |
| ≥15 to <24 months | 3.4 | 3.9 | 4.3 | 3.6 | 4.8 | 5.0 | 3.0 | 3.8 | 2.9 | 4.2 | 6.9 | 5.2 | 5.6 |
| ≥2 to <5 years | 20.6 | 14.9 | 27.6 | 28.2 | 44.9 | 34.5 | 12.5 | 23.0 | 22.2 | 27.2 | 24.1 | 22.3 | 17.9 |
| ≥5 to <10 years | 49.4 | 5.9 | 74.1 | 107.0 | 91.9 | 127.9 | 42.9 | 80.3 | 68.4 | 93.7 | 17.6 | 15.2 | 27.6 |
| ≥10 to <18 years | 44.2 | 4.3 | 52.0 | 59.3 | 72.5 | 99.5 | 30.0 | 54.2 | 96.7 | 64.5 | 16.2 | 8.0 | 31.4 |

831 were vaccinated, and 819 (>97%) completed all study visits. Local reactions and systemic events were mostly mild to moderate in severity. No serious AEs were considered PCV20-related. IgG geometric mean fold rises (GMFRs) from before to 1 month after PCV20 ranged from 27.9–1847.7 (7 additional serotypes) and 2.9–44.9 (PCV13 serotypes) in children <5 years of age, and 10.5–187.7 (7 additional serotypes) and 4.3–127.9 (PCV13 serotypes) in children ≥5 years old. OPA GMFRs from before to 1 month after PCV20 ranged from 12.4–983.6 to 2.8–52.9 in children <5 years of age and from 11.5–499.0 to 5.3–147.9 in children ≥5 years of age.

### Dr. Septimus's Annotations

In this phase 3 study, robust immune responses were elicited, with increased IgG concentrations and/or OPA titers measured 1 month after PCV20 vaccination for the 7 additional serotypes and 13 matched serotypes across age groups, suggesting potential for PCV20 to provide extended protection for children ≥15 months–<18 years of age against pneumococcal disease caused by these serotypes. IgG concentrations for serotype 12F were generally lower than for the other 7 additional serotypes after PCV20 across age groups. This finding is not anticipated to be clinically meaningful. Children <5 years of age who had not received previous PCV13 or who were vaccinated with other PCVs were not evaluated. Given the limited duration of protection and potential for hyporesponsiveness with PPSV23, and the expanded serotype protection provided by PCV20 compared with PCV13, PCV20 could be particularly useful in children at high risk of pneumococcal disease. Recent US Advisory Committee on Immunization Practices (ACIP) recommendations that PCV20 be given to children at increased risk of pneumococcal disease or partially vaccinated/unvaccinated children, regardless of risk.

**BOTTOM LINE**

**A PCV20 single dose elicited robust IgG and OPA immune responses to the 7 additional serotypes and PCV13 serotypes in children <5 years of age who had received 3 prior doses of PCV13 and in those ≥5 years regardless of prior PCV13 immunization status.**

21

## FDA Approves a Pneumococcal 21-valent Conjugate Vaccine (CAPVAXIVE) for Prevention of Invasive Pneumococcal Disease and Pneumococcal Pneumonia in Adults

June 17, 2024

This new vaccine is specifically designed for adults and covers serotypes responsible for approximately 84% of invasive pneumococcal disease in adults 50 years of age and older. The FDA approved this vaccine for active immunization for the prevention of invasive disease and pneumonia caused by S pneumoniae serotypes 3, 6A, 7F, 8, 9N, 10A, 11A, 12F, 15A, 15B, 15C, 16F, 17F, 19A, 20A, 22F, 23A, 23B, 24F, 31, 33F and 35B in individuals 18 years of age and older.

The approval was in part related to the STRIDE-3 (NCT05425732) trial, which was a double-blind, Phase 3 study which evaluated CAPVAXIVE compared to PCV20 in individuals 18 years of age and older who had not previously received

a pneumococcal conjugate vaccine. Participants 50 years of age and older were enrolled in cohort 1 (n=2,362), and participants 18 through 49 years of age were enrolled in cohort 2 (n=300). Participants were randomized to receive a single dose of either CAPVAXIVE or PCV20. Results from the study include:

- In adults 50 years of age and older (cohort 1), CAPVAXIVE was non-inferior to PCV20 for the 10 serotype polysaccharides shared with both vaccines (3, 6A, 7F, 8, 10A, 11A, 12F, 19A, 22F, 33F), as assessed by serotype-specific OPA geometric mean titers (GMTs) at 1-month postvaccination;
    - CAPVAXIVE was superior to PCV20 for 10 of 11 serotype polysaccharides included in CAPVAXIVE but not in PCV20 (9N, 15A, 16F, 17F, 20A, 23A, 23B, 24F, 31, 35B), as assessed by serotype-specific OPA GMTs 1-month postvaccination and the proportions of patients with a greater than or equal to four-fold increase in OPA from prevaccination to 1-month postvaccination;

### Dr. Septimus's Annotations

The CDC Advisory Committee on Immunization Practices (ACIP) is expected to meet later this month to discuss and make recommendations for the use of CAPVAXIVE in adults. CAPVAXIVE includes eight unique serotypes not covered by other currently approved pneumococcal vaccines.

**BOTTOM LINE**

**CAPVAXIVE may offer an advantage over PCV 20 for adults ≥50 years of age.**

22

## Delays to Antibiotics in the Emergency Department and Risk of Mortality in Children With Sepsis

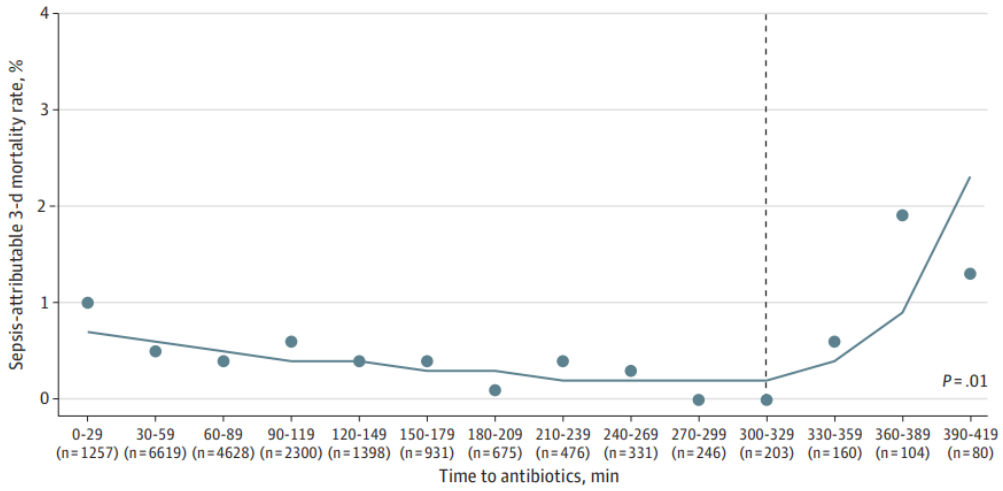
JAMA Network Open. 2024;7(6):e2413955.
doi:10.1001/jamanetworkopen.2024.13955

This was a retrospective cohort study which captured data from 51 US children's hospitals in the Improving Pediatric Sepsis Outcomes collaborative. Participants included patients aged 29 days to less than 18 years with sepsis recognized within 1 hour of emergency department arrival, from January 1, 2017, through December 31, 2021. Piecewise regression was used to identify the inflection point for sepsis-attributable 3-day mortality, and logistic regression was used to evaluate odds of sepsis-attributable mortality after adjustment for potential confounders. The primary outcome was sepsis-attributable 3-day mortality. Sepsis-attributable 30-day mortality was a secondary outcome.

