Infectious Diseases Watch

February 2024

Ed Septimus, MD

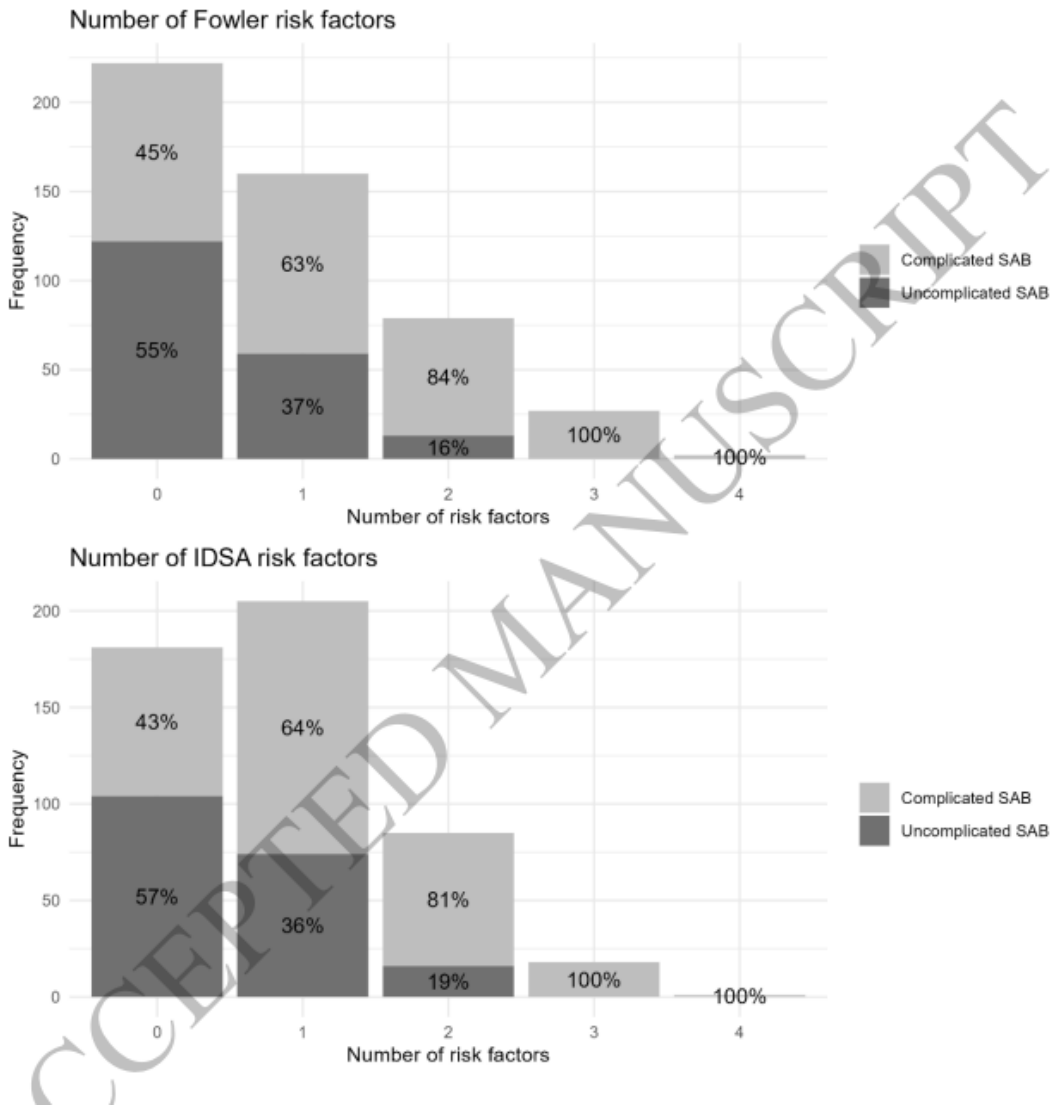
General Infectious Diseases

The utility of risk factors to define complicated Staphylococcus aureus bacteremia(SAB) in a setting with low MRSA prevalence Clin Infect Dis published online December 29, 2023

DOI: 10.1093/cid/ciad784

This is a prospective cohort with patients with SAB. They were categorized as complicated or uncomplicated through adjudication (ID physicians). Associations and predictive values of 9 risk factors [These include: 1) community acquisition of bacteremia; 2) persistent fever after 72 hours 3) skin manifestations suggestive of systemic infection; 4) positive follow-up blood cultures after 48 hours; 5) presence of permanently implanted prosthetic material; 6) hemodialysis dependence; 7) an unknown focus of infection at presentation; 8) history of endocarditis, active IV drug use, or a heart condition predisposing for endocarditis; 9) delay in start of effective antimicrobial therapy of 48h or more after collection of first positive blood culture] were determined, compared to the reference definition, as was accuracy of IDSA criteria that include 4 risk factors [The IDSA classifies SAB as complicated if any of the following characteristics are present: endocarditis or metastatic infection, presence of permanently implanted prosthetic material, skin findings suggestive of systemic infection, positive follow-up blood cultures after 48 hours and persistent fever after 72 hours (Clin infect Dis 2011;52(3):e18-55)], and the projected consequences of applying IDSA criteria on antibiotic use. Using the definition described by Fowler et al., all patients who either had infection-related mortality, or a complicated infection present at the time of initial hospitalization (e.g.: endocarditis, septic arthritis, deep tissue abscesses), or embolic stroke, or relapse of infection within 90 days, were categorized as complicated SAB. [Arch Intern Med. 2003;163:2066-72]

Among 490 patients, 296 (60%) had complicated SAB. In multivariable analysis, persistent bacteremia (odds ratio (OR) 6.8 (95% CI 3.9 – 12.0)), community-acquisition of SAB (OR 2.9 (95% CI 1.9 – 4.7)) and presence of prosthetic material (OR 2.3 (95%CI 1.5 – 3.6)) were associated with complicated SAB. Presence of any of the four risk factors in the IDSA definition of complicated SAB had Positive Predictive Value of 70.9% (95%CI 65.5 – 75.9) and Negative Predictive Value of 57.5% (49.1 – 64.8). Compared to the reference, IDSA criteria yielded 24 (5%) false-negative and 90 (18%) false-positive classifications of complicated SAB. Median duration of antibiotic treatment of these 90 patients was 16 days (IQR 14 – 19), all with favorable clinical outcome.



Comment: Using risk factors to define complicated SAB, as recommended by IDSA guidelines, may increase the proportion of SAB patients with complicated SAB by 20%. As classification is used to guide the duration of antibiotic treatment this may inadvertently lead to unnecessary prolonged antibiotic use. They suggest that in patients with SAB better criteria, in addition to reliable additional diagnostic procedures, are needed to optimize clinical management. The low prevalence of MRSA and IV-drug use in the cohort may decrease generalizability to other settings. See next review.

Efficacy and safety of an early oral switch in low-risk Staphylococcus aureus bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial Lancet Infect Dis published online January 17, 2024

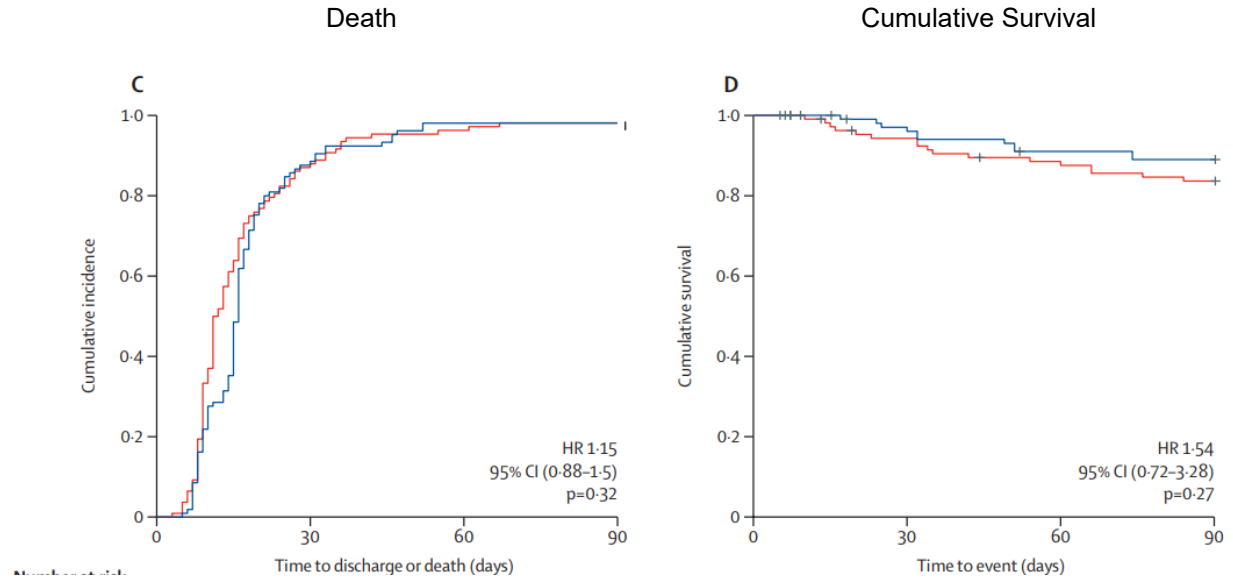
doi.org/10.1016/ S1473-3099(23)00756-9

The investigators assessed the efficacy and safety of an early switch to oral therapy in patients at low risk for complications related to S aureus bloodstream(SAB) infection. This was an international, open label, randomized, controlled, non-inferiority trial done in 31 tertiary care hospitals in Europe. Adult patients (aged ≥18 years) with S aureus isolated from at least one blood culture were eligible if they had received 5–7 days of appropriate intravenous antimicrobial therapy, initiated within 72 h after the first positive blood culture was drawn, and at least one follow-up blood culture obtained within 24–96 h after the start of appropriate antimicrobial therapy. Blood cultures taken in this period had to be negative for S aureus for the patient to be included. Patients were excluded if signs and symptoms of complicated S aureus bloodstream infection were present before enrolment, such as a deep-seated focus (e.g., endocarditis, pneumonia, infected implant, undrained abscess, empyema, and osteomyelitis), septic shock within 4 days before random assignment, prolonged bacteremia (defined as a positive blood culture obtained >72 h after start of adequate antimicrobial therapy, even if there was a negative follow-up blood culture thereafter), and a body temperature higher than 38°C measured on both days before random assignment. Patients were excluded if intravascular catheters were not removed within 4 days after the first positive blood culture was drawn. Patients with a higher a-priori risk for complications related to S aureus bloodstream infection were also excluded—namely, patients with a recent history of S aureus bloodstream infection within the preceding 3 months, injection drug use, severe immunodeficiency or severe immunosuppression, or presence of a prosthetic heart valve or deep-seated vascular graft.

Adult patients with low-risk SAB infection were randomly assigned after 5–7 days of intravenous antimicrobial therapy to oral antimicrobial therapy or to continue intravenous standard therapy. Randomization was done via a central web-based system, using permuted blocks of varying length, and stratified by the study center. The main exclusion criteria were signs and symptoms of complicated S aureus bloodstream infection, non-removable foreign devices, and severe comorbidity. The composite primary endpoint was the occurrence of any complication related to SAB infection (relapsing SAB infection, deep-seated infection, and mortality attributable to infection) within 90 days, assessed in the intention-to-treat population by clinical assessors who were masked to treatment assignment. Adverse events were assessed in all participants who received at least one dose of study medication (safety population). Due to slow recruitment, the scientific advisory committee decided on Jan 15, 2018, to stop the trial after 215 participants were randomly assigned (planned sample size was 430 participants) and to convert the planned interim analysis into the final analysis. The decision was taken without knowledge of outcome data, at a time when 126 participants were enrolled. The new sample size accommodated a non-inferiority margin of 10%; to claim non-inferiority, the upper bound of the 95% CI for the treatment difference (stratified by center) had to be below 10 percentage points.

Of 5063 patients with SAB infection assessed for eligibility, 213 were randomly assigned to switch to oral therapy (n=108) or to continue intravenous therapy (n=105). Of 108 participants in

the oral switch group, 63 (58%) received cotrimoxazole, 35 (32%) received clindamycin, nine (8%) received linezolid, and one (1%) did not receive any study medication. Of 105 participants in the intravenous group, 46 (44%) received cefazolin, 45 (43%) received intravenous flucloxacillin or cloxacillin, seven (7%) received vancomycin, five (5%) received daptomycin, and two (2%) did not receive any study medication. Mean age was 63·5 (SD 17·2) years and 148 (69%) participants were male and 65 (31%) were female. In the oral switch group, 14 (13%) participants met the primary endpoint versus 13 (12%) in the intravenous group, with a treatment difference of 0·7 percentage points (95% CI –7·8 to 9·1; p=0·013). In the oral switch group, 36 (34%) of 107 participants in the safety population had at least one serious adverse event compared with 27 (26%) of 103 participants in the intravenous group (p=0·29). The length of hospital stay was longer in the 16 participants with MRSA bacteremia (median 19 days [IQR 14–28]) than in the 197 participants with MSSA (median 15 days [9–18]; p=0·016).



Comment: This study is the first randomized controlled trial to show non-inferiority of early oral antimicrobial switch therapy compared with standard intravenous treatment in patients with low-risk SAB infection. The findings support results from observational studies that reported similar outcomes between groups. Patients with low-risk SAB infection represent a subgroup of patients with SAB infection, and a careful assessment of the individual patient is a prerequisite for assigning the low-risk category. The challenge is low-risk SAB is an increasingly uncommon [Clin Microbiol Infect 2023;29: e9-1197] and similarly low recruitment rates were observed in other randomized trials focusing on uncomplicated SAB. The slow enrolment to SABATO ultimately resulted in the termination of trial enrolment at just half of the original target population. With this decrease in power, the original non-inferiority margin of 5% was increased to 10% for the primary analyses. This margin, when coupled with the infrequent event rates, limits the ability of SABATO to definitively answer the question unfortunately. This study included only a few patients with MRSA, which might limit generalizability of the results to patients with bloodstream infection caused by MRSA. Despite these concerns, previous studies in bone and joint infections and infective endocarditis have demonstrated that oral switch can be safe and effective. [N Engl J Med 2019; 380:425-436; N Engl J Med 380:415-424] Additional data are anticipated within the next few years. The SNAP trial is enrolling patients with SAB, both uncomplicated and complicated.

Bottom line: The investigators found that an early oral switch was non-inferior to standard intravenous antimicrobial therapy in patients with low-risk SAB infection. This study supports an early switch to oral antimicrobial therapy in patients with low-risk SAB infection provided a rigorous clinical assessment and close monitoring for complications are done.

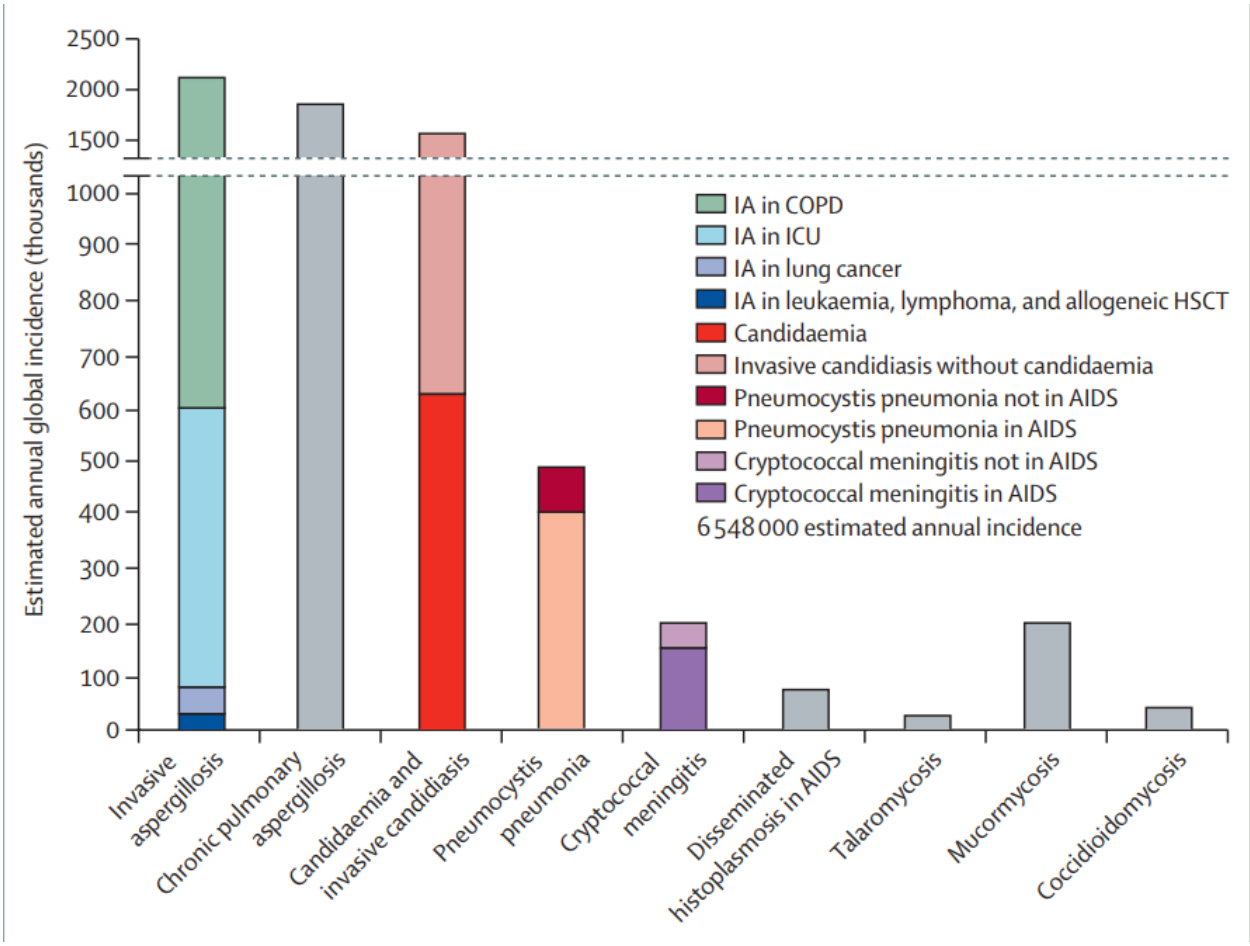
Global incidence and mortality of severe fungal disease Lancet Infect Dis published online January 12, 2024

doi.org/10.1016/ S1473-3099(23)00692-8

Using data from literature published from 2010 through 2023, along with 85 papers on individual country and global disease burden, the review estimates that over 6.55 million people annually are affected by invasive fungal infection, including over 2.1 million with invasive aspergillosis, 1.8 million with chronic pulmonary aspergillosis, and 1.5 million with a *Candida* bloodstream infection or invasive candidiasis, 500,000 with Pneumocystis pneumonia, and 194,000 with Cryptococcal meningitis. These infections lead to more than 3.75 million deaths annually, of which 2.55 million are directly attributable to the fungal infection. The review also estimates that fungal asthma affects approximately 11.5. million people annually, with 92,000 asthma deaths linked to fungal allergy and 46,000 directly attributable.

The mortality figures are higher than the prior estimates of 1.5 million to 2 million annual deaths, in part because many fungal infections are associated with diseases such as leukemia, lung cancer, Covid-19, and AIDS, and deaths have often been attributed to those diseases. In addition, many fungal diseases go undiagnosed and untreated because of limited access to diagnostics.

But the new estimates, based on a combination of untreated mortality, the proportion of patients who are treated, and percentage survival in treated patients, suggest that invasive aspergillosis could be responsible for up to one-third of the 3.23 million annual deaths from chronic obstructive pulmonary disease, while 340,000 (28%) of the more than 1.2 million deaths from tuberculosis may have been attributable to chronic pulmonary aspergillosis.



