ID WATCH

by Ed Septimus, MD

Editor's Choice

LOOK FOR THE YELLOW BANNER

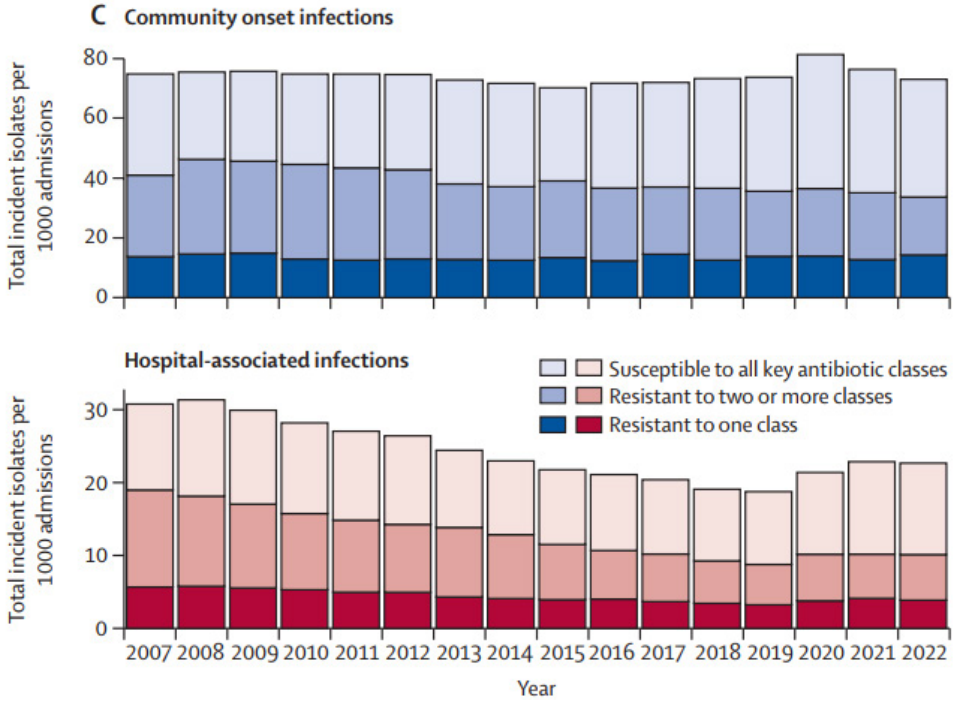
1

Trends in infection incidence and antimicrobial resistance in the US Veterans Affairs Healthcare System: a nationwide retrospective cohort study (2007–22)

Lancet Infectious Disease published online August 13, 2024
DOI: 10.1016/S1473-3099(24)00416-X

This was US nationwide retrospective cohort study, which analyzed clinical microbiology data from electronic health records from all patients admitted to all 138 Veterans Affairs (VA) Medical Centers with acute care wards across the US from February 1, 2007, to March 31, 2022. They quantified inpatient antibiotic use as days of therapy (DOT) per 1000 patient-days and antimicrobial resistance by resistance proportion (proportion of incident isolates identified as resistant) and phenotypic incidence (incidence of infections per 1000 admissions classified as resistant, susceptible, or missing). To analyze trends before the Covid-19 pandemic and during the Covid-19 pandemic, they used generalized estimating equation models and reported average annual percentage changes (AAPC).

They collected 991,527 30-day incident isolates from 507,760 patients in 138 VA Medical Centers and 50 states in the US. Between February 1, 2007, and December 31, 2019, infection incidence and antimicrobial resistance declined for many pathogens and pathogen–drug combinations. The proportion of MRSA decreased from 57.7% (11,876 of 20,584 incident isolates) to 44.6% (5916 of 13,257) over these 13 years (AAPC −1.8%; 95% CI −2.4 to −1.2; p<0.0001), and vancomycin-resistant Enterococcus faecium (VRE) infections decreased from 77.8% (2555 of 3285) to 65.1% (893 of 1371; AAPC −1.2%; 95% CI −2.5 to 0.0; p=0.052). Fluoroquinolone resistance declined in both proportion and incidence for most pathogens. These trends correlated with substantial reductions in fluoroquinolone use, from 125 DOT per 1000 patient-days to 20 DOT per 1000 patient-days. Third generation cephalosporin resistance increased significantly in E coli infections from 6.7% (942 of 14042) in 2007 to 15.3% (2153 of 14,053) in 2019 (AAPC 8.5%; 95% CI 6.2 to 10.7; p<0·0001). Carbapenem resistance proportion increased in Enterobacter cloacae infections from 1.1% (30 of 2852) in 2007 to 7.3% (212 of 2919) in 2019 (AAPC 19.8%; 95% CI 13.7 to 26.2; p<0·0001) but remained low for K pneumoniae and E coli. During the Covid-19 pandemic between January 1, 2020, and March 31, 2022, several pathogen–drug combinations increased in both incidence and resistance for hospital-associated infections (HAIs). For some pathogen–drug combinations, trends in incidence of resistant and susceptible infections were divergent, whereas for other combinations, these trends were in the same direction.



Dr. Septimus's Annotations

Resistance proportions between 2007 and 2019 declined for many, but not all pathogen–drug combinations. A consistent finding for all nine species was a decrease in fluoroquinolone resistance proportions between 2007 and 2019. Similar to the CDC antimicrobial resistance threats report from 2019, infections caused by extended-spectrum β-lactamases (ESBL)- producing and carbapenem-resistant Enterobacterales increased in this study. [Antibiotic resistance threats in the United States, 2019. https://stacks.cdc.gov/view/cdc/82532] For HAIs E coli and third generation cephalosporins, resistance proportion increased, and the incidence of susceptible infections declined. The decline in fluoroquinolone resistance paralleled a substantial decline in fluoroquinolone use in the VA Medical Centers during the same period. The Veterans Health Administration launched infection control and stewardship initiatives between 2007

and 2014 [JAMA Netw Open 2020; 3: e1920464] that might have affected rates of transmission between patients who are hospitalized as well as the risk of clinical infection among individuals colonized with the bacteria. [JAMA Netw Open 2021; 4: e21097] Substantial reductions in HAIs suggests that hospital infection control measures have been effective and should be continued. They observed an increase in the use of third generation cephalosporins across VA facilities, a corresponding consistent rise in resistance across pathogens might be expected.

This study is in contrast to the study reviewed in September 2024 ID Watch [Am J Infect Control published online July 26, 2026] entitled "Clusters of Emerging Multidrug-Resistant Organisms in United States Healthcare Facilities During the Initial Months of the SARS-CoV-2 Pandemic." They observed increased clusters of MDRO during the Covid-19 pandemic. A 2022 CDC report [COVID-19 : U.S. impact on antimicrobial resistance, special report 2022 (cdc. gov)] found that hospital-onset CRAB cases increased by 78% in 2020 compared with 2019, CRE cases by 35%, multidrug-resistant P aeruginosa by 32%, and combined hospital and community-onset C auris by 60%. Surges in Covid-19 patients, overcrowding, increased antibiotic use, and actual shortages of HCWs and PPE likely played a role in these increases. The good news is the last CDC report comparing 2021 to 2022 showed healthcare onset (HO) CRE, HO-CRAB, HO-VRE, HO-ESBL, and MDR-Pseudomonas all have stabilized. There was a decrease in HO-MRSA, but a rise in C auris.

"...[S]ignificant reductions in [methicillin-resistant Staphylococcus aureus], [vancomycin-resistant enterococc], and fluoroquinolone resistance across multiple pathogens suggest that control and stewardship efforts have influenced resistance."

The current study population was limited to enrolled veterans in the US with access to the VA Healthcare System. Time trend analysis estimates for the pandemic period show large uncertainties due to a small number of three timepoints. They do not have sufficient information about infection control practices, strain characteristics, or colonization data to assess the effect of the Covid-19 pandemic on antimicrobial resistance. However, significant reductions in MRSA, VRE, and fluoroquinolone resistance across multiple pathogens suggest that control and stewardship efforts have influenced resistance.

AR Threats

	Threat	Change in Rates or Number of Infections***			
		2020 vs. 2019	2021 vs. 2020	2022 vs. 2021	2022 vs. 2019
URGENT*	Hospital-onset CRE	▲ Increase	▲ Increase	— Stable	▲ Increase
URGENT*	Hospital-onset Carbapenem-resistant *Acinetobacter*	— Stable	— Stable	— Stable	▲ Increase**
URGENT*	Clinical Cases of *C. auris*	▲ Increase	▲ Increase	▲ Increase	▲ Increase
SERIOUS*	Hospital-onset MRSA	▲ Increase	— Stable	▼ Decrease	— Stable
SERIOUS*	Hospital-onset VRE	▲ Increase	▲ Increase	— Stable	▲ Increase
SERIOUS*	Hospital-onset ESBL-producing Enterobacterales	▲ Increase	— Stable	— Stable	▲ Increase
SERIOUS*	Hospital-onset MDR *Pseudomonas aeruginosa*	▲ Increase	▲ Increase	— Stable	▲ Increase

BOTTOM LINE

The rise in extended-spectrum β-lactamases (ESBL) Enterobacterales and recent surge in hospital-associated infections emphasize the need for ongoing surveillance, diagnostic and antimicrobial stewardship, and evidenced-based infection prevention practices.