A total of 19,515 cases (median [IQR] age, 6 [2-12] years) were included. The median (IQR) time to antibiotic administration was 69 (47-116) minutes. The estimated time to antibiotic administration at which 3-day sepsis-attributable mortality increased was 330 minutes. Patients who received an antibiotic in less than 330 minutes (19,164 patients) had sepsis-attributable 3-day mortality of 0.5% (93 patients) and 30-day mortality of 0.9% (163 patients). Patients who received antibiotics at 330 minutes or later (351 patients) had 3-day sepsis-attributable mortality of 1.2% (4 patients), 30-day mortality of 2.0% (7 patients), and increased adjusted odds of mortality at both 3 days (odds ratio, 3.44; 95% CI, 1.20-9.93; P = .02) and 30 days (odds ratio, 3.63; 95% CI, 1.59-8.30; P = .002) compared with those who received antibiotics within 330 minutes. Of the 2054 patients with bacteremia who received an antibiotic within 180 minutes of ED arrival (10.5%), the estimated inflection point of time to antibiotic administration at

which 3-day sepsis-attributable mortality changed from decreasing to increasing was 90 minutes. Although this finding was not considered statistically significant, the investigators say patients with bacteremia are most likely to benefit from timely antibiotic administration and should be a focus of future research.

Figure 1. Time to Antibiotics and 3-Day Sepsis-Attributable Mortality Among Children With Sepsis




## Dr. Septimus's Annotations

This study found that children with sepsis who received antibiotics more than 5.5 hours after ED arrival had a more than three-fold increase in the odds of sepsis-attributable 3- and 30-day mortality. The Pediatric Surviving Sepsis Campaign International Guidelines for the Management of Septic Shock and Sepsis-Associated Organ Dysfunction recommend antibiotic administration within 1 hour of recognition of septic shock and within 3 hours of recognition of sepsis-associated organ dysfunction without shock. [Pediatr Crit Care Med. 2020;21(2):e52-e106] Of the 2054 patients with bacteremia who received an antibiotic within 180 minutes of ED arrival (10.5%), the estimated inflection point of time to antibiotic administration at which 3-day sepsis-attributable mortality changed from decreasing to increasing was 90 minutes. Although this finding was not considered statistically significant, the investigators say patients with bacteremia are most likely to benefit from timely antibiotic administration and should be a focus of future research. There were exclusions and missing data which may have introduced selection bias. There was a lack of microbiological data. As you can see, mortality rates were very low.

Another challenge is that sepsis has many phenotypes, and we know that prompt recognition, action followed by appropriate responses are key; how to get a consistent and measurable sequence given the tools available today is an ongoing challenge.

### BOTTOM LINE

**While the study does provide new insights into antibiotic timing in pediatric sepsis patients, the optimization of sepsis management should ideally focus on identifying patients with predicted bacterial infection who are likely to deteriorate and need rapid antimicrobial therapy.**

23

## Global antimicrobial resistance and antibiotic use in COVID-19 patients within health facilities: a systematic review and meta-analysis of aggregated participant data

J Infect published online May 14, 2024
doi.org/10.1016/j.jinf.2024.106183

The authors conducted a systematic review to determine the prevalence of antimicrobial resistance (AMR) and antibiotic usage among Covid-19 patients receiving treatment in healthcare facilities. Their search encompassed the PubMed, Web of Science, Embase, and Scopus databases, spanning studies published from December 2019 to May 2023. They utilized random-effects meta-analysis to assess the prevalence of multidrug-resistant organisms (MDROs) and antibiotic use in Covid-19 patients, aligning with both the WHO's priority list of MDROs and the AWaRe list of antibiotic products. Estimates were stratified by region, country, and country income. Meta-regression models were established to identify predictors of MDRO prevalence and antibiotic use in Covid-19 patients.

173 studies involving nearly 900,000 Covid-19 were included in the review. MDROs were observed in 42.9% (95% CI 31.1%-54.5%, I2=99.90%) of Covid-19 patients: 41.0% (95% CI 35.5%-46.6%) for carbapenem-resistant organisms (CRO), 19.9% (95% CI 13.4%-27.2%) for MRSA, 24.9% (95% CI 16.7%-34.1%) for ESBL organisms, and 22.9% (95% CI 13.0%- 34.5%) for VRE, respectively. Overall, 76.2% (95% CI 69.5%-82.9%, I2=99.99%) of Covid-19 patients were treated with antibiotics: 29.6% (95% CI 26.0%-33.4%) with "Watch" antibiotics, 22.4% (95% CI 18.0%-26.7%) with "Reserve" antibiotics, and 16.5% (95% CI 13.3%-19.7%) with "Access" antibiotics. The MDRO prevalence and antibiotic use were significantly higher in low- and middle-income countries than in high-income countries, with the lowest proportion of antibiotic use (60.1% (95% CI 52.1%-68.0%)) and MDRO prevalence (29.1% (95% CI 21.8%-36.4%)) in North America, the highest MDRO prevalence in the Middle East and Africa (63.9% (95% CI 46.6%-81.2%)), and the highest proportion of antibiotic use in South Asia (92.7% (95% CI 90.4%-95.0%)). Most studies were conducted in Europe and Central Asia (n = 81, 46.8%), followed by the Middle East & North Africa (n = 26, 15.0%) and South Asia (n =25, 14.5%). The majority of studies (137, 79.2%) were conducted in tertiary hospitals. Among these, 86 (49.7%) focused exclusively on patients in ICUs. The meta-regression identified antibiotic use and ICU admission as a significant predictor of higher prevalence of MDROs in Covid-19 patients.

Macrolides were the most commonly prescribed category of antibiotics (34.7%), followed by glycopeptides (33.1%) and third-generation cephalosporins (31.5%). The most commonly used antibiotics were azithromycin (46.2%), ceftriaxone (38.3%), and vancomycin (34.7%).

### Dr. Septimus's Annotations

The results underscore the challenge facing global efforts to prevent and control AMR amidst the backdrop of a pandemic. These results serve as a warning to highlight the urgent need to enhance antimicrobial stewardship strategies. There was high heterogeneity in the included studies due to variations in study settings and study design. The study participants of the included studies were biased toward hospitalized patients.

