Infectious Diseases Watch

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General Infectious Diseases

An Open-Label, Randomized Trial Comparing Fidaxomicin With Oral Vancomycin for the Treatment of Clostridioides difficile Infection in Hospitalized Patients Receiving Concomitant Antibiotics for Concurrent Infections Clin Infect Dis published online October 5, 2023

https://doi.org/10.1093/cid/ciad606

Patients with *Clostridioides difficile* infection (CDI) who are receiving concomitant antibiotics (CA) for a different infection are at increase risk for treatment failure and recurrent CDI. To test if fidaxomicin is more efficacious than vancomycin for such patients, investigators randomized participants to receive fidaxomicin (74 patients; 46% male, 69% younger than 65) or vancomycin (70 patients; 50% male, 57% younger than 65) and the proportions achieving clinical cure were assessed in the two groups.

The between-group difference in clinical cure at the end of therapy did not meet not statistically significant even though fidaxomicin had a 10% higher cure rate: [73% (fidaxomicin) and 63% (vancomycin)]. Duration of hospital stay (5 and 6 days), but recurrence rate was only 3% and 4%, and likelihood of sustained clinical cure (87% and 84%) also were comparable between groups.

Comment: These investigators found that in patients with CDI on CA, fidaxomicin had a 10% higher proportion of participants who achieved cure; however, it did not reach statistical significance due to the inability to reach target enrollment numbers decreasing the statistical power. The recurrent rate was very low compared to other studies and most patients were <65. In a recent publication the authors compared the management of CDI in adults of current IDSA/SHEA, ESCMID and ASID guidelines. Updated IDSA/SHEA and ESCMID guidelines now reflect the increased efficacy of fidaxomicin in preventing recurrence and have both promoted fidaxomicin to first-line therapy with an initial CDI episode in both non-severe and severe disease and endorsed the role of bezlotoxumab in the prevention of recurrent infection. Vancomycin remains an acceptable alternative and metronidazole is not preferred. [J Antimicrob Chemother 2023; 78: 21–30]

Bottom line: Fidaxomicin may be the best choice; however, the question of how best to treat patients with CDI on CA remains unclear.

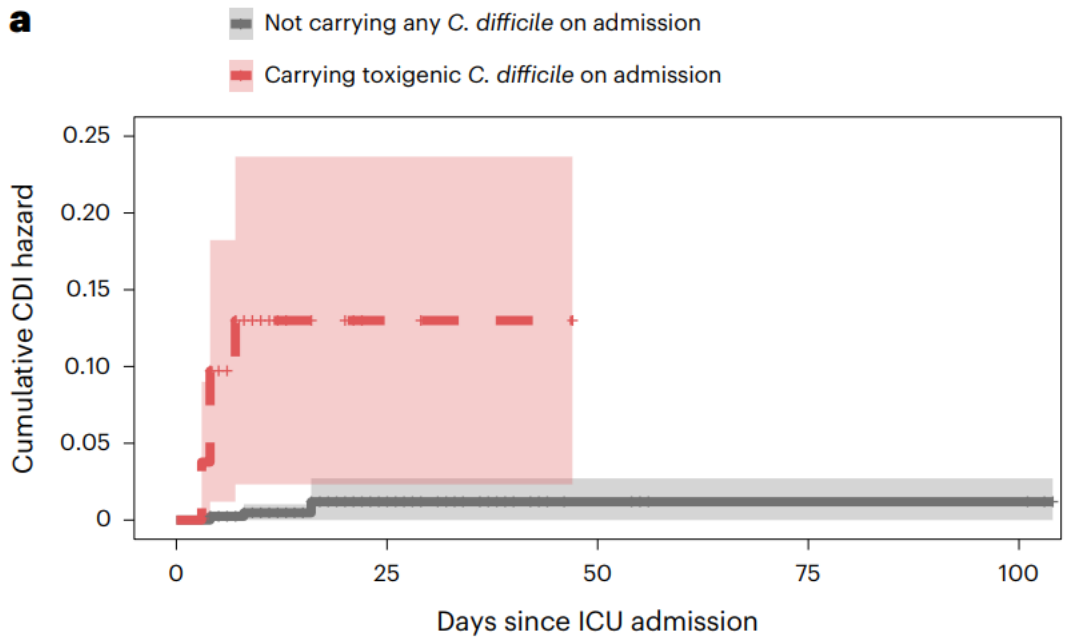
Editor's Choice

Longitudinal genomic surveillance of carriage and transmission of *Clostridioides difficile* in an intensive care unit Nat Med 2023; 29:2526-2534 suggested by Mary Hayden

doi.org/10.1038/s41591-023-02549-4

To improve the understanding of asymptomatic carriers' contribution to *C. difficile* spread, the investigators conducted admission and daily longitudinal culture-based screening for *C. difficile* in a US-based ICU over nine months and performed whole-genome sequencing on all recovered isolates.

In this longitudinal, observational study they collected 3,952 rectal swab and stool samples from 1,289 unique ICU admissions and 1,111 unique patients; 448 *C. difficile* isolates were recovered via enrichment culture for toxigenic and non-toxigenic strains. Despite a high burden of carriage, with 9.3% of admissions having toxigenic *C. difficile* detected in at least one sample, only 1% of patients culturing negative on admission to the unit acquired *C. difficile* via cross-transmission. While patients who carried toxigenic *C. difficile* on admission posed minimal risk to others, they themselves had a 24-times greater risk for developing a healthcare-onset *C. difficile* infection than noncarriers.



Comment: Their data showed that although transmission of *C. difficile* leading to acquisition within the ICU probably occurred, it was uncommon, with only six genomically supported acquisitions over the nine-month study. Modeling evaluation and one quasi-experimental study supported the effectiveness of asymptomatic screening for reducing rates of CDI. [Infect. Control Hosp. Epidemiol. 2014; 35:1043–1050] While the current study was not designed to directly address this question—and only includes screening on ICU admission rather than hospital admission—they demonstrated that among 67 asymptomatic importers of toxigenic C. difficile in this study only one was genomically linked to an acquisition that may have resulted in CDI during hospitalization in this nine-month study period. These results suggest that implementation of basic infection prevention practices, such as hand hygiene and environmental cleaning and disinfection, and single-patient rooms, can minimize cross-transmission from asymptomatic carriers of C. difficile within the ICU. This observation might not hold in other molecular epidemiological contexts, such as when the epidemic hospital-associated strain ribotype 027 or NAP1 was observed to cause as many as 30% of *C. difficile* infections in the US.[now <20%] While more studies are needed, some interventions that have shown promise in preventing CDI in carriers include administration of probiotics [Cochrane Database Syst. Rev. 2017;12: CD006095, fidaxomicin prophylaxis [Clin. Infect. Dis.2019; 68: 196–203], and FMTs. These results cannot be generalized to the entire hospital or to other healthcare settings, such as long-term care facilities, or to other countries. They did not have isolates from clinically diagnosed CDI, so they could not verify whether colonizing strains were genomically matched to those from later infections, although the limited existing data from previous reports suggest high concordance between colonizing and subsequent infecting strain types. [Clin. Infect. Dis. 2019; 69:1801–1804]

Bottom line: While current infection prevention practices can limit cross-transmission, these results indicate that further reductions in hospital-onset CDI will require developing more effective strategies to interrupt the transition from colonization to clinical infection. See next review.

The role of the hospital bed in hospital-onset Clostridioides difficile: A retrospective study with mediation analysis

Infect Control & Hospital Epidemiol published online December 13, 2023

doi:10.1017/ice.2023.254

This was a retrospective cohort study, which used a real-time location system to track the movement of hospital beds in 2 academic hospitals from April 2018 to August 2019. They abstracted patient demographics, clinical characteristics, and C. difficile PCR results from the medical record. They defined patients as being exposed to a potentially “contaminated” bed or room if, within the preceding 7 days from their HO-CDI diagnosis, they resided in a bed or room respectively, that held an occupant with C. difficile in the previous 90 days. They used multivariable logistic regression to determine whether residing in a contaminated bed was associated with HO-CDI after controlling for time at risk and requiring intensive care. They assessed mediation and interaction from a contaminated hospital room.

Of 25,032 hospital encounters with 18,860 unique patients, they identified 237 cases of HO-CDI. Exposure to a contaminated bed was associated with HO-CDI in unadjusted analyses

(odds ratio [OR], 1.8; 95% confidence interval [CI], 1.4–2.31) and adjusted analyses (OR, 1.5; 95% CI, 1.2–2.0). Most of this effect was due to both mediation from and interaction with a contaminated hospital room.

Figure 1. Exposure to a *Clostridioides difficile* "contaminated" bed. Beds are considered contaminated (red) starting with the positive *C. difficile* test of an occupant (green occupant). The bed remains contaminated for 90 days and "resets" every time a new patient with *C. difficile* is identified in that bed. Subsequent occupants (blue and orange) are considered to have an associated hospital-onset *C. difficile* infection (HO-CDI) if they develop their infection ≥3 days after being admitted and while residing in the contaminated bed or within 7 days of leaving the contaminated bed (orange occupant with star).

Comment: Residing in a hospital bed or room that previously had a patient with C. difficile increases the risk of HO-CDI. Prior studies have described an increased odds ratio of 1.1 to 4.5 for HO-CDI when residing in a room where a prior occupant was diagnosed with C. difficile. [Am J Infect Control 2022; 50:1352–1354] They did not account for clinical severity, which could affect the degree of spore transmission and contamination to the next bed occupant. Similarly, their outcome of HO-CDI did not capture asymptomatic on admission or acquisition of C. difficile or episodes of C. difficile that occurred after hospital discharge.

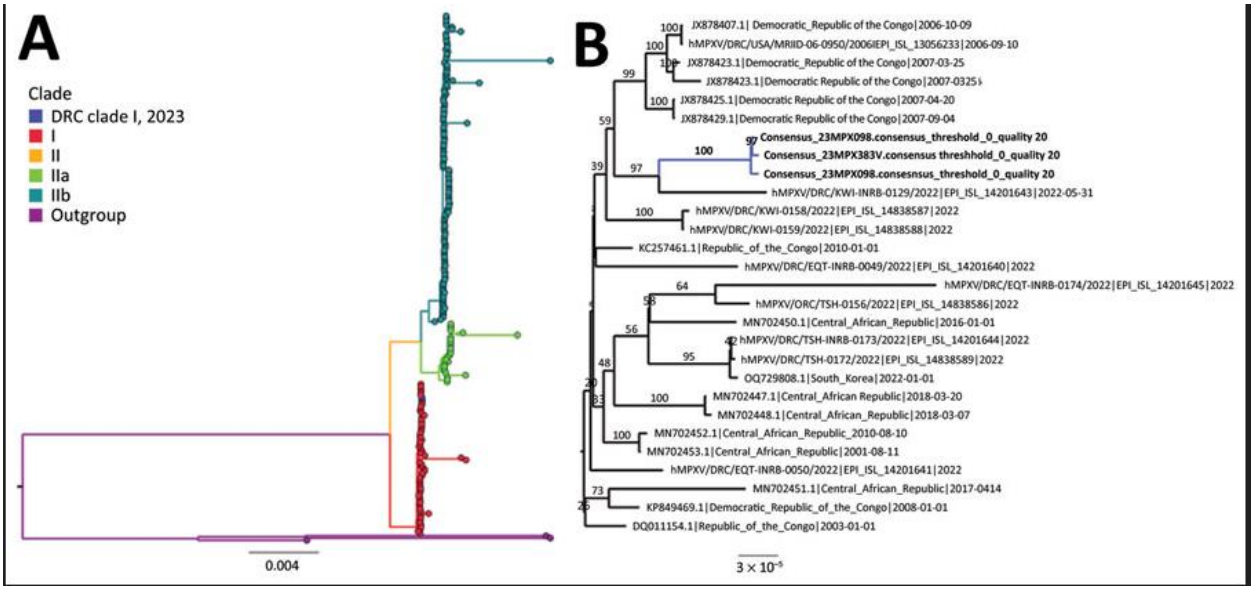
Increased attention to cleaning and disinfecting the healthcare environment may reduce hospital transmission of C. difficile. New technologies or cleaning and disinfection methods with better compliance should improve eradication C. *difficile* spores from a hospital bed and/or the surrounding healthcare environment which should lead to reductions in healthcare transmission of *C. difficile* and decrease rates of HO-CDI. Further studies involving genomic sequencing is needed to directly link possible bed contamination and developing HO-CDI. The study above in an ICU used daily longitudinal culture-based screening for *C. difficile* with whole-genome sequencing (WGS).

Bottom line: Increased attention to disinfecting the environment may reduce HO-CDI, but additional longitudinal studies using WGS are needed.

Clade I–Associated Mpox Cases Associated with Sexual Contact, the Democratic Republic of the Congo Emerg Infect Dis early release January 2024

Investigators in the Democratic Republic of the Congo (DRC) have confirmed a cluster of clade I MPXV-associated infections reported to be sexually transmitted. Case patient 1 had sexual contact with the source patient (thought to be European) 1 week before returning to the DRC. Patient 1 exhibited genital pruritis, vesicular skin eruptions, and genital and perianal ulcerations typical of mpox. This patient reported having sexual contact with 9 partners, in whom screening

revealed 3 cases (all positive for MPXV by PCR). Phylogenetic analysis defined these MPXV infections as clade I.



Comment: Mpox virus (MPXV) is endemic in several regions of Central and West Africa; in 2022, however, >86,000 cases were reported in non-endemic areas, and the epidemic was deemed a public health emergency by WHO. MPXV has been subclassified into two clades (I and II, further subdivided into IIa and IIb). The 2022 outbreak was attributed to clade IIb, and >90% of infections were linked to sexual contact among men who have sex with men. Clade I infections are associated with greater disease severity and more pronounced rash and had demonstrated increased human-to-human transmission compared with clade II before the global emergence of clade IIb. [Clin Infect Dis. 2014; 58:260–267]

Bottom line: This outbreak demonstrates clade I MPXV can be easily transmitted by sexual contact. Clade I has been associated with higher morbidity making it clear we should employ all potential interventions especially MPXV vaccination for high risk individuals. See next review

Multi-country outbreak of mpox WHO report December 22, 2023

A total of 906 new laboratory-confirmed cases of mpox were reported globally in November 2023 from 26 countries. The most affected regions, ordered by number of laboratory-confirmed cases, were the WHO Region of the Americas, the European Region, the Western Pacific Region, the South-East Asia Region and the African Region. Based on the data reported through global surveillance, the mpox outbreak continues in most WHO regions.

Table 1. Number of cumulative confirmed mpox cases and deaths reported to WHO, by WHO Region, from 1 January 2022 through 30 November 2023

WHO Region	Total confirmed cases	Total deaths	Cases in last month	Monthly change in cases (%)
Region of the Americas	60 400	136	308	+110
European Region	26 654	7	259	+58
Western Pacific Region	2 760	3	172	-15
African Region	2 126	22	58	-1.7
South-East Asia Region	748	2	109	-25.0
Eastern Mediterranean Region	95	1	0	-
Total	92 783	171	906	+25.7

Comment: In general, it is important to maintain awareness of mpox among communities at risk for infection, health care professionals and sexual health service providers in order to strengthen case detection, contact tracing, and management of cases; offer testing and treatment as needed; promote vaccination; and mitigate stigma and discrimination associated with mpox that may cause additional harm to individuals experiencing symptoms, and deter them from seeking appropriate care.

Bottom line: Mpox continues to slowly circulate, and the incidence is rising. High risk individuals [gay men, bisexual men, other men who have sex with men, trans and gender diverse people, and sex workers] should be offered vaccination.

Transmission of Mpox to Nonsexual Close Contacts — Two U.S. Jurisdictions, May 1–July 31, 2022 MMWR 2023; 72:1351-1352

During August–September 2022, CDC requested that US jurisdictions submit aggregate or deidentified individual level data on the number of reported nonsexual contacts of mpox patients with cases occurring during May 1–July 31. Most jurisdictions either reported no nonsexual contacts during the specified period or were unable to categorize contacts as nonsexual because of contact tracing limitations. Two jurisdictions, Tennessee, and the District of Columbia (DC), reported aggregate data on the number of adult and pediatric nonsexual contacts identified during May 1–July 31, 2022. The secondary attack rate among nonsexual close contacts was defined as the percentage of nonsexual close contacts of mpox patients who became symptomatic within 21 days of exposure to the primary patient.

During May 1–July 31, a total of 278 mpox cases were reported by the two jurisdictions, and 662 nonsexual contacts of these patients were identified (average = 2.4 nonsexual contacts per patient. Among 563 nonsexual close contacts reported by DC, 162 (28.8%) were interviewed after exposure. The primary exposure settings for nonsexual contacts in DC were large gatherings (e.g., festivals) (230; 40.9%), unknown settings (119; 21.1%), place of employment (71; 12.6%), or home (44; 7.8%). In Tennessee overall, a total of 10 people who reported nonsexual close contact with an mpox patient experienced symptoms within 21 days after exposure (secondary attack rate = 1.5%).

Comment: During the 2022 multinational mpox outbreak, U.S. mpox cases primarily occurred among adult gay, bisexual, and other men who have sex with men. [MMWR Morb Mortal Wkly Rep 2022; 71:1018–22] Among all cases, 94% of patients reported exposure through sexual or other intimate contact. Currently, little is known about less common nonsexual mpox transmission. Although sexual or intimate contact was the primary mode of transmission in the 2022 multinational mpox outbreak, limited nonsexual transmission also occurred. The secondary attack rate reported from this investigation is consistent with that reported among nonsexual contacts in regions with endemic mpox. [PLoS Negl Trop Dis 2019;13:e0007791]

Age-specific information was not reported for nonsexual contacts; therefore, this report cannot distinguish between pediatric and adult nonsexual contacts. Fewer than one half of nonsexual contacts in one jurisdiction were interviewed after exposure, which might have resulted in underreporting of secondary cases. Data was incomplete for many nonsexual close contacts. Finally, because this investigation did not collect mpox laboratory test results for nonsexual close contacts who became symptomatic 21 days after exposure to the primary case, the secondary attack rate might be inflated.