Comment: It is likely that over 6.55 million people globally have a life-threatening fungal infection each year. These new estimates show major shifts in incidence from generally accepted figures used in the last decade. Both severe influenza and Covid-19 have led to a substantial increase in the incidence of invasive pulmonary aspergillosis [J Infect Dis 2021; 224: 1631–40]and, in the case of Covid-19, Candida bloodstream infection [Mycoses 2023; 66: 483–87] and mucormycosis.

Bottom line: The incidence of fungal disease is substantially more frequent than previously thought. Improved clinical awareness, appropriate sampling, and timely laboratory diagnostic testing, combined with imaging, could definitively reduce the substantial number of mostly avoidable premature deaths from life-threatening fungal disease.

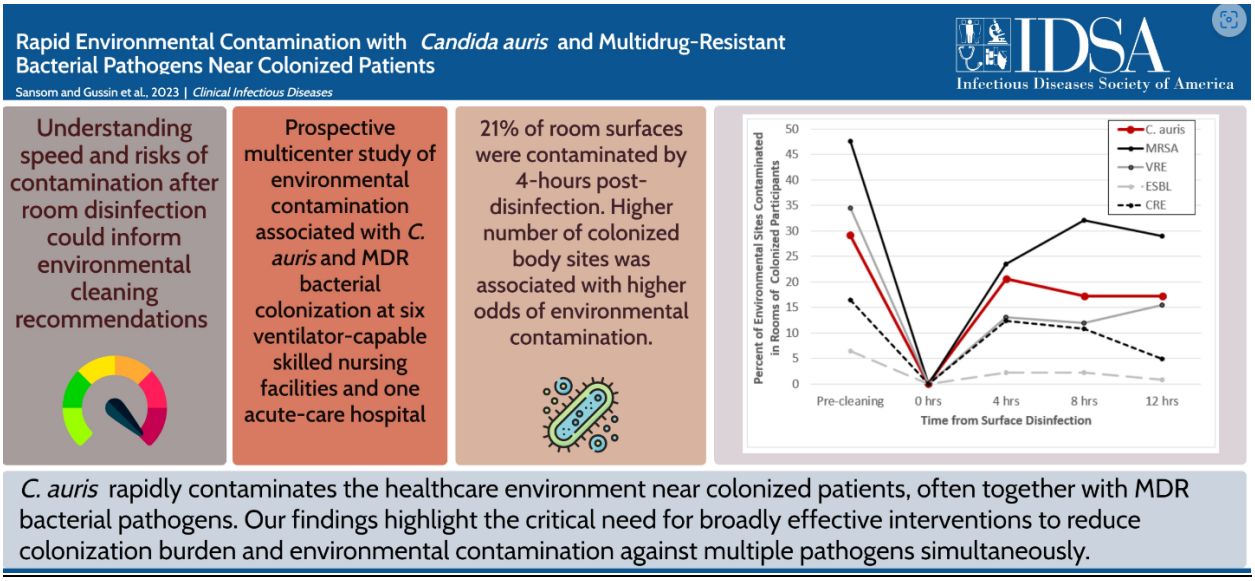
Editor's Choice

Rapid Environmental Contamination with Candida auris and Multidrug-Resistant Bacterial Pathogens Near Colonized Patients Clin Infect Dis published online December 6, 2023

DOI: 10.1093/cid/ciad752

The investigators conducted a prospective multicenter study of environmental contamination associated with C. auris colonization at six ventilator-capable skilled nursing facilities and one acute-care hospital in Illinois and California. Known C. auris carriers were sampled at five body sites followed by sampling of nearby room surfaces before disinfection and at 0, 4, 8, and 12-hours post-disinfection. Samples were cultured for C. auris and bacterial multidrug-resistant organisms (MDROs). Odds of surface contamination after disinfection were analyzed using multilevel generalized estimating equations.

Among 41 known C. auris carriers, colonization was detected most frequently on palms/fingertips (76%) and nares (71%). C. auris contamination was detected on 32.2% (66/205) of room surfaces pre-disinfection and 20.5% (39/190) of room surfaces by 4-hours post disinfection. A higher number of C. auris-colonized body sites was associated with higher odds of environmental contamination at every time point following disinfection, adjusting for facility of residence. In the rooms of 38 (93%) C. auris carriers co-colonized with a bacterial MDRO, 2%-24% of surfaces were additionally contaminated with the same MDRO by 4-hours post disinfection. Among C. auris carriers, body co-colonization with bacterial MDROs (i.e., MRSA, VRE, ESBL, CRE) was common, with at least one bacterial MDRO detected in 93% (38/41) of C. auris colonized participants. There were 28 ESBL (68%), 25 VRE (61%), 21 MRSA (51%) and 17 CRE (41%) co-colonized participants identified.



Comment: Contamination of the healthcare environment has been well described for bacterial pathogens, but information for C. auris has been limited. The investigators report that contamination due to C. auris occurs rapidly after disinfection of the immediate environment near known C. auris carriers. Most environmental contamination occurred within 4- hours of

disinfection, suggesting that twice-daily or even thrice-daily cleaning would not suffice to mitigate contamination that could lead to C. auris spread. Their prior work in SNFs demonstrated that cleaning compliance was often poor, with < 25% of high-touch surfaces adequately cleaned each day [J Am Geriatrics Soc 2012; 60: 1012-8] Practical limits to cleaning frequency could potentially be overcome with the use of long-acting disinfectants, antimicrobial surfaces, or use of no touch technologies. Basic infection prevention strategies, including rigorous hand hygiene and barrier precautions (e.g., gowns, gloves), should be employed for C. auris containment. In addition, nearly all C. auris carriers were co-colonized with bacterial MDROs that also shed heavily into the nearby environment. While routine CHG bathing has been an effective component of MRSA prevention bundles [Infect Control Hosp Epidemiol 2023: 1-29], the effects of CHG skin antisepsis in controlling C. auris has not been proven. [Clin Infect Dis 2020; 71(11): e718-e25]. However, the investigators have previously demonstrated that CHG concentrations sufficient to reduce C. auris skin colonization can be achieved with appropriate bathing technique. [OFID, 2019] We clearly need better solutions to combat both patient colonization and environmental contamination. They did not monitor the activity within patient rooms or interactions with healthcare workers during each 12-hour study period.

Bottom line: C. auris can contaminate the healthcare environment rapidly after disinfection, highlighting the challenges associated with environmental disinfection. Future research should investigate long-acting disinfectants, antimicrobial surfaces, and more effective patient skin antisepsis to reduce the environmental reservoir of C. auris and bacterial MDROs in healthcare settings.

Efficacy and safety of rezafungin and caspofungin in candidaemia and invasive candidiasis: pooled data from two prospective randomised controlled trials

Lancet Infect Dis published online November 23, 2023

doi.org/10.1016/ S1473-3099(23)00551-0

ReSTORE was a multicenter, double-blind, double-dummy, randomized phase 3 trial conducted at 66 tertiary care centers in 15 countries. STRIVE was a multicenter, double-blind, double-dummy, randomized phase 2 trial conducted at 44 centers in 10 countries. Adults (≥18 years) with candidemia or invasive candidiasis were treated with once-a-week intravenous rezafungin (400 mg and 200 mg) or once-a-day intravenous caspofungin (70 mg and 50 mg). Efficacy was evaluated in a pooled modified intent-to-treat (mITT) population. Primary efficacy endpoint was day 30 all-cause mortality (tested for non-inferiority with a pre-specified margin of 20%). The secondary efficacy endpoint was mycological response. Safety was also evaluated.

ReSTORE was conducted from October 12, 2018, to October 11, 2021, and STRIVE from July 26, 2016, to April 18, 2019. The mITT population, pooling the data from the two trials, comprised 139 patients for rezafungin and 155 patients for caspofungin. Day 30 all-cause mortality rates were comparable between groups (19% [26 of 139] for the rezafungin group and 19% [30 of 155] for the caspofungin group) and the upper bound of the 95% CI for the weighted treatment difference was below 10% (−1·5% [95% CI −10·7 to 7·7]). Mycological eradication occurred by day 5 in 102 (73%) of 139 rezafungin patients and 100 (65%) of 155 caspofungin patients (weighted treatment difference 10·0% [95% CI −0·3 to 20·4]). Safety profiles were similar across

groups. The secondary and exploratory efficacy findings suggest that rezafungin can have an early treatment benefit, including higher mycological eradication rates at earlier timepoints and potentially a faster time to negative culture, particularly in patients with a positive blood culture proximal to randomization. Analyses of all-cause mortality at day 30 among subgroups of patients favored caspofungin in patients younger than 65 years but favored rezafungin in those aged 65 years or older; and favored caspofungin in patients with normal renal function to mild renal impairment but rezafungin in patients with moderate to severe renal impairment.

Comment: Rezafungin is a new FDA approved echinocandin, which is structurally similar to the other three approved echinocandins with an established mechanism of action, but with stability and pharmacokinetics that allow once-weekly intravenous administration and front-loaded dosing. Echinocandins are recommended as a first-line treatment in candidemia and invasive candidiasis. [Clin Infect Dis. 2016; 62: 1-50] Echinocandins act via concentration-dependent killing**.** The early eradication seen with rezafungin versus caspofungin could therefore be attributed to the higher front-loaded exposure of rezafungin versus caspofungin. The treatment differences between caspofungin and rezafungin in all-cause mortality rates from the exploratory subgroup analyses warrant further investigation.

Bottom line: This analysis supports the efficacy and safety of rezafungin in treating candidemia and invasive candidiasis. The availability of rezafungin as a new antifungal is a valuable addition to candidemia and invasive candidiasis treatments and may help to address the growing challenge of treatment-resistant Candida strains and species such as Candida auris.

Sink-traps are a major source for carbapenemase producing *Enterobacteriaceae* transmission

Infect Control Hosp Epidemiol published online December 27, 2023

doi:10.1017/ice.2023.270

Researchers set out to assess the extent and persistence of sink-drain and sink-outlet contamination in their facility and trace the possible transmission to patients. From 2017 to 2019, they sampled 592 patient-room sinks in 34 departments and analyzed isolates from sinks and patients.

A total of 144 (24%) of 592 sinks were contaminated with CPE in 25 of 34 departments, and repeated sampling showed that 52% to 100% were contaminated at least once during the sampling period. During the study period, 318 patients acquired CPE during their hospitalization, with *K pneumoniae* (46%), *E coli* (23%), and *Enterobacter* spp. (23%) the most common species.

In 127 (40%) of these patients, no index case was detected but a contaminated sink was identified with the same CPE strain. In 57 additional cases, researchers identified CPE-contaminated sinks with a different bacterial species than that acquired by the patient but with the same carbapenemase gene (*bla*), which suggests the sink could have been the source of transmission. For 20 cases with an identical sink-patient strain, sink-to-patient transmission was assumed because the sink was contaminated before the patient was hospitalized, and the

patient's initial screening for CPE was negative. The genomic sequencing of two sink-patient isolate pairs identified two plasmids that were nearly identical. During 2 years of follow-up, repeated sink sampling showed that contamination of sink traps with CPE was persistent.

Table 1. CPE Isolates Acquired by 318 Patients According to CP Genes and the Attributed Factor

Acquisition of CPE Genes	No.	Attributed to Another Index Case, No. (%)	Possibly Attributed to a Contaminated Sink, No. (%)[a]	Probably Attributed to a Contaminated Sink, No. (%)[b]	Genetically Identical Sink-Patient Isolates, n/N[c]
KPC	144	20 (13.8)	24 (16.7)	69 (47.9)	12/60
NDM-1	115	19 (16.5)	31 (26.9)	42 (36.5)	16/34
OXA-48	41	5 (12.2)	2 (4.9)	10 (24.4)	7/7
VIM	27	6 (22.2)	1 (1.8)	11 (40.7)	4/6

Note. CPE, carbapenemase-producing Enterobacteriaceae; CP, carbapenemase producing; KPC, carbapenemase-producing *Klebsiella pneumoniae*; NDM-1, New Delhi metallo β-lactamase-1; VIM, Verona integron-encoded; PFGE, pulsed-field gel electrophoresis.
[a]Sink contaminated by a different bacterial specie but with an identical CP gene and no index case suggested.
[b]Sink contaminated by an identical bacterial specie with an identical CP gene and no index case suggested.
[c]No. of patient-sink identical isolates per no. of pairs assessed by PFGE.

Comment: In this study, the investigators have reported the frequency of CPE-contaminated sinks in an acute-care hospital, and they have demonstrated that they are frequently and persistently contaminated with a dominant clone. Most importantly, they have shown that CPE contaminated sinks are not only a source of outbreaks in high-risk units, but that sink-traps serve as an important environmental niche of gram-negative MDRO (specifically CPE) that play a major role in CPE transmission in nonoutbreak settings. Using sequencing methods, they have demonstrated that the sink isolates carried similar plasmids as those found among patients hospitalized in the same hospital room. Particularly disturbing is the lack of reported successful interventions to eliminate sink-trap and wastewater contamination. In their experience, as in previous reports, sink-trap and even full pipe replacement resulted only in a temporary resolution. Similarly poor results were reported with other interventions such as weekly cleaning with acetic acid, bleach, or hydrogen peroxide. Currently, the only effective means to prevent sink-to-patient MDRO transmission may be structural aspects (e.g., eliminating sinks that are not necessary) together with education to address the infectious risks of sinks and prevention of their misuse (no flushing of any substance into the sink and sole use for hand washing).

Not all bacterial isolates were genetically characterized. Furthermore, only in 20 cases could they define the temporal relation, providing direct evidence of sink-to-patient transmission. Frequently, the sinks were sampled only after a CPE carrier patient was already detected. Last, the genetic characterization of the isolates included only PFGE and further genomic investigation of the isolates may lead to further elucidation of the route of transmission between sinks and patients.

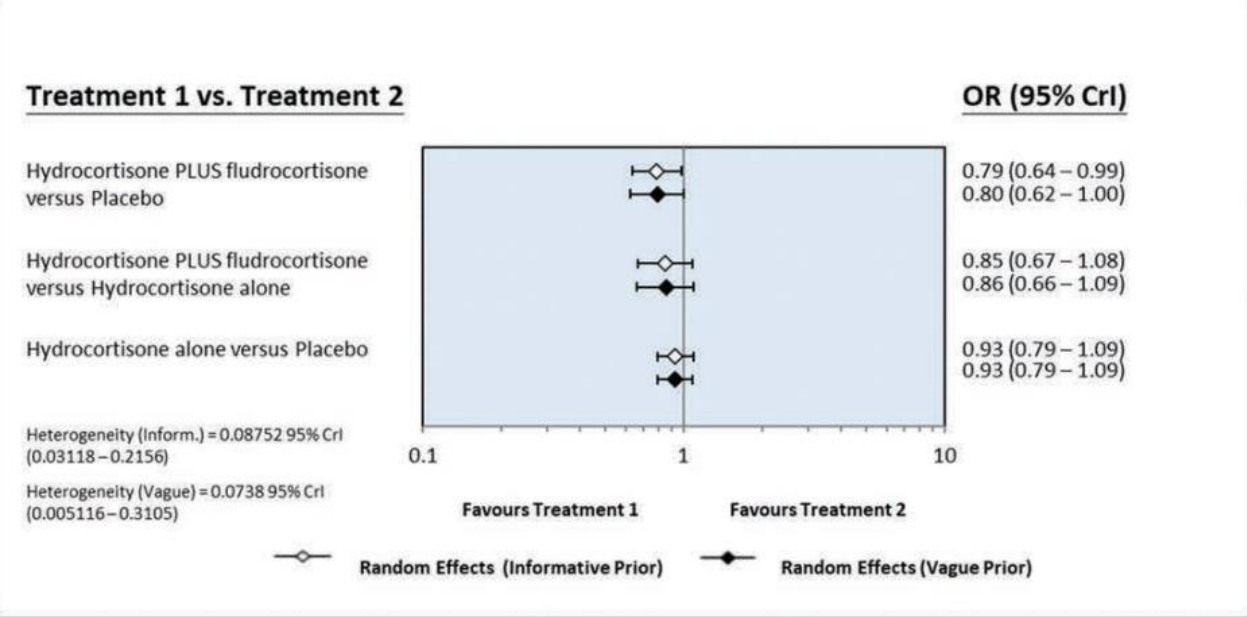
Bottom line: This report adds to the accumulating data indicating the significant role of sinks in CPE transmission and suggests a paradigm change, in which infection control interventions to prevent CPE and other water bound organisms dissemination should focus on environmental control and appropriate behavior regarding the sink and its surroundings.

Do We Need to Administer Fludrocortisone in Addition to Hydrocortisone in Adult Patients With Septic Shock? An Updated Systematic Review With Bayesian Network Meta-Analysis of Randomized Controlled Trials and an Observational Study With Target Trial Emulation Crit Care Med published online December 29, 2023

DOI: 10.1097/CCM.0000000000006161

This is a systematic review and Bayesian network meta-analysis evaluating the efficacy and safety of hydrocortisone combined with fludrocortisone or hydrocortisone alone, compared with placebo in adult patients with septic shock. They extended a prior Cochrane review, databases, including PubMed, Embase, the Cochrane Library, and ClinicalTrials.gov, along with other relevant websites, were searched until August 31, 2023. Randomized controlled trials (RCTs) and observational studies using target trial emulation were included. The primary outcome was short-term mortality with an emphasis on 28- or 30-day mortality as the main measure and in-hospital or ICU mortality as the nearest surrogate of this measure. Three of the most common adverse events, namely, gastroduodenal bleeding, superinfection, and hyperglycemia, were also considered.

A total of 19 studies involving 95,841 patients were included. Hydrocortisone plus fludrocortisone showed the lowest short-term mortality versus placebo (odds ratio [OR]: 0.79; 95% credible interval [CrI], 0.64–0.99; 9; number needed to treat [NNT]: 21, range: 12–500; low certainty of evidence). The surface under the cumulative ranking curve values for hydrocortisone plus fludrocortisone, hydrocortisone alone, and placebo were 0.9469, 0.4542, and 0.0989, respectively. Consistent results were observed in RCTs alone and those using a daily 200-mg dose of hydrocortisone. Although gastroduodenal bleeding or superinfection showed no clear increase, hyperglycemia risk increased. The ORs were 0.53 for placebo versus hydrocortisone plus fludrocortisone and 0.64 for placebo versus hydrocortisone alone, with very low certainty of evidence.



Comment: In adults with septic shock, hydrocortisone plus fludrocortisone improved short-term survival with minimal adverse events compared with hydrocortisone alone or placebo. However, the authors conclude these findings were based on limited certainty of evidence. Their findings indicate that hydrocortisone alone demonstrated marginal benefits over placebo. However, in a recent systematic review, the investigators concluded that the administration of hydrocortisone significantly reduced the 28-day mortality rate among patients with refractory septic shock. [Cureus 2019; 11: e4914] The current paper excluded certain outcomes, such as time to wean off vasopressors, ICU stay length, ventilator-free days, and kidney replacement.

Bottom line: In adults with septic shock, hydrocortisone plus fludrocortisone improves short-term survival with an increased risk of hyperglycemia. However, these findings are not definitive due to the limited certainty of evidence and wide NNT range. Additional large-scale, placebo controlled RCTs are needed to provide more conclusive evidence. In the meantime, I see no reason not to add fludrocortisone.

Transition to Oral Antibiotic Therapy for Hospitalized Adults With Gram-Negative Bloodstream Infections JAMA Network Open. 2024;7(1): e2349864.