**BOTTOM LINE**

**This comprehensive and systematic assessment of AMR and antibiotic use during the Covid-19 pandemic provides evidence to highlight the global issue of serious AMR.**

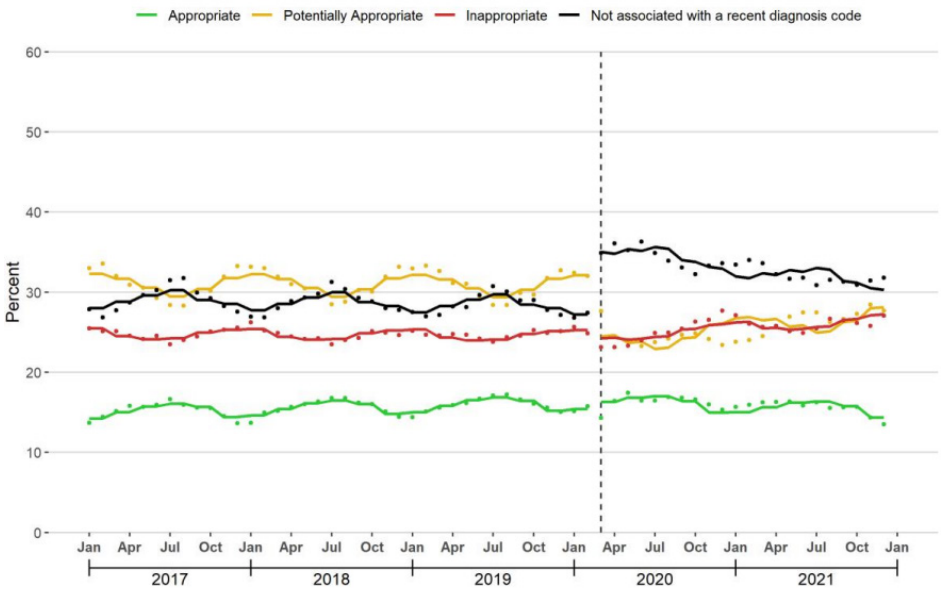
24

## Changes in the Appropriateness of US Outpatient Antibiotic Prescribing After the Coronavirus Disease 2019 Outbreak: An Interrupted Time Series Analysis of 2016–2021 Data

Clin Infect Dis published online April 22, 2024
doi.org/10.1093/cid/ciae135

This was an interrupted time series analysis of Optum's de-identified Clinformatics Data Mart Database, a national commercial and Medicare Advantage claims database. Analyses included prescriptions for antibiotics dispensed to children and adults enrolled during each month during 2017–2021. For each prescription, they applied previously developed antibiotic appropriateness classification scheme to ICD-10 Clinical Modification diagnosis codes on medical claims occurring on or during the 3 days prior to dispensing. Outcomes included the monthly proportion of antibiotic prescriptions that were inappropriate and the monthly proportion of enrollees with ≥1 inappropriate prescription. Using segmented regression models, they assessed for level and slope changes in outcomes in March 2020.

Analyses included 37,566,581 enrollees, of whom 19,154,059 (51.0%) were female. The proportion of enrollees with ≥1 inappropriate prescription decreased in March 2020 (level decrease: −0.80 percentage points [95% confidence interval {CI}, −1.09% to −.51%]) and subsequently increased (slope increase: 0.02 percentage points per month [95% CI, .01%–.03%]), partly because overall antibiotic dispensing rebounded and partly because the proportion of antibiotic prescriptions that were inappropriate increased (slope increase: 0.11 percentage points per month [95% CI, .04%–.18%]). In December 2021, the proportion of enrollees with ≥1 inappropriate prescription equaled the corresponding proportion in December 2019.




### Dr. Septimus's Annotations

Despite an initial decline, the proportion of enrollees exposed to inappropriate antibiotics returned to baseline levels by December 2021. Their database did not include the Medicaid population or the uninsured and is not representative of all privately insured or Medicare Advantage enrollees. Their database did not report information on race, ethnicity, or socioeconomic status.

BOTTOM LINE

**Their findings underscore the continued importance of outpatient antibiotic stewardship initiatives in preventing unnecessary morbidity and morbidity associated with antimicrobial adverse events including accelerating antimicrobial resistance.**

25

## FDA approves Moderna's RSV shot for older adults

The FDA has approved Moderna's RSV mRNA vaccine for adults older than 60 years. The approval makes RSV the second disease for which an mRNA vaccine has been greenlighted. There are two other RSV vaccines approved for adults older than 60: Arexvy by GSK and Abrysvo by Pfizer.

FDA approval was based off a multinational study involving around 37,000 adults older than 60 across 22 countries. The study found that mRESVIA had an efficacy against RSV lower respiratory tract disease of 83.7 percent. This reported efficacy exceeds the vaccine efficacy rates reported for Pfizer and GSK's RSV vaccines, 77.8 percent and 74.6 percent, respectively. The most common side effects reported from mRESVIA were injection site pain, fatigue, headache, muscle pain and join stiffness.

Dr. Septimus's Annotations

Approval of mRESVIA for the prevention of lower respiratory tract disease caused by RSV in individuals 60 years of age and older provides another available vaccine for the prevention of this potentially life-threatening disease in high-risk individuals.

26

## FDA Expands Approval of GSK's RSV Vaccine To Adults 50 To 59

June 7, 2024

The FDA approved the expanded use of GSK's RSV vaccine in adults aged between 50 and 59, making it the first RSV vaccine endorsed for that age group. Pfizer and Moderna are already approved for people aged 60 and older for the virus. The CDC has to sign off on the use of GSK's vaccine in the expanded patient population. CDC's panel of independent experts will convene between June 26-28, 2024.

Dr. Septimus's Annotations

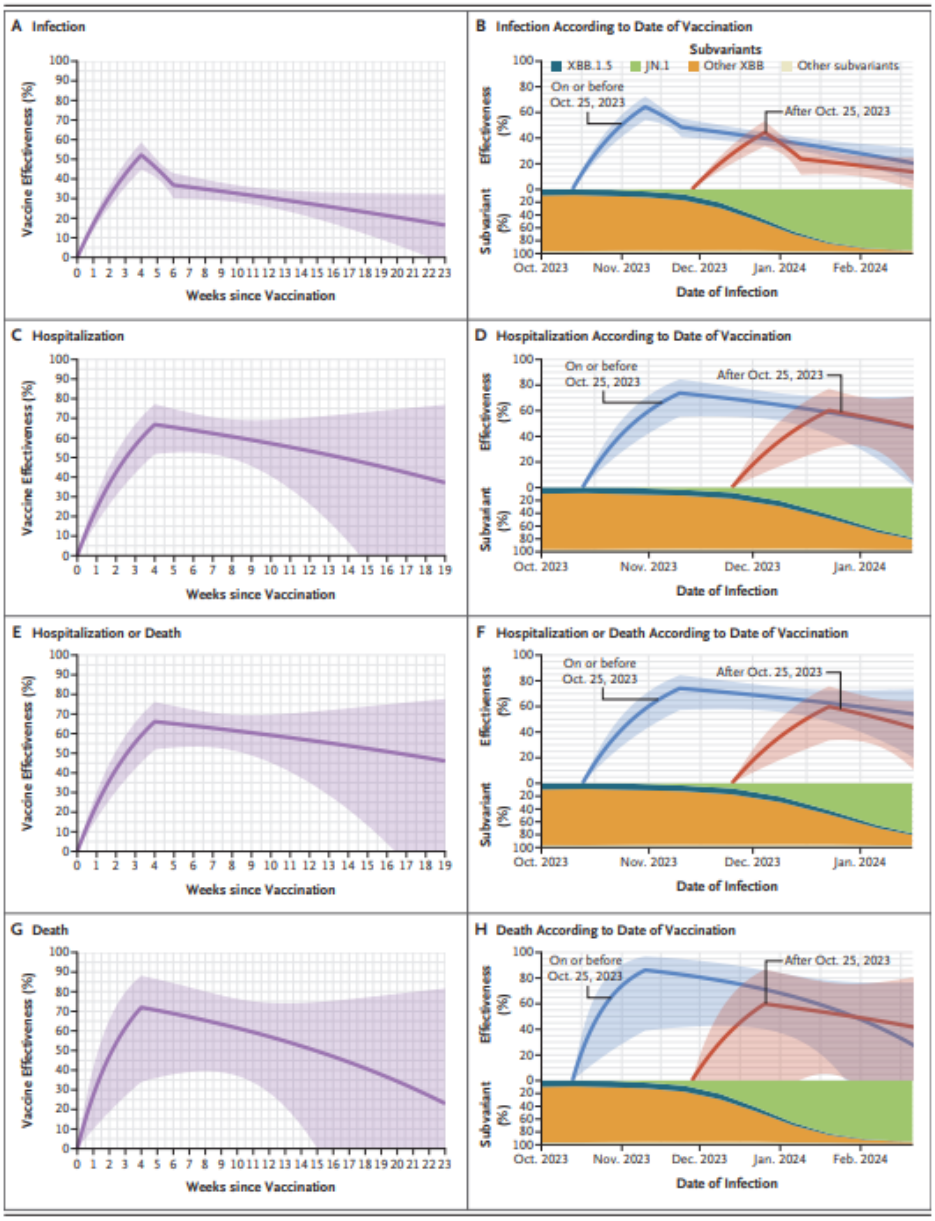
To date uptake of current RSV vaccines has been disappointing. Healthy adults <60 years old are unlikely to benefit, but high-risk individuals may. Will wait to see ACIP recommendations for individuals <age 60.