Bottom line: We need more data from nonsexual close contacts, including factors associated with an increased risk for infection and behaviors that increase the risk for transmission, which can help guide development and implementation of recommendations to prevent nonsexual transmission.

Editor's Choice

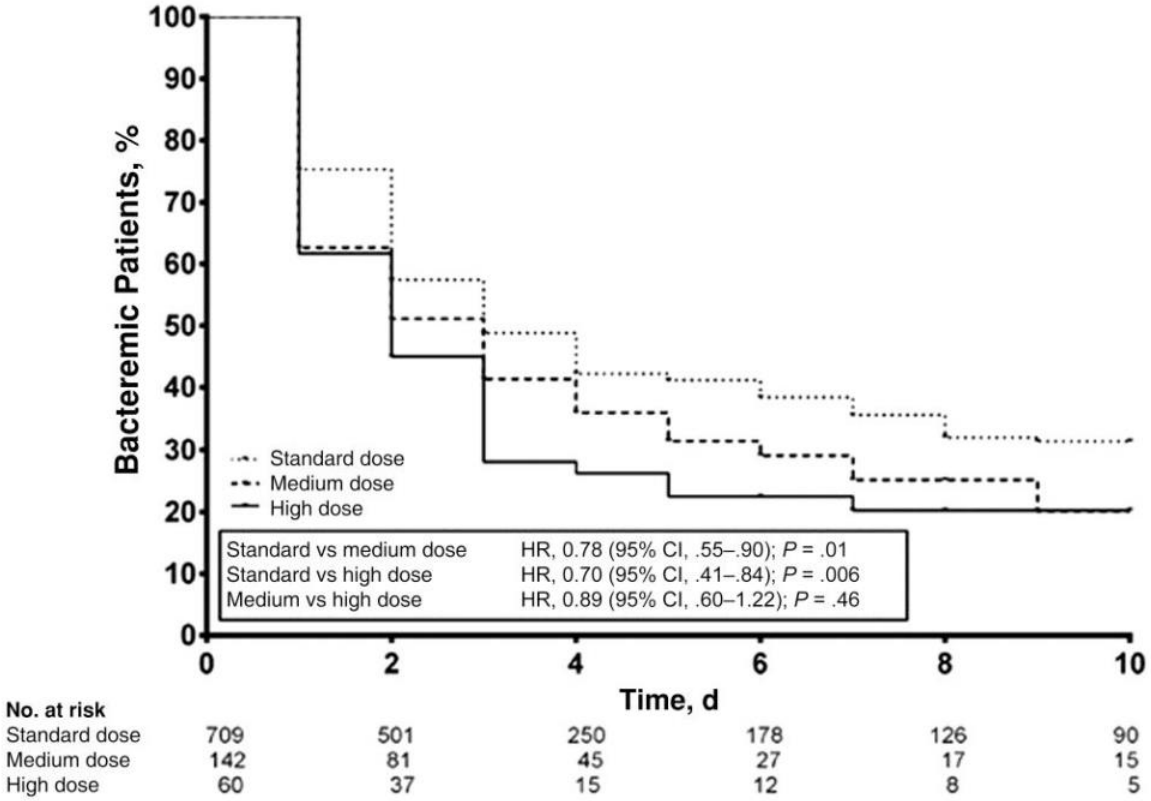
State-of-the-Art Review: Persistent Enterococcal Bacteremia Clin Infect Dis published online November 29, 2023. Highlights

doi.org/10.1093/cid/ciad612

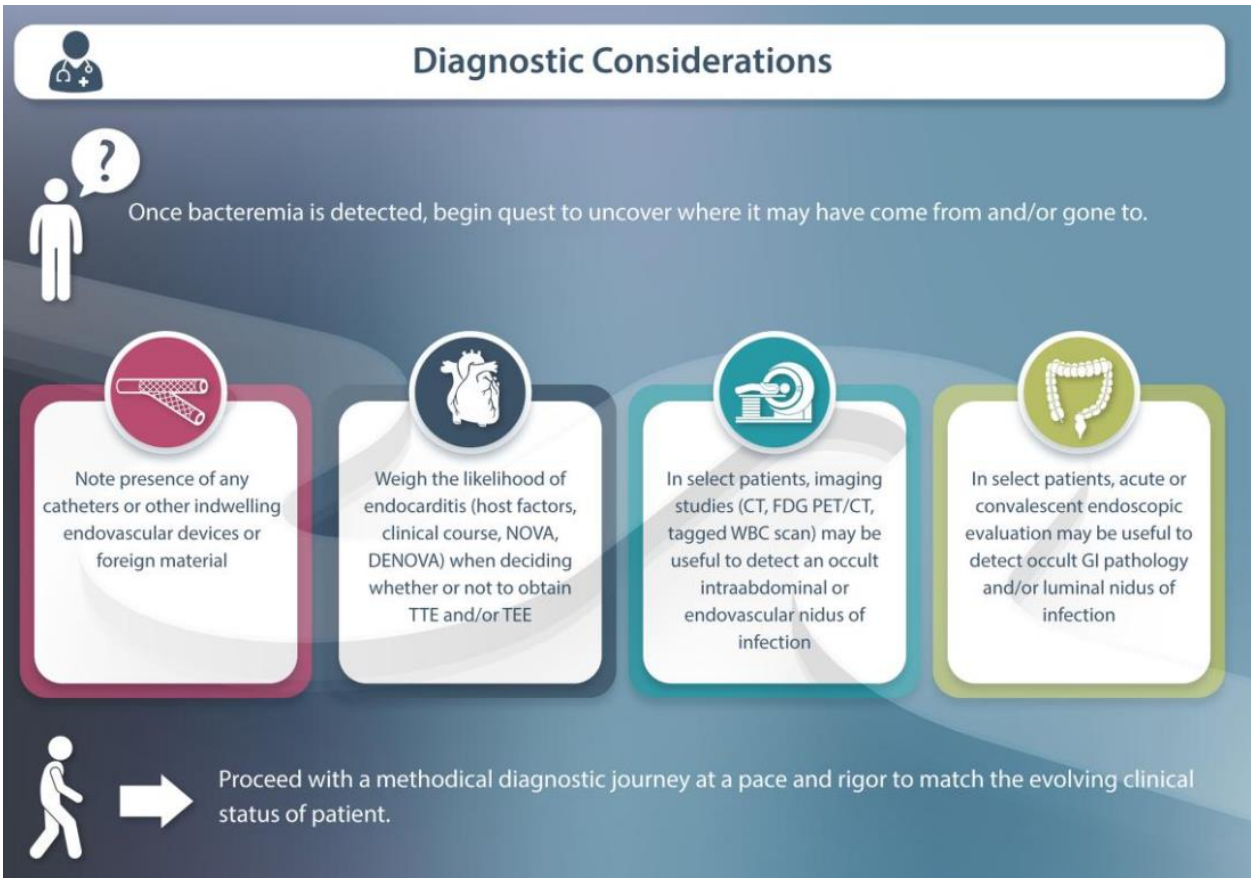
Enterococcus species, in particular *E. faecalis* and *E. faecium*, are now among the most prevalent causes of bacteremia, trailing behind only *Escherichia coli* as well as *Staphylococcus*, *Streptococcus*, and *Klebsiella* species. [Emerg Infect Dis 2021; 27:2560–9] Enterococcal bacteremia is associated with a significant 20%–35% 30-day mortality rate, likely at least in some part due to the advanced age, multiple comorbid conditions, and/or underlying immunocompromised state typical among patients affected by enterococcal bacteremia. [J Clin Microbiol 2022; 60: e0242921.] Persistent enterococcal bacteremia despite seemingly appropriate antimicrobial treatment is a common occurrence in clinical practice, at times due to inadequate source control of infection, but also occurring without any such identified uncontrolled source. Current best practices for management of persistent enterococcal bacteremia are understudied.

First, how does one define persistent enterococcal bacteremia. Recent larger studies describing cohorts that include hospitalized patients with any episode of enterococcal bacteremia, found a mean duration of bacteremia of 4 days, another found that 12.0% of patients had persistently positive blood cultures for ≥5 days, and another found that 13.5% of patients had persistently positive blood cultures after ≥72 hours of appropriate antimicrobials. [Ann Med Surg (Lond) 2022; 80: 104258; J Glob Antimicrob Resist 2022; 29:386–9] A recent large multicenter prospective study directly compared the rates of persistent VRE and

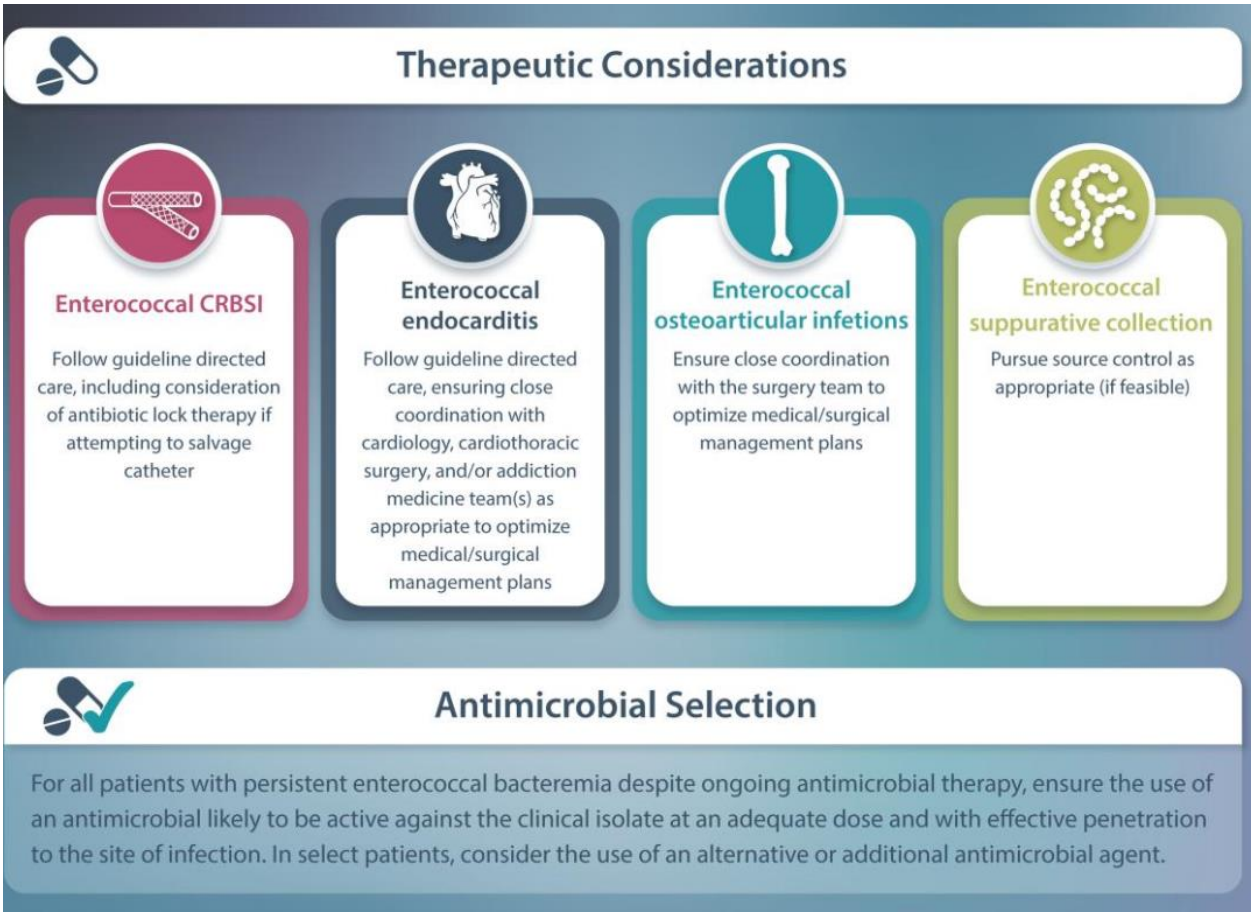
vancomycin-susceptible enterococcal (VSE) bacteremia (defined as persistent positive blood cultures for ≥4 days while receiving ≥48 hours of appropriate antimicrobials) and found slightly higher rates among patients with VRE compared with VSE bacteremia (21.4% vs 15.3%). [Open Forum Infect Dis 2022; 9: ofab616] In a large subset of patients with VRE bacteremia who were treated with daptomycin provides a more detailed look at the distribution of duration of bacteremia among this group. [Clin Infect Dis 2017; 64:605–13] See below.



In a large recent report describing a group of patients with enterococcal endocarditis found that only 13.4% of patients had persistent bacteremia after ≥7 days of antimicrobial therapy, which was similar to the rate of persistent bacteremia (11.4%) among patients with all other causes of endocarditis (e.g., *Staphylococcus* and *Streptococcus* spp.) in the entire cohort. [J Am Coll Cardiol 2020; 75:482–94]. Regardless of your definition of persistent bacteremia, once detected, it should alert treating clinicians to the high risk for adverse clinical outcomes and the need for aggressive source control and optimization of antimicrobial therapy.



Understanding susceptibility to antimicrobial agents is central to informed treatment of *E. faecalis* and *E. faecium* infections. For *E. faecalis*, this difference from streptococci is manifested by a reduced susceptibility without frank resistance to penicillin and ampicillin and resistance to the antistaphylococcal penicillins. For *E. faecium*, most strains express high-level resistance to all β-lactam antimicrobials, including ampicillin. In both species, intrinsic resistance is associated with expression of a single, low-affinity penicillin-binding protein (PBP), PBP4 (*E. faecalis*) or PBP5 (*E. faecium*). *E. faecalis* and *E. faecium* also exhibit a clinically important tolerance to cell-wall active antimicrobials like ampicillin and vancomycin. “Tolerance” can be defined as a large disparity between the antimicrobial concentration required to inhibit growth of a bacterial strain in vitro and that required to kill the strain. It was recognized that combining penicillin with streptomycin resulted in in vitro synergistic bactericidal activity, the clinical use of cell wall active agents and aminoglycosides has resulted in cure rates of 70% or greater for enterococcal endocarditis. The downside of aminoglycoside combinations is the intrinsic toxicity of aminoglycosides as well as the spread of high-level resistance conferred by acquired aminoglycoside-modifying enzymes. More recently, it has been shown that the use of ceftriaxone-ampicillin combinations results in cure rates similar to those of cell wall agent–aminoglycoside combinations when treating *E. faecalis* endocarditis. [Clin Infect Dis 2013; 56:1261–8.] The mechanism for achieving this result is unclear but may be the result of more complete inhibition of all PBPs than can be achieved with either agent alone.



Enterococci are commonly considered pathogens of “lower” virulence than more aggressive pathogens like *S. pyogenes*, *S. pneumoniae,* and *Staphylococcus aureus*. Still, there are defined mechanisms by which enterococci move from commensal to pathogen, which include their ability to multiply in the gastrointestinal (GI) tract, their ability to attach to epithelial cells of the GI tract, the urinary tract, heart valves, and prosthetic material. One virulence characteristic that is particularly relevant to this discussion is the formation of biofilm. Biofilm formation is important in many different types of infections including enterococci. [Nat Rev Microbiol 2019; 17:82–94] It is likely that enterococci can enter a “persister state” when present in a biofilm, making them less susceptible to antimicrobials. In addition, in vitro experiments have shown that minimum inhibitory concentrations for some antimicrobials are higher in biofilm cells than in planktonic cells and increase with the duration of the biofilm (which in many clinical infections is prolonged)

Enterococci are present in the normal human GI flora in substantial numbers, but they represent a relatively small percentage of bacteria in the gut. Under the influence of antimicrobials, especially those that achieve high concentrations in the GI tract, enterococci can become predominant, leading to increased translocation into the bloodstream and increased contamination of the perineal region, predisposing to infections, particularly in immunocompromised patients and in those with instrumented urinary tracts. In particular, cephalosporins secreted by the GI tract, such as ceftriaxone (which achieves biliary concentrations exceeding 5000 µg/mL with normal dosing), and drugs with potent activity

against anaerobic bacteria have been associated with enterococcal colonization and infection. [Ann Intern Med 2001; 135: 175–83]

Certain host factors may help predict persistent enterococcal bacteremia, including neutropenia, active hematologic cancer, and ongoing hemodialysis. The most efficient diagnostic strategy to Identify all patients with enterococcal endocarditis remains unsettled. The NOVA and DENOVA scores were developed to help "rule out" endocarditis and avoid the need for transesophageal echocardiography (TEE) in patients at very low risk for endocarditis; the diagnostic performance of these scores is good but not perfect. [Clin Infect Dis 2015; 60:528–35; Infection 2019; 47:45–50] The Duke–International Society for Cardiovascular Infectious Diseases (ISCVID) criteria for the diagnosis of infective endocarditis were recently updated and now newly include *E. faecalis* as a typical pathogen for endocarditis. [Clin Infect Dis 2023; 77:518–26.] See below.