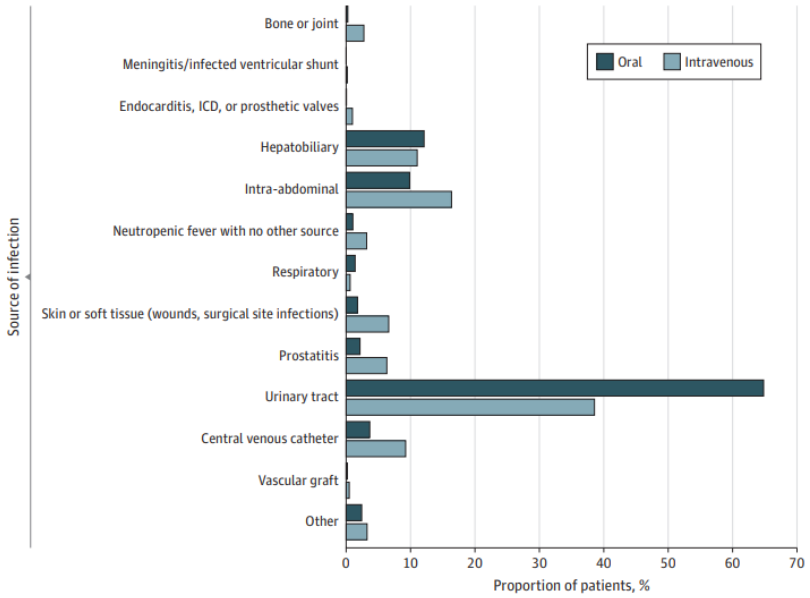
doi:10.1001/jamanetworkopen.2023.49864

This was a retrospective cohort study including 4581 hospitalized adults with GN-BSIs at 24 US hospitals between January 1 and December 31, 2019. Patients were excluded if they died or went into hospice care within 72 hours. Patients were excluded from the oral therapy group if transition occurred after day 7. Baseline characteristics and clinical parameters reflecting severity of illness were evaluated in groups receiving oral and IV therapy. The prevalence of transition from IV to oral antibiotics by day 7, median day of transition, sources of infection, and oral antibiotic selection were assessed. The time limit for evaluating patients' transition to oral therapy was chosen given evidence favoring the duration of only 7 days of antibiotic therapy for uncomplicated GN-BSIs. [Clin Infect Dis. 2019; 69:1091-1098; Clin Infect Dis. 2019; 69:2011-2014]

Of a total of 4581 episodes with GN-BSIs (median age, 67 years [IQR, 55-77 years]; 2389 men [52.2%]), 1969 patients (43.0%) receiving IV antibiotics were transitioned to oral antibiotics by day 7. Patients maintained on IV therapy were more likely than those transitioned to oral therapy to be immunosuppressed (833 of 2612 [31.9%] vs 485 of 1969 [24.6%]; P < .001), require intensive care unit admission (1033 of 2612 [39.5%] vs 334 of 1969 [17.0%]; P < .001), have fever or hypotension as of day 5 (423 of 2612 [16.2%] vs 49 of 1969 [2.5%]; P < .001), require kidney replacement therapy (280 of 2612 [10.7%] vs 63 of 1969 [3.2%]; P < .001), and less likely to have source control within 7 days (1852 of 2612 [70.9%] vs 1577 of 1969 [80.1%]; P < .001). Transitioning patients from IV to oral therapy by day 7 was highly variable across hospitals, ranging from 25.8% (66 of 256) to 65.9% (27 of 41). A total of 4109 patients (89.7%) achieved clinical stability within 5 days. For the 3429 episodes (74.9%) with successful source control by day 7, the median day of source control was day 2 (IQR, 1-3 days) for the oral group and day 2 (IQR, 1-4 days) for the IV group. Common infection sources among patients administered oral therapy were the urinary tract (1277 of 1969 [64.9%]), hepatobiliary (239 of 1969 [12.1%]), and intra-abdominal (194 of 1969 [9.9%]). The median day of oral transition was 5 (IQR, 4-6 days). Total duration of antibiotic treatment was significantly shorter among the oral group than the IV group (median, 11 days [IQR, 9-14 days] vs median, 13 days [IQR, 8-16

days]; P < .001]. Fluoroquinolones (62.2% [1224 of 1969]), followed by β-lactams (28.3% [558 of 1969]) and trimethoprim-sulfamethoxazole (11.5% [227 of 1969]), were the most prescribed oral antibiotics.

Figure 2. Source of Infection Among Patients Transitioned to Oral Antibiotic Therapy vs Intravenous Therapy



ICD indicates implantable cardiac device.

Comment: In this cohort study of 4581 GN-BSI episodes at 24 US hospitals, 43.0% of patients were transitioned to oral antibiotics by day 7; day 5 was the median day of oral transition, most commonly with fluoroquinolones (62.2%). Patients maintained on IV therapy had more severe illness and more comorbidities; however, 89.7% of patients were clinically stable within 5 days and the median day of source control was day 2 for all patients with successful source control by day 7. Most GN-BSI episodes were from urinary sources with Enterobacterales, an area of practice with literature supporting the safety and efficacy of oral transition therapy. Data from the UTI literature, including randomized clinical trials, demonstrate the utility of oral antibiotics and treatment duration of 7 days. [JAMA. 2000; 283:1583-1590] Another retrospective Enterobacterales bacteremia study showed that clinical outcomes with oral transition compared with continued IV therapy did not demonstrate any differences in 30-day all-cause mortality or recurrence of bacteremia and was associated with a decreased length of stay. [Ann Pharmacother. 1996; 30:596-602] This analysis did not assess if there were no active oral agents in each episode that precluded oral transition, which may explain why those with Pseudomonas or extended-spectrum β-lactamase pathogens that have limited oral treatment options typically continued to receive IV therapy. Finally, most GN-BSI episodes in this cohort were secondary to the urinary tract, which may limit generalizability to all cases of GN-BSI. Future prospective research is also needed to provide additional data for developing evidence-based guidelines on the optimal approach to transition to oral antibiotic therapy in GN-BSIs.

Bottom line: There appear to be opportunities for earlier and more frequent oral antibiotic transitions if patients demonstrate clinical stability by day 5 and there is a good oral alternative. Antimicrobial stewardship teams can consider developing targeted education on when transition to oral antibiotics can be considered for GN-BSIs. See next review

Early Switch From Intravenous to Oral Antibiotics for Patients With Uncomplicated Gram-Negative Bacteremia JAMA Network Open. 2024;7(1): e2352314.

doi:10.1001/jamanetworkopen.2023.52314

This was a cohort study conducted using the target trial emulation framework included observational data from adults with uncomplicated gram-negative bacteremia in 4 hospitals from January 1, 2018, through December 31, 2021. The duration of follow-up was 90 days. Eligibility criteria included a blood culture positive for growth of gram-negative bacteria, clinical stability within 4 days of initial blood culture, an available susceptibility report on day 4, and initiation of appropriate empirical IV antibiotic treatment within 24 hours of blood culture. Switching to oral antibiotics within 4 days after initial blood culture was compared with continuing IV antibiotic treatment for at least 5 days after initial blood culture. Choice of IV and oral antibiotic agent after availability of the susceptibility report was at the discretion of the treating physician but had to comply with the susceptibility result. Antibiotic treatment had to be maintained for 7 to 14 days. Individuals who were immunosuppressed (receiving corticosteroid treatment with ≥20 mg of prednisolone equivalent per day for >14 days, HIV positive, having received chemotherapy for <28 days, neutropenia [<1000 μL) , organ transplant recipient, or receiving biological response modifier therapy), transitioned to hospice care within 4 days of the initial blood culture, had an established uncontrolled focus of infection, or had a blood culture with polymicrobial growth or growth of either Acinetobacter, Burkholderia, Pseudomonas, Brucella, or Fusobacterium species were excluded. The main outcome was 90-day all-cause mortality. Inverse probability of treatment weighting was applied to adjust for confounding. Intention-to-treat and per-protocol analyses were performed.

A total of 914 individuals were included in the target trial emulation analysis (512 [56.0%] male; median age, 74.5 years [IQR, 63.3-83.2 years]); 433 (47.4%) transitioned early to oral antibiotic treatment, and 481 (52.6%) received prolonged IV treatment. Ninety-nine individuals (10.8%) died during follow-up. The proportion of individuals who died was higher in the group receiving prolonged IV treatment (69 [14.3%] vs 30 [6.9%]). In the intention-to-treat analysis, 90-day all-cause mortality risk was 9.1% (95% CI, 6.7%-11.6%) for the early-switch group and 11.7% (95% CI, 9.6%-13.8%) for the group receiving prolonged IV treatment; the RD[risk difference] was −2.5% (95% CI, −5.7% to 0.7%) and RR[risk ratio] was 0.78 (95% CI, 0.60-1.10). In the per-protocol analysis, the RD was −0.1% (95% CI, −3.4% to 3.1%) and RR was 0.99 (95% CI, 0.70-1.40).

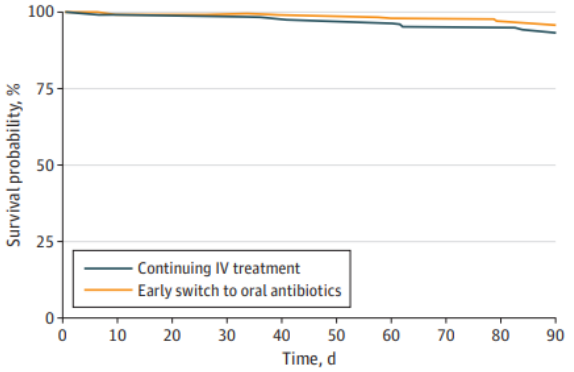
C

Table 3. Inverse Probability–Weighted 90-Day Risk of All-Cause Mortality Among Individuals With Gram-Negative Bacteremia Continuing IV Antibiotic Therapy vs Early Switch to Oral Antibiotic Therapy

Analysis	90-d Risk of all-cause mortality, % (95% CI)		90-d Risk difference (95% CI)	90-d Risk ratio (95% CI)
	Early oral switch	Continuing IV treatment		
Intention-to-treat	9.1 (6.7-11.6)	11.7 (9.6-13.8)	−2.5 (−5.7 to 0.7)	0.78 (0.60 to 1.10)
Per-protocol	9.6 (6.7-12.4)	9.7 (7.6-11.8)	−0.1 (−3.4 to 3.1)	0.99 (0.70 to 1.40)

Abbreviation: IV, intravenous.

Figure 2. Weighted Survival Curves for Individuals Who Continued or Switched to Early Oral Antibiotics



No. at risk										
Continuing IV treatment	481	367	346	340	333	327	323	319	318	315
Early switch to oral antibiotics	433	381	378	375	371	370	366	365	360	360

IV indicates intravenous.

Comment: This study used a target trial framework to estimate the potential effectiveness of early oral stepdown therapy in individuals with uncomplicated gram-negative bacteremia. Overall, they found comparable rates of 90-day all-cause mortality between clinically stable individuals transitioning early to oral antibiotics compared with individuals receiving prolonged IV antibiotic treatment. As anticipated, individuals in this study who received prolonged IV antibiotics were older, had more severe progression of bacteremia, and had a higher burden of comorbidities compared with individuals switching early to oral treatment. Although IPTW [inverses probability treatment weights]adjusted for these differences at baseline, the investigators hypothesized that receiving antibiotics beyond the defined total treatment duration might indicate a more complex disease progression. The observed larger RD in the intention-to-treat analysis compared with the per-protocol analysis may be indicative of these underlying factors. Not surprisingly, they found a higher mortality risk in the intention-to-treat analysis in the subgroup including patients older than 75 years, as the older subpopulation was more likely to have severe disease progression and a higher burden of comorbidities. However, the per-protocol analysis yielded the same absolute risk as the main analysis, suggesting no difference in risk between the 2 treatment groups despite the age difference.

Prior studies reported success for patients with uncomplicated bacteremia switching to oral treatment within 3 to 5 days. [Int J Antimicrob Agents. 2016; 48:498-503; Int J Antimicrob Agents. 2018; 51:687-692] Recent studies recommend a total treatment duration of 7 days for uncomplicated gram-negative bacteremia.

As with any observational study based on information from electronic health records, important confounders may have been incompletely recorded or absent, and it is possible that we were

unable to consider all variables affecting the decision to switch patients to oral stepdown treatment. The incidence of MDR-GN infections in this study was small.

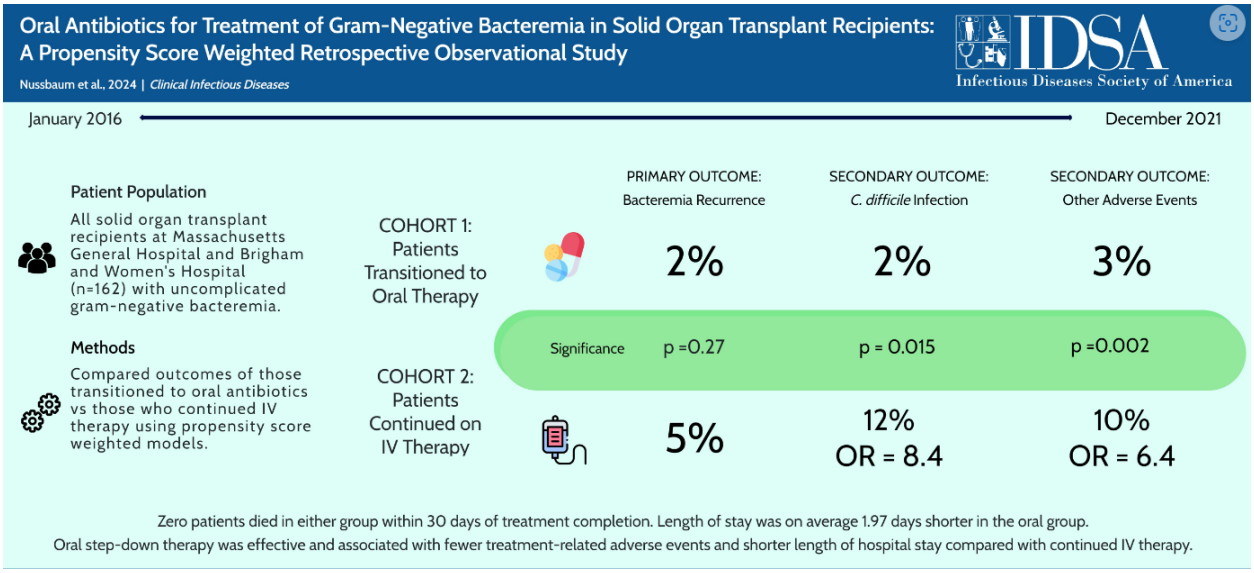
Bottom line: As other studies reviewed in this edition of ID Watch and recent prior studies, IV to PO step down is as effective and possibly safer if we have an appropriately active PO alternative. See next review.

Oral Antibiotics for Treatment of Gram-Negative Bacteremia in Solid Organ Transplant Recipients: A Propensity Score Weighted Retrospective Observational Study Clin Infect Dis published online January 9, 2024

DOI: 10.1093/cid/ciae007

The investigators identified all solid organ transplant recipients within the Massachusetts General and Brigham and Women's Hospital systems from 2016-2021 with uncomplicated gram-negative bacteremia involving an organism susceptible to an acceptably bioavailable oral antibiotic agent. Using inverse probability of treatment-weighted(IPTW) models based on propensity scores adjusting for potential clinical confounders, they compared outcomes of those transitioned to oral antibiotics vs those who continued IV therapy for the duration of treatment. Primary endpoints were mortality, bacteremia recurrence and re-initiation of IV antibiotics. Secondary endpoints included length of stay, C. difficile infection, treatment associated complications and tunneled central venous catheter placement.

120 bacteremia events from 107 patients met inclusion criteria in the oral group and 42 events from 40 patients in the IV group. There were no significant differences in mortality, bacteremia recurrence, or re-initiation of IV antibiotics between groups. Patients transitioned to oral antibiotics had an average length of stay that was 1.97 days shorter (95% CI -0.39, 3.56 days. p=0.005). Odds of developing C. difficile and other treatment associated complications were 8.4 times higher (95% CI 1.5, 46.6, p=0.015) and 6.4 times higher (95% CI 1.9-20.9, p=0.002), respectively, in the IV group. 55% of patients in the IV group required tunneled catheter placement. There was no difference in treatment duration between groups.



Comment: This study demonstrated there were no significant differences in mortality, bacteremia recurrence or re-initiation of IV therapy between the oral and IV groups. IV treatment was in fact associated with an increased incidence of C difficile infection as well as other treatment-related adverse events. In addition, the majority (55%) of patients in the IV group required placement of new tunneled central venous catheters to facilitate continued IV treatment. The retrospective nature of this study raises the concern that treating clinicians may have chosen healthier patients to transition to oral therapy, potentially reserving continued IV therapy for patients in whom there was greater clinical concern. The investigators aimed to mitigate this concern as much as possible via use of IPWT models, using propensity scores incorporating the factors they thought might influence the decision to use oral vs. continued IV therapy, as well as other validated tools such as the Pitt bacteremia score and Charlson comorbidity index. Patients transitioning to oral therapy actually had a higher median admission Pitt bacteremia score (0.92 vs 0.74) and higher median Charlson comorbidity score (6 vs 5.5), suggesting that it was not healthier patients transitioning to oral therapy. The study is limited by a small sample size, particularly in the IV cohort. The majority of patients in both groups were kidney transplant recipients with a urinary source, which may have implications for the generalizability of our findings, though 41% of patients in the oral group had a source of infection outside of the urinary tract.

Bottom line: Oral step-down therapy was effective and associated with fewer treatment-related adverse events in this immunocompromised patient population. This is one of many recent articles demonstrating oral therapy involving an organism susceptible to an acceptably bioavailable oral antibiotic agent is safe and effective.

Prosthetic joint infections: 6 weeks of oral antibiotics results in a low failure rate J Antimicrob Chemother published online December 19, 2022

doi.org/10.1093/jac/dkad382

Evidence suggests that shorter antibiotic courses and early oral antibiotic therapy (OAT) may provide similar outcomes as prolonged intravenous courses, although results have been inconsistent. Investigators in France performed a multisite retrospective study involving 172 patients (60% male) and 38 orthopedic surgeons. PJI most often affected the knee (50%) and hip (35%), and *Staphylococcus* spp. comprised the most common pathogen genus. In 76% of patients, implants were retained after surgical debridement. Most patients (77%) initially received parenteral antibiotic therapy (typically daptomycin plus piperacillin-tazobactam and vancomycin-based therapy) for a median 5 days. OAT was initiated first in 40 patients (most commonly fluroquinolone + rifampicin) for a median total duration of 42 days. Failure rates were 16% for patients receiving >3 days of initial parenteral therapy and 9% for patients receiving OAT after <3 days of parenteral treatment. Risk factors for treatment failure included PJI in the knee, polymicrobial infection, and vancomycin-based therapy.

Comment: This study shows that early OAT in the right hands represents a viable option to IV therapy. The analysis reflects the experience of 3 ID docs with extensive experience. Larger more heterogenous prospective studies should help provide further guidance. Based on this study, OAT should focus on non-knee PJI and monomicrobial infections.

Efficacy and safety of a structured de-escalation from antipseudomonal β-lactams in bloodstream infections due to Enterobacterales (SIMPLIFY): an open-label, multicentre, randomised trial Lancet Infect Dis published online January 9, 2024

doi.org/10.1016/ S1473-3099(23)00686-2

This was an open-label, pragmatic, randomized trial performed in 21 hospitals. Patients with bacteremia caused by Enterobacterales susceptible to one of the de-escalation options and treated empirically with an antipseudomonal β-lactam were eligible. Patients were randomly assigned (1:1; stratified by urinary source) to de-escalate to ampicillin, trimethoprim–sulfamethoxazole (urinary tract infections only), cefuroxime, cefotaxime or ceftriaxone, amoxicillin– clavulanic acid, ciprofloxacin, or ertapenem in that order according to susceptibility (de-escalation group), or to continue with the empiric antipseudomonal β-lactam (control group). Oral switching was allowed in both groups. The primary outcome was clinical cure 3–5 days after end of treatment in the modified intention-to-treat (mITT) population, in patients who received at least one dose of study drug. Safety was assessed in all participants. Non-inferiority was declared when the lower bound of the 95% CI of the absolute difference in cure rate was above the –10% non-inferiority margin.