27

# Durability of XBB.1.5 Vaccines against Omicron Subvariants

N Engl J Med published online May 29, 2024
DOI: 10.1056/NEJMc2402779

In the fall of 2023, the updated Moderna and Pfizer–BioNTech mRNA vaccines (i.e., 2023–2024 formulas) against Covid-19 containing the SARS-CoV-2 omicron XBB.1.5 subvariant were authorized by the FDA for all doses administered to persons 6 months of age or older in the US. In addition, the updated Novavax adjuvanted vaccine against Covid-19 containing the spike protein from the XBB.1.5 subvariant was authorized by the FDA for use in persons 12 years of age or older. This report explored the clinical data on the durability of protection conferred by these updated vaccines against circulating omicron subvariants over a 5-month period. To reduce confounding bias caused by changing infection rates over time, they compared the risk of disease between recipients and nonrecipients of the XBB.1.5 vaccines on the same date. To further reduce confounding bias, they included the time since previous vaccination, the time since previous infection, and demographic characteristics (sex, age, race, ethnic group, and socioeconomic status) as covariates. They calculated the vaccine effectiveness for each end point as one minus the hazard ratio.



The updated monovalent XBB.1.5 COVID-19 vaccines were effective against Omicron subvariants circulating during the most recent respiratory virus season, but their effectiveness waned over time. The three vaccines developed by Moderna, Pfizer-BioNTech and Novavax were 66.8% effective against hospitalization at 4 weeks, decreasing to 57.1% after 10 weeks. Additionally, data appeared to point to lower effectiveness against infection, hospitalization, and death after the arrival of the JN.1 subvariant, the dominant strain in the US at the end of March of this year.

## Dr. Septimus's Annotations

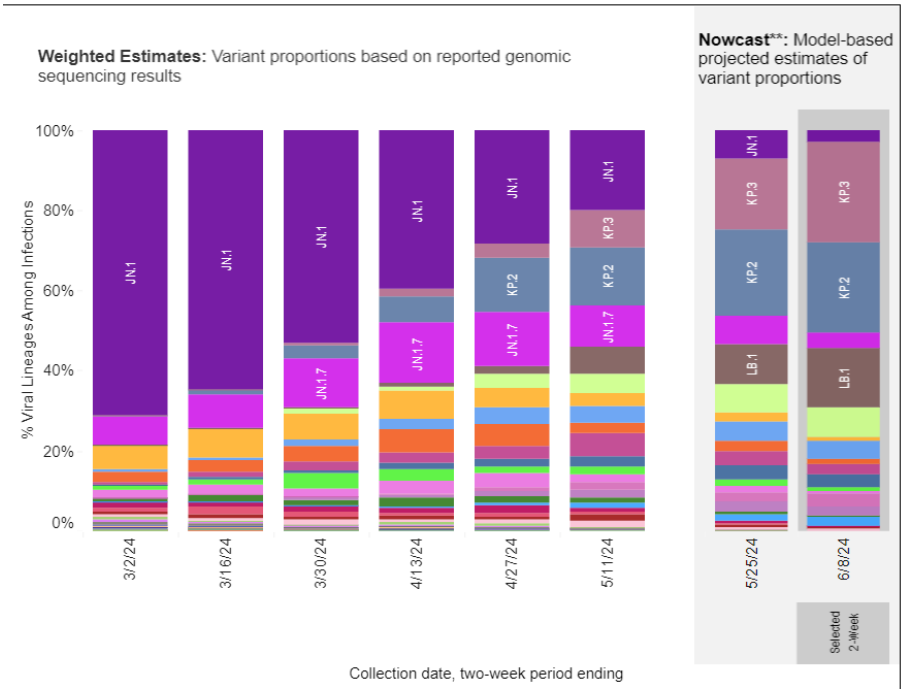
The XBB.1.5 vaccines were less protective against JN.1 than against other XBB sublineages. This study included primarily symptomatic SARS-CoV-2 infections and did not include the results of at-home Covid-19 antigen tests. KP.2 and KP.3 now make up almost 50% of variants and JN.1 is now <10%. There has been an uptick in ED visits for Covid-19 in the last few weeks. See Covid-19 by the Numbers below. In an article reviewed in May's ID Watch [BioRxiv posted April 26, 2024] the findings suggest that the increased immune resistance ability of KP.2 partially contributes to the higher Ro more than previous variants including JN.1.