Clinical Data	2023 Duke-ISCVID Criteria[a]	NOVA[a]	DENOVA[a]
Positive blood culture	Major criteria: *E. faecalis* bacteremia in ≥2 blood culture sets OR other enterococcal bacteremia in ≥3 blood culture sets	N represents *number* of positive blood cultures suggestive of continuous bacteremia (3 of 3 or majority of >3); O, *origin* of bacteremia unknown	N represents *number* of positive blood cultures suggestive of continuous bacteremia (2 of 2 or majority of >2); O, *origin* of bacteremia unknown
Evidence of endocardial involvement	Major criteria: echocardiogram and/or cardiac CT showing vegetation, perforation or other suppurative complication, or significant new regurgitation OR PET/CT showing abnormal metabolic activity involving valve	V represents prior *valve* disease, including native valve disease, previous endocarditis, or presence of a valve prosthesis	V represents prior *valve* disease, including native valve disease, previous endocarditis, or presence of a valve prosthesis
Predisposition	Minor criteria: prior endocarditis, prosthetic valve or valve repair, CHD or HOCM, more than mild stenosis or regurgitation, endovascular CIED, or injection drug use	A represents *auscultation* of a heart murmur	A represents *auscultation* of a heart murmur
Fever	Minor criteria: temperature >38.0°C	…	D represents *duration* of any symptoms compatible with endocarditis for ≥7 d
Vascular phenomena	Minor criteria: major arterial emboli, septic pulmonary infarcts, cerebral or splenic abscess, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, or Janeway lesions	…	E represents *embolization* as determined with clinical examination or imaging
Immunologic phenomena	Minor criteria: glomerulonephritis, Osler nodes, Roth spots, or rheumatoid factor	…	…
Microbiologic evidence	Minor criteria: positive enterococcal blood cultures that do not meet major criteria OR positive enterococcal culture from other sterile site	…	…
Imaging criteria	Minor criteria: abnormal PET/CT metabolic activity at prosthetic valve within 3 mo of implantation	…	…

Abbreviations: CHD, congenital heart disease; CIED, cardiovascular implantable electronic device; CT, computed tomography; *E. faecalis*, *Enterococcus faecalis*; HOCM, hypertrophic obstructive cardiomyopathy; ISCVID, International Society for Cardiovascular Infectious Diseases; PET, positron emission tomography.

[a]The 2023 Duke-ISCVID criteria describe definite infective endocarditis as the presence of 2 major, 1 major and 3 minor, or 5 minor clinical criteria [43]. The NOVA score assigns points to clinical criteria (N, 5 points O, 4 points; V, 2 points; A, 1 point) and describes a very low risk for endocarditis with total scores <4 points [40]. The DENOVA score assigns points to clinical criteria (1 point for each of the 6 DENOVA criteria) and describes a very low risk for endocarditis with total scores <3 points [42].

It is important to note that enterococcal endocarditis is primarily due to *E. faecalis* rather than *E. faecium* or other enterococci, with one large cohort finding *E. faecalis* as the cause of 91% of enterococcal endocarditis cases. [J Am Coll Cardiol 2020; 75:482–94] The correct identification of patients with enterococcal endocarditis is critical, as the recommended management typically will include 2 antimicrobial agents rather than a single agent. One group assessed a large

cohort of patients with *E. faecalis* bacteremia (defined as ≥1 positive culture) and found that 26% had definite endocarditis. Attempts to identify occult sources for enterococcal bacteremia are also important. Consideration of endoscopic evaluation (colonoscopy) may help identify luminal GI pathology responsible for translocation of GI flora; importantly, this can also serve to identify occult noninfectious processes (e.g., GI cancer) in need of different treatment. Despite a thorough evaluation there are many cases where an underlying source of infection is not found. A recent large study described a cohort of patients with persistent enterococcal bacteremia (defined as positive blood cultures after ≥72 hours of antibiotics) and found that 39% had no identifiable source of infection beyond primary bacteremia, but it is unclear how extensive the diagnostic evaluations were in these cases. [J Glob Antimicrob Resist 2022; 29:386–9] Regardless of whether a source of persistent enterococcal bacteremia immediately apparent, infectious disease consultation should be obtained to assist with diagnostic and management efforts, as this has been consistently associated with a decrease in mortality rate.

For treatment, a 7-day course of antimicrobials after catheter removal may be adequate treatment for enterococcal CRBSI without endocarditis. [Eur J Clin Microbiol Infect Dis 2022; 41:1203–6.] For endocarditis, ampicillin plus ceftriaxone for 6 weeks is preferred over penicillin plus gentamicin due to toxicity. Enterococcal osteoarticular infections may also serve as a source for persistent enterococcal bacteremia, as well as a source of clinical management challenges. In particular, the optimal treatment of enterococcal prosthetic joint infections remains uncertain. At issue is the choice between debridement with implant retention or 1- or 2-stage implant exchange, optimal choice of antimicrobial therapy (single vs combination therapy), and whether there is a role for subsequent suppressive antimicrobial therapy in some or all cases. Persistent enterococcal bacteremia without an evident underlying source of infection despite an appropriate or exhaustive workup is also a relatively common diagnostic and therapeutic dilemma. Despite extensive investigation, the ideal antimicrobial for the initial treatment of VRE bacteremia is not yet well defined. [For VRE daptomycin 10-12 mg/kg q 24h or linezolid can be administered.]

Bottom line: This is an excellent review. Ongoing research is needed to further elucidate specific factors intrinsic to host immunity or enterococcal virulence that contribute to persistent bacteremia and severe infections. What is the role of combination antimicrobial therapy or early antimicrobial escalation strategies for severe enterococcal infection without endocarditis?

Conventional vs Short Duration of Antibiotics in Patients With Moderate or Severe Cholangitis: Noninferiority Randomized Trial Am J Gastro published online October 9, 2023

DOI: 10.14309/ajg.0000000000002499

In 120 patients with moderate (77%) or severe (23%) acute cholangitis urgent biliary drainage was accomplished within 48 hours of admission. Investigators then randomized them to receive either 4 days or 8 days of IV antibiotics. All patients also had received antibiotics pre drainage. Antibiotics were continued beyond the randomized duration in any patient who did not meet predefined clinical stability criteria.

Clinical cure at 30 days (defined as no recurrent cholangitis and >50% reduction in bilirubin from initial level) was similar in both groups (≈80%), as was hospital length of stay (≈3 days) and mortality (≈10%, with most deaths occurring prior to completing antibiotics). Lack of clinical cure and mortality were both associated significantly with malignant etiology of cholangitis and hypotension that required pressors.

Comment: For acute cholangitis, guidelines suggest 4 to 7 days of antibiotics after successful biliary drainage [J Hepatobiliary Pancreat Sci 2018; 25:3] but randomized trials of antibiotic duration were lacking until this trial. Although this was a single center study and unblinded it provides randomized data on short-duration antimicrobial therapy after source control as long as patients are improving.

Bottom line: 4 days of antimicrobial therapy is appropriate after source control in keeping with "less is more."

Editor's Choice

Maternal Vaccine Effectiveness Against Influenza-Associated Hospitalizations and Emergency Department Visits in Infants JAMA Pediatr published online December 18, 2023

doi:10.1001/jamapediatrics.2023.5639

This was a prospective, test-negative case-control study using data from the New Vaccine Surveillance Network from the 2016 to 2017 through 2019 to 2020 influenza seasons. Infants younger than 6 months with an ED visit or hospitalization for acute respiratory illness were included from 7 pediatric medical institutions in US cities. Control infants with an influenza-negative molecular test were included for comparison. Data were analyzed from June 2022 to September 2023. They estimated maternal vaccine effectiveness against hospitalizations or ED visits in infants younger than 6 months, those younger than 3 months, and by trimester of vaccination. Maternal vaccination status was determined using immunization information systems, medical records, or self-report. Vaccine effectiveness was estimated by comparing the odds of maternal influenza vaccination 14 days or more before delivery in infants with influenza vs those without.

Of 3764 infants (223 with influenza and 3541 control infants), 2007 (53%) were born to mothers who were vaccinated during pregnancy. Overall vaccine effectiveness in infants was 34% (95% CI, 12 to 50), 39% (95% CI, 12 to 58) against influenza-associated hospitalizations, and 19% (95% CI, −24 to 48) against ED visits. Among infants younger than 3 months, effectiveness was 53% (95% CI, 30 to 68). Effectiveness was 52% (95% CI, 30 to 68) among infants with mothers who were vaccinated during the third trimester and 17% (95% CI, −15 to 40) among those with mothers who were vaccinated during the first or second trimesters.

Comment: Maternal vaccination was associated with reduced odds of influenza-associated hospitalizations and ED visits in infants younger than 6 months. Effectiveness was greatest among infants younger than 3 months, for those born to mothers vaccinated during the third trimester, and against influenza-associated hospitalizations. They did not capture data on

influenza vaccination prior to conception or postpartum which may confer some protection to infants and could impact the strength of the association observed. Accurate vaccine record systems are needed to support pregnancy-specific vaccine recommendations, which include the Tdap, influenza, Covid-19, and respiratory syncytial virus (RSV) vaccine. The FDA/CDC approved RSV vaccine for pregnant persons, with an indication between 32 to 36 weeks' gestation for neonatal benefit. OB-Gyn, primary care, and pediatric clinicians should collaborate to share effective approaches in their communities to enhance access, confidence, and coverage of vaccines and preventive care.

Bottom line: This is another example of the benefit of vaccination in pregnancy and protection of infants born to vaccinated women.

Clinical Practice Guideline by the Pediatric Infectious Diseases Society (PIDS) and the Infectious Diseases Society of America (IDSA): 2023 Guideline on Diagnosis and Management of Acute Bacterial Arthritis in Pediatrics J Pediatr Inf Dis Soc published online December 12, 2023 Highlights

https://doi.org/10.1093/jpids/piad089

- In children with suspected acute bacterial arthritis (ABA), they recommend performing blood culture prior to administration of antimicrobial therapy (strong recommendation, moderate certainty of evidence).
- In children with suspected ABA, they suggest against measuring serum procalcitonin (conditional recommendation, low certainty of evidence).
- In children with suspected ABA, they recommend obtaining plain radiography of the affected joint and adjacent bones rather than not performing plain radiographs (strong recommendation, moderate certainty of evidence).
- In children with suspected ABA in whom further imaging studies are required to assess the extent of inflammation and infection, including adjacent osteomyelitis and pyomyositis, they suggest performing an MRI study rather than other imaging modalities (e.g., CT or bone scintigraphy) (conditional recommendation, very low certainty of evidence).
- In children with suspected ABA, they suggest collecting synovial fluid from the affected joint by arthrocentesis prior to starting empiric antimicrobial therapy (conditional recommendation, moderate certainty of evidence).[this should be a strong recommendation if patient clinically stable]
- On joint fluid obtained by arthrocentesis, they recommend performing white blood cell count and differential and routine microbiological cultures (aerobic bacterial culture and Gram stain) (strong recommendation, moderate certainty of evidence).
    - Further diagnostic testing may be beneficial in certain situations: 1) molecular testing for specimens from which no pathogen has been identified by Gram stain and aerobic bacterial culture, (particularly in preschool-aged children at higher risk of K. kingae infection); and 2) more extensive scope of microbial testing, beyond aerobic bacterial culture (e.g., anaerobic, fungal, and/or mycobacterial cultures and stains; molecular testing, which may include metagenomic next-

generation sequencing), in children who are immunocompromised or who have a history of penetrating injury.

- In children with presumed ABA who are ill-appearing or have rapidly progressive infection, we recommend immediately starting empiric antimicrobial therapy (after blood cultures are obtained if possible) rather than withholding antibiotics until invasive diagnostic procedures are performed (strong recommendation, moderate certainty of evidence) In children with presumed ABA who do not appear clinically ill, they suggest withholding antimicrobial therapy, while under careful observation, until an initial joint aspirate is collected for diagnostic purposes (conditional recommendation, very low certainty of evidence).
- In children with suspected ABA, they recommend using empiric antimicrobial therapy active against S. aureus (strong recommendation, moderate certainty of evidence). Comment: Antimicrobials with activity against community-acquired MRSA (CA-MRSA) should be considered based on local susceptibility data and severity of disease.
- In infants and preschool aged children (6 to 48 months of age) with suspected ABA, they suggest selecting empiric therapy to include activity against K. kingae rather than only targeting S. aureus (conditional recommendation, very low certainty of evidence).
- In children with presumed or confirmed ABA who demonstrate a poor clinical and laboratory response within 48-96 hours (continued fever, persistent bacteremia and/or rising CRP) after initial invasive procedures (open or arthroscopic) and initiation of appropriate antimicrobial therapy, they suggest performing MRI if not previously obtained (conditional recommendation, very low certainty of evidence). If evidence suggests persisting foci of infection (ineffective source control), they suggest additional invasive procedures to ensure adequate source control.
- In children with presumed or confirmed ABA who require a surgical procedure, they recommend against the routine use of intra-articular antimicrobial agents (strong recommendation, very low certainty of evidence) and against using adjunctive corticosteroid therapy (conditional recommendation, very low certainty of evidence).
- In children with presumed or confirmed ABA receiving antimicrobial therapy with or without surgical intervention, in addition to serial clinical evaluation, they suggest performing CRP at initial evaluation followed by sequential monitoring of CRP to assess response to therapy, rather than relying solely on clinical evaluation (conditional recommendation, low certainty of evidence).
- For children with presumed or confirmed ABA who respond to initial intravenous antibiotic therapy, they recommend transition to an oral antibiotic regimen rather than OPAT when an appropriate, well-tolerated oral antibiotic option is available, and that antibiotic is active against the confirmed or presumed pathogen(s) (strong recommendation; low certainty of evidence).
- In children with confirmed primary ABA without adjacent osteomyelitis with rapid clinical improvement and consistent, progressive decrease in CRP by the end of the first week of treatment, they suggest treating for a total duration of antimicrobial therapy (parenteral plus oral) as short as 10 to 14 days for common pathogens (S. aureus, S. pyogenes, S. pneumoniae, and H. influenzae type b), rather than for longer courses of 21 to 28 days (conditional recommendation, low certainty of evidence). For children with slower clinical response, inadequate source control, or persistently elevated CRP, courses of therapy of 21 to 28 days may be preferred.

Bottom line: This guideline provides common sense evidence-based recommendations including duration of therapy. See next review

Multicenter evaluation of the BIOFIRE Joint Infection Panel for the detection of bacteria, yeast, and AMR genes in synovial fluid samples J Clin Microbiol published online November 2023

DOI:10.1128/jcm.00357-23

This study was performed to evaluate the BIOFIRE JI Panel for regulatory clearance. Thirty-one species or groups of microorganisms are included in the panel, as well as eight AMR genes. See below

Gram–positive bacteria		
Anaerococcus prevotii/vaginalis	*Parvimonas micra*	*Streptococcus* spp.
Clostridium perfringens	*Peptoniphilus*	*Streptococcus agalactiae*
Cutibacterium avidum/granulosum	*Peptostreptococcus anaerobius*	*Streptococcus pneumoniae*
Enterococcus faecalis	*Staphylococcus aureus*	*Streptococcus pyogenes*
Enterococcus faecium	*Staphylococcus lugdunensis*	
Finegoldia magna		
Gram–negative bacteria		
Bacteroides fragilis	*Kingella kingae*	*Proteus* spp.
Citrobacter	*Klebsiella aerogenes*	*Pseudomonas aeruginosa*
Enterobacter cloacae complex	*Klebsiella pneumoniae* group	*Salmonella* spp.
Escherichia coli	*Morganella morganii*	*Serratia marcescens*
Haemophilus influenzae	*Neisseria gonorrhoeae*	
Yeast		
Candida		
Candida albicans		
Antimicrobial resistance genes		
CTX–M	*mecA/C* and MREJ (MRSA)	*vanA/B*
IMP	NDM	VIM
KPC	OXA–48–like	

They provided data from a multicenter evaluation of 1,544 prospectively collected residual synovial fluid (SF)samples with performance compared to standard-of-care (SOC) culture for organisms or polymerase chain reaction (PCR) and sequencing for AMR genes. A BIOFIRE JI Panel result was considered a true positive (TP) or true negative (TN) only when it agreed with the result from the comparator method. Discrepancy analysis ensued when results were discordant, i.e., false positive (FP) or false negative (FN) results. When sufficient specimen volume was available, discordant specimens were investigated using additional, independent PCR assays. For some discrepant results, additional testing was performed on clinical isolates (additional, independent PCR assays or Vitek2).

Two hundred two specimens were positive by culture for at least one on-panel organism, and 242 specimens were positive by the BIOFIRE JI Panel for at least one organism. The overall performance of the BIOFIRE JI Panel for organisms was 90.5% sensitivity and 99.6% specificity. For the FN discrepancies, 20 results were positive by culture/negative by the BIOFIRE JI Panel, and for the FP discrepancies, 70 results were negative by culture/positive by the BIOFIRE JI Panel. A total of 70 specimens grew 75 off panel microorganisms (not included in the panel), and these results were not considered as FNs. The overall performance of the BIOFIRE JI Panel for AMR genes was 100% PPA and 98.8% NPA. Performance for the organisms was additionally stratified by specimens collected from native joints (*N* = 850) and specimens collected from prosthetic joints (PJ) (*N* = 442). For specimens collected from native joints, sensitivity and specificity were 88.2% and 99.6%, respectively. For specimens collected from prosthetic joints, overall organism sensitivity and specificity were 92.0% and 99.4%.

Comment: The BIOFIRE JI Panel provides an improvement over SOC culture, with a substantially shorter time to result for both organisms and AMR genes with very good sensitivity/PPA and specificity/NPA. In a recent study investigator compared BIOFIRE JI panel with metagenomic sequencing from patients with knee arthroplasty failure including 44 who were diagnosed with a PJ infection. The performance of the test for detection of organisms on the panel was high-91% sensitivity and 100% specificity. However, the panel was less accurate for the diagnosis of infection due to high numbers of organisms not included on the panel like S. epidermidis and C acnes. [J Clin Microbiol 2022; 60: e0112622] See table 5 below

TABLE 5 Off–panel organisms identified by SOC culture (*N* = 70 specimens)

Off–Panel organism identified	Number identified
Staphylococcus epidermidis	38
Cutibacterium acnes	8
Staphylococcus capitis	5
Corynebacterium striatum	3
Staphylococcus hominis	3
Corynebacterium amycolatum	2
Staphylococcus caprae	2
Acinetobacter baumannii complex	1
Arthrobacter cumminsii	1
Bacillus licheniformis	1
Capnocytophaga canimorsus	1
Clostridium symbiosum	1
Enterococcus gallinarum	1
Enterococcus hirae	1
Klebsiella oxytoca	1
Granulicatella adiacens	1
Pasteurella multocida	1
Prevotella intermedia	1
Staphylococcus haemolyticus	1
Staphylococcus saccharolyticus	1
Staphylococcus warneri	1
Total	75

Bottom line: The panel does offer a faster turnaround and better sensitivity over SOC cultures; however, the panel will miss organisms like S epidermidis and C acnes which may be important pathogens causing PJIs.