2030 patients were screened between October 5, 2016, and January 23, 2020, of whom 171 were randomly assigned to the de-escalation group and 173 to the control group. 164 (50%) patients in the de-escalation group and 167 (50%) in the control group were included in the mITT population. 148 (90%) patients in the de-escalation group and 148 (89%) in the control group had clinical cure (risk difference 1·6 percentage points, 95% CI –5·0 to 8·2). The number

of adverse events reported was 219 in the de-escalation group and 175 in the control group. Of these, 53 (24%) in the de-escalation group and 56 (32%) in the control group were considered severe. Seven (5%) of 164 patients in the de-escalation group and nine (6%) of 167 patients in the control group died during the 60-day follow-up. There were no treatment-related deaths.

Comment: De-escalation includes discontinuation of unnecessary drugs or switching to narrower-spectrum antibiotics as targeted therapy, based on microbiological data or clinical re-evaluation. The results of the different outcomes, subgroups, and DOOR analyses were consistent and supported the noninferiority hypothesis; when time of exposure to antipseudomonal β-lactams was considered, de-escalation was actually superior. The same investigators recently performed an observational study in patients with Enterobacterales bacteremia initially treated with antipseudomonal agents, in which de-escalation was not associated with worse outcomes in a propensity score-adjusted analysis.[Clin Infect Dis 2019; 69: 956–62] The antipseudomonals have consistently been associated with an increased risk of colonization and infection with multidrug-resistant P aeruginosa and Enterobacterales.[J Antimicrob Chemother 2015; 70: 3004–13; EClinicalMedicine 2023; 57: 101871] The investigators performed an exploratory study on the acquisition of multidrug resistant Gram-negative bacteria in a small subset of patients. The results are encouraging, suggesting that once the efficacy and safety of de-escalation have been demonstrated, these variables could be a primary endpoint in future trials of de-escalation from antipseudomonal drugs. Regarding C difficile infection, they could not show any impact because the number of reported cases was very low. [see study above] A study published in 2019 showed that the use of empirical antipseudomonal β-lactams for more than 48 hours was an independent risk factor for C difficile infection. [Clin Infect Dis 2019; 69: 414–20] The various antibiotic options in both groups, reflecting actual practice, meaning the study could not be blinded. Duration of treatment in most patients was longer than recommended for Enterobacterales bacteremia based on the recent trial results supporting 7 days as an appropriate duration in most patients. [EClinicalMedicine 2023; 55: 10175031 and others] The rectal colonization study was performed on a low number of patients.

Bottom line: This trial is important because it confirms the safety of antibiotic de-escalation. De-escalation from antipseudomonal β-lactams in patients with bacteremia caused by Enterobacterales was non-inferior in clinical efficacy to continuing the initial drug. This is another study demonstrating de-escalation to an appropriate oral antibiotic is effective and perhaps safer than continuing IV broad spectrum antibiotics.

Fluoroquinolone antibiotics: Prescribe only as last resort, says UK regulator BMJ 2024;384:q183

doi.org/10.1136/bmj.q183

As of 22 January, fluoroquinolone given systemically by mouth, injection, or inhalation must be given only when there are no alternative antibiotics appropriate for use, the safety update said. Fluoroquinolones should be prescribed only when other recommended antibiotics have failed, will not work because of resistance, or are unsafe to use in individual patients, the regulator added.

Comment: This was a safety update the Medicines and Healthcare Products Regulatory Agency. The recommendations highlight serious adverse reactions to fluoroquinolones include tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy, and central nervous system effects. While I agree that fluoroquinolones can cause serious adverse effects and have been overprescribed, this recommendation may be going too far. As articles above demonstrate due to high oral bioavailability of fluoroquinolones these antimicrobials can be prescribed effectively for IV to PO stepdown de-escalation and may be safer than continuing IV broad spectrum antibiotics.

Bottom line: Fluoroquinolones have been overprescribed leading to increased resistance, therefore are not suitable for empiric therapy and have serious side effects. However, under certain situations, they may be appropriate for oral step down therapy decreasing the need for long term IV therapy.

Mortality, hospital length of stay, and recurrent bloodstream infections associated with extended-spectrum beta-lactamase-producing Escherichia coli in a low prevalence region: A 20-year population-based large cohort study Int J Infect Dis 2024; 138:84-90

doi.org/10.1016/j.ijid.2023.11.007

The study population was defined as patients aged ≥15 years with *E. coli* BSI in Queensland, Australia, from 2000 to 2019. Outcomes were defined as 30-day case fatality, hospital length of stay (LOS), and recurrent E. coli BSI.

A total of 27,796 E. coli BSIs were identified, of which 1112 (4.0%) were ESBL-producers. Patients with ESBL-Ec BSI were more frequently older, male, with comorbidity, recurrent E. coli BSI, and less likely with community-associated community-onset infections as compared to non-ESBL-Ec BSI patients. The standardized mortality rate of ESBL-Ec BSI increased 8-fold from 2000 to 2019 (1 to 8 per million residents) and case fatality was 12.8% (n = 142) at 30 days from positive blood culture. Patients with ESBL-Ec BSI were not at higher risk of 30-day case fatality (adjusted hazard ratio [HR] = 0.98, 95% CI: 0.83-1.17), but had higher risk of recurring episodes (adjusted subdistribution HR = 1.58, 95% CI: 1.29-1.92) and observed 14% longer LOS (adjusted incidence rate ratio = 1.14, 95% CI: 1.10-1.18) than non-ESBL-Ec BSI patients

Comment: The incidence of E coli producing extended-spectrum beta-lactamase (ESBL-Ec) is increasing. The standardized mortality rate of ESBL-Ec bloodstream infection (BSI) increased 8-fold from 2000 to 2019. ESBL-Ec BSI was associated with 14% longer hospital stay than non-

ESBL-Ec BSI. ESBL-Ec was associated with a higher risk of E. coli BSI recurrence than non-ESBL-Ec BSI. In patients with ESBL-Ec BSI with recurrence, median duration to next episode was 165 days. Older age, male, having comorbidity, and non-urogenital sources of infection were predictors of case fatality.

A systematic review and metanalysis of other smaller observational studies had reported higher likelihood of death in patients with ESBL-Ec BSI, however, the significance of this association did not persist when pooling adjusted effect estimates [JAC Antimicrob Resist 2021;3]. These results all suggest that while factors including older age, comorbidity, and polymicrobial infection present more frequently in patients with ESBL-Ec BSI, these factors likely have greater and direct influence on case fatality risk rather than ESBL production itself. This was a retrospective cohort study that utilized coded data collected over 20 years and the accuracy of these data could not be validated. They could not access data on antibiotic therapy for each of the E. coli BSI episodes. Current literature on the effects of delay in appropriate antibiotic therapy on clinical outcomes in patients with ESBL-Ec infections has been variable [J Clin Microbiol 2010; 48:1726–31; BMC Infect Dis 2018; 18:625; meta-analysis. Front Med (Lausanne) 2022; 9:869822] There is substantial literature demonstrating increased mortality in septic shock if there is a delay on starting appropriate antibiotics. Unfortunately, this study could not elucidate the association between ESBL-Ec BSI and case fatality when mediated by appropriateness of antibiotic therapy.

Bottom line: This population-based study reported longer hospital LOS and higher frequency of recurrent BSI in patients with ESBL-Ec BSI as compared to those with non-ESBL-Ec BSI. Many of us are seeing substantial increases in ESBL infections, especially in the ICU. This trend has compelled us to consider empiric carbapenems for ICU patients with suspected severe infections/ septic shock due to gram-negatives until culture results are available. Timely de-escalation is essential if cultures do not grow an ESBL. More studies are needed to try and identify risk factors for ESBL infections.

Coverage gaps in empiric antibiotic regimens used to treat serious bacterial infections in neonates and children in Southeast Asia and the Pacific The Lancet Regional Health - Southeast Asia Published Online October 31, 2023

doi.org/10. 1016/j.lansea.2023. 100291

To assess the coverage provided by commonly prescribed empiric antibiotic regimens for children in low and middle-income countries in Southeast Asia and the Pacific, the investigators built a weighted incidence syndromic combination antibiogram (WISCA), parameterized using data obtained from a systematic review of published literature incorporating WHO-defined SEARO and WPRO regions in Ovid MEDLINE, EMBASE, Global Health and PubMed. Susceptibility data for bacterial pathogens were extracted to provide coverage estimates for pre-specified antibiotics (aminopenicillins, gentamicin, third generation cephalosporins and carbapenems), reported at the regional level.

6648 bacterial isolates from 11 countries across 86 papers were included in the Bayesian WISCA model, which weighted bacterial incidence and antimicrobial susceptibility of relevant isolates. Coverage provided by aminopenicillins in neonatal sepsis/meningitis was 26% (80%

credible interval: 16–49) whilst gentamicin coverage was 45% (29–62). Third-generation cephalosporin coverage was only 29% (16–49) in neonatal sepsis/meningitis, 51% (38–64) in pediatric sepsis and 65% (51–77) in pediatric meningitis. Carbapenems were estimated to provide the highest coverage: 81% (65–90) in neonatal sepsis/meningitis, 83% (72–90) in pediatric sepsis and 79% (62–91) in pediatric meningitis.

The most common pathogens isolated in neonatal sepsis/meningitis were Klebsiella spp. (39%, 1337 isolates) and Escherichia coli (27%, 910 isolates), with Streptococcus agalactiae (GBS) only reported in 1% of cases (20 isolates). Acinetobacter spp. and Staphylococcus aureus were also isolated in a sizeable proportion of neonatal sepsis cases (515 [15%] and 447 [13%] of cases, respectively). In pediatric sepsis, E. coli (26%, 2538 isolates), S. aureus (20%, 1924 isolates) and Streptococcus pneumoniae (13%, 1298 isolates) were the most commonly isolated pathogens; Salmonella spp. (15%, 1464) and Klebsiella spp. (18%, 1816 isolates) were also reported. This is similar to the profile of pathogens identified in cases of pediatric meningitis, with S. agalactiae (14%, n = 136) also isolated in a sizeable proportion of cases (predominantly occurring in the post-neonatal period) whilst S. pneumoniae was the most important cause of pediatric meningitis in older children (43%, 421 isolates) followed by E. coli (27%, 269 isolates).

Antibiotic	Neonatal sepsis/ meningitis	Paediatric sepsis (>1 month)	Paediatric meningitis (>1 month)
Aminopenicillin	26 (16, 39)	37 (26, 49)	62 (51, 77)
Gentamicin	45 (29, 62)	39 (28, 51)	21 (12, 30)
Third-generation cephalosporins	29 (16, 49)	51 (38, 64)	65 (51, 77)
Carbapenems	81 (65, 90)	83 (72, 90)	79 (62, 91)

Comment: These findings reveal alarmingly high rates of resistance to commonly prescribed empirical therapies for neonatal and pediatric sepsis and meningitis in the Asia–Pacific region. While coverage estimates are informative for understanding rates of non-susceptibility to currently recommended first- and second-line antibiotic regimens, it is important to note that widespread use of carbapenem-containing antibiotic regimens may accelerate further gram-negative resistance. The microbiology in this study is somewhat different than the US experience. For early neonatal sepsis/meningitis E coli is the most common followed by GBS. In this study only 1% of cases were due to GBS. For pediatric sepsis, Salmonella is uncommon in the US. I selected this article since we live in a global community. Fortunately, the US is not seeing this level of resistance in neonates and pediatrics, but this may give us a glimpse of what may be coming if we are not proactive in addressing global AMR.

Bottom line: Currently recommended empirical regimens for neonates and children with sepsis and meningitis provide limited coverage in Southeast Asia and the Pacific. New regimens with improved efficacy to treat these common infectious conditions in children are urgently needed.

Editor's Choice

A novel antibiotic class targeting the lipopolysaccharide transporter Nature published online January 3, 2024

doi.org/10.1038/s41586-023-06873-0 R

Carbapenem-resistant Acinetobacter baumannii (CRAB) has emerged as a major global pathogen with limited treatment options. The investigators report the identification and optimization of tethered macrocyclic peptide (MCP) antibiotics with potent antibacterial activity against CRAB. The mechanism of action of this molecule class involves blocking the transport of bacterial lipopolysaccharide from the inner membrane to its destination on the outer membrane, through inhibition of the LptB2FGC complex. A clinical candidate derived from the MCP class, zosurabalpin (RG6006), effectively treats highly drug-resistant contemporary isolates of CRAB both in vitro and in mouse models of infection, overcoming existing antibiotic resistance mechanisms.

To assess the potential of zosurabalpin for the treatment of severe invasive CRAB infections, its in vitro activity was evaluated against 129 human clinical isolates of A. baumannii derived from a range of infection sites. This panel was enriched for difficult-to-treat isolates (78%)32 and MDR (80%) isolates. The MIC required to inhibit growth of 90% of these isolates was 1 mg l−1 (MIC90; range, ≤0.016–4 mg l−1). The pharmacokinetic properties of zosurabalpin were examined both in single-dose and multiple-dose pharmacokinetic studies in mice, revealing acceptable plasma exposures after s.c. administration with high clearance (51 ml min−1 kg−1), a low volume of distribution (0.7 l kg−1), a short terminal half-life (0.3 h) and moderate protein binding (fraction unbound, 37%).

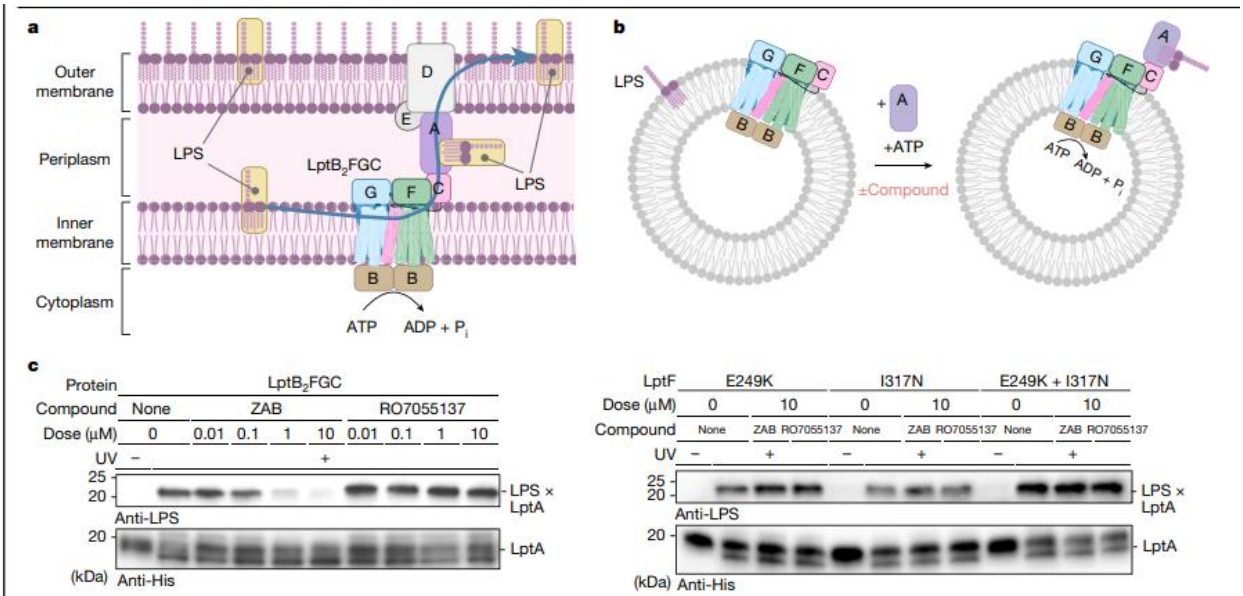


Fig. 3 | Zosurabalpin kills cells by inhibiting $LptB_2FGC$ function. a, Schematic of the trans-envelope lipopolysaccharide transporter. The inner-membrane complex $LptB_2FGC$ is an ATP-binding cassette that uses ATP hydrolysis to extract LPS from the inner membrane and transport it to the cell surface. P_i, inorganic phosphate. **b**, In vitro assay monitoring the release of LPS from proteoliposomes containing $LptB_2FGC$ complexes to $LptA^{I36pBPA}$–His7 by ultraviolet irradiation cross-linking and detection of LPS–$LptA^{I36pBPA}$–His7 adducts by LPS immunoblotting (Methods). The diagrams in **a** and **b** were created using BioRender. **c**, Zosurabalpin (ZAB) inhibits LPS transport in vitro by wild-type $LptB_2FGC$ to LptA, whereas the structurally related inactive control compound RO7055137 (Fig. 1a) displays no LPS transport inhibition at comparable doses. Two amino acid substitutions, LptF(E249K) and LptF(I317N), that decreased the susceptibility of *Acinetobacter* to zosurabalpin were tested both individually and together. All three variants were resistant to compound treatment (Extended Data Table 6). Activity assays were conducted in biological triplicate, and representative blots are shown. UV, ultraviolet irradiation.

Comment: This chemical class represents a promising treatment paradigm for patients with invasive infections due to CRAB, for whom current treatment options are limited, and additionally identifies LptB2FGC as a tractable target for antimicrobial drug development.

Bottom line: We certainly need better antimicrobial agents to treat CRAB. More studies are needed to look at safety and efficacy in humans.

Editor's Choice

Taurolidine/Heparin Lock Solution and Catheter-Related Bloodstream Infection in Hemodialysis A Randomized, Double-Blind, Active-Control, Phase 3 Study Clinical J Am Soc Nephrology 202318: 1446–1455

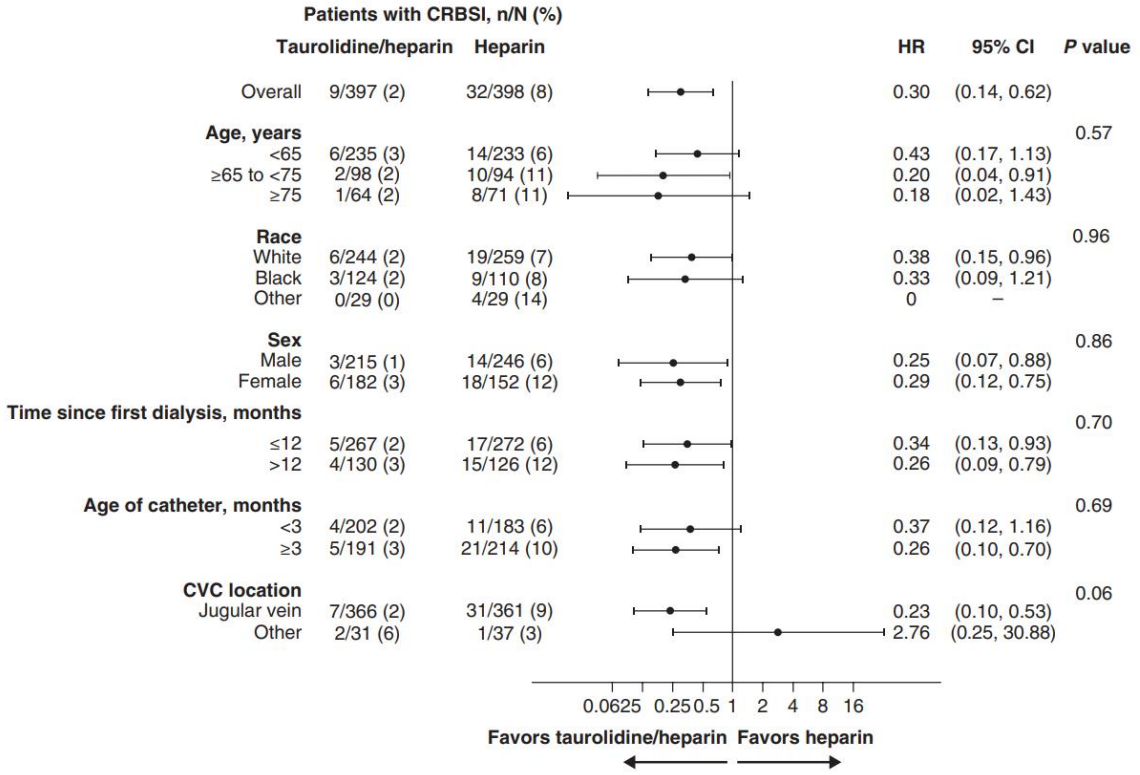
doi.org/10.2215/CJN.0000000000000278

LOCK IT-100 was a randomized, double-blind, active-control, multicenter, phase 3 study that enrolled adults with kidney failure undergoing maintenance hemodialysis via CVC from 70 US sites. Participants were randomized 1:1 to taurolidine/heparin catheter lock solution or heparin control catheter lock solution (1000 units/ml). The primary end point was time to CRBSI as assessed by a blinded Clinical Adjudication Committee. Secondary end points were catheter removal for any reason and loss of catheter patency. Eligible participants were aged 18 years or older and underwent hemodialysis >2 times per week in an outpatient hemodialysis unit.