### BOTTOM LINE

**Overall, the XBB.1.5 vaccines were effective against omicron subvariants, although less effective against JN.1. The effectiveness was greater against hospitalization and death than against infection, and it waned over time. Will the KP variants result in a summer wave?**

## 28 COVID-19 by the Numbers

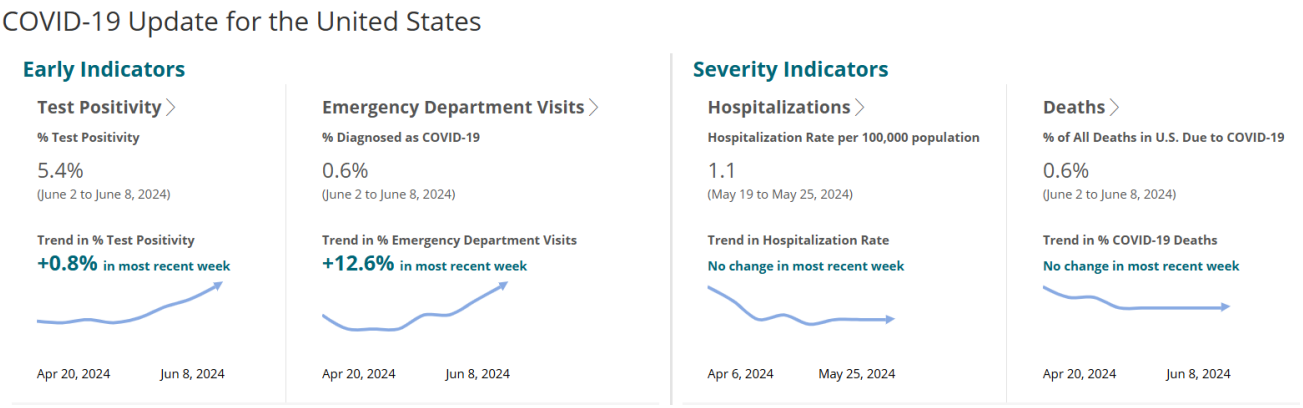
**Weighted and Nowcast Estimates in United States for 2-Week Periods in 2/18/2024 – 6/8/2024**

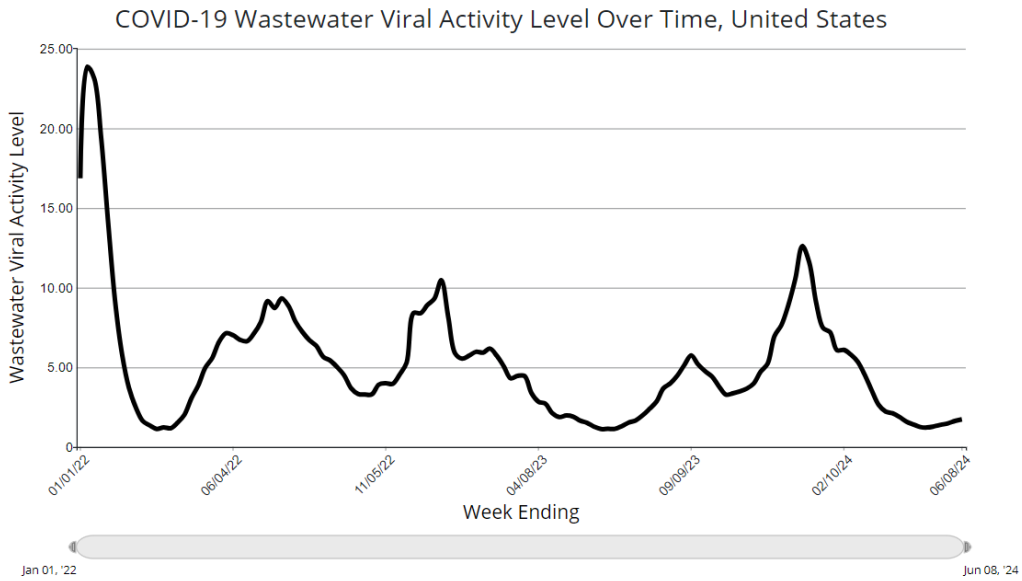



**Nowcast Estimates in United States for 5/26/2024 – 6/8/2024**

USA

| WHO label | Lineage # | %Total | 95%PI |
|---|---|---|---|
| Omicron | KP.3 | 25.0% | 15.9-36.7% |
| | KP.2 | 22.5% | 17.4-28.5% |
| | LB.1 | 14.9% | 7.6-26.6% |
| | KP.1.1 | 7.5% | 4.6-11.8% |
| | JN.1.11.1 | 4.4% | 2.6-7.3% |
| | JN.1.7 | 3.7% | 2.6-5.1% |
| | XDV.1 | 3.4% | 1.5-7.2% |
| | JN.1.16.1 | 3.3% | 2.0-5.5% |
| | JN.1 | 3.1% | 2.2-4.3% |
| | JN.1.16 | 2.4% | 1.1-4.8% |
| | KS.1 | 2.2% | 1.3-3.6% |
| | KW.1.1 | 2.0% | 0.6-5.5% |
| | JN.1.13.1 | 1.5% | 1.0-2.1% |
| | JN.1.8.1 | 0.9% | 0.6-1.4% |
| | JN.1.18 | 0.8% | 0.5-1.2% |
| | KQ.1 | 0.8% | 0.4-1.5% |
| | JN.1.32 | 0.4% | 0.3-0.6% |
| | JN.1.4.3 | 0.3% | 0.1-0.9% |
| | XDP | 0.3% | 0.1-0.5% |
| | KV.2 | 0.2% | 0.1-0.3% |
| | BA.2 | 0.0% | 0.0-0.3% |
| | BA.2.86 | 0.0% | 0.0-0.0% |
| | HV.1 | 0.0% | 0.0-0.0% |




## Dr. Septimus's Annotations

In the last few weeks there has been an increase of 12.6% in visits to the ED. So far this has not resulted in an increase in hospitalizations or deaths due to Covid-19. Wastewater surveillance is still considered low, but there is an increase in recent weeks.

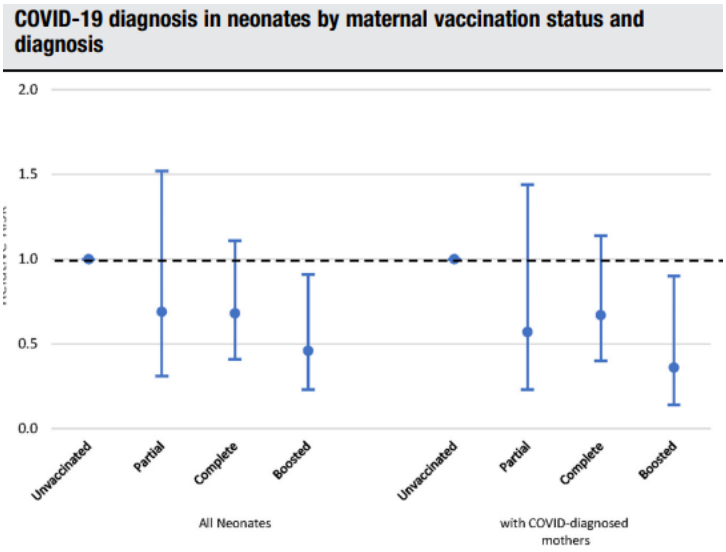
## Maternal vaccination against COVID-19 and neonatal outcomes during Omicron: INTERCOVID-2022 study

Am J Ob Gyn published online February 24, 2024
doi.org/10.1016/j.ajog.2024.02.008

This study aimed to analyze the impact of Covid-19 during pregnancy on newborns and the effects of maternal Covid-19 vaccination on neonatal outcomes when Omicron was the variant of concern. INTERCOVID-2022 was a large, prospective, observational study, conducted in 40 hospitals across 18 countries, from November 27, 2021, to June 30,

2022, to assess the effect of Covid-19 in pregnancy on maternal and neonatal outcomes and to assess vaccine effectiveness. Women diagnosed with laboratory-confirmed Covid-19 during pregnancy were compared with 2 nondiagnosed, unmatched women recruited concomitantly and consecutively during pregnancy or at delivery. Mother-newborn dyads were followed until hospital discharge. The primary outcomes were a neonatal positive test for Covid-19, severe neonatal morbidity index, severe perinatal morbidity and mortality index, preterm birth, neonatal death, referral to neonatal intensive care unit, and diseases during the neonatal period. Vaccine effectiveness was estimated with adjustment for maternal risk profile.