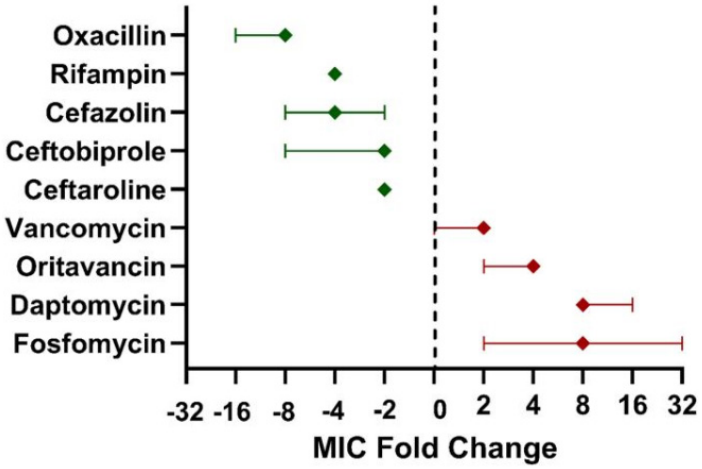
2

Comparative *in vitro* efficacy of antibiotics against the intracellular reservoir of *Staphylococcus aureus*

Journal of Antimicrobial Chemotherapy published online July 29, 2024
DOI: 10.1093/jac/dkae241

S *aureus* often causes bloodstream infections, and Kupffer cells (KCs; hepatic macrophages) can clear S. *aureus* bacteremia (SAB) by engulfing the pathogen. Nonetheless, 10% of S. *aureus* bacteria survive within such phagocytes, where they are protected from antibiotic exposure. Delayed bloodstream clearance is a well-known risk factor for mortality — and different antibiotics vary in their potency for managing SAB. Investigators assessed the efficacy of various antibiotics using an in vitro assay mimicking the intracellular milieu of phagocytes (e.g., pH 5). In a murine KC line, they also measured the intracellular accumulation of the antibiotics as well as S. aureus time-kill kinetics.

Antibiotic MIC fold change in phagolysosome-mimicking low-pH environment relative to physiological pH.



In low-pH medium compared with physiologic conditions, S. *aureus* minimum inhibitory concentrations (MICs) of oxacillin, rifampin, cefazolin, ceftobiprole, and ceftaroline decreased, whereas MICs of oritavancin, daptomycin, and fosfomycin increased. Most antibiotics accumulated in KCs (in descending order: oritavancin, fosfomycin, oxacillin, vancomycin, ceftaroline, cefazolin, and ceftobiprole); only daptomycin penetrated poorly. In 24-hour time-kill assays using S. *aureus*–infected KCs exposed to different antibiotics in physiologic concentrations, oritavancin and the combination of rifampin plus vancomycin elicited the most pronounced reductions in S. *aureus* counts. Daptomycin, ceftaroline, ceftobiprole, oxacillin, and cefazolin yielded more-modest reductions, whereas vancomycin alone was bacteriostatic.

Dr. Septimus's Annotations

In taking the pathogenic reservoir of S. aureus and the intracellular conditions within KCs into account, these assays reveal differences in S. aureus susceptibility to various antibiotics that are not merely explained by varying penetration of the agents and low pH. These results parallel clinical observations (such as the inferior effectiveness of vancomycin versus cefazolin or oxacillin for treating MSSA bacteremia). Experiments like these may help identify better strategies for treating patients with SAB.

BOTTOM LINE

These findings raise concerns about the efficacy of commonly prescribed antibiotics against intracellular S aureus reservoirs and emphasize the need to consider targeting pathogen eradication from the liver to achieve early control of S aureus bacteremia.

Association of *Staphylococcus aureus* Bacterial Load and Colonization Sites With the Risk of Postoperative *S. aureus* Infection.

Open Forum Infectious Diseases published online July 23, 2024
DOI: 10.1093/ofid/ofae414

Surgical patients aged 18 years or older were screened for *S aureus* (SA) carriage in the nose, throat, or perineum within 30 days before surgery. SA carriers and noncarriers were enrolled in a prospective cohort study in a 2:1 ratio. The primary objective of this study was to quantify the association between SA carriage and SA surgical site infection (SSI) or postoperative bloodstream infection (BSI) (SA SSI/BSI) within 90 days after surgery. Most of these surgical procedures were clean and elective procedures. SA screening samples were processed at local (hospital) laboratories on chromogenic media. For each culture sample, the bacterial load of colonizing SA was determined semiquantitatively using the quadrant streaking method, and the scoring was classified as follows: NG = no growth; 1+ = light growth; 2 + and 3+ = moderate growth; and 4+ = heavy growth. The following variables were considered potential confounders: age, sex, body mass index (BMI; defined as body weight [kg] divided by the square of body height [m2]), prior history of SA colonization or infection, preoperative decolonization treatment (if given after SA screening), use of immunosuppressive medication before surgery, Charlson comorbidity index (CCI), American Society of Anesthesiologists physical classification score (ASA score), and site.

A total of 10,570 source population patients were screened for preoperative SA colonization according to protocol. Overall, 3725 (35.2%) patients were colonized with SA before surgery. They enrolled 5004 patients in the study cohort; 3369 (67.3%) were SA carriers. 100 SA SSI/BSI events occurred during follow-up, and 86 (86%) of these events occurred in SA carriers. The number of colonized bodily sites (adjusted hazard ratio [aHR], 3.5–8.5) and an increasing SA bacterial load in the nose (aHR, 1.8–3.4) were associated with increased SA SSI/BSI risk. However, extranasal-only carriage was not independently associated with SA SSI/BSI (aHR, 1.5; 95% CI, 0.9–2.5).

Association Between Bacterial Load of Colonizing SA in the Nose and SA SSI/BSI Within 90 Days After Surgery

No. of SA Colonized Body Sites	No. of SA SSI/BSI Events/No. of Subjects (%)	Adjusted HR (95% CI)[a]
Noncarriers	14/1631 (0.9)	Reference
Carriage at 1 bodily site	53/2309 (2.3)	3.5 (1.7–7.2)
Carriage at 2 bodily sites	24/891 (2.7)	5.3 (2.1–13.4)
Carriage at 3 bodily sites	9/174 (5.2)	8.5 (2.2–33.8)

Multivariable Weighted Analysis of the Association Between the Number of SA Colonized Body Sites and the Risk of SA SSI/BSI Within 90 Days After Surgery

SA Carriage Status in the Nose and Semiquantitative Bacterial Load of Colonizing SA	Adjusted HR (95% CI)[a]
Noncolonized in the nose, but colonized extranasally	Reference
Carriage of 1+ bacterial load of SA	1.8 (1.0–2.7)
Carriage of 2+ bacterial load of SA	2.3 (1.4–3.1)
Carriage of 3+ bacterial load of SA	2.8 (1.9–3.6)
Carriage of 4+ bacterial load of SA	3.4 (2.5–4.3)

Dr. Septimus's Annotations

SA colonizes 20%–30% of the human population at different bodily sites, including the nose, throat, axilla, and perineal region. [Lancet Infect Dis 2005; 5:751–62] Earlier studies identified nasal SA carriage as an important risk factor for developing postoperative SA infection. [Clin Infect Dis 2002; 34:305–8] Earlier studies demonstrated that nasal SA carriage alone had been associated with a 2- to 10-fold increase in the risk of developing SA SSI.[Ann Pharmacother 1998; 32: S7–16] The role of extranasal-only carriage, bacterial load, and number of colonized bodily sites on the risk of developing SA SSI or postoperative BSI has not been as well studied until now.

"...[S]creening multiple bodily sites for SA colonization and then decolonizing the carriers could be a cost-effective strategy for preventing [*Staphylococcus aureus* surgical site infection]."

In this large cohort study, the prevalence of SA colonization at any bodily site was 35%. Endogenous SA carriage at any bodily site, and particularly in the nose, was independently associated with an increased risk of developing SA SSI/BSI. In addition, they observed a linear relationship between the semiquantitative bacterial load of SA in the nose and the occurrence of SA SSI/BSI. Lastly, they found that the risk for developing SA SSI/BSI increased as the number of preoperatively colonized bodily sites increased. Previous studies have shown that the nose is the primary niche for SA carriage and that nasal SA carriage is an independent risk factor for SA infection. [Lancet Infect Dis 2005; 5:751–62] The results of this study are in line with previous studies. They state that "screen-and-treat" strategy consisting of screening multiple bodily sites for SA colonization and then decolonizing the carriers could be a cost-effective strategy for preventing SA SSI. [Infect Control Hosp Epidemiol 2018; 39:1340–6] Based on this, they argue that all screen-and-treat SA decolonization strategies should include at least nasal SA screening. If feasible, the screening of additional bodily sites could be considered. The Compendium on "Strategies to Prevent Surgical Site Infections in Acute-Care Hospitals:2022 Update" recommends decolonize surgical patients with an antistaphylococcal agent in the preoperative setting for orthopedic and cardiothoracic procedures for patients colonized with either MSSA or MRSA.[Infect Control Hosp Epidemiol 2023]

BOTTOM LINE

Nasal S *aureus* (SA) carriage was associated with an increased risk of SA surgical site infection/bloodstream infections (SSI/BSI) and accounted for the majority of SA infections. Higher bacterial load, as well as SA colonization at multiple bodily sites, further increased this risk.