Catheters were required to be in place for >14 days and to have been used successfully to dialyze the participant >2 times before enrollment. Exclusion criteria included treatment with antibiotics ≤14 days of enrollment, catheter exit-site infection, thrombolytic treatment (i.e., tissue plasminogen activator) in the patient's current catheter ≤30 days of randomization, systemic immunosuppression (e.g., patients actively on immunosuppressants), or malignancy with life expectancy ≤ 6 months.

Taurolidine/heparin is a novel antimicrobial catheter lock solution that combines taurolidine 13.5 mg/ml and heparin (1000 units/ml). Taurolidine is an antibacterial and antifungal agent with a mechanism of action that does not lend itself to resistance. Taurolidine/heparin is designed to be instilled and dwell in the arterial and venous lumens of the CVC after each hemodialysis. It is aspirated before initiation of the next session, without intended systemic administration. Heparin is the current standard-of-care catheter lock solution to prevent thrombosis. Heparin, however, does not have any antimicrobial properties.

In the full analysis population (N=795), nine participants in the taurolidine/heparin arm (n5397; 2%) and 32 participants in the heparin arm (n=398; 8%) had a CRBSI. Event rates per 1000 catheter days were 0.13 and 0.46, respectively, with the difference in time to CRBSI being statistically significant, favoring taurolidine/ heparin (P < 0.001). The hazard ratio was 0.29 (95% confidence interval, 0.14 to 0.62), corresponding to a 71% reduction in risk of CRBSIs with taurolidine/heparin versus heparin. There were no significant differences between study arms in time to catheter removal for any reason or loss of catheter patency. The safety of taurolidine/heparin was comparable with that of heparin, and most treatment-emergent adverse events were mild or moderate. Based on a prespecified interim analysis, the Data and Safety Monitoring Board recommended terminating the trial early for efficacy with no safety concerns.



Comment: The finding in this study of a 71% reduction in CRBSIs with the use of taurolidine/heparin is consistent with the findings of two earlier studies in hemodialysis patients. [Semin Dial. 2012;25(2):233–238; QJM. 2014;107(12): 995–1000] Based on these studies the FDA has approved taurolidine/heparin in this population. The recent SHEA/IDSA/APIC guidelines on prevention of prevent central line-associated bloodstream infections in acute-care hospitals recommends as an additional approach that antimicrobial locks be considered for individuals with chronic CVCs who are at high risk for CRBSI.[Infect Control Hosp Epidemiol 2022;43:553-569] The availability of taurolidine/heparin will benefit patients who have no choice besides a dialysis CVC because they have run out of possible sites for arteriovenous access. Fistulas and grafts are the preferred arteriovenous access.

Bottom line: These findings support the use of taurolidine/heparin in hemodialysis patients to reduce risk of CRBSIs, which are associated with significant clinical and quality of life benefits in this population.

Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023 MMWR 2024; 72:1385-1389

During July 7–11, 2023, CDC received reports of two patients in different states with a tuberculosis (TB) diagnosis following spinal surgical procedures that used bone allografts containing live cells from the same deceased donor. An outbreak associated with a similar product manufactured by the same tissue establishment occurred in 2021. [MMWR 2021; 70:1261–3] Because of concern that these cases represented a second outbreak, after receiving the first case report, CDC notified the FDA requested that the tissue establishment quarantine any remaining tissue from this donor (i.e., same product lot). On July 11, the tissue establishment quarantined the 53 units that had not yet been distributed and provided a list of all health care facilities that had purchased tissue units from that lot. Eight hospitals and five dental offices in seven states (California, Louisiana, Michigan, New York, Oregon, Texas, and Virginia) received a total of 50 bone allograft units from this product lot during February 27–June 20, 2023CDC and the FDA worked with the tissue establishment to determine that this product was obtained from a donor different from the one implicated in the 2021 outbreak and learned that the bone allograft product was distributed to 13 health care facilities in seven states. Notifications to all seven states occurred on July 12. As of December 20, 2023, five of 36 surgical bone allograft recipients received laboratory-confirmed TB disease diagnoses; two patients died of TB! WGS demonstrated close genetic relatedness between positive Mycobacterium tuberculosis cultures from surgical recipients and unused products. Although the bone product had tested negative by nucleic acid amplification testing before distribution, M. tuberculosis culture of unused product was not performed until after the outbreak was recognized.

Comment: After the 2021 outbreak, tissue establishments considered whether to perform nucleic acid amplification testing for M. tuberculosis in tissues that retain live cells before distribution. The tissue establishment involved in both investigations voluntarily implemented such testing for bone allografts but did not detect the M. tuberculosis contamination of this second product lot. Although extremely useful for diagnosing TB disease, nucleic acid amplification tests are less sensitive than are the slower culture-based tests for identifying M. tuberculosis. [Lancet Infect Dis 2022; 22:1617–25] Therefore, more comprehensive laboratory

evaluations for M. tuberculosis in donor tissues could include culture-based testing, which can take up to 8 weeks for final confirmation. In this outbreak, M. tuberculosis was not identified from liquid cultures of the donor specimen until day 40 after inoculation. The public health response prevented up to 53 additional surgical procedures using allografts from that donor; additional measures to protect patients from tissue-transmitted M. tuberculosis are urgently needed.

Bottom line: This second outbreak of bone allograft–related TB in recent years underscores the urgent need to implement improved donor screening and culture-based testing to prevent tissue derived M tuberculosis transmission.

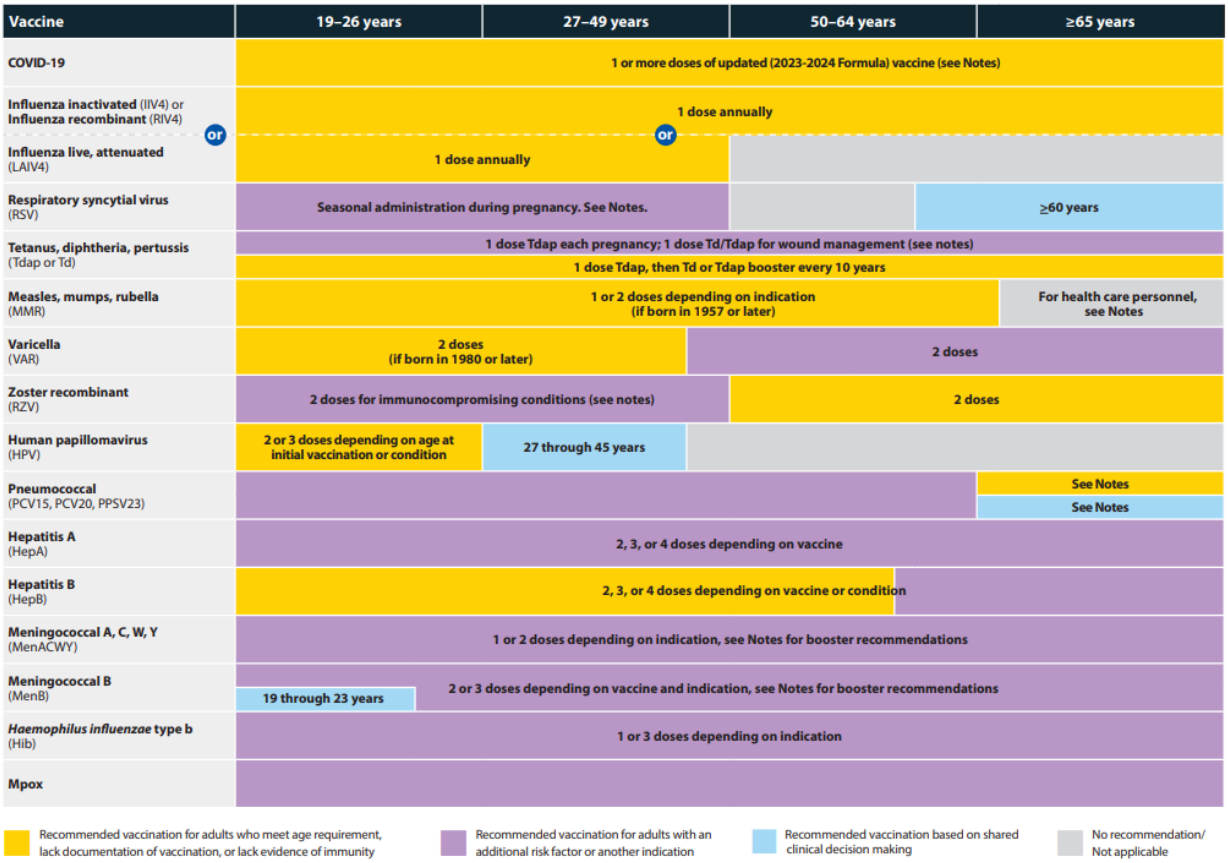
Recommended Adult Immunization Schedule, United States, 2024 Ann Intern Med published online January 12, 2024

doi:10.7326/ M23-3269

Key changes

- RSV vaccines: Two RSV vaccines are now available (Abrysvo and Arexvy). In people 60 years of age or older, either RSV vaccine can be administered, but should be based on shared decision-making that considers risk factors for severe disease, risk of exposure to RSV, patient preferences, and clinical judgement. Only Abrysvo is recommended for pregnant persons at 32 weeks through 36 weeks gestation during the 2023-2024 winter season to protect both the recipient and neonates. (Alternatively, infants can be immunized with the monoclonal antibody nirsevimab [Beyfortus]).
- COVID-19 vaccine**:** All adults should receive at least one dose of the updated 2023-2024 formula of the COVID-19 vaccine. The number of doses needed and intervals between doses may vary depending on a patient's prior vaccination history, whether they are immunocompromised, and the vaccine product used.
- Mpox vaccine: All adults in any age group who are at increased risk of becoming infected with mpox (e.g., men who have sex with men, diagnosis of a sexually transmitted infection, multiple sex partners, etc.) should receive a two-dose series of the mpox vaccine (Jynneos).
- Meningococcal vaccine: MenACWY-D (Menactra) was removed from the schedule because the product is no longer available in the U.S. The new pentavalent meningococcal vaccine MenACWY-TT/MenB-FHbp (Penbraya) was added. This vaccine can be used for additional MenACWY and MenB doses if both are given on the same clinic day and at least 6 months have elapsed since the most recent Penbraya dose.
- Polio vaccine: If adults are known or suspected to be unvaccinated or incompletely vaccinated for polio, they should complete a three-dose primary series. However, most adults who were born and raised in the U.S. can assume that they were vaccinated against polio during childhood. If previously vaccinated adults are at increased risk for exposure to polio, they may receive a single booster of inactivated poliovirus vaccine.
- Hepatitis B vaccine: People ages 60 years or older without known risk factors for hepatitis B may receive the hepatitis B vaccine series, and any adult over 60 who requests the vaccine should receive it, as well as those with risk factors.
- Flu vaccine: Routine annual vaccination continues to be recommended for all people ages 6 months and older who do not have contraindications. All seasonal influenza

vaccines for 2023-2024 are quadrivalent. People with egg allergies can receive egg-based vaccines appropriate for their age and health status.



Comment: In an editorial entitled “Quality health communication is critical to optimal adult immunization.” [Ann Intern Med published online January 12, 2024] the authors point out how difficult it is to navigate through increasingly convoluted tables. They point out the table simply “won’t do.” Given declining vaccine update the authors [and I agree] need to collaborate with professional communicators to create solutions of organizing and presenting the information to healthcare professionals. Below highlights recommendations for pneumococcal vaccination.

New ACIP Recommendations Pneumococcal Vaccination

This report summarizes all published recommendations from CDC's Advisory Committee on Immunization Practices (ACIP) for use of pneumococcal vaccines in adults aged ≥19 years in the United States. This report also includes updated and new clinical guidance for implementation from CDC.

Before 2021, ACIP recommended 23-valent pneumococcal polysaccharide vaccine (PPSV23) alone (up to 2 doses), or both a single dose of 13-valent pneumococcal conjugate vaccine (PCV13) in combination with 1–3 doses of PPSV23 in series (PCV13 followed by PPSV23), for use in U.S. adults depending on age and underlying risk for pneumococcal disease. In 2021, two new pneumococcal conjugate vaccines (PCVs), a 15-valent and a 20-valent PCV (PCV15

and PCV20), were licensed for use in U.S. adults aged ≥18 years by the Food and Drug Administration.

ACIP recommendations specify the use of either PCV20 alone or PCV15 in series with PPSV23 for all adults aged ≥65 years and for adults aged 19–64 years with certain underlying medical conditions or other risk factors who have not received a PCV or whose vaccination history is unknown. In addition, ACIP recommends use of either a single dose of PCV20 or ≥1 dose of PPSV23 for adults who have started their pneumococcal vaccine series with PCV13 but have not received all recommended PPSV23 doses. Shared clinical decision-making is recommended regarding use of a supplemental PCV20 dose for adults aged ≥65 years who have completed their recommended vaccine series with both PCV13 and PPSV23.

Updated and new clinical guidance for implementation from CDC includes the recommendation for use of PCV15 or PCV20 for adults who have received PPSV23 but have not received any PCV dose. The report also includes clinical guidance for adults who have received 7-valent PCV (PCV7) only and adults who are hematopoietic stem cell transplant recipients.

Adults aged ≥19 years with an immunocompromising condition, a CSF leak, or a cochlear implant who have received both PCV13 and PPSV23 with incomplete vaccination status are recommended to complete their pneumococcal vaccine series by receiving either a single dose of PCV20 at an interval at least 5 years after the last pneumococcal vaccine dose or ≥1 dose of PPSV23.

— When a second PPSV23 is used instead of PCV20, it should be administered ≥8 weeks after the PCV13 dose and ≥5 years after the first PPSV23 dose for adults aged 19–64 years with an immunocompromising condition but not for adults with a CSF leak or a cochlear implant. In addition, adults with an immunocompromising condition, a CSF leak, or a cochlear implant who have received both PCV13 and PPSV23 (no PCV20) but have not received a dose of PPSV23 at age ≥65 years are recommended to receive either PCV20 or a single final dose of PPSV23 at age ≥65 years and ≥5 years since the previous PPSV23 dose.

Shared clinical decision-making is recommended regarding PCV20 use for adults aged ≥65 years who have completed the recommended vaccine series with both PCV13 (at any age) and PPSV23 (which was administered at age ≥65 years). Unlike routine, catch-up, and risk-based recommendations, shared clinical decision-making vaccinations are not recommended for everyone in a particular age group or everyone in an identifiable risk group. Rather, shared clinical decision-making recommendations are individually based and guided by a decision process between the health care provider and the patient or guardian.

Adults aged ≥19 years who have received PCV13 only are recommended to receive a single dose of PCV20 at an interval ≥1 year after receipt of the PCV13 dose or to receive ≥1 dose of PPSV23 to complete their pneumococcal vaccine series.

— When PPSV23 is used instead of PCV20, the minimum recommended interval between PCV13 and PPSV23 administration is ≥8 weeks for adults with an immunocompromising condition, a CSF leak, or a cochlear implant and ≥1 year for adults without these conditions. Either PCV20 or a second PPSV23 dose is recommended ≥5 years after the first PPSV23 dose for adults aged 19–64 years with specified immunocompromising conditions but not for adults with a CSF leak or a cochlear implant. In addition, those who received both PCV13 (at any age) and PPSV23 (no PCV20) but have not received a dose of PPSV23 at age ≥65 years are

recommended to receive either PCV20 or a single and final dose of PPSV23 at age ≥65 years and ≥5 years since the previous PPSV23 dose.

Bottom line: Vaccinations to prevent vaccine preventable diseases is one of the most important advances in public health. Given the decrease in the uptake of recommended vaccinations we need a new communication plan for both healthcare professionals and as well as the public.

CDC alerts healthcare providers about measles cases January 25, 2024

The CDC urged healthcare providers to be alert for patients who have fever and rashes and have traveled abroad, following reports of 23 measles cases since December 1, 2023.

"The increased number of measles importations seen in recent weeks is reflective of a rise in global measles cases and a growing global threat from the disease," the CDC said in an email.

In other recent developments, Virginia officials warned of measles exposures at two international airports, New Jersey confirmed a case in Camden County, and Georgia reported a case in Cobb County involving an unvaccinated resident of the metro Atlanta area who had recently traveled outside the country.

Comment: Measles is among the most contagious infections, and the virus can linger in the air for up to two hours. In Europe, reported measles cases rose more than 40-fold last year compared with 2022 according to the WHO. Most cases in the US have been linked to travel outside the country. For every 1,000 cases in children, one child may become deaf or intellectually disabled, and one to three may die. Deaths from measles rose worldwide by 43 percent between 2021 and 2022 according to the WHO and CDC. For measles to remain under control, at least 95 percent of the population must be immunized. More than 1.8 million infants missed their measles vaccinations between 2020 and 2022.

Bottom line: Be on the alert for patients who have fever and rashes and have traveled abroad. Measles is a disease preventable by vaccination. We cannot let our guard down. Measles is not a benign disease.

Effectiveness of Recombinant Zoster Vaccine(RZV) Against Herpes Zoster in a Real-World Setting Ann Inten Med published online January 9, 2024

doi:10.7326/M23-2023

The study included nearly 2.0 million persons who contributed 7.6 million person-years of follow-up. After adjustment, VE of 1 dose was 64% and VE of 2 doses was 76%. After 1 dose only, VE was 70% during the first year, 45% during the second year, 48% during the third year, and 52% after the third year. After 2 doses, VE was 79% during the first year, 75% during the second year, and 73% during the third and fourth years. Vaccine effectiveness was 65% in persons who received corticosteroids before vaccination and 77% in those who did not.

Comment: Two doses of RZV were highly effective, although less effective than in the previous clinical trials. Two-dose effectiveness waned very little during the 4 years of follow-up. However,

1-dose effectiveness waned substantially after 1 year, underscoring the importance of the second dose. Herpes zoster could not be identified as accurately in these observational data as in the previous clinical trials.

Bottom line: RZV is very effective. This article highlights the importance of getting the second dose.

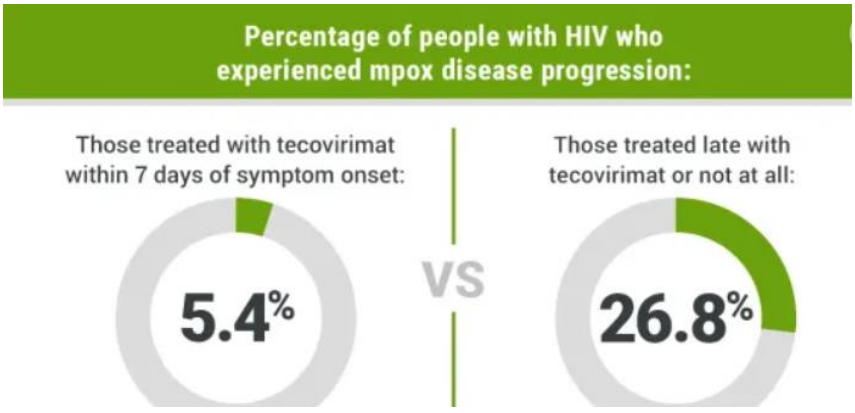
Early Tecovirimat Treatment for Mpox Disease Among People With HIV JAMA Intern Med published online January 8, 2024

doi:10.1001/jamainternmed.2023.7696

Despite limited data in humans, tecovirimat was widely prescribed to people with HIV (PWH) with mpox during the 2022 mpox epidemic, particularly PWH with low $CD4^+$ T-cell counts or severe mpox clinical manifestations. The purpose of this study was to evaluate if PWH with mpox who were treated with tecovirimat within 7 days of symptom onset were less likely to have mpox disease progression.