They enrolled 4707 neonates born to 1577 (33.5%) mothers diagnosed with Covid-19 and 3130 (66.5%) nondiagnosed mothers. Among the diagnosed mothers, 642 (40.7%) were not vaccinated, 147 (9.3%) were partially vaccinated, 551 (34.9%) were completely vaccinated, and 237 (15.0%) also had a booster vaccine. Neonates of booster vaccinated mothers had less than half the risk of being diagnosed with Covid-19 when compared with those of unvaccinated mothers; they also had the lowest rates of preterm birth, medically indicated preterm birth, respiratory distress syndrome, and number of days in the neonatal intensive care unit. Newborns of unvaccinated mothers had double the risk for neonatal death when compared with those of nondiagnosed mothers. Vaccination was not associated with any congenital malformations. Although all vaccines provided protection against neonatal test positivity, newborns of booster-vaccinated mothers had the highest vaccine effectiveness (64%; 95% confidence interval, 10%-86%). Vaccine effectiveness was not as high for messenger RNA vaccines only. Vaccine effectiveness against moderate or severe neonatal outcomes was much lower, namely 13% in the booster-vaccinated group (all vaccines) and 25% and 28% in the completely and booster-vaccinated groups, respectively (messenger RNA vaccines only). Vaccines were fairly effective in protecting neonates when given to pregnant women ≤100 days (14 weeks) before birth; thereafter, the risk increased and was much higher after 200 days (29 weeks).




## Dr. Septimus's Annotations

Neonates of booster-vaccinated mothers had less than half the risk of being diagnosed with Covid-19 than those of unvaccinated mothers; they also had the lowest rates of preterm birth, medically indicated preterm birth, respiratory distress syndrome, and number of days in the neonatal intensive care unit. All vaccines provided protection against neonatal test positivity, but vaccine effectiveness was highest among newborns of booster-vaccinated mothers. Vaccines were fairly effective in protecting neonates when given to pregnant women ≤100 days (14 weeks) before birth; thereafter, the risk increased and was much higher after 200 days (29 weeks).

### BOTTOM LINE

**At a time when Omicron was the dominant variant, neonates of unvaccinated mothers died twice as frequently as those of vaccinated mothers. Vaccines protected against preterm birth and adverse neonatal outcomes.**

30

## FDA Advisers Recommend a New COVID-19 Vaccine Formula for the Fall

June 5, 2024

A committee of advisers to the FDA voted on June 5th to update the formula for the Covid-19 vaccine ahead of an anticipated fall immunization campaign, now an annual step to try to offer better protection against versions of the virus in circulation.

The unanimous vote by the 16 advisers initially recommended a formula aimed at combating the variant JN.1, which dominated infections in the US in February. However, in recent weeks, JN.1 has been replaced by descendants known as KP.2 and KP.3. In a follow-up meeting on June 13th the FDA is now advising manufacturers to develop the 2024-2025 Covid-19 vaccines using the KP.2 strain for the vaccine.

### Dr. Septimus's Annotations

Like influenza any decision involves some educated guesswork, given that any new vaccine formula will not be available until months after a variant becomes dominant. Studies have shown that protection tends to improve as the vaccines target dominant variants.

**BOTTOM LINE**

**Current FDA will now recommend KP.2 formulation for updated Covid-19 vaccine. This change is intended to ensure that the Covid-19 vaccines (2024-2025 Formula) will be closely match the most recent circulating SARS-CoV-2 strains.**

## Masks and respirators for prevention of respiratory infections: a state of the science review

Clin Microbiol Rev published online May 22, 2024
doi.org/10.1128/cmr.00124-23

The authors reviewed over 100 published reviews and selected primary studies, including re-analyzing contested meta-analyses of key clinical trials. They agreed on seven basic key findings.

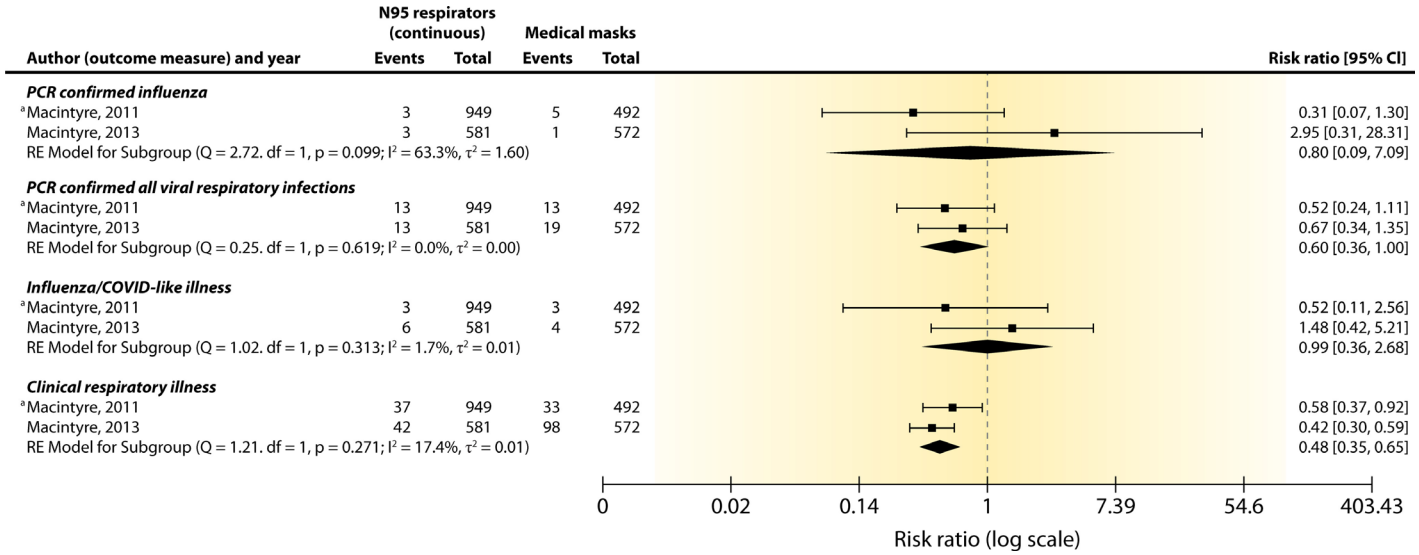
1. There is strong and consistent evidence for airborne transmission of SARS-CoV-2 and other respiratory pathogens.
2. Masks if correctly and consistently worn, are effective in reducing transmission of respiratory diseases and show a dose-response effect.
3. Respirators are significantly more effective than medical or cloth masks.
4. Mask mandates are, overall, effective in reducing community transmission of respiratory pathogens. Mask mandates have played out differently in different jurisdictions and sociocultural settings.
5. Masks are important sociocultural symbols; non-adherence to masking is sometimes linked to political and ideological beliefs and to widely circulated mis- or disinformation.
6. Although masks are not generally harmful to the general population, masking may be relatively contraindicated in individuals with certain medical conditions, who may require exemption such as patients with Alzheimer's Disease, chronic lung disease, end stage renal disease, heart failure, mental health conditions, facial conditions, infants and young children. Furthermore, certain groups (notably D/deaf people) are disadvantaged when others are masked.