4

Reaction Risk to Direct Penicillin Challenges: A Systematic Review and Meta-Analysis

JAMA Internal Medicine Published online September 16, 2024
DOI: 10.1001/jamainternmed.2024.4606

The purpose of this analysis was to evaluate the frequency of reactions to direct penicillin challenges in individuals with penicillin allergy labels and to identify factors associated with such reactions. Three electronic databases were searched (MEDLINE, Web of Science, and Scopus) from inception to July 19, 2023, for primary studies assessing patients undergoing direct penicillin challenges. Two reviewers independently selected original studies reporting the frequency of immunologically mediated reactions following a direct penicillin challenge in patients reporting a penicillin allergy. The quality of each primary study was independently assessed by teams of 2 reviewers using an adaptation of the risk-of-bias tool They excluded studies that performed direct challenges with drugs from another antibiotic class or that exclusively

assessed patients with cephalosporin allergy. They synthesized the frequency of immunologically mediated reactions and severe immunologically mediated reactions by performing a random-effects meta-analysis of log-transformed proportions. Given the infrequency of events, Bayesian meta-analytic methods were applied. They assessed heterogeneity by computing an estimate of the I2 statistic for implementation in the Bayesian context.

A total of 56 primary studies involving 9225 participants were included. Among participants, 438 experienced reactions to direct penicillin challenges without prior testing, corresponding to an overall meta-analytic frequency of 3.5% (95% credible interval [CrI], 2.5%-4.6%). Meta-regression analyses revealed that studies performed in North America had lower rates of reaction to direct challenges (odds ratio [OR], 0.36; 95% CrI, 0.20-0.61), while studies performed in children (OR, 3.37; 95% CrI, 1.98-5.98), in outpatients (OR, 2.19; 95% CrI, 1.08-4.75), and with a graded (OR, 3.24; 95% CrI, 1.50-7.06) or prolonged (OR, 5.45; 95% CrI, 2.38-13.28) challenge had higher rates of reaction. Only 5 severe reactions (3 anaphylaxis, 1 fever with rash, and 1 acute kidney injury) were reported, none of which were fatal.

Dr. Septimus's *Annotations*

In this systematic review and meta-analysis of 56 primary studies in 9225 participants, the meta-analytic frequency of reactions to direct penicillin challenges was 3.5%. Risk factors associated with positive reactions to direct penicillin challenges included challenges performed outside of North America, in children, in outpatient settings, and with multiple dosing. Most studies in this review excluded participants with severe index reactions, which may have resulted in an underestimation of the frequency of reaction to direct penicillin challenges in the general population. The primary studies largely used different definitions of low risk, limiting the performance of subgroup analysis according to allergy risk group and highlighting the need to adopt more consistent definitions of allergy risk. Lastly, the studies varied in their challenge protocols as aspects, such as the drug and dosing, which may have influenced the number of reactions captured.

BOTTOM LINE

This systematic review and meta-analysis found that reactions to direct penicillin challenges are infrequent, with rates comparable to indirect challenges after allergy testing. These findings suggest that direct challenges are safe for incorporation into penicillin allergy evaluation efforts across age groups and clinical settings.

5

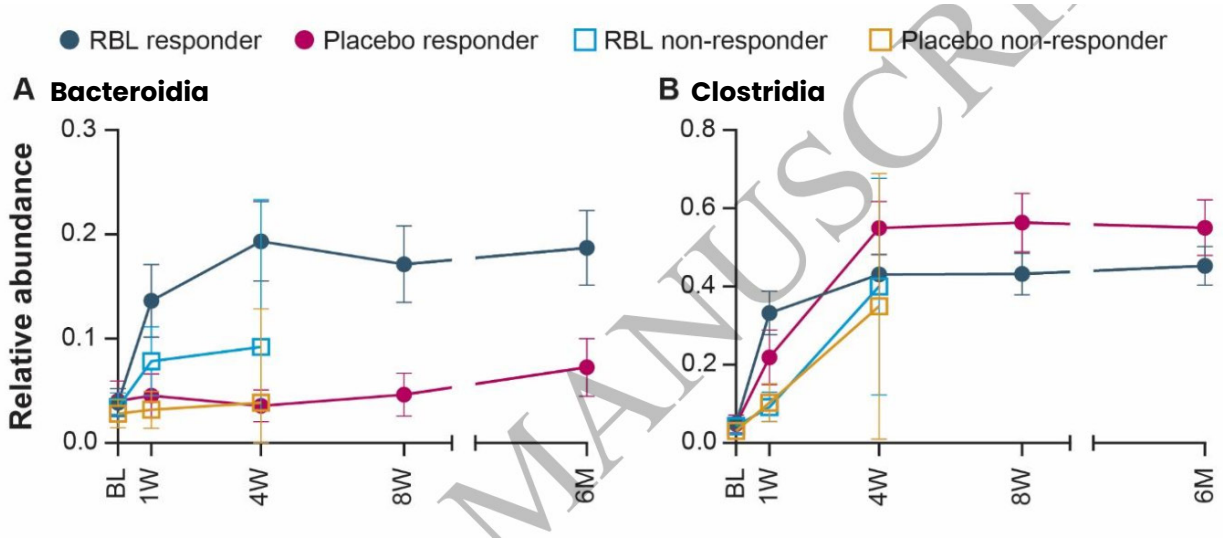
Microbiome and Metabolome Restoration After Administration of Fecal Microbiota, Live-jslm (REBYOTA®) for Preventing Recurrent Clostridioides difficile Infection

Journal of Infectious Diseases published online August 22, 2024
DOI: 10.1093/infdis/jiae418

Microbiota-based treatments are effective in preventing recurrent Clostridioides difficile infection (rCDI). Fecal microbiota, live-jslm (REBYOTA®; RBL, previously RBX2660) was shown to prevent rCDI in a phase 3, randomized, double-blinded placebo controlled clinical trial (PUNCH™ CD3).[Drugs 2022; 82(15): 1527-38] Stool samples from participants in PUNCH™ CD3 who received a single blinded dose of rectally administered RBL or placebo were sequenced to determine microbial community composition and calculate the Microbiome Health Index for post-antibiotic dysbiosis (MHI-A). The composition of bile acids (BAs) in the same samples was quantified by liquid chromatography mass spectrometry. Relationships between BA composition and microbiota community structure and correlations with treatment outcomes were assessed. Participants were aged ≥18 years with documented rCDI (≥1 recurrence after a primary episode) who

had completed at least one round of standard of care (SOC) oral antibiotic therapy, or who had ≥2 episodes of severe CDI resulting in hospitalization within the previous year. Participants were required to have had a positive stool test for the presence of C. difficile within 30 days before enrollment and were currently taking or had just been prescribed antibiotics to control CDI-related diarrhea at the time of enrollment. Participants were required to have had resolution of diarrhea prior to RBL or placebo study treatment. Participants agreed to not take non-dietary probiotics for eight weeks after receiving study treatment. Eligible participants were randomized 2:1 to receive a single dose of blinded treatment, either RBL or placebo (saline), rectally administered following an antibiotic washout period of 24 to 72 hours. The primary endpoint was treatment success — the absence of CDI diarrhea within eight weeks of study treatment. Participants were followed through six months. Participants with CDI recurrence within eight weeks of blinded treatment (treatment failure) were eligible to receive open-label RBL administration within 21 calendar days of failure determination, which could be administered after CDI antibiotics per investigator discretion.

Before administration, Gammaproteobacteria and Bacilli dominated the microbiota community and primary BAs were more prevalent than secondary BAs. Clinical success after administration correlated with shifts to predominantly Bacteroidia and Clostridia, a significant increase in MHI-A, and a shift from primary to secondary BAs. Several microbiota and BA changes were more extensive in RBL-treated responders compared to placebo-treated responders, and microbiota changes correlated with BA changes.



Dr. Septimus's Annotations

In the US, over 450,000 people are impacted by CDI at an economic cost of $5.4 billion. [N Engl J Med 2020; 382(14): 1320-30] Up to 35% of patients treated for an initial episode and up to 65% of patients with one or more prior episodes experience recurrent CDI (rCDI). [Clin Microbiol Infect 2012; 18 Suppl 6: 21-7] Colonic microbiome and metabolome disruption, termed dysbiosis, contributes to rCDI. Antibiotics are standard of care (SOC) treatment for CDI, but also may contribute to further dysbiosis and increased risk of recurrence. [Clin Infect Dis 2021; 73(5): e1029-e44] Fecal microbiota transplantation (FMT) has been extensively explored as a strategy for restoring eubiosis, with substantial promise, however, the production and administration of FMT are not standardized processes. These challenges have prompted development of standardized microbiota-based live biotherapeutics, including fecal microbiota, live-jslm (REBYOTA®; RBL, previously known as RBX2660) — the first single-dose, rectally administered, microbiota-based, biotherapeutic approved by the US FDA to prevent CDI recurrence in individuals aged ≥18 years following antibiotic treatment for rCDI. In a pivotal phase 3 trial (PUNCH™ CD3), RBL

(for prevention of rCDI) demonstrated 70.6% treatment success, defined as the absence of CDI diarrhea through eight weeks after the completion of study treatment, compared with 57.5% treatment success for placebo.[Drugs 2022; 82(15): 1527-38]

In general, patients with rCDI that received FMT shifted to Bacteroidia, Clostridia, and secondary BA predominance similar to the results in this trial. [PLoS One 2016; 11(1): e0147210] Their results are also consistent with those for other standardized microbiota-based therapeutics developed for rCDI. [N Engl J Med 2022; 386(3): 220-9] This study did not assess strain engraftment, i.e., whether newly appearing taxa after administration were derived directly from administered RBL. The downside of RBL is it needs to be rectally administered.