Editor's Choice

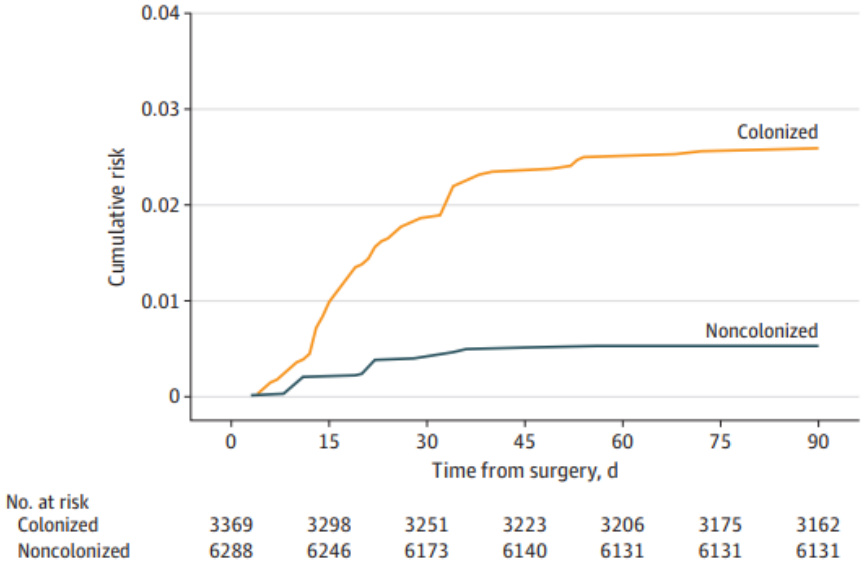
Postoperative *Staphylococcus aureus* Infections in Patients With and Without Preoperative Colonization JAMA Network Open. 2023;6(10): e2339793.

doi:10.1001/jamanetworkopen.2023.39793

This was a multicenter cohort study designed to assess surgical patients at 33 hospitals in 10 European countries who were recruited between December 16, 2016, and September 30, 2019 (follow-up through December 30, 2019). Enrolled patients were actively followed up for up to 90 days after surgery to assess the occurrence of S aureus SSIs and BSIs. Postoperative follow-up data were collected for all patients at days 7, 14, 21, 28, 60, and 90 after surgery (±3 days each) by medical record review and by contacting the participants or next of kin. Data analysis was performed between November 20, 2020, and April 21, 2022. All patients were 18 years or older and had undergone 11 different types of surgical procedures. They were screened for S aureus colonization in the nose, throat, and perineum within 30 days before surgery (source population). S aureus screening samples were analyzed locally on chromogenic culture media. All available S aureus isolates from the patients who developed S aureus SSIs and BSIs (screening isolates [n = 84; 54 patients] and infecting isolates [n = 139; 60 patients]) and from a random sample of noninfected patients (n = 221; 162 patients) were characterized by multilocus sequence typing using whole genome sequencing data Both S aureus carriers and noncarriers were subsequently enrolled in a 2:1 ratio.

In total, 5004 patients (median [IQR] age, 66 [56-72] years; 2510 [50.2%] female) were enrolled in the study cohort; 3369 (67.3%) were S aureus carriers. One hundred patients developed S aureus SSIs or BSIs within 90 days after surgery. The weighted cumulative incidence of S aureus SSIs or BSIs was 2.55% (95% CI, 2.05%-3.12%) for carriers and 0.52% (95% CI, 0.22%-0.91%) for noncarriers. Preoperative S aureus colonization (adjusted hazard ratio [AHR], 4.38; 95% CI, 2.19-8.76), having nonremovable implants (AHR, 2.00; 95% CI, 1.15-3.49), undergoing mastectomy (AHR, 5.13; 95% CI, 1.87-14.08) or neurosurgery (AHR, 2.47; 95% CI, 1.09-5.61) (compared with orthopedic surgery), and body mass index (AHR, 1.05; 95% CI, 1.01-1.08 per unit increase) were independently associated with S aureus SSIs and BSIs. For 53 patients who developed an *S aureus* infection, both colonizing and infecting *S aureus* strains were available. For 44 of these 53 patients (83.0%), the ST of the colonizing and infecting strains was identical.

Figure 2. Cumulative Incidence Function for *Staphylococcus aureus* Surgical Site Infections (SSIs) and Bloodstream Infections (BSIs) in *S aureus* Colonized vs Noncolonized Patients



Comment: This study confirms findings from previous studies that endogenous S aureus carriage is an important etiologic factor for postoperative S aureus infections. [J Clin Microbiol. 2015; 53:3478-3484; N Engl J Med. 20012001; 344:11-16] They found that certain types of surgery (mastectomy and neurosurgery), an increasing BMI, and having nonremovable implants also independently increased the risk of S aureus SSIs and BSIs. This study has compared head-to-head the risk of S aureus SSIs and BSIs of different surgical procedures from different surgical subspecialties in such a large cohort. It is important that interventions target the patient populations who have an increased risk. These data could help in the prioritization of which patient population should be targeted. Patient recruitment in certain countries and for certain surgical procedures progressed slower than we expected, which resulted in overrepresentation of patients from certain countries and surgical procedures in the study. They also expected a higher incidence of S aureus SSIs and BSIs than was observed.

Surprisingly, preoperative topical S aureus decolonization was not associated with S aureus SSIs and BSIs in any of their analyses, although there is convincing evidence supporting a protective effect of preoperative S aureus decolonization on the occurrence of S aureus SSI. [N Engl J Med. 2010; 362:9-17; JAMA. 2015; 313:2162-2171] However, the participating sites used different preoperative decolonization strategies for different surgical procedures (universal decolonization for certain procedures regardless of colonization status, targeted decolonization in case of S aureus colonization or MRSA carriage only, or no decolonization). Therefore, the use of topical S aureus decolonization could not really be assessed. The Compendium 2022 Update on strategies to prevent surgical site infections recommends as an essential practice to decolonize surgical patients with an anti-staphylococcal agent in the preoperative setting for orthopedic and cardiothoracic procedures. [Infect Control Hosp Epidemiol 2023; 44:695-720]

Bottom line: This study confirmed that S aureus SSIs and BSIs are important postoperative complications especially in colonized patients. Interventions aimed at prevention of these infections should focus on at-risk surgical patients.

Assessing the impact of discordant antibiotic treatment on adverse outcomes in community-onset UTI: a retrospective cohort study J Antimicrob Chemother published online November 17, 2023

doi.org/10.1093/jac/dkad357

Investigators in the UK performed a retrospective cohort study to evaluate discordant (antibiotic-resistant microorganism) versus appropriate (antibiotic-sensitive microorganism) antimicrobial therapy begun within 3 days of a physician consultation for UTI, and their relationship to hospital admission and need for re-consultation. UK guidelines recommend only sending urine cultures in cases of complicated UTI, treatment failure or where AMR is suspected, meaning that the subset of patients who have a urine culture sent are already deemed at higher risk of adverse outcomes. They aimed to use a dataset of linked primary care, secondary care and microbiology data to investigate the effect of discordant antibiotic treatment on adverse outcomes (hospitalization and primary care reconsultation) in the 30 days following a treated episode of culture-confirmed community-onset lower UTI (COLUTI) in primary care. The study period was April 2012 to March 2017. The following were excluded: no record of age, sex or Index of Multiple Deprivation (IMD) score; inpatient urine samples; Read code indicating upper UTI (pyelonephritis) within ±3 days; admission to hospital on day of consultation; and hospital discharge ≤30 days prior.

Among 11963 UTI episodes in 8324 patients (median age, 54), women accounted for 87% of all episodes and the most common organism was E. coli (72%). The most frequently prescribed antibiotics were trimethoprim (34%), nitrofurantoin (24%), cephalexin (17%), and amoxicillin (16%). Discordant treatment was identified in 14% of episodes. Hospital admission within 30 days occurred in 2% of appropriately treated cases and 5% of discordant cases, and re-consultation occurred in 39% and 87% of such cases, respectively. In multivariate analysis, discordant therapy was associated with increased chances of hospital admission (adjusted odds ratio, 2.3) and re-consultation (aOR, 11.2). Among patients aged ≥75, the numbers needed to treat to prevent hospital admission and re-consultation were 26 and 3, respectively.

Comment: In the UK urines are only ordered in complicated cases. The need for re-consultation was high, and although the majority of cases were women, males had higher risk of hospitalization. This may suggest the possibility of subclinical prostatitis, so clinicians need to tailor therapy in treating males especially if an older patient. The investigators saw higher levels of resistance compared with national surveillance data on community urine samples, with resistance to trimethoprim seen in 40.1% of E. coli isolates compared with 34.0% from 2017 surveillance. This cohort represents an ethnically diverse, socioeconomically deprived urban population, and the results may only be relevant to other similar populations. They found that patients of non-white ethnicity were more likely to receive discordant treatment.

Bottom line: More work is needed to identify patients at high risk for resistance and determine ways to prevent complications.

2022 National and State Healthcare-Associated Infections Progress Report. November 2023

The CDC has released the 2022 National and State Healthcare-Associated Infections (HAI) Progress Report. While some settings saw no change or increases in infections, Acute Care Hospitals reported significant decreases in some HAIs between 2021 and 2022:

- Central line-associated bloodstream infections (CLABSI) (down 9%),

    Largest decrease in ICU (21%), but increase in NICU (11%)

- Catheter-associated urinary tract infections (CAUTI) (down 12%),

- Ventilator-associated events (VAE) (down 19%),

- Hospital-onset methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia (down 16%), and

- Hospital-onset *Clostridioides difficile* (CDI) (down 3%).

- Surgical site infections (SSI) following abdominal hysterectomy and colon surgery had no significant changes

HAI Type	Acute Care Hospitals	Inpatient Rehabilitation Facilities	Long-term Acute Care Hospitals
CLABSI	↓ 9%	No Change	No Change
CAUTI	↓ 12%	No Change	No Change
VAE	↓ 19%		No Change
SSI: Colon Surgery	No Change		
SSI: Abdominal hysterect...	No Change		
LabID MRSA bacteremia	↓ 16%	No Change	No Change

Comment: This report mirrors the Leapfrog report reviewed in December 2023 ID Watch. SSIs remain unchanged, but we have seen a reversal in trends for CLABSIs, CAUTIs, and VAEs.

Bottom line: More progress needs to occur if we are to get back to pre-pandemic rates, but we are moving in the right direction. CDC noted that one in 31 patients at health care facilities and one in 43 nursing home residents contracts an HAI each day. The new report underscores the need for improvement.

Treatment effectiveness of antibiotic therapy in Veterans with multidrug-resistant Acinetobacter spp. Bacteremia Antimicrob Stewardship & Healthcare Epidemiol (2023), 3, e230, 1–7

doi:10.1017/ash.2023.500

This was a retrospective cohort study of hospitalized Veterans Affairs (VA) patients from 2012 to 2018 with a positive MDR *Acinetobacter spp.* blood culture who received antimicrobial treatment 2 days prior to through 5 days after the culture date. Only the first culture per patient was used. The association between treatment and patient characteristics was assessed using bivariate analyses. Multivariable logistic regression models examined the relationship between antibiotic regimen and in-hospital, 30-day, and 1-year mortality. Generalized linear models were used to assess cost outcomes. Fully adequate treatment was defined as receipt of only antibiotics to which the isolate was non-resistant (susceptible or intermediate). Partial adequate treatment was defined as receipt of at least one antibiotic to which the isolate was non-resistant. Inadequate treatment was defined as receipt of no antibiotics to which the isolate was non-resistant. Patient characteristics of gender, age, race, ethnicity, comorbidities, and previous healthcare exposure (previous ICU admission, past immunocompromising conditions, mechanical ventilation, previous antibiotic exposure, and previous admission) were also collected.

MDR *Acinetobacter spp.* was identified in 184 patients. Most cultures identified were *Acinetobacter baumannii* (90%). Most patients were older (mean age, 67 years), White, non-Hispanic men. Penicillin—β-lactamase inhibitor combinations (51.1%) and carbapenems (51.6%)—were the most prescribed antibiotics. Prior hospital admission (77.2%) and antibiotic exposure (90.8%) in the previous 90 days were common. From 2012 to 2018, these treatments were commonly used in accordance with recommendations from the Sanford Guide: carbapenems (51.6%), aminoglycosides (29.9%), and extended spectrum cephalosporins (31.5%). Half of cultures received combination anti-Acinetobacter therapy (50.0%), and 50.0% received monotherapy. Thirty-seven percent of patients received fully adequate treatment, 50% partially adequate, and 13% inadequate treatment. In unadjusted analysis, extended spectrum cephalosporins and penicillin—β-lactamase inhibitor combinations—were associated with a decreased odds of 30-day mortality but were insignificant after adjustment (adjusted odds ratio (aOR) = 0.47, 95% CI, 0.21–1.05, aOR = 0.75, 95% CI, 0.37–1.53). There was no association between combination therapy vs monotherapy and 30-day mortality (aOR = 1.55, 95% CI, 0.72–3.32). Half (50.5%) of the infected patients died in hospital, 44% within 30 days, and 67.9% within 1 year.

Comment: Given limited clinical data supporting the effectiveness of any single antibiotic agent, the recent IDSA guidelines recommend combination therapy including high-dose ampicillin-sulbactam for severe MDR Acinetobacter spp. infection. [Clin Infect Dis 2022; 74:2089–2114] However, prior studies have found limited improved clinical outcomes with combination therapy, however many of these involve colistin as one of the drugs [J Clin Med 2022;11:3239]

Their analysis only included patients who received treatment within −2 through 5 days of culture date, which may have resulted in missing patients who may have died before treatment, had delayed treatment, or received treatment longer than 5 days. Treatment received more than 5 days post-culture was not captured; thus, full duration of treatment was not a factor in the outcome or cost analysis, which may have resulted in underestimated costs in severely ill

patients. Additionally, the identification and reporting of bacterial susceptibilities could only be determined based on antibiotics that were tested in the microbiology panels. The authors say these findings add to evidence from some prior studies, which have found limited improved clinical outcomes with combination therapy.

Bottom line: Although this study did not find better outcomes with combination therapy, more studies are needed. In my opinion until more studies are performed to confirm this study, I would still use combination therapy for severe Acinetobacter infections.

Editor's Choice

Association Between Daily Toothbrushing and Hospital-Acquired Pneumonia A Systematic Review and Meta-Analysis. JAMA Intern Med published online December 18, 2023

doi:10.1001/jamainternmed.2023.6638

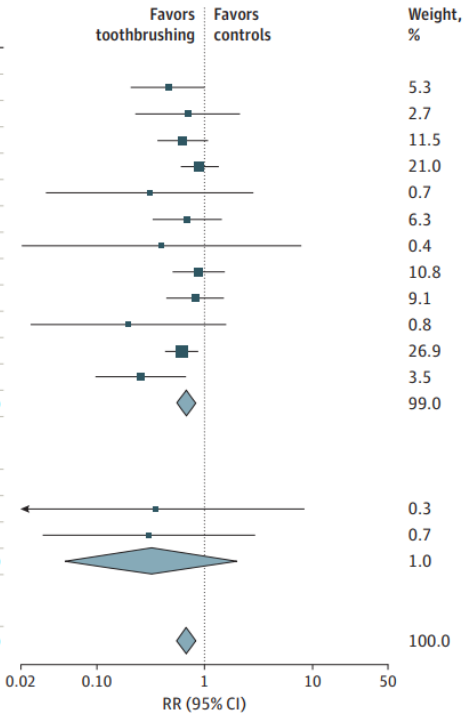
The authors reviewed 15 randomized clinical trials with an effective population size of 2,786 patients. The studies compared outcomes among hospitalized patients and oral care habits while in the hospital. All but one study focused on patients who were being treated in ICUs. Meta-analysis was performed using random-effects models. The primary outcome of this systematic review and meta-analysis was HAP. Secondary outcomes included hospital and intensive care unit (ICU) mortality, duration of mechanical ventilation, ICU and hospital lengths of stay, and use of antibiotics. Subgroups included patients who received invasive mechanical ventilation vs those who did not, toothbrushing twice daily vs more frequently, toothbrushing provided by dental professionals vs general nursing staff, electric vs manual toothbrushing, and studies at low vs high risk of bias.

Toothbrushing was associated with significantly lower risk for HAP (risk ratio [RR], 0.67 [95% CI, 0.56-0.81]) and ICU mortality (RR, 0.81 [95% CI, 0.69-0.95]). Reduction in pneumonia incidence was significant for patients receiving invasive mechanical ventilation (RR, 0.68 [95% CI, 0.57-0.82) but not for patients who were not receiving invasive mechanical ventilation (RR, 0.32 [95% CI, 0.05-2.02]). Toothbrushing for patients in the ICU was associated with fewer days of mechanical ventilation (mean difference, -1.24 [95% CI, -2.42 to -0.06] days) and a shorter ICU length of stay (mean difference, -1.78 [95% CI, -2.85 to -0.70] days). Brushing twice a day vs more frequent intervals was associated with similar effect estimates. Results were consistent in a sensitivity analysis restricted to 7 studies at low risk of bias (1367 patients). Non-ICU hospital length of stay and use of antibiotics were not associated with toothbrushing.

There is no evidence that brushing 3 or more times a day confers additional benefit over brushing 2 times a day. They were unable to answer whether the type of toothpaste or choice of toothbrushing fluid affects outcomes.