7. There are risks to the environment from single-use masks and respirators. Single-use masks and respirators contribute to non-biodegradable waste and environmental pollution, though research on recycling, reuse, and novel materials points to some potential solutions.

## BOX 1: FLAWED ASSUMPTIONS AND LOGICAL FALLACIES ABOUT AIRBORNE TRANSMISSION

The following incorrect assumptions have led to flawed conceptual models and ineffective policies (see text for details and references):

1. Absence of direct evidence in favor of airborne transmission can be taken as evidence refuting airborne transmission.
2. Because contact and droplet transmission can occur only during close contact, all close-contact transmission must be contact and droplet.
3. Because large droplets are smaller than the lumen of the smallest bronchioles, they can reach the key target cell for SARS-CoV-2 in the alveoli.
4. Particles above 5 μm in diameter are droplets and not aerosols.
5. Aerosols are produced in significant numbers from infectious patients only when aerosol-generating medical procedures (AGMPs) are done.
6. Only respiratory diseases with a high $R_0$ (such as measles) are airborne.




## Dr. Septimus's Annotations

The need for a new review on masks was highlighted by a widely publicized Cochrane Review. The masks section of a 2023 Cochrane review of non-pharmaceutical interventions was—controversially—limited to randomized controlled trials (RCTs). [Cochrane Database Syst Rev 2023; 1:CD006207] Some investigators were quick to question the review's methodology, especially key flaws in the meta-analysis and omission of a vast body of non-RCT evidence. [JAMA Netw Open 2023; 6:e2339443; BMJ Evid Based Med 2022; 27:253–260] In the end they propose an agenda for future research, including

improved characterization of the situations in which masking should be recommended or mandated; attention to comfort and acceptability; generalized and disability-focused communication support in settings where masks are worn; and development and testing of novel materials and designs for improved filtration, breathability, and environmental impact. See next review

**BOX 2: SOME SUGGESTIONS FOR A NEW GENERATION OF RESEARCH ON MASKS AND RESPIRATORS**

1. Interdisciplinary and multi-method designs which go beyond "do masks work?" and ask nuanced, multi-faceted questions such as "what kind of masks should be introduced in respiratory epidemics and pandemics, at what stage, for whom, how and with what support?"
2. Studies of how to address the mismatch between the strong and consistent evidence base on the effectiveness of masks and respirators and the lack of acceptance of this evidence by influential scientists, clinicians and policymakers.
3. Studies to improve the quality of communication when [some people are] wearing face coverings.
4. Studies to optimize acceptability, fit and comfort of masks and respirators and minimize side effects such as skin reactions and headache. We recommend a wider range of mask materials, designs and styles, including consideration of specific need groups.
5. Studies of new materials and combinations of materials for masks and respirators, with a view to optimizing filtration efficacy, breathability, fit and environmental sustainability.
6. Studies of how to address the widespread, sinister and growing phenomenon of anti-mask misinformation and disinformation on social and mainstream media.

**BOTTOM LINE**

**Masks work if worn appropriately and consistently. This article is an excellent reference and outlines future important research.**

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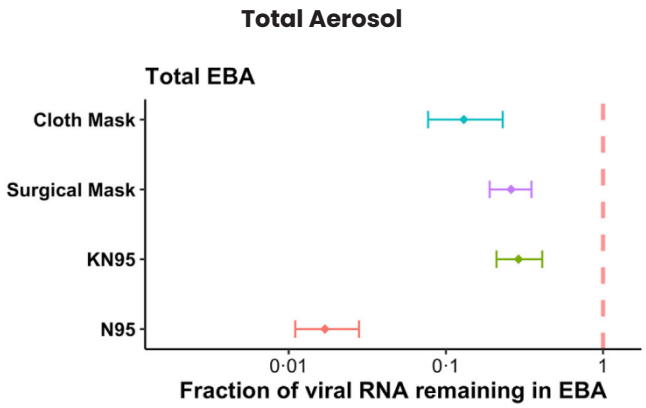
## Relative efficacy of masks and respirators as source control for viral aerosol shedding from people infected with SARS-CoV-2: a controlled human exhaled breath aerosol experimental study

eBioMedicine published online May 29, 2024
doi.org/10. 1016/j.ebiom.2024. 105157

The investigators compared efficacy of masks (cloth and surgical) and respirators (KN95 and N95) as source control for SARS-CoV-2 viral load in exhaled breath of volunteers with COVID-19 using a controlled human experimental study. Volunteers (N = 44, 43% female) provided paired unmasked and masked breath samples allowing computation of source-control factors. Each individual served as their own control and provided masked and unmasked samples on the same day, allowing the investigators to show the direct effect of each type of mask and respirators. They defined source-control factor (SCF %) as a percentage reduction in viral load released into the environment when wearing a mask and presented the SCFs for each of the four categories of masks and respirators.

All masks and respirators significantly reduced exhaled viral load, without fit tests or training. A duckbill N95 reduced exhaled viral load by 98% (95% CI: 97%–99%), and significantly outperformed a KN95 ($p < 0.001$) as well as cloth and surgical masks. Cloth masks outperformed surgical masks ($p = 0.027$) and the tested KN95 ($p = 0.014$).




Dr. Septimus's Annotations

Lab experiments using manikins have demonstrated that N95 respirators were more effective than cotton and surgical masks in reducing viral aerosol emissions. [MMWR 2021; 70: 254-257] Very few human studies have examined the relative efficacy of different types of masks and respirators as source control for SARS-CoV-2. The study population were mostly young adults, and all had mild symptoms at the time of testing. Therefore, the results may not be generalizable to those who are older or have more symptoms. The types of N95, KN95 respirators, and surgical masks that they included were limited and should not be considered representative of all N95, KN95 respirators, and surgical masks. All of the cloth masks were brought by volunteers and were mostly without brand information or homemade. Greater viral loads in the unmasked samples for those wearing N95 and K95 were because most of these samples were collected during Delta and Omicron waves, while most cloth and surgical unmasked samples were collected during earlier waves. Nonetheless, in this study after controlling for potential confounders, they demonstrated N95 respirators were significantly more efficacious as source control than all other types of masks and respirators used in this study.

BOTTOM LINE

**These results suggest that N95 respirators should be the standard of care in nursing homes and healthcare settings when respiratory viral infections are prevalent in the community and healthcare-associated transmission risk is elevated.**

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## National Academies Issue New Broad Definition of Long COVID-19

June 11, 2024

According to the 2024 NASEM(National Academies of Sciences, Engineering, and Medicine) definition of long COVID: "Long COVID is an infection-associated chronic condition that occurs after SARS-CoV-2 infection and is present for at least 3 months as a continuous, relapsing and remitting, or progressive disease state that affects one or more organ systems." People with long COVID may present with one or more of a long list of symptoms, such as shortness of breath, rapid heartbeat, extreme fatigue, post-exertional malaise, or sleep disturbance and with single or multiple diagnosable conditions, including interstitial lung disease, arrhythmias, postural orthostatic tachycardia syndrome (POTS), myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), diabetes, or autoimmune disorders. The condition can exacerbate preexisting health conditions or present as new ones. The definition does not require laboratory confirmation or other proof of initial infection. Long COVID can follow SARS-CoV-2 infection of any severity, including asymptomatic infections, whether or not they were initially recognized.