Patients were grouped according to whether they were treated with tecovirimat within 7 days of mpox symptom onset (early tecovirimat cohort) or they did not receive tecovirimat or received the drug 7 or more days after symptom onset (late or no tecovirimat cohort). Multivariable logistic regression models were used to identify factors associated with progression of mpox disease. The 2 cohorts were then matched 1:1 using propensity scores based on the identified factors, and mpox disease progression was compared.

After propensity score matching, a total of 112 PWH were included in the analysis; 56 received tecovirimat within 7 days of mpox symptom onset and 56 were either treated later or did not receive tecovirimat. In the early tecovirimat group, the median (IQR) age was 35 (30-42) years; 54 individuals (96.4%) were cisgender men, 46 (82.1%) were Black individuals, and 10 (17.9%) were individuals of other races (American Indian or Alaska Native, Asian, Native Hawaiian or Other Pacific Islander, or White) or unknown race. In the late or no tecovirimat group, the median (IQR) age was 36 (32-43) years; 54 (96.4%) were cisgender men, 49 (87.5%) were Black individuals, and 7 (12.5%) were individuals of other races or unknown race. Mpox disease progression occurred in 3 PWH (5.4%) in the early tecovirimat group and in 15 PWH (26.8%) in the late or no tecovirimat group (paired odds ratio, 13.00 [95% CI, 1.71-99.40]; $P = .002$).



Comment: Roughly 5.4% of the 56 treated and 26.8% of the 56 untreated or late-treated patients progressed, representing an odds ratio of 11.0 (95% CI, 1.4-85.1) for progression among the no/late-treated population compared with early. Progression was defined as

developing at least 1 severe mpox criterion after day 7 of symptoms. The CDC recommends tecovirimat treatment in patients with severe disease or those with involvement of anatomic areas, which might result in scarring or strictures. They also recommend that treatment be considered for those at high risk of developing severe disease, specifically those with immunocompromise, pediatric populations, pregnant or breastfeeding people, and those with conditions affecting their skin integrity. Tecovirimat is currently available in 2 ways. The CDC enables clinicians to apply via an expanded-access investigational drug application to obtain the drug for patients. While clinicians need to register, they do not have to obtain their own investigational drug application to treat patients. However, only those patients who fit the CDC recommendations for treatment are eligible for the drug. This would not include a person with HIV with a high CD4 count and undetectable viral load. A second path to the drug is that patients with mpox, regardless of their level of immunodeficiency, are eligible to enroll in a randomized placebo-controlled trial evaluating the efficacy of mpox.

Although this study has methodological rigor in matching, the study remains susceptible to the threat of selection bias and residual confounding inherent in observational studies. The wide confidence intervals reported for the odds ratio suggest statistical imprecision, likely due to small sample size. There is concern that broad use of tecovirimat could result in resistant virus. Second, mpox does not appear to be a severe disease in healthy people with HIV. Lastly efficacy data for tecovirimat through randomized clinical trials are critical for determining the appropriate uses of the drug, as well as optimal dose and duration of therapy for FDA approval.

Bottom Line: Tecovirimat should be started in all PWH especially with low CD4 counts as soon as an mpox diagnosis is suspected. Additional research is warranted to confirm these findings.

Detecting Mpox Cases Through Wastewater Surveillance — United States, August 2022–May 2023 MMWR 2024; 73:37-43

This study included samples which that collected from August 2022 through May 2023. People with mpox are assumed to shed the virus for up to 25 days after symptom onset, and the investigators wanted to determine the sensitivity and positive and negative predictive value (PPV and NPV) of wastewater mpox section.

The investigators defined PPV as the probability that at least one person was shedding virus when a wastewater detection occurred. NPV was defined as the probability that no one was shedding virus when there were zero wastewater detections.

In a single week, from samples representing thousands to millions of persons, a wastewater mpox detection had a sensitivity of 32% for detecting one or more people shedding mpox virus, 49% for detecting five or more people shedding virus, and 77% for detecting 15 or more people shedding virus.

The PPV was 72.6% for predicting a single case per day (95% confidence interval [CI], 61.8% to 81.8%) and 61.9% (95% CI, 48.8% to 73.9%) for predicting a case weekly. The NPV for predicting the absence of anyone shedding mpox virus in a county on a given day or week was 72.9% (95% CI , 70.5% to 75.2%) and 80.3% (95% CI, 76.2% to 84.0%), respectively.

Comment: When Mpox virus was detected in wastewater on a single day or week, it was likely (but not always) at least one case present in the county. On the other hand, non-detection of Mpox virus in wastewater provides reassurance to public health officials that large numbers of cases are not present in communities where wastewater surveillance is sampled.

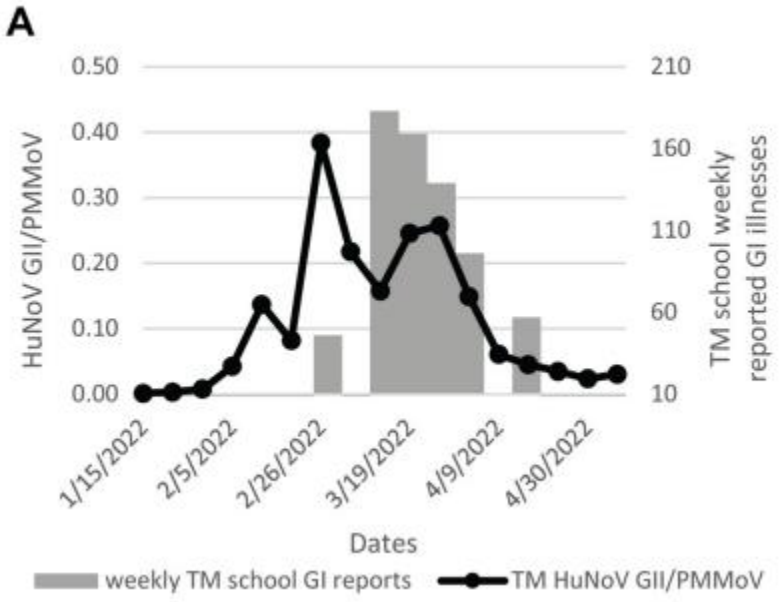
Bottom line: Wastewater surveillance is a useful public health tool to detect increase cases in the community which can lead to effective interventions such as mobile vaccination units and education. See next review.

Norovirus GII wastewater monitoring for epidemiological surveillance PLOS Water 3(1): e0000198.

doi.org/10.1371/journal. pwat.0000198

For the study, the investigators sampled wastewater samples from five communities in southeastern Michigan, mostly between July 2021 and July 2022. Communities included Ann Arbor, Flint, Jackson, Tecumseh, and Ypsilanti. They compared the detections with syndromic surveillance findings as well as digital epidemiologic sources such as search term data.

Wastewater RNA detections were highest in the winter and spring and were comparable across all five sampling sites. To assess the timeliness of norovirus wastewater testing compared with syndromic, outbreak and search term trend data for norovirus, they quantified human norovirus GII in composite influent samples from 5 wastewater treatment plants (WWTPs) using reverse transcription-digital droplet PCR and correlated wastewater levels to syndromic, outbreak, and search term trend data. Wastewater human norovirus GII RNA levels were comparable across all WWTPs after fecal content normalization using Pepper mild mottle virus (PMMoV). Norovirus wastewater signals typically led to syndromic, outbreak, and search-term trend data.



Comment: Norovirus surveillance using case reports and syndromic detection often lags rather than leads outbreaks. Wastewater sampling for norovirus can provide an early and accessible warning system that has the advantage of detecting virus from people who have mild or asymptomatic infections. Unlike other monitoring methods, wastewater tracking doesn't depend on healthcare seeking, clinical testing, or inference based on other patterns. A limitation of this and future studies is the lack of gold standard case data for norovirus which required us to consider correlations across multiple epidemiological datasets to validate wastewater detection.

Bottom line: This is another example that wastewater surveillance provides valuable signals of disease before an increase in reportable clinical cases.

Clinical Impact of Multiplex Molecular Diagnostic Testing in Children With Acute Gastroenteritis Presenting to an Emergency Department: A Multicenter Prospective Study Clin Infect Dis published online December 14, 2023

In a prospective study partially funded by the manufacturer of the multiplex PCR panel. They used the BIOFIRE FILMARRAY gastrointestinal (GI) panel assay for multiplex PCR testing. Investigators enrolled 1157 children with gastroenteritis (GE) (mean age, 4.9 years; 571 in a preintervention group [clinician-based testing] and 586 in an intervention group [stool samples assessed with molecular testing]). Return visits to healthcare providers within 10 days were documented.

During the preintervention period, diagnostic testing was performed in 14.0% of participants and a treatable pathogen was detected in 2.5%. During the intervention period, 627 pathogens (most often viral) were detected in 74.0% of participants. C difficile was the only pathogen detected in 8 (preintervention) versus 23 (intervention) children aged ≥2 years. Univariate analysis showed no difference in likelihood of return visits in the preintervention and intervention groups (32% and 30%), and no between-group difference in proportion of children who received antibiotics. Multivariate adjusted analysis showed a 21% drop in return healthcare visits in the intervention group, but no difference in return emergency department (ED) visits or hospitalizations. Season at enrollment and racial/ethnic composition differed between groups.

Multiplex molecular testing substantially increased detection of potential pathogens, including treatable pathogens and those that warranted withholding of empiric antibiotics. The pre-intervention and intervention periods were not balanced by a number of key variables associated with diarrheal disease.

Pathogen	Pre-Intervention		Intervention	
	Standard-of-Care Clinician-Ordered Tests (N = 571)	Multiplex PCR (N = 375), Clinician Blinded to Results	Standard-of-Care Clinician-Ordered Rests (N = 586)	Multiplex PCR (N = 586), Results Available to Clinician
Bacteria				
Campylobacter	4 (0.7%)	13 (3.5%)	1 (0.2%)	11 (1.9%)
Salmonella	2 (0.4%)	11 (2.9%)	6 (1.0%)	18 (3.1%)
Shigella/enteroinvasive E. coli	9 (1.6%)	33 (8.8%)	4 (0.8%)	24 (4.1%)[a]
Plesiomonas	…	0 (0)	…	2 (0.3%)
Yersinia	…	0 (0)	…	2 (0.3%)
Shigatoxin-producing *E. coli*	4 (0.7%)	14 (3.7%)	1 (0.2%)	14 (2.4%)
Escherichia coli O157	4 (0.7%)	3 (0.8%)	1 (0.2%)	3 (0.5%)
Enterotoxigenic *E. coli*	…	10 (2.7%)	…	6 (1.0%)
Enteroaggregative *E. coli*	…	21 (5.6%)	…	36 (6.1%)
Enteropathogenic *E. coli*	…	76 (20%)	…	67 (11.4%)
Clostridioides difficile	2 (0.4%)	43 (11.5%)	6 (0.6%)	94 (16.0%)[b]
C. difficile no virus and aged ≥2 y	1 (0.2%)	8 (2.1%)	1 (0.2%)	23 (3.9)
Viruses				
Adenovirus F 40/41	1 (0.2%)	33 (8.8%)	1 (0.2%)	61 (10.4%)
Astrovirus	…	6 (1.6%)	…	43 (7.3%)[a]
Norovirus GI/GII	…	57 (15.2%)	…	148 (25.3%)[a]
Rotavirus	2 (0.4%)	16 (4.3%)	1 (0.2%)	12 (2.0%)
Sapovirus	…	31 (8.3%)	…	66 (11.3%)
Any viral pathogen	3 (0.6%)	135 (36%)	2 (0.4%)	294 (50%)[a]
Protozoa	…	18 (3.1)	…	23 (3.9%)
Cryptosporidium	…	10 (2.7%)	…	14 (2.4%)
Cyclospora	…	0 (0)	…	0 (0)
Giardia	…	9 (2.4%)	…	9 (1.5%)
At least 1 potential pathogen	19 (3.3%)	262 (70%)	15 (3%)	434 (74%)
Any treatable pathogen[c]	14 (2.5%)	65 (17.3%)	5 (0.9%)	61 (10.4%)
Any clinically relevant pathogen[d]	16 (2.8%)	84 (22.4%)	12 (2%)	88 (15%)

During the pre-intervention period, multiplex PCR testing was performed on stored stool specimens and not available to clinicians. During the intervention period, multiplex testing was performed in real time and available to clinicians.

Abbreviation: PCR, polymerase chain reaction.

[a] $P < .01$ for difference between pre-intervention and intervention prevalence by multiplex PCR.

[b] $P < .05$ for difference between pre-intervention and intervention prevalence by multiplex PCR.

Comment: Advantages of molecular diagnostics over traditional stool culture include increased sensitivity for pathogen detection and faster turnaround time, potentially resulting in improvements in appropriate use of antibiotics. They found that multiplex molecular testing of all patients identified a potentially treatable pathogen in a higher proportion (17.3%) of patients during the pre-intervention period compared with clinician-ordered testing (3.2%) as well as clinically relevant pathogens (22% vs 2.8%). However, they did not detect a significant improvement in overall appropriate antibiotic prescribing among children with a treatable pathogen. In this study the main benefit of using molecular diagnostics in children with GI disease was a 21% reduction in return visits with no effect on antimicrobial use, ED visits, or hospitalization. A study limitation included a major Shigella outbreak at one site and group imbalance. Nonetheless this study highlights the need to examine cost-effectiveness of GI molecular platforms and if these tests provide differences in meaningful outcomes. Cost savings attributable to a multiplex diagnostic panel have been shown in an inpatient population [J Clin Microbiol 2018; 56: e01457-17; Pediatrics 2021; 147:e2020036954; J Clin Microbiol 2019; 57:e01775-18] and in a study of adults [J Clin Microbiol 2023; 61: e0162822] but, to my knowledge, not among pediatric ED patients.

Bottom line: Routine molecular multiplex testing for all children who presented to the ED with acute gastroenteritis did detect more clinically relevant pathogens and led to a 21% decrease in return visits, but no differences in antimicrobial use or hospitalizations. Additional research is needed to define patients most likely to benefit from testing in ED setting.

Burden of medically-attended diarrhea and outpatient *Clostridioides difficile* infection among persons in two large integrated healthcare settings, 2016-2021 OFID published online January 11, 2024

DOI: 10.1093/ofid/ofad680

This was a retrospective cohort study among patients ≥18 years of age from Kaiser Permanente Southern California (KPSC) and Northwest (KPNW) from 01/01/2016–12/31/2021. Medically attended diarrhea (MAD) was identified by outpatient diarrheal ICD-10 diagnosis codes, and CDI through positive laboratory results. Outpatient CDI was defined by no hospitalization ≤7 days after specimen collection. Incidence rates (IRs) of outpatient CDI were stratified by select demographic and clinical variables. Outpatient CDI burden 12 months following index date was measured by CDI-associated healthcare visits, and CDI testing and treatment.

They identified 777,533 MAD episodes; 12.1% (93,964/777,533) were tested for CDI. Of those CDI-tested, 10.8% (10,110/93,964) were positive. Outpatient CDI IR was 51.0 (95% confidence interval [CI]: 49.8–52.2) per 100,000 PY, decreasing from 58.2 (95% CI: 55.7–60.7) in 2016 to 45.7 (43.7–47.8) in 2021. 44.1% (n=4,200) received an antibiotic 30 days prior to index date and 84.1% (n=8,006) CDI were 'community-associated' (no hospitalizations 12 weeks prior to index date). 6.7% (n=526) of outpatient CDIs had a CDI-associated hospitalization ≤12 months.

Comment: There was a high incidence of outpatient CDI despite infrequent CDI testing among patients with MAD. The majority of those with outpatient CDI had no recent antibiotic use and no recent hospitalization. The lack of recent antibiotic use or hospitalization among many of the identified outpatient CDI cases suggests other factors, such as transmission within households, could be contributing to the occurrence of CDI in the general community. Further studies are needed to understand the source and management of medically attended outpatient CDI. They were unable to completely capture a history of long-term care facility or nursing home stays, thus it is possible that some outpatient CDI cases occurred among patients within those settings and that some cases classified as community-associated actually had a history of a stay in a healthcare facility in the weeks and months preceding their CDI diagnosis. Although this study showed that patients with outpatient CDI do not utilize high levels of healthcare, this study could not directly measure illness severity or the impact of CDI on their quality-of-life.

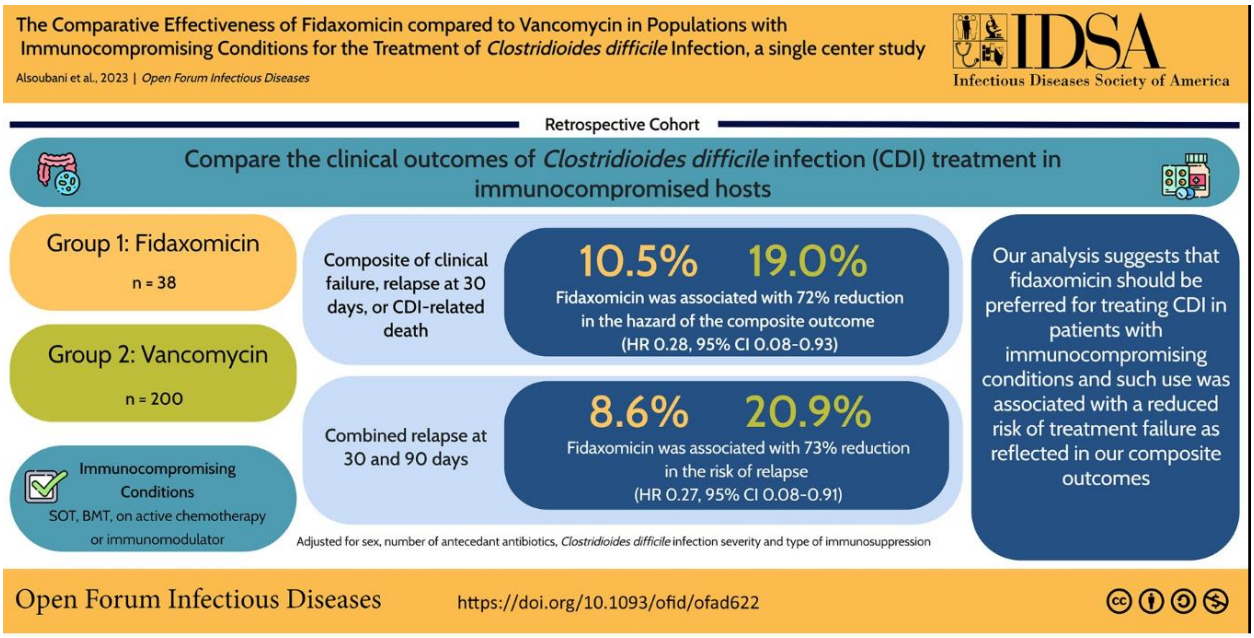
Bottom line: Outpatient CDI may be more common than previously thought. Additional studies are needed to define risk factors.