Figure 3. Association of Toothbrushing With Hospital-Acquired Pneumonia (HAP)

Source	Experimental group No. of events	Experimental group No. of patients	Control group No. of events	Control group No. of patients	RR (95% CI)	Weight, %
1.1.1 VAP						
Bellissimo-Rodrigues et al,[42] 2014	8	98	17	96	0.46 (0.21-1.02)	5.3
Chacko et al,[44] 2017	5	104	7	102	0.70 (0.23-2.14)	2.7
de Lacerda Vidal et al,[41] 2017	17	105	28	108	0.62 (0.36-1.07)	11.5
Falahinia et al,[39] 2016	19	34	21	34	0.90 (0.61-1.35)	21.0
Félix,[51] 2016	1	30	3	28	0.31 (0.03-2.82)	0.7
Gong et al,[31] 2018	9	40	13	40	0.69 (0.33-1.43)	6.3
Khan et al,[49] 2017	0	4	1	5	0.40 (0.02-7.82)	0.4
Lorente et al,[45] 2012	21	217	24	219	0.88 (0.51-1.54)	10.8
Pobo et al,[46] 2009	15	74	18	73	0.82 (0.45-1.50)	9.1
Salarzehi et al,[32] 2021	1	30	5	30	0.20 (0.02-1.61)	0.8
Singh et al,[43] 2022	32	110	52	110	0.62 (0.43-0.88)	26.9
Yao et al,[44] 2011	4	28	14	25	0.26 (0.10-0.67)	3.5
Subtotal	132	**874**	203	**870**	**0.68 (0.57-0.82)**	99.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{11} = 10.37$ ($P = .50$); $I^2 = 0\%$						
Test for overall effect: $z = 4.13$ ($P < .001$)						
1.1.2 NV-HAP						
Bellissimo-Rodrigues et al,[42] 2014	0	29	1	31	0.36 (0.02-8.39)	0.3
Giuliano et al,[47] 2021	1	393	3	360	0.31 (0.03-2.92)	0.7
Subtotal	1	**422**	4	**391**	**0.32 (0.05-2.02)**	1.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_1 = 0.01$ ($P = .94$); $I^2 = 0\%$						
Test for overall effect: $z = 1.21$ ($P = .23$)						
Total	133	**1296**	207	**1261**	**0.67 (0.56-0.81)**	100.0
Heterogeneity: $\tau^2 = 0.00$; $\chi^2_{13} = 11.01$ ($P = .61$); $I^2 = 0\%$						
Test for overall effect: $z = 4.23$ ($P < .001$)						
Test for subgroup differences: $\chi^2_1 = 0.63$ ($P = .43$); $I^2 = 0\%$						



Comment: These findings suggest that daily toothbrushing may be associated with lower rates of pneumonia and ICU mortality, particularly among patients undergoing invasive mechanical ventilation; programs and policies to encourage daily toothbrushing are warranted. This study represents an important contribution to infection prevention and reinforces the notion that routine toothbrushing is an essential component of standard of care in ventilated patients. However, there is still uncertainty regarding NV-HAP since the investigators could only identify 2 studies. The NEVER Trial will hopefully answer this question. The studies were not double blind which may have biased their assessments. Second, duration of follow-up was short in some studies, potentially leading to under detection of pneumonia. They did not have patient-level data to assess whether effects differed for patients with oral vs nasal vs tracheal intubations or whether these effects differed by age group.

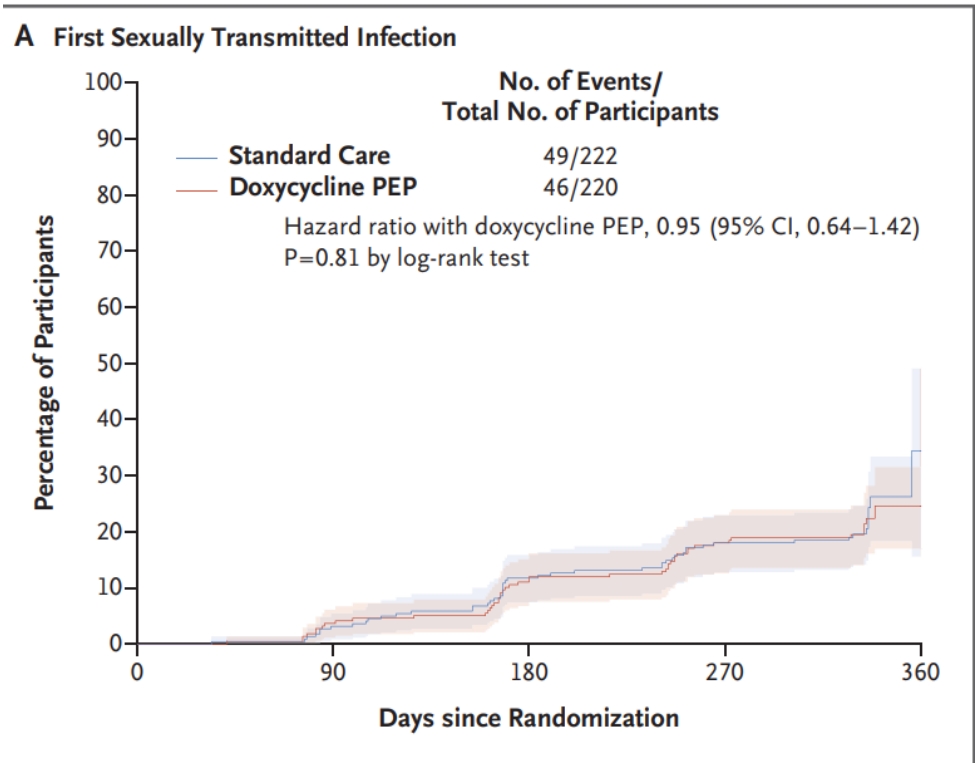
Bottom line: Toothbrushing should be an essential practice for patients on invasive mechanical ventilation. More studies are needed regarding if toothbrushing prevents NV-HAP.

Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women N Engl J Med 2023;389:2331-40.

DOI: 10.1056/NEJMoa2304007

The investigators conducted a randomized, open-label trial comparing doxycycline PEP (doxycycline 200 mg taken within 72 hours after unprotected sex) with standard care among Kenyan women 18 to 30 years of age who were receiving preexposure prophylaxis against HIV. [tenofovir-emtricitabine] The primary end point was any incident infection with Chlamydia trachomatis, N gonorrhoeae, or Treponema pallidum. Hair samples were collected quarterly for objective assessment of doxycycline use.

A total of 449 participants underwent randomization; 224 were assigned to the doxycycline-PEP group and 225 to the standard-care group. Participants were followed quarterly over 12 months. A total of 109 incident STIs occurred (50 in the doxycycline-PEP group [25.1 per 100 person-years] and 59 in the standard-care group [29.0 per 100 person-years]), with no significant between-group difference in incidence (relative risk, 0.88; 95% confidence interval [CI], 0.60 to 1.29; P=0.51). Among the 109 incident STIs, chlamydia accounted for 85 (78.0%) (35 in the doxycycline-PEP group and 50 in the standard-care group; relative risk, 0.73; 95% CI, 0.47 to 1.13). No serious adverse events were considered by the trial investigators to be related to doxycycline, and there were no incidents of HIV infections. Among 50 randomly selected participants in the doxycycline-PEP group, doxycycline was detected in 58 of 200 hair samples (29.0%). All N. gonorrhoeae–positive isolates were resistant to doxycycline! According to hair-sample analysis for doxycycline only 29% of samples showed the drug present.



Comment: In May 2023 ID Watch reviewed a study which found that among men who have sex with men and transgender women, doxycycline taken after intercourse substantially reduces risk for bacterial STIs. [N Engl J Med 2023; 388:1296-1306] However, among cisgender women, the incidence of STIs was not significantly lower with doxycycline PEP than with standard care. According to hair-sample analysis, the use of doxycycline PEP among those assigned to receive it was low. The results of this study were disappointing. It showed that a successful intervention in men may not work for women. The question is why. Possible explanations include antimicrobial-resistant N gonorrhoeae [Prevalence of the tet(M) gene, which confers high-level tetracycline-resistant N. gonorrhoeae, was 100% at baseline (in 16 enrollment visits in which DNA samples were tested) and 100% at the follow-up visits in the doxycycline-PEP group versus 27% resistance in earlier study in men] and inadequate adherence. Tetracycline-resistant C. trachomatis was not detected in the current trial. Syphilis was too uncommon to permit assessment of effectiveness.

Bottom line: No additional trials are in process for cisgender women, who bear the highest global burden of complications from STIs. Further trials investigating doxycycline PEP among persons who had been assigned a female sex at birth are warranted.

Respiratory Viruses in Wastewater Compared with Clinical Samples, Leuven, Belgium. Emerg Infect Dis. January 2024

DOI: 10.3201/eid3001.231011

Investigators screened 112 wastewater samples collected weekly over a 2-year period at a large regional treatment plant in Leuven for the presence of respiratory pathogens with an in-house–developed multiplex quantitative PCR respiratory panel. They then investigated whether respiratory viruses found in wastewater corresponded to their detection in samples from patients with respiratory infections at the University Hospitals Leuven (UZL). At UZL, patient samples were only tested with the respiratory panel in case of serious lower respiratory tract infection in immunocompromised or critically ill patients.

Influenza A was repeatedly identified during mid-February–mid-May 2022. This pattern aligned with positive clinical samples at UZL, which showed an influenza A peak during March–May 2022 and few cases outside that period. The onset of the 2022–23 influenza epidemic, with cocirculation of influenza A and B, was reflected in positive wastewater samples as of mid-December.

The off-season peak of RSV in the spring of 2021, visible in clinical samples at UZL was reflected in positive wastewater samples during March–July 2021. They detected RSV in almost all wastewater samples from mid-October 2021 until the end of July 2022. After August 2022, RSV reappeared in wastewater; levels were elevated in November and December 2022. The number of positive clinical samples in UZL remained low until the end of October 2022, followed by a strong RSV epidemic in November and December 2022.

During late September–December 2021, human metapneumovirus was almost continuously detectable in wastewater, which corresponded with high numbers of positive samples at UZL. Human metapneumovirus reappeared in wastewater in late October 2022, followed by an increase in positive samples at UZL in November and December.

Parainfluenzavirus (PIV) type 1 was predominantly found in wastewater samples during fall 2022, coinciding with a rise in positive cases at UZL. PIV-2 was sporadically detected in wastewater beginning in fall 2021, corresponding with low positive case numbers at UZL during November 2021–November 2022. PIV-3 was almost always detected in wastewater samples; a clear peak occurred during February–May 2021, in concordance with positive sample numbers at UZL. PIV-4 was detectable during August–December 2021 and September–December 2022, and occurred sporadically in between. The data also demonstrated an association with numbers of positive samples at UZL.

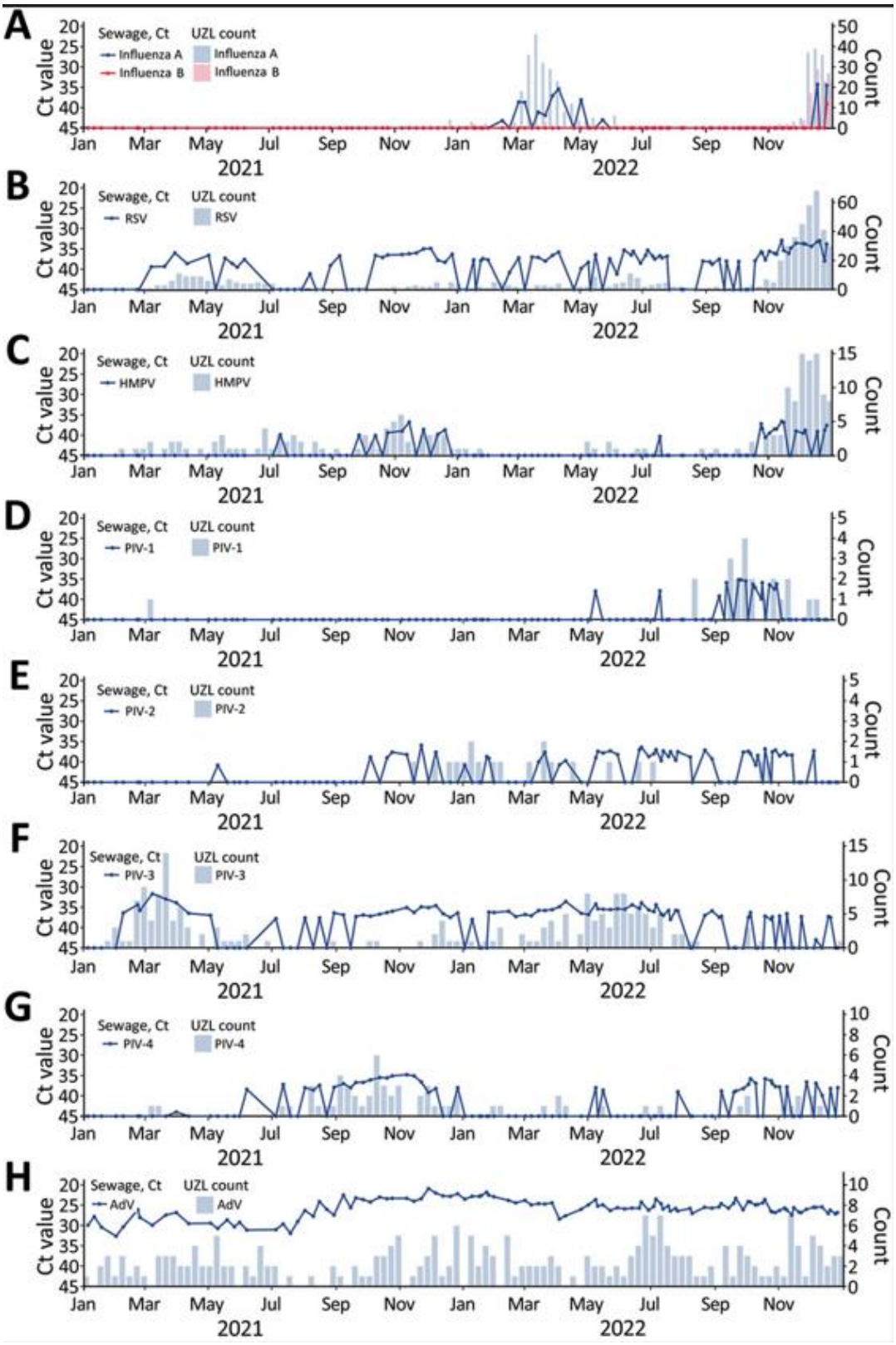
They detected adenovirus and human bocavirus (HBoV) consistently and in high concentrations in all wastewater samples. The continuous high-level detection of adenovirus and HBoV in wastewater does not align with the low numbers of positive samples found in ARI patients at UZL. Of the 4 HBoV genotypes, HBoV1 is mainly associated with respiratory symptoms in children with ARI and HBoV2 is linked to gastroenteritis. All HBoV genotypes are known to be present in stool and can frequently be detected in wastewater samples. Adenovirus infections can cause gastrointestinal symptoms, even when the primary site of involvement is the respiratory tract. The presence of HBoV and adenovirus in wastewater samples is likely linked to enteric rather than respiratory infections.

Enterovirus/rhinovirus were continuously detected in wastewater, but enterovirus D68 (EV-D68) was only present during early September–December 2021; the highest concentrations were detected in October 2021. Those findings suggest a regional EV-D68 outbreak during fall 2021, in line with increasing EV-D68 infections in Europe in September 2021. At UZL, 33 EV-D68–positive samples were detected during the study period, most during October 2021–January 2022. In mid-September 2022, EV-D68 reappeared in wastewater; only a small number of positive samples were reported at UZL. Detection of EV-D68 in wastewater preceded positive cases in the same region, indicating that wastewater surveillance can be used as a sensitive early warning signal for EV-D68 circulation.

Human parechovirus (HPeV) infections are common in children; illnesses can range from gastroenteritis and respiratory infections to neurologic disease, particularly in neonates. [J Clin Virol. 2009;45:1–9]We detected HPeV consistently in almost all wastewater samples throughout the study but detected few positive clinical samples. HPeV's presence in wastewater could be associated with enteric infections or paucisymptomatic respiratory infections with limited spillover to hospitals.

The SARS-CoV assay in the respiratory panel did not detect SARS-CoV-2 until late September 2021. Their assay targets a conserved region in the open reading frame 1ab polyprotein gene to enable detection of SARS-CoV-1 and SARS-CoV-2, resulting in a lower sensitivity. The assay is, however, not sensitive enough for environmental surveillance. Of the 4 endemic seasonal coronaviruses infecting humans, human coronavirus (HCoV) NL63 was primarily detected in wastewater during fall and winter of 2022, whereas HCoV-229E and HCoV-OC43 were present in most samples year-round. HCoV-HKU-1 was mainly detected between winter of 2021 and summer of 2022; all positive clinical samples were also reported during this period. Low numbers of HCoV positive clinical samples were detected in UZL, particularly for HCoV-NL63

and HCoV-229E, likely because of the mild nature of endemic coronavirus infections (typically not requiring hospitalization) rather than because of absence of circulation.