BOTTOM LINE

Clinical response to RBL(Fecal microbiota) administration is associated with restoration of gut microbiota and bile acid compositions to a greater extent than placebo administration.

6

A randomized controlled trial of efficacy and safety of Fecal Microbiota Transplant for preventing recurrent Clostridioides difficile infection.

Clinical Infectious Diseases published online September 13, 2024
DOI: 10.1093/cid/ciae467

Between 2018 and 2022, Veterans across the Veterans Health Administration system with recurrent C difficile infection (CDI) who responded to antibiotic treatment were randomized in a 1:1 ratio to oral FMT or placebo capsules. Randomization was stratified by the number of prior CDI recurrences (1 or ≥2). The primary endpoint was clinical recurrence by day 56, defined as >3 unformed stools daily for ≥2 days with or without laboratory confirmation of C. difficile, or death within 56 days.

A CDI episode was defined as laboratory confirmation of C. difficile AND either (a) >3 loose/watery stools/24 hours for 2 consecutive days, not explained by another diagnosis, or (b) ileus or toxic megacolon. Veterans were treated with standard of care antibiotics by their local treating clinicians. Potential study participants had to report resolution or symptom improvement for 48 hours during treatment of their most recent CDI episode and be able to be randomized within the enrollment window, without signs of recurrence before randomization. The enrollment window was 2-14 days after completion of antimicrobial therapy for CDI or 30 days after the onset of CDI, whichever was longer. FMT and placebo capsules were manufactured by the Microbiota Therapeutics Program at the University of Minnesota. Microbiota isolated from fecal material obtained from 4 standardized donors was lyophilized using a procedure previously demonstrated to preserve bacterial viability across the taxonomic spectrum. The primary endpoint was the incidence of recurrent CDI (definite or possible) or death, within 56 days of randomization. All study subjects experiencing loose or watery stools were instructed to submit a stool sample, which was processed at a central laboratory at the Iowa VA for detection of C. difficile toxin. Definite CDI recurrence was defined as: new onset of more than 3 loose or watery stools in 24 hours for 2 consecutive days with laboratory confirmation of a positive C. difficile toxin test from a stool specimen in the absence of another diagnosis. Possible recurrence was defined as above but without laboratory confirmation of C. difficile. Safety endpoints included all serious adverse events (SAEs) through 180 days, occurrence of certain pre-specified adverse events (AEs) queried at days 2 and 14 through chart review and participant telephone follow up, and spontaneously volunteered adverse events which occurred within the first 14 days or which were judged potentially related.

The study was stopped due to futility after meeting pre-specified criteria. Of 153 participants (76 FMT, 77 placebo) with an average age of 66.5 years, 25 participants (32.9%) in the FMT arm and 23 (29.9%) in the placebo arm experienced the primary endpoint of diarrhea and possible or definite CDI recurrence or death within 56 days of capsule administration (absolute difference 3.0%; 95% CI [-11.7%, 17.7%]). Stratification by number of recurrences revealed no statistically significant differences. There were no clinically important differences in adverse events.

Dr. Septimus's Annotations

In this randomized double-blind clinical trial enrolling Veteran participants from across the US, they found no difference in the rates of recurrent CDI or death between FMT and placebo recipients after successful antimicrobial therapy. Among other trials evaluating FMT, the results in this trial were similar to Hota et al, who compared open-label FMT administered by enema to a tapered course of vancomycin in 30 participants. [Clin Infect Dis 2017; 64: 265-71 Their findings, however, contrasted with an open-label trials comparing FMT to another modality of delivery, or FMT to antimicrobial therapy.[N Engl J Med 2013; 368: 407-15; Gastroenterology 2019; 156: 1324-32 e3] In these studies, recurrence rates after FMT are significantly lower than the non-FMT comparators, or in the case of oral FMT being compared to another modality of administration, both modalities have shown excellent results. [Clin Infect Dis 2014; 58: 1515-22]

It should be pointed out that most of the participants in this trial had a positive C. difficile PCR test at enrollment instead of a toxin test, which may be more likely to represent colonization vs. active infection. The choice of the primary endpoint for possible recurrence was based on symptoms with or without laboratory confirmation which was considered "pragmatic." They included patients with one or multiple recurrences, and it is possible that the benefit of FMT may be seen in trials with a higher proportion of patients with multiple recurrences. They did observe a 12.5% decrease in recurrence with FMT among participants with ≥2 recurrences (37.5% vs. 50%), but this was not statistically significant. In a recent trial, investigators reported a recurrence rate of 12% with SER-109 (a stool derived oral capsule product composed of purified Firmicutes spores) compared to 40% with placebo.[N Engl J Med 2022; 386: 220-9] However, in addition to using a different product and administration schedule (4 capsules daily for 3 days following 10 mg magnesium citrate) the study population had 3 or more recurrences, whereas most of the participants (78%) in this study experienced only one recurrence.

BOTTOM LINE

FMT therapy vs. placebo did not reduce CDI recurrence or death at 56 days. However, FMT may perform better in patients with multiple recurrences. There were no meaningful differences in adverse events between treatment groups.

7

The Contribution of 18F FDG PET-CT for the Investigation of Fever of Unknown Origin and Inflammation of Unknown Origin.

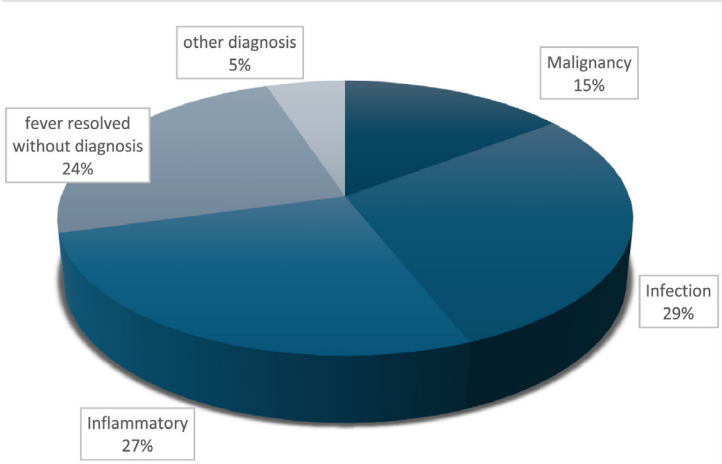
The American Journal of Medicine 2024; 137:629-639
DOI: 10.1016/j.amjmed.2024.03.017

Fever of unknown origin (FUO) and inflammation of unknown origin are highly challenging diagnostic conditions. The investigators aimed to assess the contributory effect of PET-CT to the diagnosis and compare it with the contributory effect of CT alone. FUO; defined as temperature >38.3°C on multiple occasions, symptom duration of ≥3 weeks, and no diagnosis after extensive evaluation) and inflammation of unknown origin (IUO; defined as prolonged inflammatory syndrome without fever but with elevated acute-phase reactants such as C-reactive protein).

In this systematic review and meta-analysis of 36 studies that involved 3500 patients, researchers evaluated the contributory effect of positron-emission tomography CT (PET-CT) in diagnosing causes of FUO or IUO. PET-CT was defined as contributory if was positive and led to a final diagnosis or if it was completely negative (in accord with a final diagnosis).

Most studies were retrospective and included FUO patients only. Final diagnoses were infectious diseases (29%), noninfectious inflammatory conditions (27%), cancers (15%), or other conditions (5%); the remaining 24% resolved without diagnosis. The pooled contribution of PET-CT was 75%; the pooled contribution of total-body CT was 68%. Sensitivity and specificity for PET-CT were 86% and 60%; sensitivity and specificity for total-body CT were 63% and 84%.

Final diagnosis classified as infectious, noninfectious inflammatory, malignancies, and resolution of fever of unknown origin without diagnosis and other.



PET-CT contributed to establishing diagnoses in three quarters of patients with FUO and IUO — better than the result for total-body CT. PET-CT also had higher sensitivity but lower specificity than total-body CT. Notably, prior research has shown that negative PET-CT is associated with spontaneous resolution of FUO [Intern Emerg Med 2023; 18:367]. Whether total-body CT or PET-CT should be the first imaging modality for these patients remains to be determined. This evaluation had limitations. First, the included studies were heterogeneous with respect to different types of world populations and different years. In addition, the comparison of PET-CT and CT was only based on different components of the same test, and only in 5 studies. There was no study that directly compared CT and PET-CT. They could not assess the contributory effect of PET-CT on specific subgroups of patients. Lastly, most facilities do not have PET-CT capability.

BOTTOM LINE

PET-CT had a contributory effect of 75% for the diagnosis of fever of unknown origin and inflammation of unknown origin. PET-CT had superior sensitivity and inferior specificity vs the CT scan.

8

Duration of antibiotic therapy for multidrug resistant Pseudomonas aeruginosa pneumonia: is shorter truly better?

BMC Infectious Diseases 2024 24:911
DOI: 10.1186/s12879-024-09600-w

In this retrospective study, investigators compared outcomes in two groups of patients who had been treated for hospital-acquired/ventilator-associated pneumonia (HAP/VAP) caused by MDR P aeruginosa from 2017 through 2020. MDR P. aeruginosa was defined as isolates that were non-susceptible (intermediate or resistant) to one or more drugs in at least three of the following categories: extended spectrum (ES) cephalosporins (i.e. cefepime, ceftazidime), ES penicillin with beta lactamase inhibitor (i.e. piperacillin/tazobactam), fluoroquinolones, aminoglycosides, and/or carbapenems. One group received 8 days or less of antibiotic therapy, which is roughly in line with the duration recommended by Infectious Diseases Society of America (IDSA) guidelines (7 days)[[Clin Infect Dis 2016; 63: e61–111] and the other group received more than 8 days' worth.