Dr. Septimus's Annotations

There is a clear benefit for a more uniform long Covid-19 case definition. However, I have some concerns over the new definition. A person can meet these proposed long COVID criteria by merely having one symptom that does

not have any negative impact on the person's functioning or quality of life. The failure to list any thresholds of frequency or severity of symptoms, so that the symptoms are not trivial, has major consequences for an infection that is as widespread as Covid-19. If the majority of individuals may be eligible for a long COVID diagnosis given their prior infection, and the threshold criteria for being diagnosed is so low, then the prevalence of long COVID could increase significantly. I hope there is still a chance to make this proposed case definition narrower. The new definition does not eliminate clinical judgment. See next review

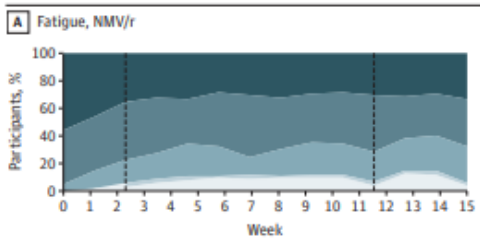
**BOTTOM LINE**

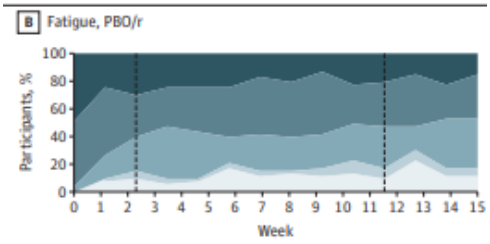
**Case definitions are crucial for science, and even more critical for diseases like long COVID that lack a consistent definition or biomarker. There is a clear benefit for a more uniform long COVID case definition, because currently physicians make this diagnosis on a case-by-case basis with a mix of definitions and their judgment. But there are potential negative consequences of an overly broad long COVID case definition.**

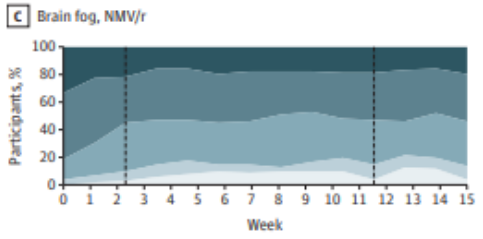
## Nirmatrelvir-Ritonavir and Symptoms in Adults With Postacute Sequelae of SARS-CoV-2 Infection: The STOP-PASC Randomized Clinical Trial.

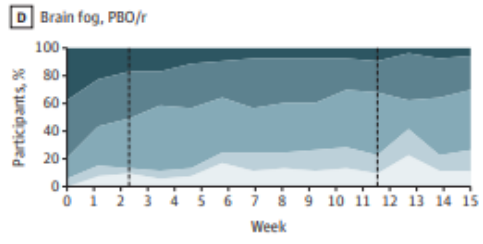
JAMA Intern Med published online June 7, 2024
doi:10.1001/jamainternmed.2024.2007

This was a 15-week blinded, placebo-controlled, randomized clinical trial conducted from November 2022 to September 2023. The participants were adults with moderate to severe PASC symptoms of 3 months or longer duration. Participants were randomized 2:1 to treatment with oral nirmatrelvir-ritonavir (NMV/r, 300 mg and 100 mg) or with placebo-ritonavir (PBO/r) twice daily for 15 days. Key exclusion criteria included pregnancy or breastfeeding, severe liver disease, SARS-CoV-2 infection, and use of SARS-CoV-2–specific treatment within 30 days of randomization, SARS-CoV-2 vaccination within 28 days, or other vaccine within 14 days of randomization, or medications that interact with study drug. Primary outcome was a pooled severity of 6 PASC symptoms (fatigue, brain fog, shortness of breath, body aches, gastrointestinal symptoms, and cardiovascular symptoms) based on a Likert scale score (where 0 is none, 1 mild, 2 moderate, 3 severe) at 10 weeks. Secondary outcomes included symptom severity at different time points, symptom burden and relief, patient global measures, Patient-Reported Outcomes Measurement Information System (PROMIS) measures, orthostatic vital signs, and sit-to-stand test change from baseline and Patient Global Impression of Severity (PGIS) and Patient Global Impression of Change (PGIC) at day 15, week 5, week 10, and week 15 in NMV/r vs PBO/r groups.

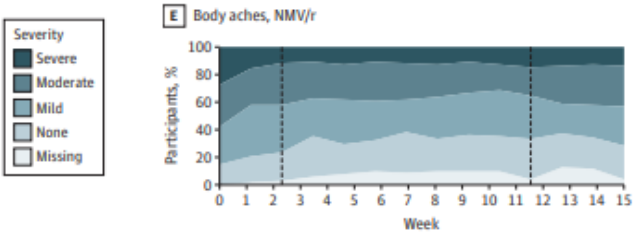




Of the 155 participants (median age, 43 [34-54] years; 59% females), 102 were randomized to the NMV/r group and 53 to the PBO/r group. Nearly all participants (n = 153) had received the primary series for Covid-19 vaccination. The mean time between index SARS-CoV-2 infection and randomization was 17.5 months. There was no statistically significant difference in the model-derived severity outcome pooled across the 6 core symptoms at 10 weeks between the

NMV/r and PBO/r groups. No statistically significant between-group differences were found at 10 weeks in the Patient Global Impression of Severity or Patient Global Impression of Change scores, summative symptom scores, and change from baseline to 10 weeks in PROMIS fatigue, dyspnea, cognitive function, and physical function measures. Adverse event rates were similar in NMV/r and PBO/r groups.




## Dr. Septimus's Annotations

This randomized clinical trial including 155 participants with PASC symptoms (≥3 months' duration) found that a 15-day course of nirmatrelvir-ritonavir in a highly vaccinated study cohort was generally safe, but did not show significant benefit in improving fatigue, brain fog, body aches, cardiovascular symptoms, shortness of breath, or gastrointestinal symptoms. They found that many participants with PASC in the PBO/r group improved over time, as did a control group in another trial in PASC. Therefore, an effective intervention needs to substantially hasten that process to see a meaningful difference. The investigators admit a smaller sample size than was originally planned due to early enrollment closure. The high rate of exclusion due to eligibility criteria, such as drug-drug interaction, also limited generalizability and potentially misses subgroups of patients who could be responders. Severity of the acute Covid-19 infection may impact outcomes and was not captured in depth aside from hospitalization status. Evaluation for molecular and digital biomarkers from the STOP-PASC trial is forthcoming.

### BOTTOM LINE

**This randomized clinical trial did not find a significant benefit of nirmatrelvir-ritonavir for a subset of PASC symptoms among a highly vaccinated cohort with prolonged PASC symptoms.**