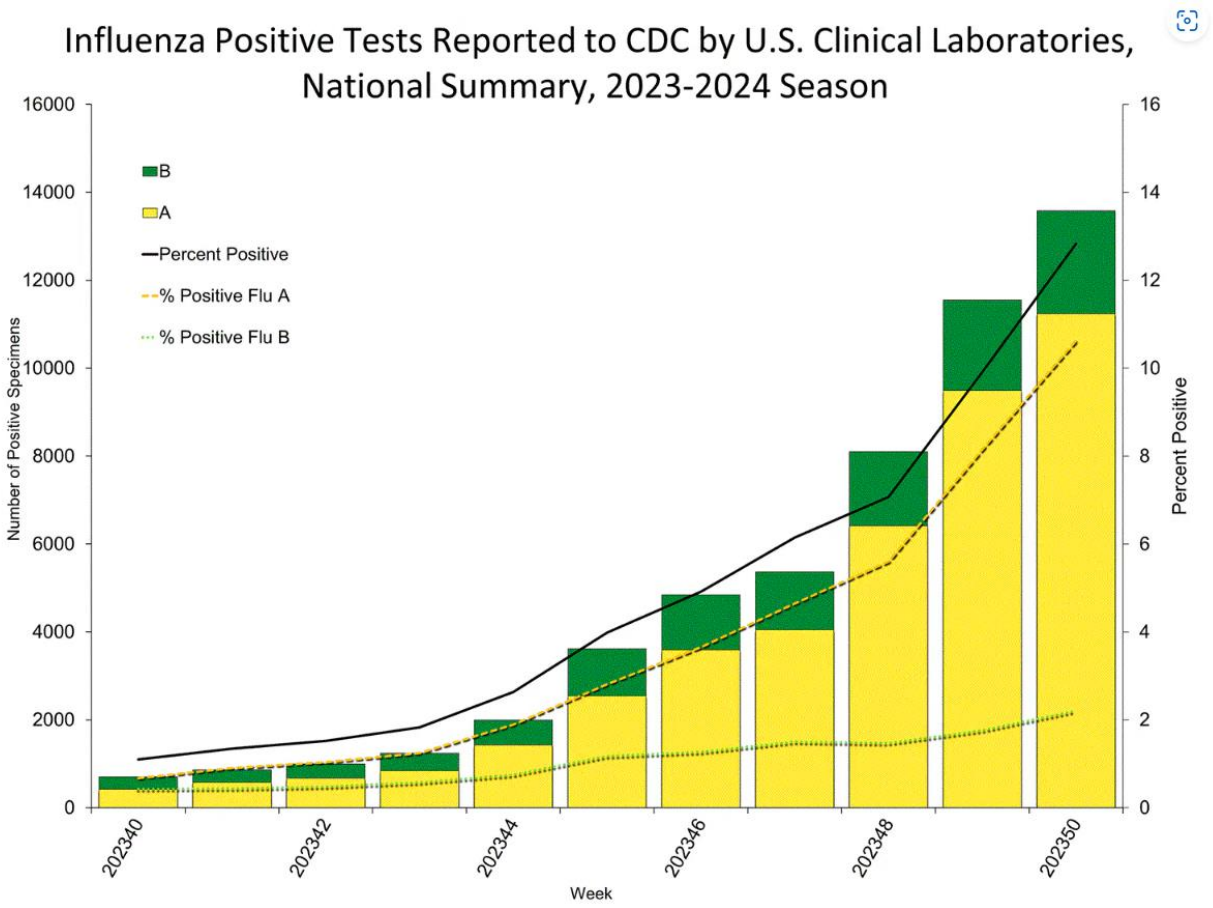


Comment: By using an in-house respiratory panel to test a 2-year wastewater sample collection, the investigators detected the presence and seasonal variations of most tested respiratory viruses. These findings demonstrate wastewater sampling's potential for population-level pathogen monitoring and early outbreak detection. This study underscores the role of wastewater-based epidemiology in supplementing clinical surveillance for respiratory viruses, enhances understanding of community virus circulation, and supporting public health efforts. Since they only sampled severe illness in the hospital the clinical samples may not be entirely representative of locally circulating respiratory pathogens, especially when those pathogens cause mainly mild infections.

Bottom line: This article supports the use of wastewater surveillance in predicting circulating viral pathogens. This tool was invaluable during the SARS-CoV-2 pandemic. Next targets to consider include detecting antibiotic resistance genes, C auris, and mpox.

Respiratory Viruses by the Number

Influenza

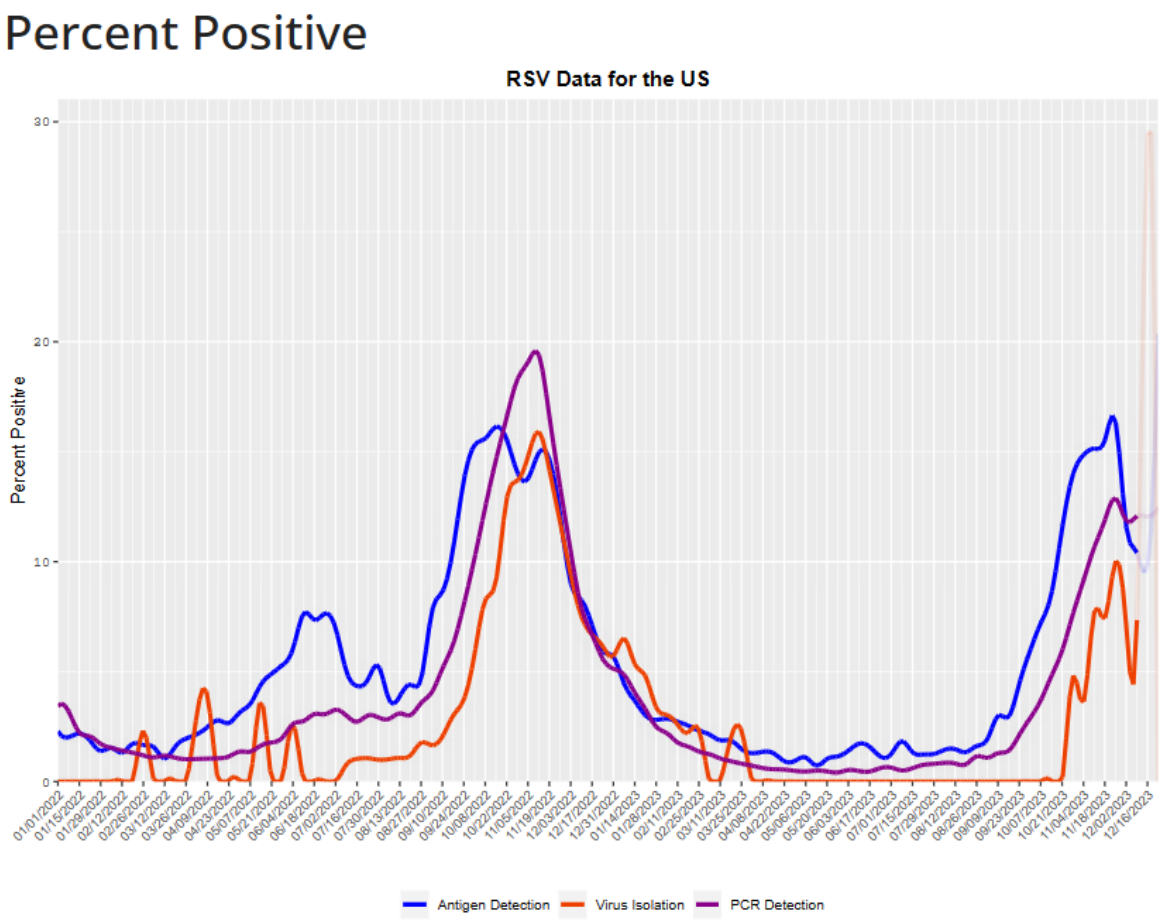


Comment: Seasonal influenza activity is elevated and continues to increase in most parts of the country. The number of weekly flu hospital admissions continues to increase. During Week 50,

of the 1,050 viruses reported by public health laboratories, 860 (81.9%) were influenza A and 190 (18.1%) were influenza B. Of the 481 influenza A viruses subtyped during week 50, 376 (78.2%) were influenza A(H1N1) and 105 (21.8%) were A(H3N2). CDC estimates that there have been at least 5.3 million illnesses, 54,000 hospitalizations, and 3,200 deaths from flu so far this season.

Bottom line: Flu activity is up. CDC recommends that everyone 6 months and older get an annual flu vaccine. It is not too late to get vaccinated.

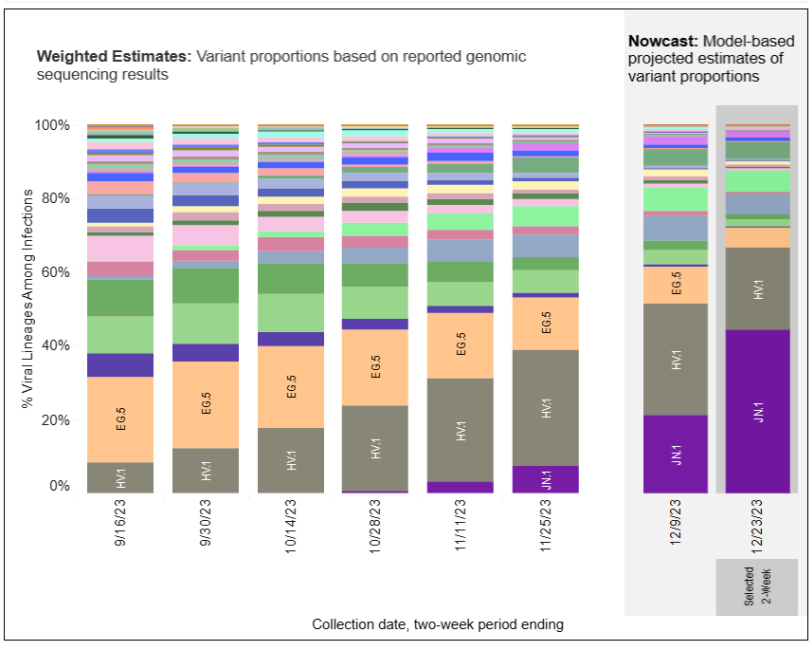
RSV



Comment: Overall RSV activity has peaked and is beginning to decrease. RSV vaccination remains low-see MMWR report below.

COVID-19

First detected in September, the latest Covid-19 variant to emerge, JN.1, has rapidly spread and now accounts for 44.1% of cases in the U.S. Less than two weeks ago, around December 13th JN.1 accounted for only 21% of cases. Trailing JN.1 is another variant, HV.1, making up 22.1% of cases nationally. CDC does not think that JN.1 presents an increased risk to public health relative to other currently circulating variants.



USA

WHO label	Lineage #	%Total	95%PI
Omicron	JN.1	44.2%	38.8-49.7%
	HV.1	22.1%	19.9-24.5%
	JD.1.1	5.6%	4.6-6.9%
	HK.3	5.5%	4.9-6.2%
	EG.5	5.5%	4.7-6.3%
	JG.3	4.8%	4.0-5.8%
	BA.2.86	2.0%	1.5-2.7%
	FL.1.5.1	1.9%	1.6-2.3%
	JF.1	1.4%	1.1-1.8%
	XBB.1.16.6	1.2%	0.9-1.5%
	XBB.1.9.1	0.7%	0.5-1.0%
	XBB.1.16.11	0.7%	0.5-1.0%
	XBB.2.3	0.6%	0.5-0.8%
	GK.1.1	0.6%	0.4-0.7%
	XBB.1.16	0.5%	0.3-1.0%
	XBB.1.5.70	0.5%	0.4-0.8%
	HF.1	0.5%	0.3-0.7%
	XBB.1.16.15	0.3%	0.2-0.5%
	BA.2	0.3%	0.0-2.1%
	XBB	0.3%	0.2-0.3%
	GE.1	0.2%	0.1-0.3%
	GK.2	0.1%	0.1-0.2%
	CH.1.1	0.1%	0.0-0.1%
	EG.6.1	0.1%	0.1-0.1%
	XBB.1.5	0.1%	0.0-0.1%
	XBB.1.16.1	0.1%	0.0-0.1%
	XBB.1.42.2	0.0%	0.0-0.1%
	XBB.1.5.68	0.0%	0.0-0.0%
	XBB.2.3.8	0.0%	0.0-0.1%
	XBB.1.9.2	0.0%	0.0-0.0%
	XBB.1.5.72	0.0%	0.0-0.0%
	XBB.1.5.10	0.0%	0.0-0.0%
	XBB.1.5.59	0.0%	0.0-0.0%
	FD.1.1	0.0%	0.0-0.0%
Other	Other*	0.0%	0.0-0.1%

Comment: The most recent data from the CDC details more than 25,000 new Covid-19 hospitalizations, a 10% jump from the previous week. There was also a 3% jump in deaths linked to the virus during that week. Although Covid-19 hospitalizations and deaths have risen for several weeks in a row, the numbers are still lower than they were during this same period in 2022, and they're significantly lower than they were during Covid's peak two years ago. Some major health systems are bringing back mask requirements to stop the spread of infections. Vaccinations remain low. See next review.

Influenza, Updated COVID-19, and Respiratory Syncytial Virus Vaccination Coverage Among Adults — United States, Fall 2023 MMWR 2023; 72;1377-1382.

CDC researchers reviewed fall 2023 data from the National Immunization Survey-Adult Covid Module (NIS-ACM), a random phone survey of US adults used to track Covid-19, flu, and RSV coverage.

By December 9, about 42.2% and 18.3% of adults reporting receiving a flu and Covid-19 shot, respectively, while 17.0% of older adults and 21.4% of those with chronic conditions said they were vaccinated against RSV. About 27% and 41% of adults and 53% of older adults said they would definitely, probably, or were unsure whether they would receive the three vaccines.

The proportion of unvaccinated adults who said they definitely would get vaccinated fell as uptake rose, from 33.2% to 9.4% for flu, and 28.2% to 14.1% for Covid-19. The decline was less for RSV vaccine, from 20.9% to 14.1%. The percentage of unvaccinated adults who reported they probably or definitely would not get vaccinated was lowest for RSV, while the proportion of those who were unvaccinated and said they probably would get vaccinated or were unsure was highest for RSV.

Immunization rates for all vaccines was lowest among uninsured respondents, while uptake and intent to be vaccinated climbed with age and were higher among those living in urban and suburban areas than in rural areas.

Flu vaccine uptake was higher among White and Asian adults than among most other racial groups, but the proportion reporting that they probably or definitely would not get vaccinated against flu was comparable among White and Black adults (both 32.2%) and lower among Hispanic respondents (24.0%).

Updated Covid-19 and RSV vaccine uptake was higher among White people than among most other racial groups, but a higher proportion of White adults said they probably or definitely would not receive a Covid-19 vaccine (43.2%) than Black (31.3%) and Hispanic (34.7%) adults.

Likewise, a higher percentage of White respondents reported that they probably or definitely would not get vaccinated against RSV (32.5%) than Black (15.3%) and Hispanic (19.3%) adults. Uptake of all vaccines varied by region, from 15.6% to 54.8% for flu, 2.4% to 35.6% for Covid-19, and 1.9% to 32.4% for RSV.

Comment: Although influenza, updated Covid-19, and RSV vaccination has slowed for the 2023–24 respiratory season, vaccination is still recommended while viruses are circulating. The response rates for NIS-ACM were relatively low (<25%). All responses were self-reported; vaccination receipt, and month and year of receipt of most recent dose might be subject to recall or social desirability bias.

Bottom line: Vaccination rate for these 3 respiratory viruses is very disappointing. We should use this data to better understand vaccination patterns and to guide planning, implementation, and acceptance in the future.

Outcomes of Pediatric SARS-CoV-2 Omicron Infection vs Influenza and Respiratory Syncytial Virus Infections JAMA Pediatr published online December 26, 2023

doi:10.1001/jamapediatrics.2023.5734

This multicenter, retrospective cohort study used 5 population-based data sources and included all 3 pediatric EDs in Stockholm, Sweden, covering approximately 500 000 individuals younger than 18 years. They identified individuals younger than 18 years attending the ED from August 1, 2021, to September 15, 2022, with a PCR positive for SARS-CoV-2, influenza A/B, or RSV from 1 day before to 1 day after the ED visit. Multiplex PCR testing of all 3 viruses was introduced February 2021, and more than 99% of the study population was tested for all 3 viruses. s. For the cohort with Omicron, only visits from December 27, 2021, onward were included, a period when Omicron was the dominating variant. They excluded patients testing positive for more than 1 virus. Two infectious diseases physicians reviewed diagnoses to include visits likely due to respiratory infections. Criteria. Outcomes were hospitalization, ICU admission, and 30-day all-cause mortality. Hospitalizations with admission due to infection were included. Logistic regression models adjusted for age, sex, and comorbidities were used to compare hospitalizations for RSV and influenza vs Omicron.

They included 2596 pediatric patients (896 [34.5%] with Omicron, 426 [16.4%] with influenza A/B, and 1274 [48.0%] with RSV). Of patients with RSV, 990 (77.7%) were younger than 2 years vs 648 (72.3%) with Omicron and 81 (19.0%) with influenza (Table 1). Hospitalization rates were 31.5% (n = 282) for Omicron, 27.7% (n = 118) for influenza, and 81.7% (n = 1041) for RSV. For infants aged 0 to 1 year, odds ratios (ORs) for hospitalization were 11.29 (95% CI, 8.91-14.38) for RSV vs Omicron and 1.67 (95% CI, 1.03- 2.68) for influenza vs Omicron. For children aged 2 to 4 years, ORs were 3.96 (95% CI, 2.25-7.01) and 0.31 (95% CI, 0.15-0.65), respectively. For youths aged 5 to 17 years, ORs were 5.22 (95% CI, 2.40-11.81) and 1.10 (95% CI, 0.69-1.77), respectively. ICU admission rates were 0.7% (n = 6) for Omicron, 0.9% (n = 4) for influenza, and 2.9% (n = 37) for RSV. Three patients died within 30 days: 2 (0.2%) with Omicron and 1 (0.1%) with RSV.

Table 2. Age-Stratified Hospital Admission Rates in the Cohorts With SARS-CoV-2 Omicron, Influenza A/B, or RSV Infection[a]

	Hospital admissions, No./total No. (%)		
Age, y	Omicron (n = 648)	Influenza (n = 81)	RSV (n = 990)
13-17	14/47 (29.8)	22/89 (24.7)	8/11 (72.7)
7-12	26/95 (27.4)	27/115 (23.5)	11/16 (68.8)
5-6	5/25 (20.0)	18/61 (29.5)	16/21 (76.2)
2-4	34/81 (42.0)	17/80 (21.2)	181/236 (76.7)
1	31/79 (39.2)	6/17 (35.3)	118/156 (75.6)
0	172/569 (30.2)	28/64 (43.8)	707/834 (84.8)
Overall	282/896 (31.5)	118/426 (27.7)	1041/1274 (81.7)

Comment: Hospitalization rates were higher in patients infected with RSV vs Omicron in all age groups, but no differences were observed between influenza and Omicron. Patients infected with influenza were older, highlighting difficulties in comparing these patient

populations. This was a retrospective design with potential underreporting of respiratory illness provided and patients with mild disease might have been missed since they were not tested by PCR. The CDC estimates that RSV leads to 58,000-80,000 hospitalizations and 100-300 deaths each year in children under 5 years of age.