The primary outcome was clinical success at the end of therapy, defined as resolution of signs and symptoms of infection and no need for additional antibiotic treatment. Secondary outcomes included 30-day and 90-day mortality and relapsed pneumonia within 30 days of index culture. Relapse is one of the concerns when treating HAP/VAP caused by MDR P aeruginosa with a short course of antibiotics, particularly in immunocompromised patients. Exclusion criteria were inmates, those with polymicrobial pneumonia, community-acquired pneumonia, and infections requiring prolonged antibiotic therapy (empyema, lung abscesses, or other pulmonary complications secondary to pneumonia), non-P. aeruginosa infection and/or patients requiring prolonged antibiotic therapy (>21 days) for a different indication).

Of 427 patients with MDR P. aeruginosa respiratory isolates, 85 patients were included. Baseline characteristics were similar among groups with a median age of 65.5 years and median APACHE 2 score of 20. Roughly 75% had ventilator-associated pneumonia. Compared to those who received≤8 days of therapy, no difference was seen for clinical success in patients treated for more than 8 days (80% vs. 65.5%, p=0.16). The number of 30-day and 90-day in-hospital mortality, 30-days relapse, and other secondary outcomes did not significantly differ among the treatment groups.

Dr. Septimus's Annotations

The investigators found longer courses of antibiotics (>8 days) did not result in any significant difference in outcomes compared to those treated with shorter therapy. This is contrary to a recent randomized controlled trial conducted by Bougle et al. where non-inferiority of short duration (8 days) in the treatment of P. aeruginosa VAP was not demonstrated compared to long duration (15 days) due to significant higher rate of recurrence in the shorter duration group, however this study was limited due to its lack of power.[Intensive Care Med. 2022;48:841–849] The clinical success at the end of therapy in patients treated with 8 days of antibiotics (80%) in this study was very similar to that of the REPROVE trial where 79.5% of their patients with P. aeruginosa VAP were successfully treated with ceftazidime-avibactam for 7–14 days. [Lancet Infect Dis. 2018; 18:285–95] Furthermore, all-cause mortality in this study (26.7%) was similar to patients being treated with 14 days of imipenem-relebactam for P. aeruginosa HAP/VAP in the RESTORE-IMI 2 trial (33.3%). [Clin Infect Dis. 2021;73:e4539–48]

"The investigators found longer courses of antibiotics (>8 days) did not result in any significant difference in outcomes compared to those treated with shorter therapy. "

The use of combination therapy for severe pseudomonal infections has been considered standard of practice by many clinicians due to in-vitro antibiotic synergy and potential prevention of resistance emergence while receiving therapy. In this study the choice of antibiotics for treatment of MDR P. aeruginosa HAP/VAP was dictated by the susceptibility patterns, with the majority using monotherapy. They did not see any trend favoring combination therapy over monotherapy. This finding was similar to the meta-analysis conducted by the IDSA expert panels including 7 randomized trials which found that combination therapy offered no benefit in reducing mortality beyond monotherapy (RR, 0.94; 95% CI, 0.76– 1.16). [Clin Inf Dis. 2016;63: e61–111] After exclusion of patients receiving inappropriate empiric treatment regimen, mortality was not different among groups who were treated with monotherapy vs. combination (23.1% vs. 33.2%, adjusted HR 0.9; 95% CI 0.5–1.63). [Crit Care Med. 2007;35(8):1888–95]

Sample sizes were small; and were may not powered to detect the difference in outcomes among treatment groups. Additionally, since this was a retrospective study, clinical diagnosis of pneumonia was largely dependent on provider documentation, which did not always detail the specific rationale for the diagnosis and thus it was hard to retrospectively differentiate between pneumonia and possible colonization. They were unable to capture mortality or re-admission events outside our hospital; and thus, the incident rate may represent an underestimation.

BOTTOM LINE

This result favors the approach of treating patients with MDR P. aeruginosa HAP/VAP for ≤8 days, instead of a longer duration, to prevent the development of resistance and adverse drug events.

The evidence base for the optimal antibiotic treatment duration of upper and lower respiratory tract infections: an umbrella review

The Lancet Infectious Disease published online September 4, 2024
DOI: 10.1016/ S1473-3099(24)00456-0

To evaluate the current evidence base for shortening antibiotic duration in respiratory tract infections (RTIs), investigators conducted an umbrella review of systematic reviews addressing antibiotic treatment durations for CAP, AECOPD, hospital-acquired pneumonia (HAP), acute sinusitis, and streptococcal pharyngitis, tonsillitis and pharyngotonsillitis. The primary outcomes of interest were clinical and bacteriologic cure, microbiologic eradication, mortality, relapse rate, and adverse events.

Of the 30 reviews identified by the investigators, 14 (of which 8 were meta-analyses) found moderate-quality evidence that 5 days of antibiotics is clinically non-inferior to a longer course for non-ICU CAP, but the evidence was insufficient to support anything shorter than 5 days. For AECODP, 8 reviews (including 5 meta-analyses) found sufficient evidence supporting a treatment duration of 5 days, but evidence for shorter durations was scarce. The quality of the reviews was generally low, and the quality of evidence varied between type of infection, the available evidence for non-ICU CAP and AECOPD supports a short-course treatment duration of 5 days in patients who have clinically improved. Evidence for shorter durations for non-ventilator-associated HAP and acute sinusitis was limited. Only three reviews of HAP were included, and notably, individual studies included high percentages of patients with ventilator-associated pneumonia (VAP). Although some studies show that a short 3-day course of therapy for HAP did not result in worse clinical outcomes than longer course treatment, and guidelines for HAP recommend an antibiotic treatment duration of 7 days or fewer, future RCTs are needed to determine optimal antibiotic treatment duration for HAP in non-ventilated patients.[Clin Infect Dis 2016; 63: e61–111] Only four reviews encompassing 13 RCTs addressed acute bacterial rhinosinusitis (ABRS) treatment. Despite the low quality of the reviews, similar clinical and microbiological outcomes were reported for short versus longer treatment durations, justifying current guidelines that recommend a 5–7-day treatment course for uncomplicated ABRS.[Clin Infect Dis 2012;54: e72–112] For pharyngotonsillitis (8 reviews, of which 6 did a meta-analysis), the analysis found sufficient evidence to support short-course cephalosporin but not short-course penicillin when dosed three times a day.

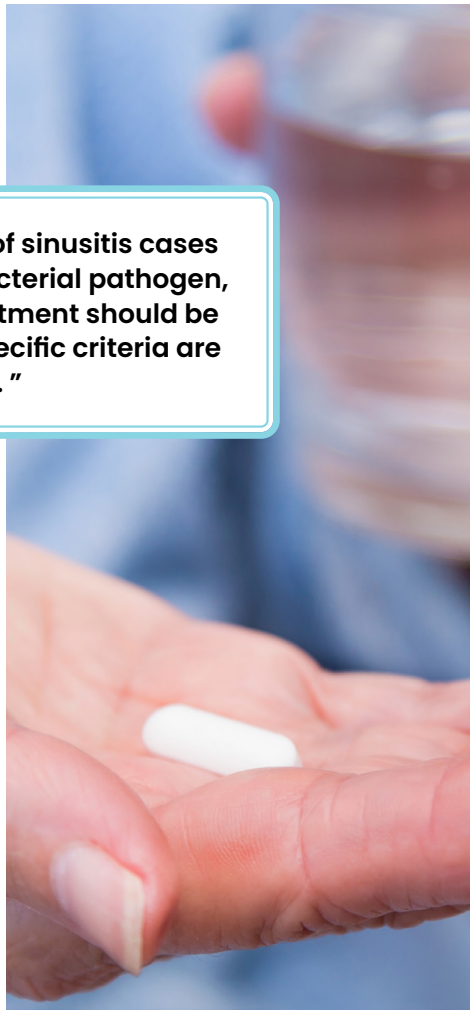
Dr. Septimus's Annotations

In this paper, 30 reviews were identified studying a short-course antibiotic treatment for RTIs, of which 21 performed meta-analyses. They reported that in general, the risk of bias was unclear or high and the resulting evidence base for short-course treatment differed per condition. For CAP, there is moderate-quality evidence that shorter courses of antibiotic therapy are clinically non-inferior to longer courses. Overall, the evidence supports a treatment duration of no more than 5 days. Patients who were immunocompromised or in the ICU were under-represented, so the optimal treatment duration for CAP in patients who are immunocompromised or in the ICU has not been established.

Meta-analyses on AECOPD were of low quality and contained RCTs of mostly unclear risk of bias; however, reviews concluded that short-course treatment (3–6 days) was non-inferior to long-course treatment. Many cases of AECOPD are viral.