Comparative Effectiveness of Fidaxomicin vs Vancomycin in Populations With Immunocompromising Conditions for the Treatment of *Clostridioides difficile* Infection: A Single-Center Study OFID published online December 8, 2023

This was a single-center retrospective study evaluating patients with CDI between 2011 and 2021. The primary outcome was a composite of clinical failure, relapse at 30 days, or CDI-related death. A multivariable cause-specific Cox proportional hazards model was used to test

the relationship between treatment and the composite outcome, adjusting for confounders and treating death from other causes as a competing risk. CDI was defined as a diarrheal illness with a positive stool assay for C difficile that was associated with the initiation of treatment by the treating provider. The investigators reviewed physician notes to confirm that the presence of diarrhea, abdominal pain, or ileus on clinical presentation was consistent with CDI for each case. A test result was considered positive if glutamate dehydrogenase antigen and toxin assays were positive or if a nucleic acid amplification test (NAAT) result was positive. Clinical failure was defined as any conversion or additional use of antimicrobials >72 hours after initiation of therapy by the treating physician for perceived treatment failure. Relapse at 30 days was defined as recurrence of diarrhea and/or the need to restart CDI treatment within 30 days of stopping therapy for the index CDI case, as determined by the treating physician with or without a positive test result. Relapse at 90 days was defined as recurrence of diarrhea and/or the need to restart CDI treatment between 30 and 90 days of stopping therapy for the index CDI case, as determined by the treating physician with or without a positive test result. Severe CDI was defined per the criteria of the Infectious Diseases Society of America (IDSA): leukocytosis with white cell count ≥15 000 cells/mL or serum creatinine >1.5 mg/dL. Hospital-acquired CDI was defined as infection diagnosed after 48 hours following admission to the hospital. Health care–associated CDI was defined as exposure to a health care facility within 30 days prior to diagnosis.

The study analyzed 238 patients who were immunocompromised and treated for CDI with oral fidaxomicin (n = 38) or vancomycin (n = 200). There were 42 composite outcomes: 4 (10.5%) in the fidaxomicin arm and 38 (19.0%) in the vancomycin arm. After adjustment for sex, number of antecedent antibiotics, CDI severity and type of immunosuppression, fidaxomicin use significantly decreased the risk of the composite outcome as compared with vancomycin (10.5% vs 19.0%; hazard ratio, 0.28; 95% CI, .08–.93). Furthermore, fidaxomicin was associated with 70% reduction in the combined risk of 30- and 90-day relapse following adjustment (hazard ratio, 0.27; 95% CI, .08–.91).



Comment: The findings of this study suggest that the use of fidaxomicin for treatment of CDI reduces poor outcomes in patients who are immunocompromised. However, this was a retrospective single-center study with a limited sample size. All treatment decisions were determined by the treating physician, which may have led to confounding by indication. Although they adjusted for potential confounders, it is possible that residual confounding remained. They performed a sensitivity analysis excluding patients treated with vancomycin for >30 days and demonstrated results similar to the primary analysis. The guidelines of the IDSA and European Society of Clinical Microbiology and Infectious Diseases were updated to recommend fidaxomicin as the first line of treatment. [Clin Infect Dis 2021; 73: e1029–44; Clin Microbiol Infect 2021; 27(suppl 2): S1–21]

Bottom line: Their analysis suggests that fidaxomicin should be the first line for treating CDI in patients with immunocompromising conditions. Future multicenter studies are needed to confirm their findings.

The combined effect of systemic antibiotics and proton pump inhibitors on *Clostridioides difficile* infection and recurrence

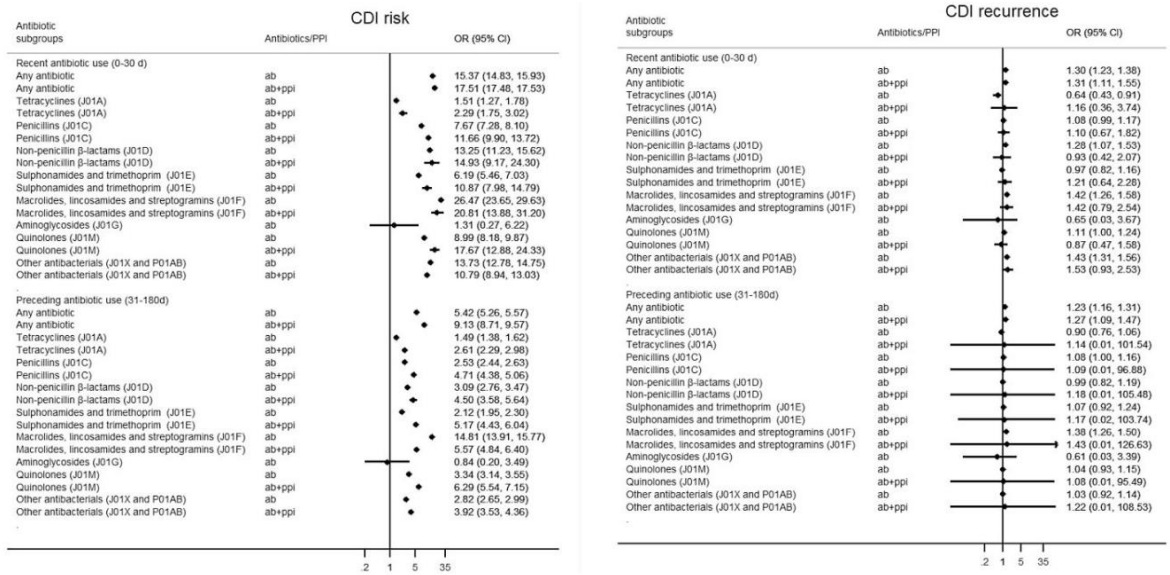
J Antimicrob Chemother published online January 24, 2024

doi.org/10.1093/jac/dkae012

This is a population-based study including all 43152 patients diagnosed with CDI in Sweden (2006–2019), and 355,172 matched population controls without CDI. The impact of antibiotics and PPIs on CDI risk and recurrence was explored for recent (0–30 days) and preceding (31–180 days) use prior to their first CDI diagnosis, using multivariable conditional logistic regression presented as odds ratios (ORs) and 95% confidence interval, adjusted for demographics, comorbidities, and other drugs.

Overall, 63% and 39% of patients with CDI were at some point exposed to antibiotics and PPIs before infection, respectively, compared with 16% and 14% of controls. When recently exposed to both, the odds for CDI were 17.51 (95% confidence interval [CI], 17.48 to 17.53) higher than among those not exposed, while the odds ratio [OR] was 15.37 (95% CI, 14.83 to 15.93) for antibiotics alone and 2.65 (95% CI, 2.54 to 276) for PPI alone. The effect of preceding use was less pronounced, with an OR of 9.13 (95% CI, 8.71 to 9.57) for combined use, 5.42 (95% CI, 5.26 to 5.57) for antibiotics alone, and 2.08 (95% CI, 2.01 to 2.15) for PPI alone.

While recent antibiotic use resulted in slightly higher odds of recurrent CDI (OR, 1.30; 95% CI, 1.23 to 1.38), recent PPI use was not associated with CDI recurrence (OR, 1.03; 95% CI, 0.94 to 1.12), and the combined effect was no different than the effect of antibiotics alone. Recent macrolides/lincosamides(clindamycin)/streptogramins, other antibacterials including nitroimidazole derivates, non-penicillin beta lactams, and FQs showed the strongest association with CDI risk and recurrence, particularly for recent use.



Comment: This large Swedish population-based study showed that recent and preceding outpatient use of all antibiotic classes, except for the rarely used aminoglycosides and tetracyclines to a lesser extent, was associated with a significantly increased risk of CDI with macrolides, lincosamides(clindamycin) and streptogramins showing the largest increase (OR= 26). There was an interaction with PPIs, particularly with FQs, for which the OR of CDI went up from 9 to 18 compared to population controls. Compared to those with CDI yet without recurrence, antibiotic use prior to the first episode seemed predictive for only some antibiotic classes with limited interaction with PPIs.

Bottom line: These findings stress the need to reconsider the risk-benefit of both antibiotics and PPIs, which are both still over-prescribed.

Respiratory Viruses by the Numbers

Numbers for all three of the main respiratory viruses declined this past week, and new data from the CDC suggest that the current flu season has been moderate so far and that people with chronic conditions continue to make up the bulk of flu hospitalizations.

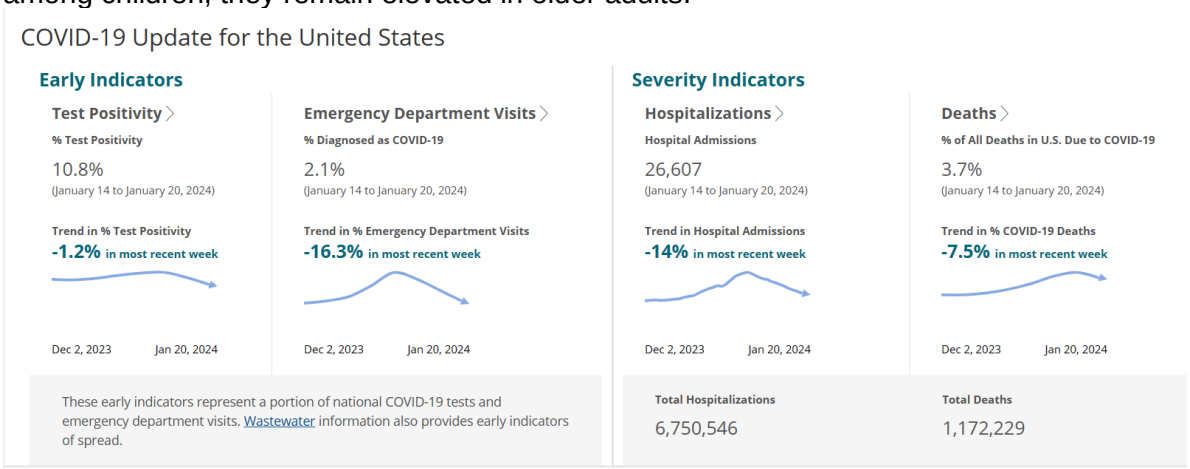
In its respiratory virus snapshot, the CDC said activity is still elevated but decreasing across most of the country. More specifically, flu and Covid-19 activity are stabilizing or decreasing, and RSV infections continue to decline.

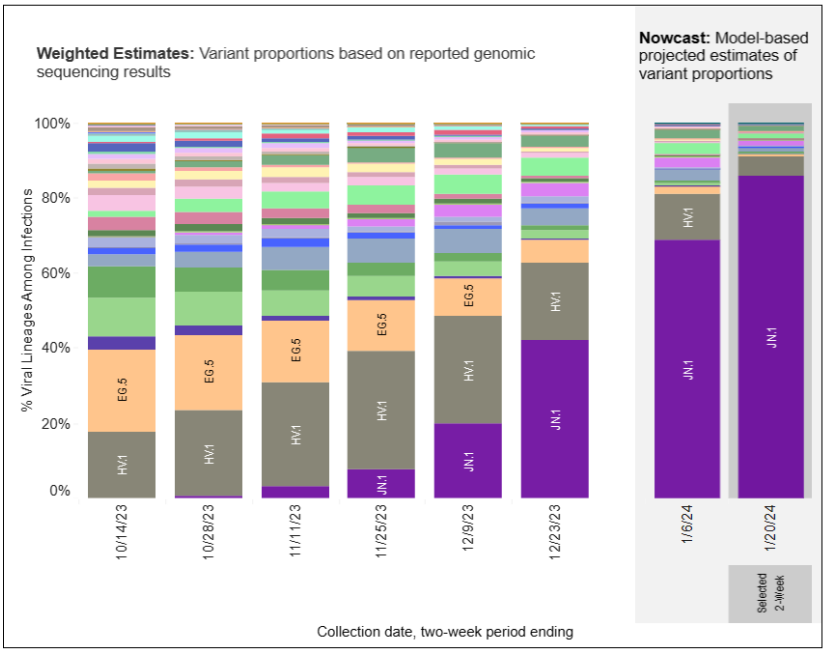
Most flu indicators, including outpatient visits for flulike illness, declined for the third week in a row. Though deaths from flu trended downward overall, the CDC reported 10 more pediatric flu deaths, raising the season's total to 57. The fatalities were reported between the week ending December 23 and the week ending January 13. Six involved influenza A, and three involved influenza B. Of subtyped influenza A viruses, all were 2009 H1N1. CDC estimates that there

have been at least 18 million cases, 210,000 hospitalizations, and 13,000 deaths so far this season

The CDC's wastewater surveillance system dashboard shows that SARS-CoV-2 detections are still listed as very high but have declined steadily since the start of 2024. Despite continued high wastewater levels, Covid-19 infections appear to be causing less severe disease than prior surges earlier in the pandemic. Hospital bed occupancy and intensive care unit capacity for all patients remains stable nationally. JN.1 now makes up 86% of SARS-CoV-2 variants. See review below

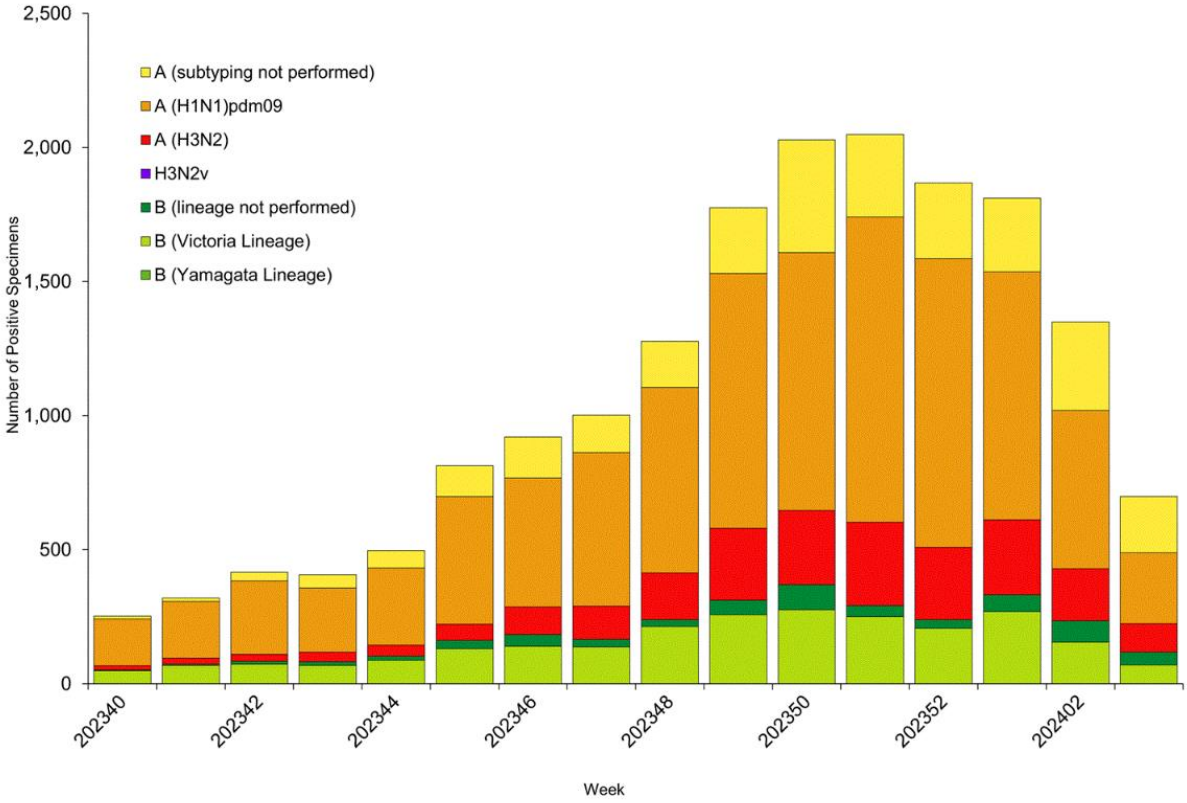
RSV indicators continue to decline in some areas, and though hospitalizations are decreasing among children, they remain elevated in older adults.





USA

WHO label	Lineage #	%Total	95%PI
Omicron	JN.1	85.7%	82.9-88.2%
	HV.1	5.3%	4.4-6.4%
	JD.1.1	1.6%	1.4-2.0%
	BA.2.86	1.5%	1.1-2.1%
	JG.3	1.5%	1.2-1.9%
	HK.3	1.5%	1.2-1.8%
	EG.5	0.6%	0.5-0.8%
	GE.1	0.4%	0.1-1.5%
	JF.1	0.2%	0.2-0.3%
	FL.1.5.1	0.2%	0.2-0.3%
	EG.5.1.8	0.2%	0.2-0.3%
	BA.2	0.1%	0.0-0.6%
	XBB.1.16.6	0.1%	0.1-0.2%
	XBB.1.16.17	0.1%	0.1-0.3%
	XBB.1.5.70	0.1%	0.1-0.2%
	XBB.1.16.11	0.1%	0.1-0.1%
	GK.1.1	0.1%	0.1-0.1%
	XBB	0.1%	0.0-0.1%
	XBB.1.9.1	0.1%	0.0-0.1%
	HF.1	0.1%	0.0-0.1%
	XBB.1.16.15	0.1%	0.0-0.1%
	XBB.2.3	0.0%	0.0-0.1%
	XBB.1.16	0.0%	0.0-0.0%
	GK.2	0.0%	0.0-0.0%
	CH.1.1	0.0%	0.0-0.0%
	XBB.1.5	0.0%	0.0-0.0%
	EG.6.1	0.0%	0.0-0.0%
	XBB.1.16.1	0.0%	0.0-0.0%
	XBB.1.5.68	0.0%	0.0-0.0%
	XBB.1.9.2	0.0%	0.0-0.0%
	XBB.2.3.8	0.0%	0.0-0.0%
	XBB.1.42.2	0.0%	0.0-0.0%
	XBB.1.5.72	0.0%	0.0-0.0%
	XBB.1.5.59	0.0%	0.0-0.0%
Other	Other*	0.0%	0.0-0.0%



Comment: If this holds up, the worse may be behind us, but we still need to be vigilent. Although flu and Covid-19 activity is declining, it is still not too late to be vaccinated.

COVID-19

Virological characteristics of the SARS-CoV-2 JN.1 variant Lancet published online January 3, 2025

doi.org/10.1016/ S1473-3099(23)00813-7

The SARS-CoV-2 BA.2.86 lineage, identified in August 2023, is phylogenetically distinct from the recently circulating SARS-CoV-2 omicron XBB lineages, including EG.5.1 and HK.3. Compared with XBB and BA.2, BA.2.86 carries more than 30 mutations in the spike protein, indicating a high potential for immune evasion. BA.2.86 has evolved and its descendant, JN.1 (BA.2.86.1.1), emerged late last year. JN.1 harbors Leu455Ser and three mutations in non-spike proteins. The spiked protein mutation Leu455Ser is a hallmark mutation of JN.1. In this paper the investigators studied the virological properties of JN.1.

They estimated the relative effective reproductive number of JN.1 using genomic surveillance data from France, the UK, and Spain, where more than 25 sequences of JN.1 have been reported, using a Bayesian multinomial logistic model. The reproductive number of JN.1 in these three countries was higher than that of BA.2.86.1 and HK.3, one of the XBB lineages with the highest growth advantage at the end of November 2023.

The in vitro ACE2 binding assay showed that the dissociation constant value of the JN.1 receptor-binding domain (RBD) was significantly higher than that of the BA.2.86 RBD, suggesting that Leu455Ser decreases binding affinity to the human ACE2 receptor. In contrast the pseudovirus assay showed that the infectivity of JN.1 was significantly higher than that of BA.2.86. They then performed a neutralization assay using rodent sera infected with BA.2.86 or immunized with BA.2.86 spike protein. In both cases, the 50% neutralization titer (NT50) against JN.1 was similar to that against BA.2.86, suggesting that Leu455Ser does not affect the antigenicity of BA.2.86. On the other hand, the NT50 of breakthrough infection sera with XBB.1.5 and EG.5.1 against JN.1 was significantly lower than that of HK.3.