Bottom line: RSV can be dangerous for both infants and young children is well-known, reflected by major differences in hospitalization rates observed for RSV compared with both SARS-CoV-2 and influenza. No difference between Omicron and influenza A/B across all age groups were surprising.

COVID-19

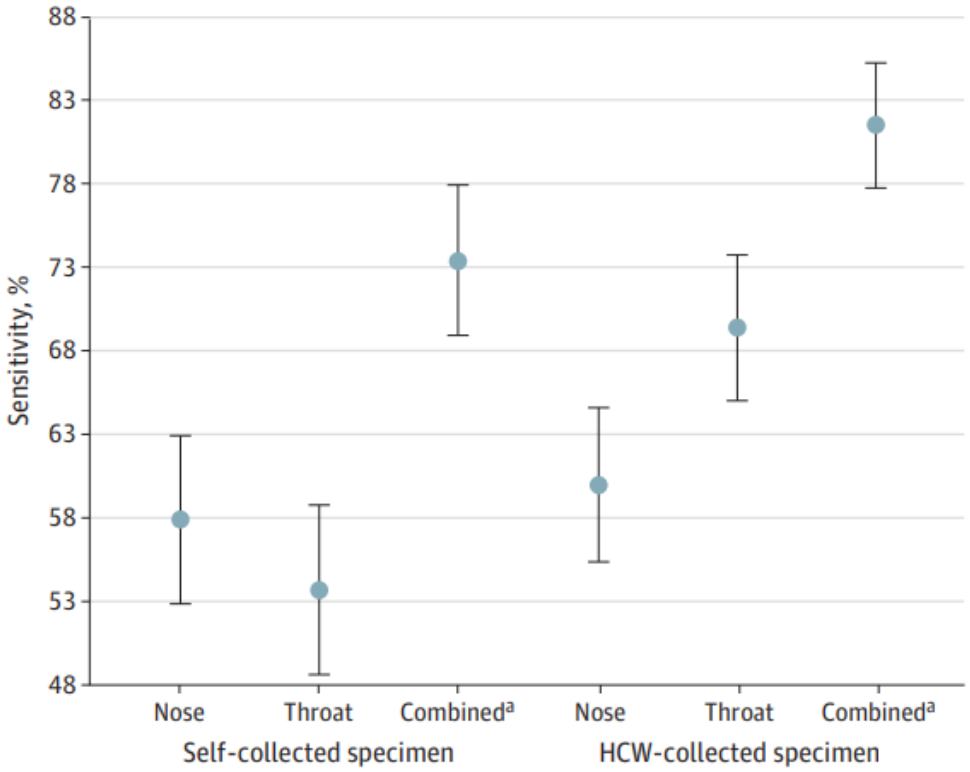
COVID-19 Rapid Antigen Tests With Self-Collected vs Health Care Worker–Collected Nasal and Throat Swab Specimens A Randomized Clinical Trial

JAMA Network Open. 2023;6(12):e2344295.

doi:10.1001/jamanetworkopen.2023.44295

For the trial, investigators randomly assigned 2,674 people aged 16 and older being tested for Covid-19 by PCR to self- or HCW-collected throat and nasal swabs for rapid antigen tests (RAT) in February and March 2022. Four samples (two HCW-collected nose and throat swabs for PCR and two self- or HCW-collected swabs for RAT) were collected per participant at two urban Covid-19 outpatient test centers in Copenhagen, and additional HCW-collected throat and nose swabs were used as the reference standard.

Of 2941 participants enrolled, 2674 (90.9%) had complete test results and were included in the final analysis (1535 [57.4%] women; median age, 40 years [IQR, 28-55 years]); 1074 (40.2%) had Covid-19 symptoms, and 827 (30.9%) were positive for SARS-CoV-2 by PCR. HCW collected throat specimens had higher mean sensitivity than HCW-collected nasal specimens for RAT (69.4% [95% CI, 65.1%-73.6%] vs 60.0% [95% CI, 55.4%-64.5%]). However, a subgroup analysis of symptomatic participants found that self-collected nasal specimens were more sensitive than self-collected throat specimens for RAT (mean sensitivity, 71.5% [95% CI, 65.3%-77.6%] vs 58.0% [95% CI, 51.2%-64.7%]; P < .001). Combining nasal and throat specimens increased sensitivity for HCW- and self-collected specimens by 21.4 and 15.5 percentage points, respectively, compared with a single nasal specimen (both P < .001).



Comment: HCW-collected throat specimens may have higher sensitivity than HCW-collected nasal specimens for Covid-19 RAT, while the sensitivity of self-collected specimens may improve by combining nasal and throat specimens. They cannot directly generalize the reported combined nasal and throat specimen sensitivity to a setting where the same swab was used to collect both specimens. A previous study demonstrated improved sensitivity for rapid antigen testing of specimens from separate nasal and throat swabs as well as using the same swab to collect both specimens. [Microbiol Spectr. 2022;10(4):e0021722]

Editor's Choice

A synbiotic preparation (SIM01) for post-acute COVID-19 syndrome in Hong Kong (RECOVERY): a randomised, double-blind, placebo-controlled trial Lancet Infect Dis published online December 7, 2023

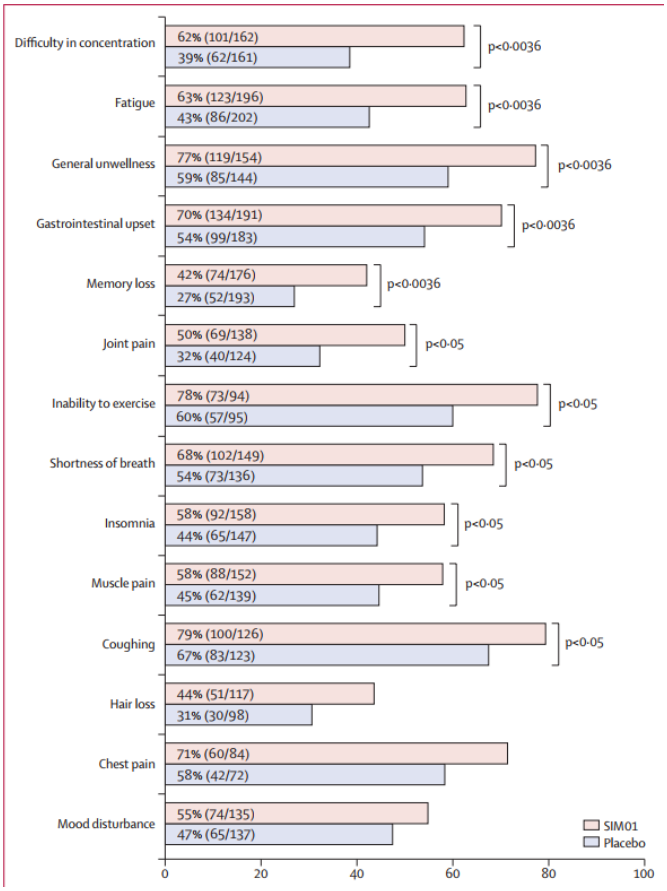
doi.org/10.1016/ S1473-3099(23)00685-0

SIM01 contains strains of anaerobic *Bifidobacterium* bacteria (which are probiotics) and soluble fibers (prebiotics) to alter the gut microbiome and possibly modify immune response. SIM01 is a synbiotic preparation of three lyophilized *Bifidobacteria* strains and three prebiotic compounds soluble fibers (prebiotics).

From June 2021 to August 2022, investigators randomly assigned 463 adult long-COVID patients at a single hospital in a 1:1 ratio to receive SIM01 or a vitamin C placebo by mouth

twice daily for 6 months. The median interval between infection and random assignment was 4 months. The investigators clinically assessed participants at baseline for symptoms, quality of life, and physical activity level. At 6 months, interviewers administered a 14-item symptom questionnaire to participants and collected blood and fecal samples to assess changes in the gut microbiome and blood cytokines.

At 6 months, significantly higher proportions of the SIM01 group had alleviation of fatigue (OR 2·273, 95% CI 1·520–3·397, p=0·0001), memory loss (1·967, 1·271–3·044, p=0·0024), difficulty in concentration (2·644, 1·687–4·143, p<0·0001), GI upset (1·995, 1·304–3·051, p=0·0014), and general unwellness (2·360, 1·428–3·900, p=0·0008) compared with the placebo group. Adverse event rates were similar between groups during treatment (SIM01 22 [10%] of 232 *vs* placebo 25 [11%] of 231; p=0·63). Treatment with SIM01, infection with omicron variants, vaccination before Covid-19, and mild acute Covid-19, were predictors of symptom alleviation (p<0·0036). Fecal metagenomic analyses showed that the gut microbiome was more diverse, including more short-chain acid-producing bacteria and fewer antimicrobial resistant genes at 6 months than at baseline in SIM01 recipients but not the placebo group. Correlation of microbial changes with symptoms showed that relief of specific symptoms was tied to distinct compositional and functional changes in the microbiome. Cytokine analyses yielded no significant results. In addition, the present study did not identify a significant difference in quality of life and physical activity between the two groups at 6 months.



Comment: In this study, treatment with SIM01 alleviates multiple symptoms of PACS. Their findings have implications on the management of PACS through gut microbiome modulation. Antibiotics are an important confounder and are known to have a profound effect on the gut microbiome. Most (87%) individuals in their cohort did not receivea antibiotics. They found that the gut microbiome of patients who had not had antibiotics also showed decreased bacteria diversity and reduced abundance of different *Bifidobacterium* strains, suggesting that SARS-CoV-2 infection might also have a direct effect on the gut microbiome. Prebiotic compounds in SIM01, including galactooligosaccharides, xylo-oligosaccharides, and resistant dextrin, can contribute to beneficial compositional shifts in gut microbiome composition. Human studies have shown that galacto-oligosaccharides can increase the abundance of different *Bifidobacteria* species in patients with irritable bowel syndrome, whereas xylooligosaccharides and resistant dextrin were shown to promote the growth of *Bifidobacterium* and *Lactobacillus* strains in in-vivo and in-vitro studies. [Int J Food Sci Nutr 2015; 66**:** 919–22. Am J Clin Nutr 2019; 109**:** 1098–111] Resistant dextrin was also able to reduce the abundance of *Clostridium* and *Bacteroides* strains. Importantly, their previous metagenomic analysis suggested that *Bifidobacteria* and *Lactobacilli* species were negatively correlated whilst *Clostridium* and *Bacteroides* species were positively correlated with different symptoms of PACS. [Gut 2022; 71: 544–52] Taken altogether, these data support the synergistic effect of probiotics and prebiotics in modulating the gut microbiome. The extent to which SIM01 is beneficial to all patients with varying severity during acute Covid-19 was explored by post-hoc subgroup analysis. On post-hoc analysis of patients who stayed in hospital during acute Covid-19, they observed a similar numerical trend in favor of SIM01 treatment, although the differences did not reach statistical significance, probably due to an insufficient sample size. A study limitation is the lack of a universally accepted long-Covid-19 symptom assessment tool and reliance on subjective symptom reports complicates interpretation of these findings. There are now several studies showing that probiotics, consisting of beneficial bacteria such as *Lactobacillus* and *Bifidobacterium* species, might enhance gut health, modulate inflammation, and improve immune function. In the context of Covid-19, these effects are promising, with some studies suggesting a potential role of probiotics in recovery from acute viral acute viral infection. [Cochrane Database Syst Rev. 2022; 8Cd006895] Additionally, given the study's single-center design and that the composition of SIM01 is based on the gut flora of healthy Chinese populations, the relevance of the findings to ethnically and geographically diverse cohorts worldwide warrants further investigation. The proposed mechanism of symptom improvement—through a reduction in systemic inflammation via increased gut microbial diversity—is intriguing but remains speculative without direct evidence for this mechanism, given that no differences were observed in plasma cytokine profiles between placebo and SIM01 groups at 6 months.

Bottom line: Their findings have implications on the management of PACS through gut microbiome modulation. Further studies are warranted to explore the beneficial effects of SIM01 in other populations.

Viral dynamics of the SARS-CoV-2 Omicron Variant in Paediatric Patients; A prospective cohort study Clin Infect Dis published online December 12, 2023

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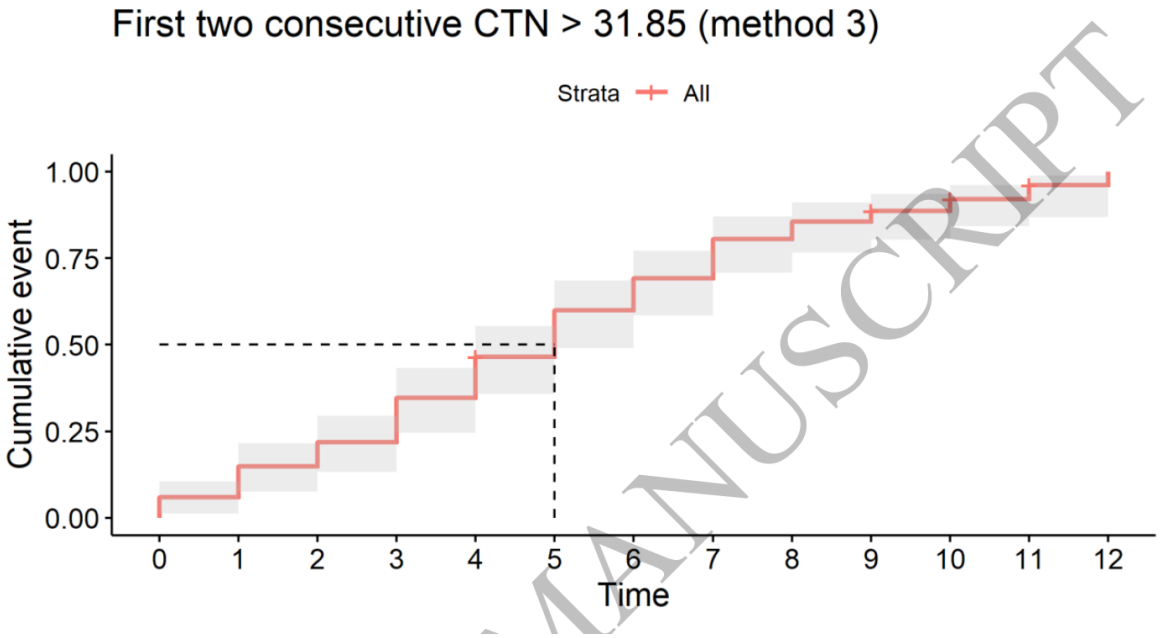
The investigators conducted a prospective cohort study of children 18 years and younger with PCR confirmed SARS-CoV-2 between February 1, 2022, and March 14, 2022. SARS-CoV-2 testing occurred on daily samples for 10 days; a subset of participants completed daily rapid antigen testing (RAT). Viral RNA trajectories were described in relation to symptom onset and resolution. The primary outcome was the SARS-CoV-2 viral load, expressed in log10RNA copies/ml, which was determined using the standard curve of the Ct N-gene (CTN) result from the Seegene Allplex 2019-nCoV assay. The associations between both time since symptom onset/resolution and non-infectious viral load were evaluated using a Cox proportional hazards model.

Among 101 children aged 2 to 17 years, the median time to study-defined non-infectious viral load was 5 days post symptom onset, with 75% meeting this threshold by 7 days, and 90% by 10 days. On the day of and day after symptom resolution, 43 of 87 (49%) and 52 (60%) had met the non-infectious thresholds, respectively. Of the 50 participants completing RAT, positivity at symptom onset and on the day after symptom onset was 67% (16/24) and 75% (14/20). On the first day where the non-infectious threshold was met, 61% (n=27/44) of participant RAT results were still positive.

There was no difference in time to symptom resolution by Omicron subvariant BA.1 compared to BA.2 (p=0.3) or sex (p=0.2). The most common presenting symptoms included sore throat (n=56, 55%), fever (n=41, 41%), fatigue / muscle aches (n=22, 22%) and headache (n=18, 18%). At the end of the 10 days follow-up the most common persistent symptoms were cough (n=9, 9%) and runny nose (n=12, 12%). After the threshold of non-infectiousness was met, the most common persistent symptoms were runny nose (n=41, 41%), cough (n=28, 28%) and sore throat (n=11, 11%).



Comment: This is the first prospective study of viral dynamics of SARS-CoV-2 in children, and the first to describe the period of infectiousness of children, using quantitative PCR viral load as a surrogate for infectiousness. One in four children had not reached the threshold for study-defined noninfectiousness by 7 days post symptom onset and 10% of children had not reached the threshold by 10 days, suggesting that some children who are infected with the Omicron variant shed potentially culturable virus beyond 5 days of symptom onset. Cough, beyond a time threshold were not predictive of infectiousness. They found that RATs in children lacked sensitivity early on in the course of infection, with only 67% testing positive on the day of symptom onset, increasing to 75% on the day after symptom onset. This suggests limited utility for early use of RATs in the detection of SARS-CoV-2 in symptomatic children and reinforces the need for a repeated test after a few days of symptoms to confirm infection as other studies have shown. [see ID Watch August 2023 Ann Intern Med July 4, 2023]

Since most participants in this study had symptomatic SARS-CoV-2 infection, these findings may not be applicable to children with asymptomatic infections. Participants were also otherwise healthy children, limiting the generalizability to children with immunocompromising conditions or medications. The use of quantitative PCR methods to infer infectiousness, rather than performing viral culture to demonstrate the presence of potential transmissible virus, is a further limitation. While both PCR viral load and viral culture are used to assess transmission, no agreed upon threshold exists for either method. Infectiousness is not binary, but on a spectrum that decreases over time.