The reviews on HAP only included studies on VAP and, therefore, they did not provide evidence on the optimal treatment duration for non-ventilator-associated HAP. Based on studies on patients with VAP the IDSA guidelines advise an antibiotic treatment duration of 7 days or less. [Clin Infect Dis 2016; 63: e61–111]

It should be emphasized that only a minority of sinusitis cases are caused by a bacterial pathogen, and antibiotic treatment should be withheld unless specific criteria are met. The IDSA guidelines advise the treatment of acute sinusitis with antibiotics to be restricted to patients with persistent symptoms (≥10 days), severe symptoms (≥3–4 days), or worsening of symptoms after initial improvement of typical viral upper RTI (≥3–4 days). 5-7 days of treatment is recommended for uncomplicated ABRS. [Clin Infect Dis 2012; 54: e72–112]



"...only a minority of sinusitis cases are caused by a bacterial pathogen, and antibiotic treatment should be withheld unless specific criteria are met."

For streptococcal pharyngitis, tonsillitis, or pharyngotonsillitis results showed that with a 5-day course of cephalosporins, clinical and microbiological cure can be achieved, but penicillin for 5 days leads to an inferior clinical and microbiological cure rate in comparison with 7–10 days of treatment. However, cephalosporins are unnecessarily broad. A recent RCT showed that clinical cure can be achieved with shorter durations of penicillin V when dosed every 6 h, to achieve more time above the minimum inhibitory concentration. [BMJ 2019; 367: l5337]

BOTTOM LINE

In general, shorter is better, however, there is a need for high-quality RCTs to provide evidence on treatment durations of less than 5 days for CAP and acute exacerbation COPD (AECOPD), to assess the optimal treatment duration for non-ventilator healthcare-acquired pneumonia (HAP) and sinusitis, and to support short-course treatment with a more frequent dosing scheme of penicillin in patients with pharyngotonsillitis.

10

Diagnostic Discordance, Uncertainty, and Treatment Ambiguity in Community-Acquired Pneumonia: A National Cohort Study of 115 U.S. Veterans Affairs Hospitals

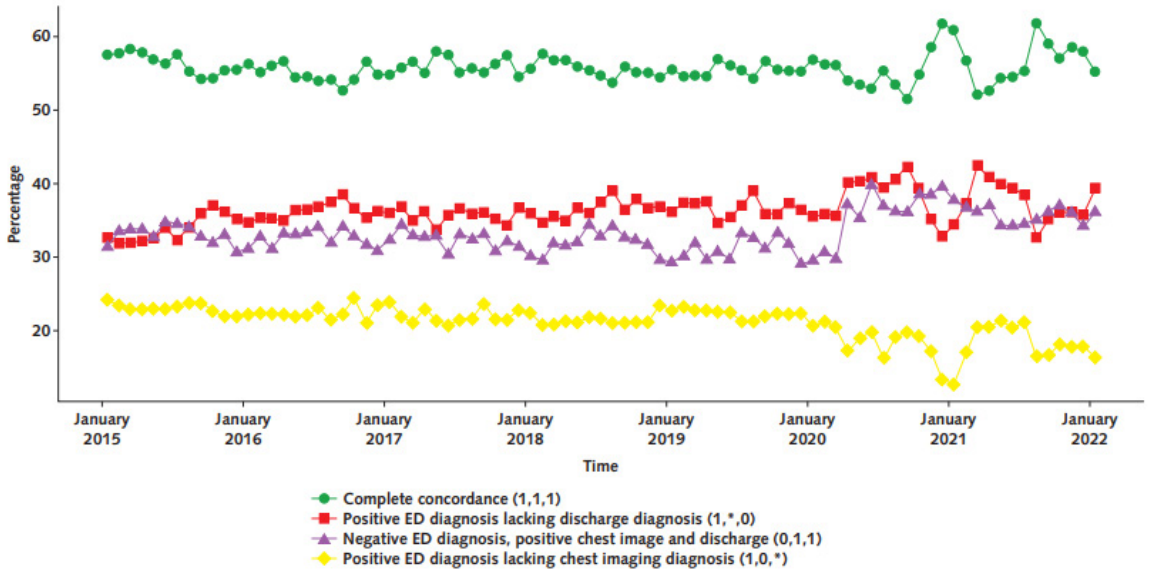
Annals of Internal Medicine published online August 4, 2024
DOI: 10.7326/M23-2505

The purpose of this study was to examine the evolution of pneumonia diagnoses among patients hospitalized from the emergency department (ED). This was a retrospective nationwide cohort of 118 U.S. Veterans Affairs medical centers. Patients aged 18 years or older and hospitalized from the ED between 1 January 2015 and 31 January 2022 were included. They looked for discordances between initial pneumonia diagnosis, discharge diagnosis, and radiographic diagnosis identified by natural language processing of clinician text, diagnostic coding, and antimicrobial treatment. Expressions of uncertainty in clinical notes, patient illness severity, treatments, and outcomes were also compared.

Among 2,383,899 hospitalizations, 13.3% received an initial or discharge diagnosis and treatment of pneumonia: 9.1% received an initial diagnosis and 10.0% received a discharge diagnosis. Discordances between initial and discharge occurred in 57%. Among patients discharged with a pneumonia diagnosis and positive initial chest image, 33% lacked an initial diagnosis. Among patients diagnosed initially, 36% lacked a discharge diagnosis and 21% lacked positive initial chest imaging. Uncertainty was frequently expressed in clinical notes (58% in ED; 48% at discharge); 27% received diuretics, 36% received corticosteroids, and 10% received antibiotics, corticosteroids, and diuretics within 24 hours. Patients with discordant diagnoses had

greater uncertainty and received more additional treatments, but only patients lacking an initial pneumonia diagnosis had higher 30-day mortality than concordant patients (14.4% [95% CI, 14.1% to 14.7%] vs. 10.6% [CI, 10.4% to 10.7%]). Patients with diagnostic discordance were more likely to present to high-complexity facilities with high ED patient load and inpatient census.

Figure 3. Monthly trends in diagnostic discordance, 1 January 2015 to 31 March 2022.



Dr. Septimus's Annotations

Pneumonia is the leading cause of death from infectious diseases. [Lancet Infect Dis. 2017; 17:1133-1161] In addition more than 1.5 million adults are hospitalized in the US annually for pneumonia, the most common infection for admission to the hospital. [Chest. 2019; 156:255-268] Appropriate management requires accurate diagnosis, but current guidelines (ATS/IDSA) focus on treatment. [Am J Respir Crit Care Med. 2019;200: e45-e67] Diagnosis is increasingly recognized as an important target for quality improvement, but most patients admitted for CAP do not identify the etiology with conventional diagnostics. This makes it difficult to improve care where clinicians who make the initial diagnosis of pneumonia rarely learn the ultimate diagnosis or ensuing treatment decisions for their patients. These findings highlight substantial diagnostic uncertainty and treatment ambiguity in pneumonia that requires attention by clinicians and patients. The tradeoffs between "overdiagnosis" versus "underdiagnosis" are real and require study. Overdiagnosis and treatment ambiguity have important consequences on patient outcomes, including adverse effects of unnecessary antibiotics.

Large-scale retrospective analysis of clinical data from the EHR results depends on data quality. Combining ICD codes with clinical text demonstrated high but imperfect accuracy. In addition, the VA population overrepresents male, older patients with comorbidities and may not be generalizable to the general population.

BOTTOM LINE

This study suggests that diagnostic discordance, uncertainty, and treatment are common features of clinical care for patients hospitalized with pneumonia with important bearings on patient care and outcomes. This study highlights the importance of linking diagnostic and antimicrobial stewardship to reduce diagnostic uncertainty and improve pathogen specific treatment.

11

Preventability of Hospital Deaths in Patients with Non-Ventilator Hospital-Acquired Pneumonia

Clinical Infectious Diseases published online August 19, 2024
DOI: 10.1093/cid/ciae418

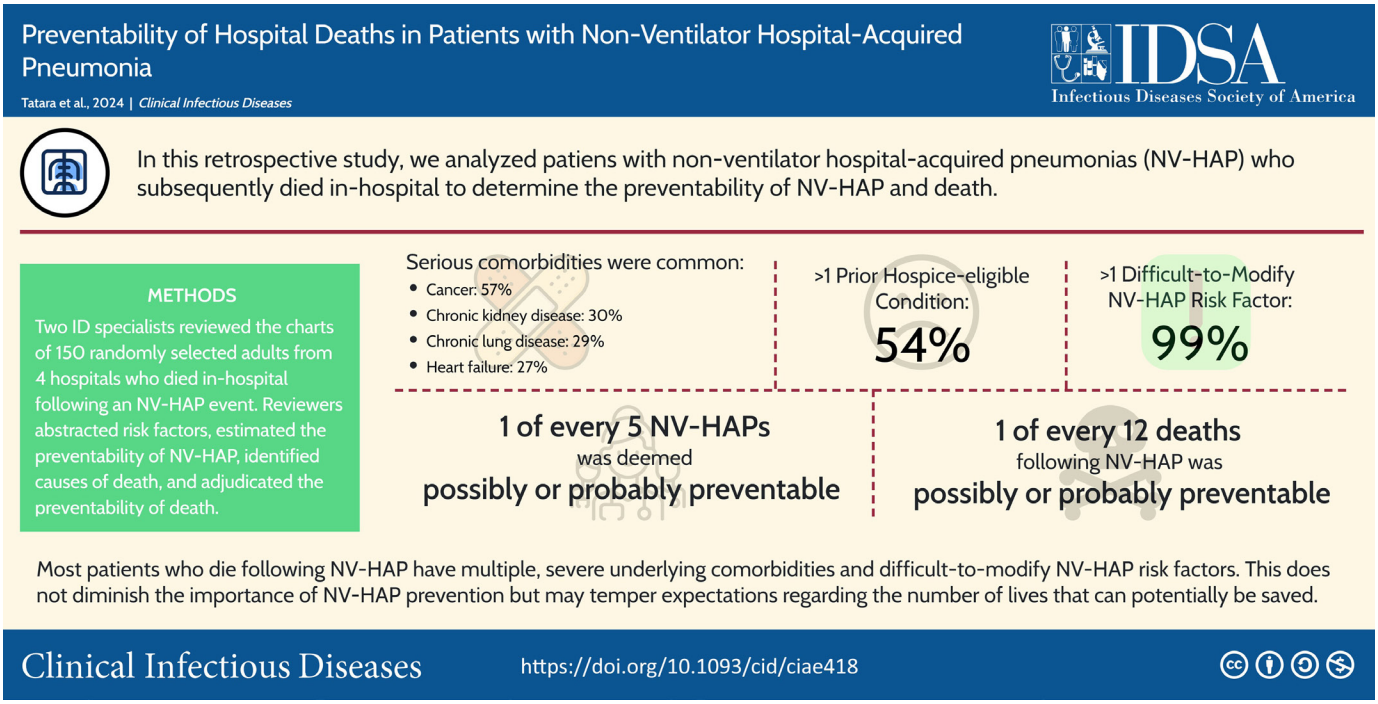
There is uncertainty regarding the preventability of NV-HAP deaths, and the immediate causes of death in patients with NV-HAP who die. To better understand these questions, the investigators undertook detailed clinical analyses using full text chart reviews of 150 patients who died in hospital following a possible NV-HAP. Their goals were to better characterize this population's underlying clinical characteristics, risk factors for NV-HAP, the extent to which NV-HAP might have been preventable, patients' immediate cause of death, and the potential preventability of deaths following NV-HAP.