Comment: These results suggest that JN.1 is one of the most immune evading variants to date. Our results suggest that Leu455Ser contributes to increased immune evasion, which partly explains the increased reproductive number of JN.1. Given growth advantage it is not surprising that JN.1 has become the dominant lineage worldwide. In the US JN.1 accounts for >85% of circulating variants.

Bottom line: JN.1 is now the predominant variant, but Covid-19 infections appear to be causing less severe disease than prior surges earlier in the pandemic.

Symptoms, Viral Loads, and Rebound Among Coronavirus Disease 2019 (COVID-19) Outpatients Treated With Nirmatrelvir/Ritonavir(N/R) Compared With Propensity Score–Matched Untreated Individuals

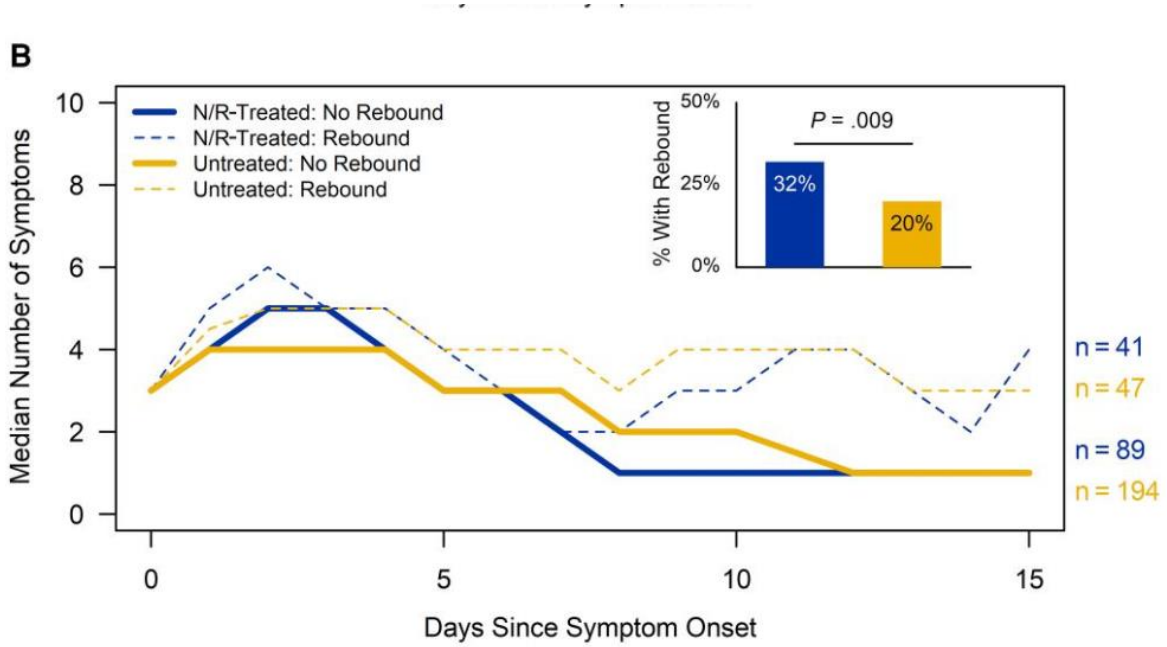
Clin Infect Dis published online November 14, 2023

https://doi.org/10.1093/cid/ciad696

The investigators identified symptomatic participants who tested SARS-CoV-2 positive and were N/R eligible from a Covid-19 household transmission study. Index cases from ambulatory settings and their households contacts were enrolled. They collected daily symptoms, medication use, and respiratory specimens for quantitative PCR for 10 days during March 2022—May 2023. Participants who completed N/R treatment (treated) had propensity score matched to untreated participants. They compared symptom rebound, viral load (VL) rebound, average daily symptoms, and average daily VL by treatment status measured after N/R treatment completion or 7 days after symptom onset if untreated.

Treated (n = 130) and untreated participants (n = 241) had similar baseline characteristics. After treatment completion, treated participants had greater occurrence of symptom rebound (32% vs 20%; P = .009) and VL rebound (27% vs 7%; P < .001). Average daily symptoms were lower among treated participants without symptom rebound (1.0 vs 1.6; P < .01) but not statistically

lower with symptom rebound (3.0 vs 3.4; P = .5). Treated participants had lower average daily VLs without VL rebound (0.9 vs 2.6; P < .01) but not statistically lower with VL rebound (4.8 vs 5.1; P = .7).



Comment: Individuals who completed N/R treatment experienced fewer symptoms and lower VL but rebound occurred more often compared with untreated individuals. Last month ID Watch reviewed an article from MMWR [2023; 72:1357-1364]. That publication suggests that SARS-CoV-2 rebound occurs initially as a mild illness 3–7 days after resolution of the initial acute illness, occurs in both treated and untreated patients, and is not associated specifically with receiving N/R. Other studies found that individuals who completed N/R treatment had fewer symptoms and lower VL than individuals who did not receive treatment. However, after completing treatment, N/R recipients were more likely to experience symptoms and VL rebound compared with untreated participants. [N Engl J Med 2022; 387:1045–7; Clin Infect Dis 2023; 76: e526–e9] Medications and symptoms were self-reported; there could have been unreported COVID-19 medication use, causing misclassification and bias in symptom reporting. Second, daily symptoms and VL were available for 10 days following enrollment. This may be insufficient follow-up time to detect all outcomes.

Bottom line: Despite risk of rebound, clinical trials show reduction in severe outcomes following N/R treatment and support that N/R treatment be prescribed for all high-risk individuals. Future studies are needed to understand rebound predictors and their association with Covid-19 treatments.

Editor's Choice

The effectiveness of COVID-19 vaccines to prevent long COVID symptoms: staggered cohort study of data from the UK, Spain, and Estonia Lancet Respir Med published online January 11, 2024

doi.org/10.1016/ S2213-2600(23)00414-9

The investigators wanted to evaluate the overall effect of vaccination to prevent long COVID symptoms and assess comparative effectiveness of the most used vaccines (ChAdOx1 and BNT162b2).[AstraZeneca and Pfizer] They conducted a staggered cohort study using primary care records from the UK [GOLD and AURUM], Catalonia, Spain, and national health insurance claims from Estonia.. Vaccination status was used as a time-varying exposure, staggered by vaccine rollout period. Vaccinated people were further classified by vaccine brand according to their first dose received. The primary outcome definition of long Covid-19 was defined as having at least one of 25 WHO-listed symptoms between 90 and 365 days after the date of a PCR-positive test or clinical diagnosis of COVID-19, with no history of that symptom 180 days before SARS-CoV-2 infection. Propensity score overlap weighting was applied separately for each cohort to minimize confounding. Sub distribution hazard ratios (sHRs) were calculated to estimate vaccine effectiveness against long Covid-19, and empirically calibrated using negative control outcomes. Random effects meta-analyses across staggered cohorts were conducted to pool overall effect estimates.

Compared with unvaccinated people, overall HRs for long Covid-19 symptoms in people vaccinated with a first dose of any Covid-19 vaccine were 0·54 (95% CI 0·44–0·67) in GOLD, 0·48 (0·34–0·68) in AURUM, 0·71 (0·55–0·91) in Spain, and 0·59 (0·40–0·87) in Estonia. A slightly stronger preventative effect was seen for the first dose of BNT162b2 than for ChAdOx1 (sHR 0·85 [0·60–1·20] in GOLD and 0·84 [0·74–0·94] in AURUM).

Comment: This study of more than 10 million vaccinated people and 10 million unvaccinated people showed that Covid-19 vaccination reduced the risk of developing long Covid-19. These findings were consistent across three different European countries and four databases, covering different health-care settings and national healthcare policies. All vaccines reduced the risk of developing long Covid-19 symptoms, with BNT162b2 showing slightly better effectiveness than ChAdOx1. Given the observational nature of their data, they cannot guarantee the absence of confounding, which could partly account for some of their findings. In addition, vaccine waning probably leads to lesser effects over time, and research on the protective effects of vaccination against long Covid-19 in the long term remains necessary.

Bottom line: Vaccination against Covid-19 consistently reduced the risk of long Covid-19 symptoms, highlighting yet another benefit of vaccination, particularly in adults even if they are less at risk of severe outcomes.

Editor's Choice

Hybrid immunity to SARS-CoV-2 during pregnancy provides more durable infant antibody responses compared to natural infection alone J Infect Dis published online December 21, 2023

DOI: 10.1093/infdis/jiad592

The investigator studied if hybrid immunity (infection plus vaccination) increased maternally derived SARS-CoV-2 antibody responses and durability vs. infection alone. Prospective cohort of pregnant participants with prior SARS-CoV-2 infection (anti-nucleocapsid IgG+, RT-PCR+ or antigen+) and their infants had blood collected in pregnancy, delivery/birth, and postpartum tested for anti-spike (anti-S) IgG and neutralizing antibodies (neutAb).

Among 107 participants at enrollment, 40% were unvaccinated and 60% were vaccinated (received ≥1 dose); 102 had previous SARS-CoV-2 infection in pregnancy (median 19 weeks gestation); 5 were diagnosed just prior to prior to pregnancy (median 8 weeks). At delivery, fewer unvaccinated participants (87% anti-S IgG+, 86% neutAb) and their infants (86% anti-S IgG+, 75% neutAb) had anti-S IgG+ or neutAb compared to vaccinated participants and their infants (100%, p≤0.01 for all). By 3-6 months postpartum, 50% of infants of unvaccinated participants were anti-S IgG+ and 14% had neutAb, vs. 100% among infants of vaccinated participants (all p <0.01) with lower median antibody responses (anti-S IgG log10 1.95 vs. 3.84 AU /ml, p<0.01; neutAb log10 1:1.34 vs. 1:3.20, p=0.11).

Comment: Investigators demonstrated among individuals with SARS-CoV-2 infection during or immediately before pregnancy and their infants, hybrid immunity was associated with a greater likelihood of having detectable anti-spike IgG+ and neutralizing antibodies at delivery for both pregnant women and their infants. They showed fewer unvaccinated women and their infants had anti-spike IgG+ or neutralizing antibodies compared with vaccinated participants. In addition, investigators found 100% of infants born to participants with hybrid immunity before delivery retained anti-spike IgG+ and neutralizing antibodies until 6 months compared to only 50% of infants born to pregnant people with a prior infection alone. Prior studies have described longitudinal anti-N and anti-S IgG responses in pregnancy and transplacental transfer in the setting of infection or vaccine, although few evaluated hybrid immunity. [J Infect Dis. 2023; 227:236–45] This study enrolled participants with initial SARS-CoV-2 infection prior to availability of bivalent vaccines potentially limiting generalizability to the current era of vaccine boosters. The number of infants with samples available at 3-6 months of age was limited, particularly among infants born to unvaccinated individuals. The investigators focused their primary comparisons between pregnant people who received ≥1 vaccine and those who remained unvaccinated, and due to limited sample size did not have power in most cases to detect significant differences by vaccine states further stratified by different vaccine uptake (i.e. partial, full, boosted).

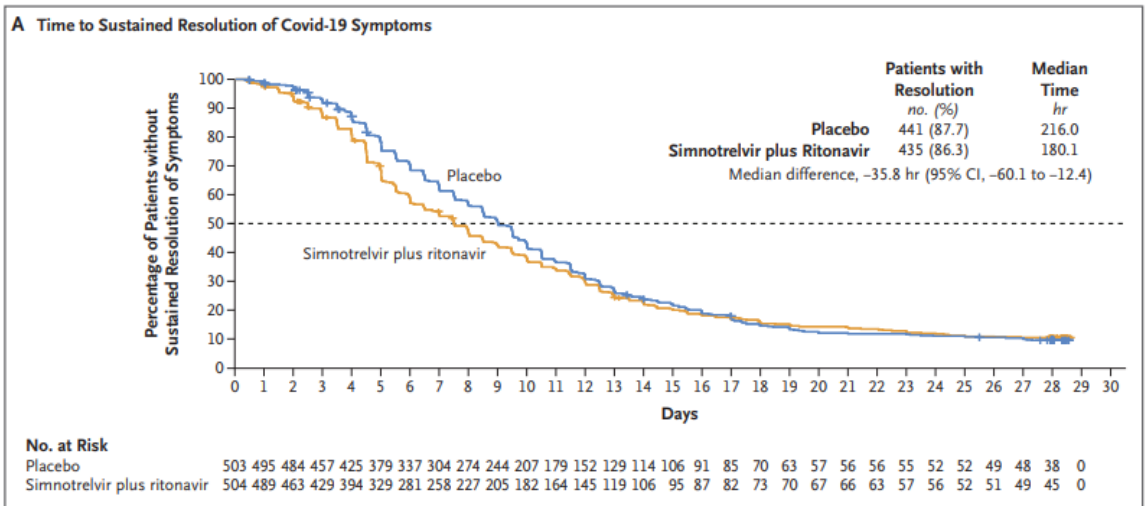
Bottom line: In pregnant people with prior SARS-CoV-2, vaccination before delivery provided more durable maternally derived antibody responses than infection alone in infants through 6 months. This data further supports vaccination in pregnancy prior to delivery, including after infection, to ensure protection for both pregnant people and their infants.

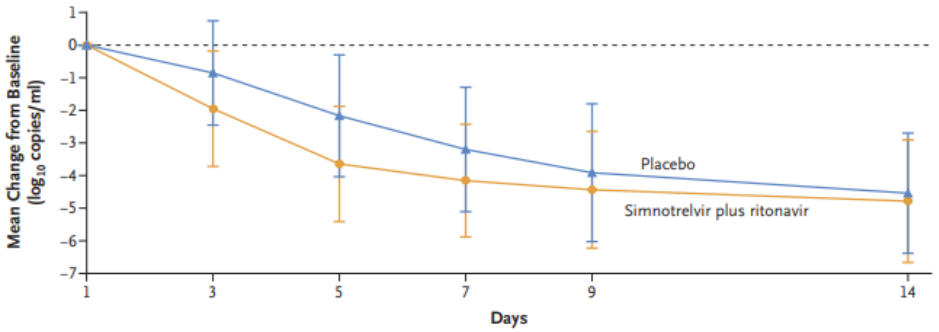
Oral Simnotrelvir for Adult Patients with Mild-to-Moderate Covid-19 N Engl J Med 2024; 390:230-41.

DOI: 10.1056/NEJMoa2301425

Simnotrelvir is an oral 3-chymotrypsin–like protease inhibitor that has been found to have in vitro activity against SARS-CoV-2. This publication reports the results on the phase 2–3, double-blind, randomized, placebo-controlled trial. They assigned patients who had mild-to-moderate Covid-19 and onset of symptoms within the past 3 days in a 1:1 ratio to receive 750 mg of simnotrelvir plus 100 mg of ritonavir or placebo twice daily for 5 days. The primary efficacy end point was the time to sustained resolution of symptoms, defined as the absence of 11 Covid-19–related symptoms for 2 consecutive days. Safety and changes in viral load were also assessed. Nasopharyngeal or oropharyngeal swab specimens were obtained on days 1, 3, 5 (end-of-treatment visit), 7, 9, and 14 for quantitation of SARS-CoV-2 RNA through RT-PCR assay at a central laboratory.

A total of 1208 patients were enrolled; 603 were assigned to receive simnotrelvir and 605 to receive placebo. Among patients in the modified intention-to-treat population who received the first dose of trial drug or placebo within 72 hours after symptom onset, the time to sustained resolution of Covid-19 symptoms was significantly shorter in the simnotrelvir group than in the placebo group (180.1 hours [95% confidence interval {CI}, 162.1 to 201.6] vs. 216.0 hours [95% CI, 203.4 to 228.1]; median difference, −35.8 hours [95% CI, −60.1 to −12.4]; P=0.006). On day 5, the decrease in viral load from baseline was greater in the simnotrelvir group than in the placebo group (mean difference [±SE], −1.51±0.14 log10 copies per milliliter; 95% CI, −1.79 to −1.24). The incidence of adverse events during treatment was higher in the simnotrelvir group than in the placebo group (29.0% vs. 21.6%). Most adverse events were mild or moderate. The most frequent adverse event that occurred at a higher incidence in the simnotrelvir group than in the placebo group was an increase in the blood triglyceride level. This adverse event is also common in association with other 3CLpro inhibitors, including nirmatrelvir.





No. at Risk						
Placebo	311	297	283	273	232	82
Simnotrelvir plus ritonavir	300	288	284	249	201	48
Change from Baseline						
Mean (±SE)		−1.10±0.13	−1.51±0.14	−0.98±0.14	−0.55±0.15	−0.27±0.27
95% CI		−1.36 to −0.84	−1.79 to −1.24	−1.24 to −0.71	−0.86 to −0.25	−0.81 to −0.26

Comment: In this phase 2–3 trial of treatment for mild-to-moderate Covid-19, simnotrelvir plus ritonavir shortened the time to sustained symptom resolution by approximately 1.5 days among patients who received treatment within 3 days after symptom onset. Simnotrelvir had more benefits for the alleviation of respiratory symptoms than placebo. In addition, simnotrelvir was associated with an additional decrease in viral load until day 9. For patients with mild-to-moderate Covid-19, viral replication and direct viral damage are important drivers of disease. [Circ Res 2020; 126:1443-55] Observational studies have indicated that even in the vaccinated population, nirmatrelvir use is associated with lower mortality among older persons or persons at increased risk for disease progression. [N Engl J Med 2022; 387:790-8] Because of the absence of in this trial events, they could not determine the effect of simnotrelvir on reducing the risk of disease progression. The population in this study was relatively young. Therefore, efficacy and safety among older patients still warrants investigations.

Bottom line: Early administration of simnotrelvir plus ritonavir shortened the time to the resolution of symptoms among adult patients with Covid-19, without significant safety concerns. More studies are needed for older high-risk populations.

SARS-CoV-2 Vaccination and Neuroimmunological Disease A Review JAMA Neurol published online January 16, 2024

doi:10.1001/jamaneurol.2023.5208

The authors performed an extensive literature search for this narrative review in the PubMed and Scopus databases, with no limitation on the time period searched, using the MeSH search terms “COVID-19” OR “SARS-CoV-2” AND “vaccination” AND “autoimmune,” returning 1005 articles in PubMed and 1364 articles in Scopus. Relevant studies for inclusion were identified by 2 investigators who independently screened all titles and abstracts. A hierarchical selection was used where only high-quality epidemiological studies exploring millions of participants or vaccine doses were included to review the highest certainty evidence.

Data from international cohorts including millions of vaccinated individuals suggest that there is a probable association between the adenovirus-vectored (AV) vaccines and Guillain-Barré syndrome (GBS). Further associations between other SARS-CoV-2 vaccines and GBS or Bell palsy have not been clearly demonstrated in large cohort studies, but the possible rare occurrence of Bell palsy following messenger RNA vaccination is a topic of interest. It is also yet to be clearly demonstrated that any other neurological diseases, such as central nervous system demyelinating disease or myasthenia gravis, have any causative association with vaccination against SARS-CoV-2 using any vaccine type, although it is possible that vaccination may rarely trigger a relapse or worsen symptoms or first presentation in already-diagnosed or susceptible individuals.

Comment: In this review, the investigators found there was a small increased risk of GBS following AV-based SARS-CoV-2 vaccines. High-quality UK studies of large cohorts convincingly reproduced consistent similar numerical associations for the AV-based ChAdOx1 vaccine, and these have been replicated in other international studies. The risk of Bell palsy following SARS-CoV-2 vaccination was unclear. No quantifiable excess risk was identified for myasthenia gravis, multiple sclerosis, or neuromyelitis optica spectrum disorders. There were substantial confounding factors in all of the studies, limiting the certainty of their conclusions.

Bottom line: The associated risk between SARS-CoV-2 vaccination and GBS, and possibly Bell palsy, is very small, and this should not change the recommendation for individuals to be vaccinated. It is very clear that the reductions in illness episodes, hospitalizations, and deaths were the result in large part conferred benefits of SARS-CoV-2 vaccination.