Bottom line: Children often meet the study-defined non-infectiousness threshold on the day after symptom resolution. RAT tests were often negative early in the course of illness and should not be relied on to exclude infection but should be repeated.

Developmental impairment in children exposed during pregnancy to maternal SARS-CoV2: A Brazilian cohort study Int J Infect Dis published online December 5, 2023

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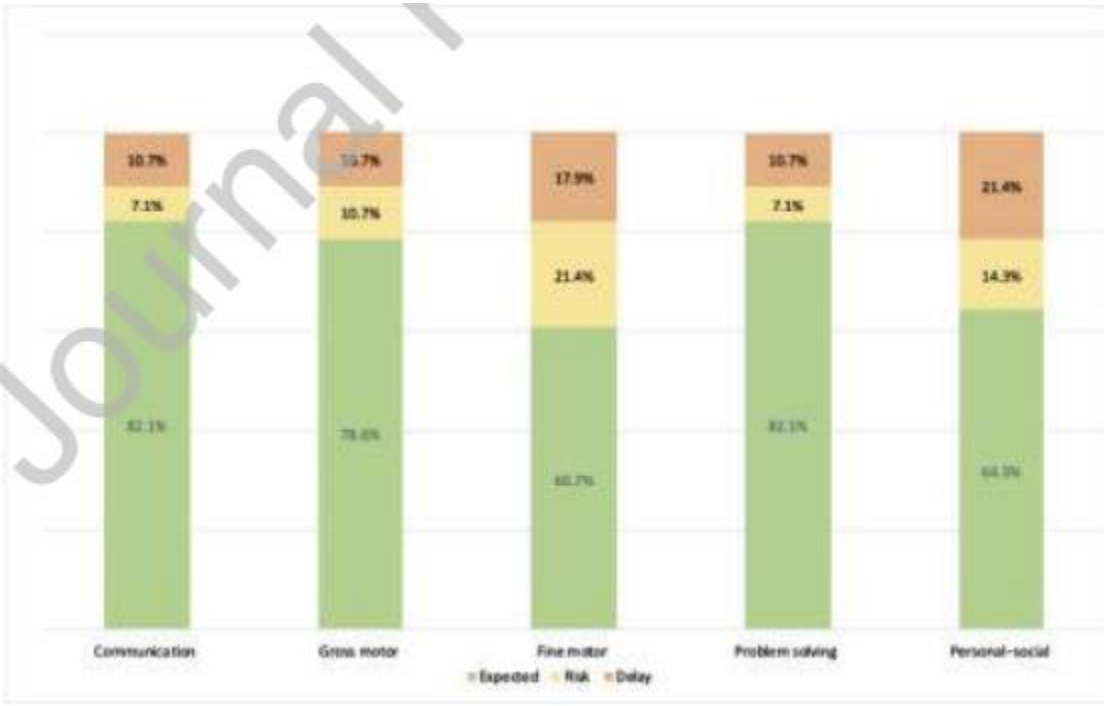
This is a progressive cohort of women assessed from April 2020 to July 2021. Investigators compared outcomes among a case group of 69 children who were exposed to lab-confirmed Covid-19 in utero compared to 68 children who served as controls and had no known exposure to Covid-19 in utero. All mothers were unvaccinated at the time of cohort inclusion, and maternal demographics were similar in the two groups.

At 12 months, 20.3% of Covid-exposed children and 5.9% of the controls received a diagnosis of neurodevelopmental delay (risk ratio, 3.44; 95% confidence interval, 1.19 to 9.95). For the exposed group, the prevalence of neurodevelopment impairment using the Ages & Stages Questionnaire (ASQ-3) was 35.7% at 4 months, 7.0% at 6 months, and 32.1% at 12 months. In follow-up of exposed infants, the researchers found 10% had an abnormal result on cranial ultrasonography, mainly mild ventriculomegaly. Below ASQ-3 at 12 months



Comment: Studies on the consequences of in-utero exposure to maternal SARS-CoV-2 infection are still limited. Recent evidence suggests that maternal SARS-CoV-2 infection during pregnancy may be associated with a greater rate of neurodevelopmental impairment during the first year of life, [JAMA Netw Open. 2022;5(6):e2215787 ; PLoS ONE. 2022; 17(5): e0267575], while other research was unsuccessful in demonstrating this association. [JAMA Netw Open.

2023;6(4): e23739]. The mechanisms underlying the potential impact of maternal Covid-19 infection on fetal brain development encompass both direct pathways, such as vertical transmission, and indirect routes, as a result of either uteroplacental insufficiency or as a consequence of the maternal immune and inflammatory responses during the prenatal period. [Aust N Z J Psychiatry. 2021; 55(8): 750–762] In this cohort, the ASQ-3 scores at 6 months were remarkably better than the scores at 4 and 12 months. They hypothesized that the improvement in the fine motor and problem-solving subdomains at 6 months was most likely due to the individual interventions that the mothers of infants below the appropriate score received after the 4-month evaluation. The ASQ-3 evaluations were not available for the control group; and they couldn't make a definitive diagnosis of congenital infection with the available criteria, as none of the infants performed SARS-CoV-2 PCR tests after birth. The number of participants in both groups was small, limiting the ability to identify differences between subgroups. Lastly, the participants were recruited from 2020 to 2021, the majority were unvaccinated, so the outcomes may vary depending on vaccination status or Covid-19 variant types.

Bottom line: SARS-CoV-2 exposed infants had an increased risk of neurodevelopmental impairment. It is important to understand the maternal infection impact on infant exposed developmental trajectories to identify the need to recommend early interventions.

WHO designates JN.1 as separate COVID-19 variant of interest December 19, 2023

Due to its rapid growth and potential to add to the respiratory virus burden in Northern Hemisphere countries, the WHO today designated JN.1, part of the BA.2.86 SARS-CoV-2 lineage, as its own variant of interest. JN.1, first detected on August 25, contains L455S mutation in the spike protein, compared to the parent BA.2.86 variant. The mutation is thought to enhance JN.1's immune-evasion capabilities.

Over the past month, the proportion of JN.1 viruses has rapidly increased, rising from 3.3% in early November to 27.1% by early December. Countries reporting the highest proportions include France, the United States, Singapore, Canada, and the UK. The WHO said JN.1 doesn't appear to cause a higher public health risk than other SARS-CoV-2 variants, but it warned that it could trigger a surge in COVID-19 alongside rises in other viral infections, especially in countries entering their winter seasons.

The WHO said JN.1 appears to have higher immune-evasion properties than the BA.2.86 parent virus. The agency added that, despite some reduction in JN.1 neutralization, evidence so far suggests that the monovalent XBB.1.5 vaccines are likely effective. The WHO also recommends universal masking in health facilities, with appropriate masks, respirators, and other personal protective equipment for HCWs caring for patients who have suspected or confirmed Covid-19.

Comment: In its last variant proportion update on December 16, the US CDC singled JN.1 out from BA.2.86 tracking, noting a dramatic jump in JN.1 detections over a 2-week period: from 8.1% to 21.4% to 44%. JN.1 levels are now the most common variant with HV.1, part of the XBB.1.9.2 lineage now second. Preliminary research shows that the latest Covid-19

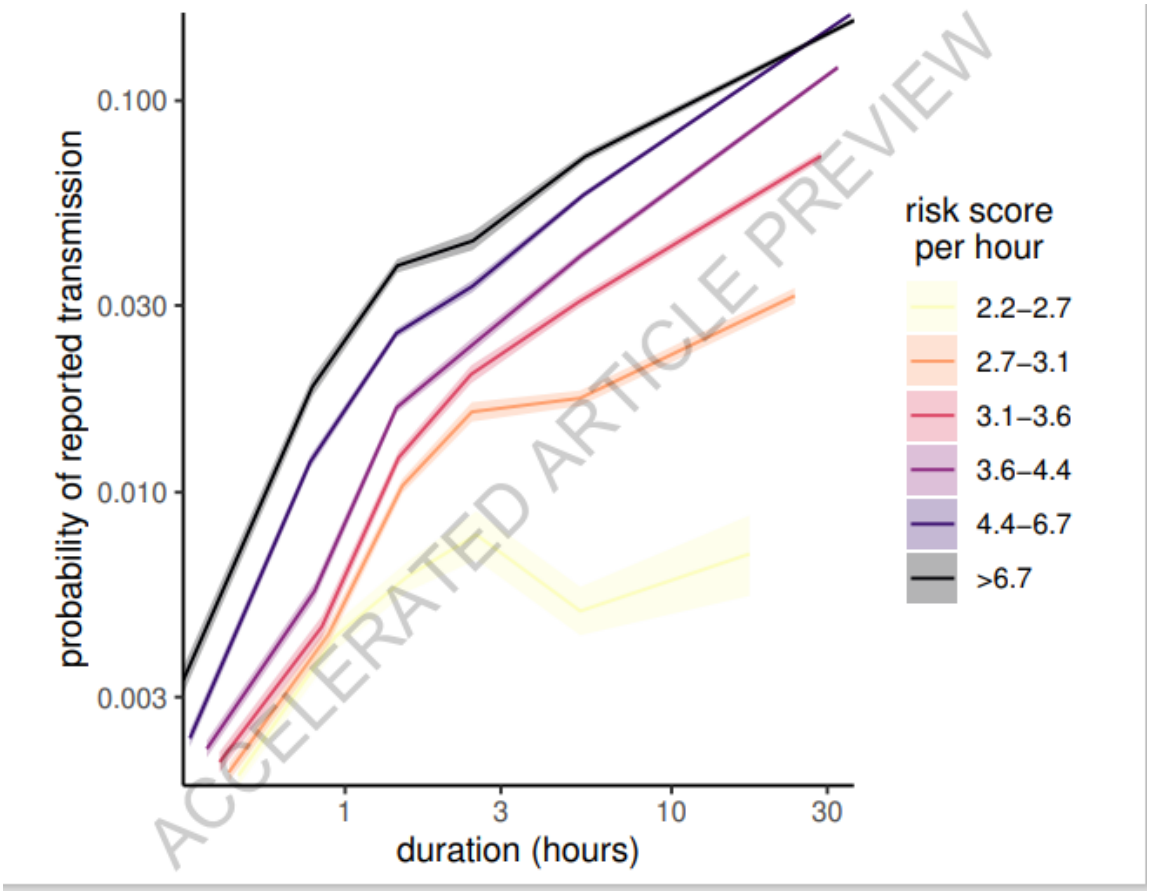
vaccines produce a robust immune response against JN.1. See respiratory virus by the numbers above.

Digital measurement of SARS-CoV-2 transmission risk from 7.2 million contacts.
Nature published online December 20, 2023

doi.org/10.1038/s41586-023-06952-2 (2023)

A team led by University of Oxford researchers evaluated data from the National Health Service (NHS) Covid-19 contact-tracing smartphone app in England and Wales to estimate how well app measurements correlated with real-life transmissions. Using Bluetooth signal strength and 240,000 positive Covid-19 tests, the NHS notified the contacts of confirmed patients of exposures from April 2021 to February 2022 and recorded data on whether contacts also tested positive. Contacts were individuals exposed to confirmed cases if within the 2-metre [6.6 feet] for at least 15-minutes. The NHS Covid-19 app assessed the transmission risk for a contact by partitioning the full exposure event into a set of non-overlapping 'exposure windows', each lasting at most 30 minutes. For each window, the app calculated a risk score: Risk score = proximity score × duration within the 30-minute window × infectiousness score.

They analyzed 7 million contacts notified by the NHS Covid-19 app. Empirical metrics and statistical modelling showed a strong relation between app-computed risk scores and actual transmission probability. Longer exposures at greater distances had similar risk to shorter exposures at closer distances. The probability of transmission confirmed by a reported positive test increased initially linearly with duration of exposure (1.1% per hour) and continued increasing over several days. While most exposures were short (median 0.7 hours, IQR 34 0.4-1.6), transmissions typically resulted from exposures lasting one hour to several days (median 6 hours, IQR 1.4-28). Households accounted for about 6% of contacts but 40% of transmissions.



Comment: An analysis of 7 million contacts of Covid-19 patients in the UK estimates that most transmissions resulted from exposures lasting 1 hour to several days and that households accounted for 40% of spread. Taking this into account, contact tracing would have been less disruptive and still have identified 80% of contacts if the duration guideline were 1 hour or more rather than 15 minutes. The main limitation of their analysis is the absence of data on the context of an exposure: setting, immunity, level of ventilation etc. Some of these factors might affect the risk score recorded by the app and the true risk in different ways: for example, being indoors is linked to poorer ventilation, which increases true risk but not risk score. Another limitation of their study is the inclusion of exposures only when their risk score crossed the app's notification threshold, excluding transmissions resulting from a large number of very low-risk exposures. These transmissions are likely to play a role in the spreading of SARS-CoV-2 in specific settings but are unlikely to be a major driver of the epidemic.

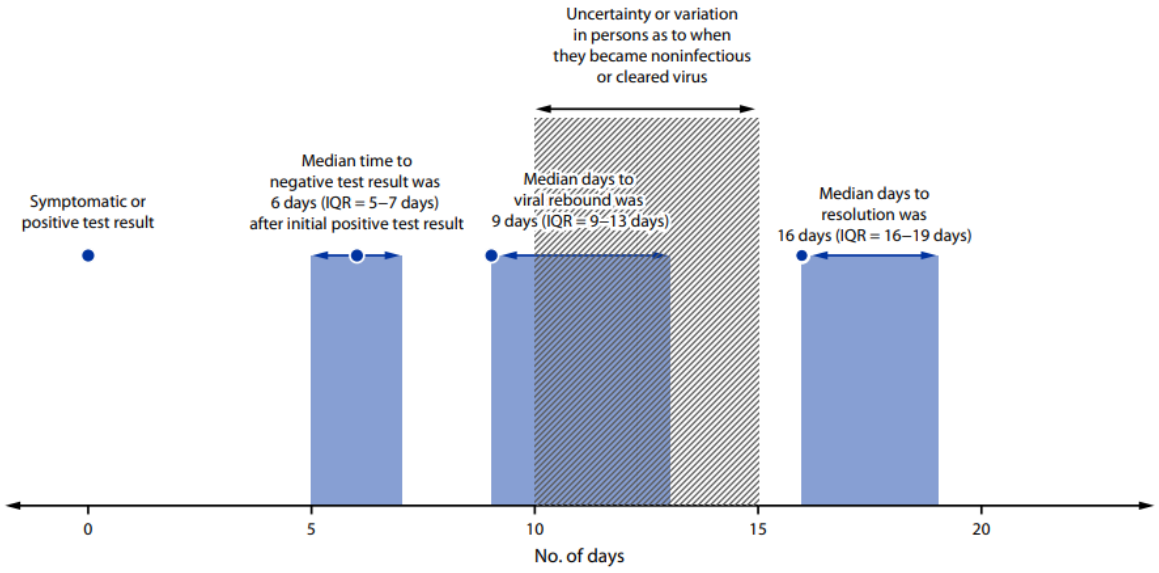
Bottom line: Empiric metrics and statistical modeling revealed a strong relationship between app-computed risk scores and the likelihood of real-world transmission. Most transmissions resulted from exposures lasting 1 hour to several days and households accounted for 40% of spread.

SARS-CoV-2 Rebound With and Without Use of COVID-19 Oral Antivirals MMWR 2023;72:1357-1364

SARS-CoV-2 rebound is typically described as recurrence of signs or symptoms or a new positive viral test result after initial recovery from COVID-19. In May 2022, CDC issued a health advisory alert that described case reports of SARS CoV-2 rebound among patients who completed the recommended 5-day course of nirmatrelvir/ritonavir. To better understand rebound, CDC reviewed SARS-CoV-2 rebound studies published during February 1, 2020–November 29, 2023. Overall, seven of 23 studies that met inclusion criteria, one randomized trial and six observational studies, compared rebound for persons who received antiviral treatment with that for persons who did not receive antiviral treatment.

In four studies, including the randomized trial, no statistically significant difference in rebound rates was identified among persons receiving treatment and those not receiving treatment. Depending on the definition used, the prevalence of rebound varied. No hospitalizations or deaths were reported among outpatients who experienced rebound, because Covid-19 signs and symptoms were mild. However, they say persons receiving antiviral treatment might be at higher risk for rebound compared with persons not receiving treatment because of host factors or treatment-induced viral suppression early in the course of illness.

FIGURE 2. Timing of viral rebound and resolution during SARS-CoV-2 infection among 22 patients*,† — February 1, 2020–November 29, 2023



Comment: Current evidence, including randomized controlled trial and observational data, 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 nirmatrelvir/ ritonavir. Viral rebound might occur in people on anti-viral treatment because they are at high risk for severe disease and might have host factors, such as immunosuppression, that contribute to the natural variability in viral dynamics. [Nat Rev Microbiol 2023; 21:147–61] Another important consideration is that persons receiving antiviral

treatment might be at higher risk for experiencing rebound given the viral suppression related to use of treatment early in the disease course and resumption of viral replication after completion of treatment because of delayed viral clearance. This elevated risk could be due to early discontinuation of antiviral treatment or the need for longer courses of treatment among certain persons, such as those who are immunocompromised. [Leuk Lymphoma 2023; 64:1054–6] Rebound probably does not represent reinfection or resistance to treatment.

Standardized definitions for symptom, viral, and clinical rebound were not used across studies. In observational studies it is the difficult in verifying whether antiviral treatment courses were completed and whether vaccination status and previous infection were documented accurately. Lastly, ascertainment bias is also possible given that persons receiving antiviral treatment are closely followed, and more likely to report recurrent symptoms.

Bottom line: Concern about rebound should not deter clinicians from prescribing lifesaving antiviral treatments when indicated to prevent morbidity and mortality from Covid-19.