They identified patients with possible NV-HAP using a validated electronic surveillance definition for NV-HAP predicated upon acute onset of worsening oxygenation >2 days after admission, an abnormal temperature or white blood cell count, an order for chest imaging, and starting new antibiotics and continuing them for at least 3 days. [6, 14, 17, 18] They identified the subset of patients who died during the index hospitalization in which NV-HAP occurred and then randomly selected 150 patients for review.

Each patient was independently reviewed between May 2022 and July 2023 by two infectious diseases clinicians. Reviewers assessed admission notes, progress notes, consultation notes, daily vital signs, laboratory test results, radiographic images, pathology reports, and autopsies if done. Reviewers abstracted the reason for admission, admitting service, location at time of death, co-morbidities, NV-HAP risk factors, use of aspiration precautions, clinical evidence for NV-HAP, most likely etiology of NV-HAP, immediate cause of death, underlying condition leading to death, presence of care restrictions such as "Do Not Resuscitate" orders, and possible errors in NV-HAP management, including delay or lack of appropriate treatment per reviewers' judgement.

Reviewers defined NV-HAP as a new lung infiltrate with at least two concurrent clinical signs (fever, change in the quantity or quality of sputum such as new purulence, and/or an abnormal white blood cell count), and new oxygen impairment >48 hours following admission. The immediate cause of death was defined as the final illness or event that led to the patient's demise while the underlying cause of death was defined as the disease or injury that initiated the chain of events that led to death. Reviewers assessed the preventability of NV-HAP using a five-point Likert scale after considering each patient's functional status, co-morbidities, modifiable risk factors, non-modifiable risk factors, and possible medical errors. 22 NV-HAP events were ranked as 1) Definitely not preventable; 2) Probably not preventable; 3) Possibly preventable; 4) Probably preventable; and 5) Definitely preventable. In addition, reviewers assessed the preventability of hospital death after taking into account each patient's functional status, co-morbidities, and prognosis prior to NVHAP using a Likert scale with the following categories: 1) Very unlikely to be a preventable death; 2) Unlikely a preventable death; 3) Uncertain- medical error may have been present, but unclear if it would have changed the outcome; 4) Likely a preventable death; and 5) Very likely a preventable death. If assessments were conflicting, reviewers discussed the case specifics and attempted to find consensus with a senior infectious disease physician.

There were 264,843 adult patients hospitalized for ≥3 days during the study period. Of these, 2,406 (0.91%) met electronic NV-HAP criteria, of whom 720 (29.9%) died in-hospital. Amongst 150 deaths randomly selected for chart review, average age was 69.3 years (IQR 60.7-77.4) and 43.3% were female. Most patients were hospitalized a median of two times (IQR 1-3) in the year preceding the admission in which they developed NV-HAP with a median interval since last hospitalization of 25 days (IQR 10-86). Almost one in five patients was transferred from another acute care hospital; 6.0% were admitted from a skilled nursing facility. NV-HAP developed a median of 6 (IQR 3-12) days after admission. Patients' median age was 69.3 (IQR 60.7-77.4) and 43.3% were female. Comorbidities were common: 57% had cancer, 30% chronic kidney disease, 29% chronic lung disease, and 27% heart failure. At least one hospice-eligible condition was present before NV-HAP in 54% and "Do Not Resuscitate" orders in 24%. Most (99%) had difficult-to-modify NV-HAP risk factors: 76% altered mental status, 35% dysphagia, and 27% nasogastric/orogastric tubes. NV-HAP was deemed possibly or probably preventable in 21% and hospital death likely or very likely preventable in 8.6%.



Dr. Septimus's *Annotations*

Most patients who die following NV-HAP have multiple, severe underlying comorbidities and difficult-to-modify risk factors for NV-HAP. Only 1 in 5 NV-HAPs that culminated in death and 1 in 12 deaths following NV-HAP were judged potentially preventable. This study confirms prior studies that have reported very high mortality rates for patients who develop NV-HAP.[5-8] This study demonstrated that NV-HAP is usually not the immediate cause of death amongst patients who die following NV-HAP, that the signs and symptoms of NV-HAP have resolved in up to a quarter of patients before they die, most patients who die following NV-HAP had a very poor prognosis even before NV-HAP, and most of these deaths may not be preventable. However, while most NV-HAP events and deaths were not thought to be preventable, some NV-HAPs and deaths are probably preventable, with potentially modifiable risk factors identified. Some hospitals have reported significant reductions in NV-HAP rates following implementation of quality improvement programs. [Infect Control Hosp Epidemiol 2020; 41(5): 547-52] Two interventions have received the most amount of attention: oral care and mobility. A recent meta-analysis of 15 randomized trials reported that regular toothbrushing in hospitalized patients was associated with a 33% decrease in hospital-acquired pneumonia and a 19% decrease in ICU mortality. [JAMA Intern Med 2024; 184: 131-42] In a recent quasi-experimental study, the investigators looked the incidence of HAP before and after implementing a bundle, which included mobilization, upright feeding, swallowing evaluation, sedation restrictions, elevated head of bed, oral care, and tube care. [Infect Control Hosp Epidemiol 2020; 41:547–552] This bundle reduced NV-HAP, attributable mortality, and antimicrobial use. In a nonrandomized controlled trial, mobilizing patients in two geriatric and respiratory wards, the investigators reported a significant decrease in pneumonia rates compared with

"Most patients who die following [Non-Ventilator Hospital-Acquired Pneumonia] have multiple, severe underlying comorbidities and difficult-to-modify risk factors for NV-HAP... However, while most NV-HAP events and deaths were not thought to be preventable, some NV-HAPs and deaths are probably preventable, with potentially modifiable risk factors identified."

usual care; however, falls were significantly more frequent in the intervention group. In another quasi-experimental trial, the investigators began an intensified postoperative physical therapy intervention, which included daily supervised early mobilization and coached deep breathing exercises in elderly patients undergoing hip fracture surgery and compared outcomes to historical controls. [Clin Interv Aging 2020; 15:1821–1829] There was a significantly lower incidence of HAP in the physical therapy group (P = 0.002) and significantly shorter length of stay than the control group (P = 0.022). These results need to be confirmed with randomized control trials (RCTs) looking at benefits versus potential harm. The primary limitation of this analysis is the subjectivity and uncertainty of determining preventability in retrospect. Even under the best of circumstances, diagnosing NV-HAP is incredibly challenging.

BOTTOM LINE

Mortality rates associated with NV-HAP are high suggesting a critical need for programs to prevent NV-HAP. Detailed analyses of patients who die following NVHAP, however, suggest that most have severe comorbid illnesses at baseline, more than half have hospice-qualifying conditions, NV-HAP is the immediate cause of death in less than half, and death was likely or very likely preventable in only 1 in 12. These findings should not lessen the need for implementing NV-HAP prevention programs. More research is needed.

Urinary Retention Evaluation and Catheterization Algorithm for Adult Inpatients.

JAMA Network Open. 2024;7(7): e2422281.
DOI: 10.1001/jamanetworkopen.2024.22281

The investigators set out to develop an algorithm for screening and management of urinary retention (UR) among adult inpatients. They used the RAND/UCLA Appropriateness Method and qualitative interviews, an 11-member multidisciplinary expert panel of nurses and physicians from across the US used a formal multi-round process from March to May 2015 to rate 107 clinical scenarios involving diagnosis and management of adult UR in postoperative and medical inpatients.

A summary of the final algorithm is summarized below:

- Bladder scanning is preferred over catheterization for evaluating symptomatic patients or asymptomatic patients who have not voided after 3 hours.
- If bladder scanning is unavailable, using an intermittent straight catheter (ISC) or indwelling urinary catheter (IUC) is appropriate, with ISC initially preferred over IUC.
- Bladder scanner volumes that should prompt catheterization are ≥300 mL in symptomatic patients and ≥500 mL in asymptomatic patients.
- A patient who requires an ISC more often than every 4 hours or whose output is ≥500 mL every 4 hours could be appropriately transitioned to an IUC.

Dr. Septimus's Annotations

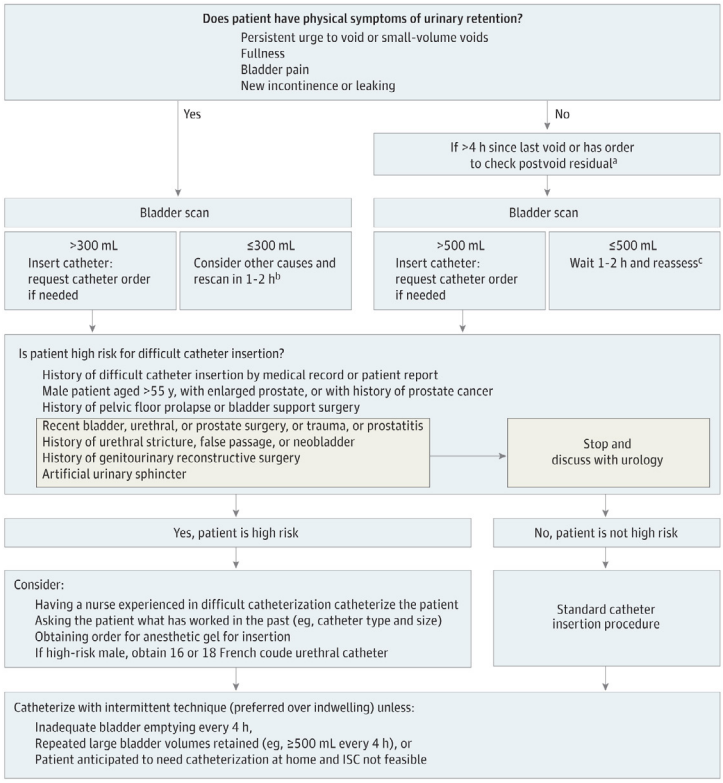
In this study using a systematic, multidisciplinary, evidence- and expert opinion–based approach, a UR evaluation and catheterization algorithm was developed to improve patient safety by increasing appropriate use of bladder scanners and catheterization. This study adds to the literature by providing practical guidance on assessing and managing UR based on both available evidence and by expert opinion. Generally, bladder scanner is accurate for clinical purposes;

however, some conditions can interfere with obtaining objective data from bladder scanners used for decisions within the algorithm, such as ascites (leading to erroneous volume assessment by ultrasonography) or very low urine output due to kidney failure (extending the time needed to fill the bladder). Algorithm implementation must consider clinical context to accommodate patient variability. Although they systematically assessed the relevant literature, the evidence was not of optimal quality, lacking randomized clinical trials to guide appropriateness ratings. The panel focused on decision-making based on postvoid residual volumes and did not consider voided volumes or calculations of voiding efficiency, which can be relevant in patients with low bladder capacities.

BOTTOM LINE

This algorithm provides a practical approach on how best to manage urinary retention among inpatients. Future efforts should focus on whether implementation of such algorithms improves patient safety by minimizing the harms of urinary retention and catheterization.

Final Evaluation and Catheterization Algorithm to Manage Urinary Retention Among Inpatients

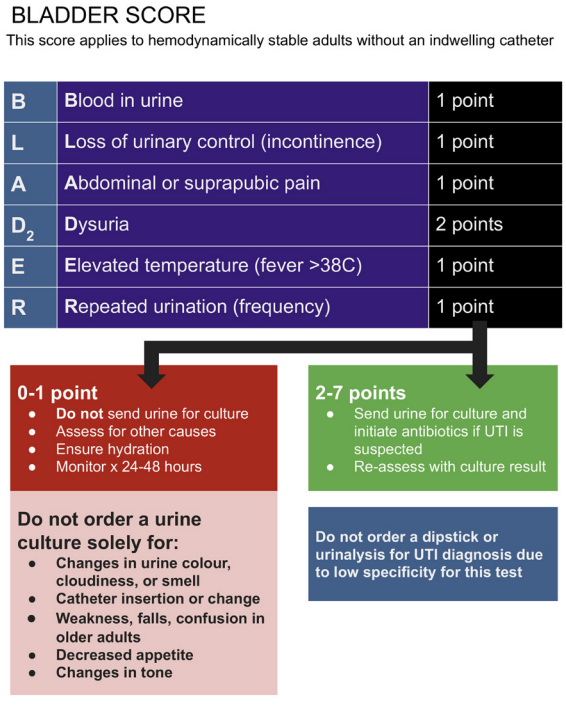


13

BLADDER score: evaluating a tool to support urinary diagnostic and antibiotic stewardship in hospitalized adults.

Infection Control & Hospital Epidemiology published online August 28, 2024
DOI: 10.1017/ ice.2024.93

This was a quasi-experimental study using interrupted time series with segmented regression to evaluate urine culturing and urinary antibiotic use and length of stay (LOS), acute care transfers, and mortality 18 months before and 16 months after the intervention in a 134-bed complex continuing care and rehabilitation hospital in Canada. The tool was developed to address noncatheterized patients, the main population from which urine cultures are sent in their population. (only 15% had a urinary catheter) They developed an intervention focusing on a 6-item mnemonic scoring tool called the BLADDER score which was developed based on existing minimum criteria for prescribing antibiotics in patients with presumed UTI. The BLADDER score was combined with ward- and prescriber-level feedback and education. Each of the letters BLADDER in the score represents a possible symptom representative of UTI (B, blood in urine; L, loss of urinary control or incontinence; A, abdominal or flank pain; D, dysuria or pain on urination; E, elevated temperature or fever; R,

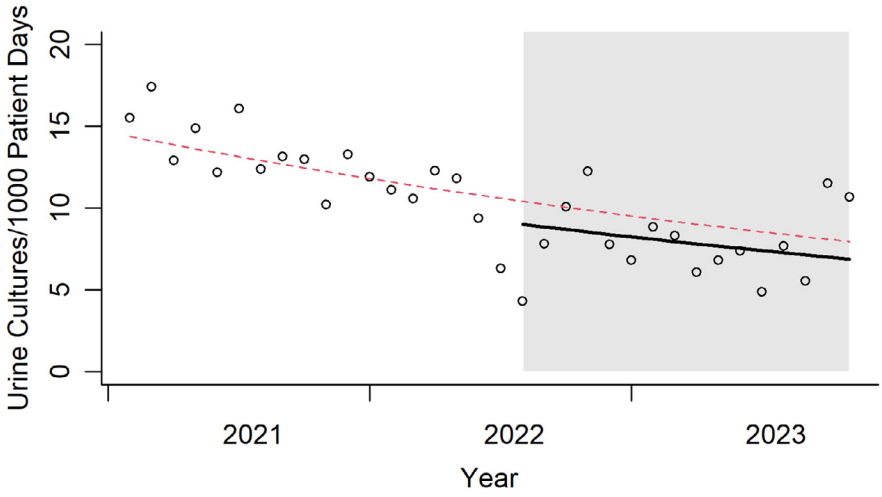


repeated urination or frequency). See figure below When patients are evaluated for possible UTI, 1 point is given for each letter in the algorithm (all symptoms receive a score of 1 except dysuria which is 2 points). A score of 2 or more should prompt a urine culture, whereas a score below 2 suggests careful monitoring and investigation for other etiologies to explain their symptoms rather than a urine culture.

The main outcomes were the number of urine cultures sent per 1,000 patient days, volume of urinary antibiotics (ciprofloxacin, nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin) measured in defined daily doses (DDDs) per 1,000 patient days, and proportion of all antibiotic DDDs that were urinary. We also evaluated urine culture percent positivity throughout the study period. Secondary measures included total systemic antibiotic DDDs per 1,000 patient days.

Before the intervention, the mean rate of urine cultures was 12.47 cultures per 1,000 patient days; after the intervention, the rate was 7.92 cultures per 1,000 patient days (IRR 0.87; 95% CI, 0.67–1.12). Urinary antibiotic use declined after the intervention from a mean of 40.55 DDD per 1,000 patient days before and 25.96 DDD per 1,000 patient days after the intervention (IRR 0.68; 95% CI, 0.59–0.79). There was no change in mean patient LOS, acute care transfers, or mortality.

Final Evaluation and Catheterization Algorithm to Manage Urinary Retention Among Inpatients



Dr. Septimus's Annotations

Implementation of the BLADDER score along with a multifaceted approach including education and audit and feedback was associated with a 32% reduction in urinary antibiotic prescribing in this rehabilitation hospital. There was no signal of unintended harm as inpatient LOS, acute care transfers, and mortality did not significantly change during the intervention. Antimicrobial/diagnostic stewardship initiatives have focused on improving urine culturing in adults, most of which have resulted in significant reductions in urine culturing and antibiotic prescribing. [JAMA Intern Med 2023; 183:933; BMJ 2023;380: e072319] The implementation of a scoring tool may be a useful adjunct to further explore in addition to other diagnostic stewardship strategies. Such a tool may be particularly useful as part of order entry in the electronic health record which should remind clinicians to be more judicious when ordering urine cultures.

BOTTOM LINE

The BLADDER score is a safe and effective tool to support improved diagnostic and antimicrobial stewardship to reduce unnecessary treatment for asymptomatic bacteriuria.

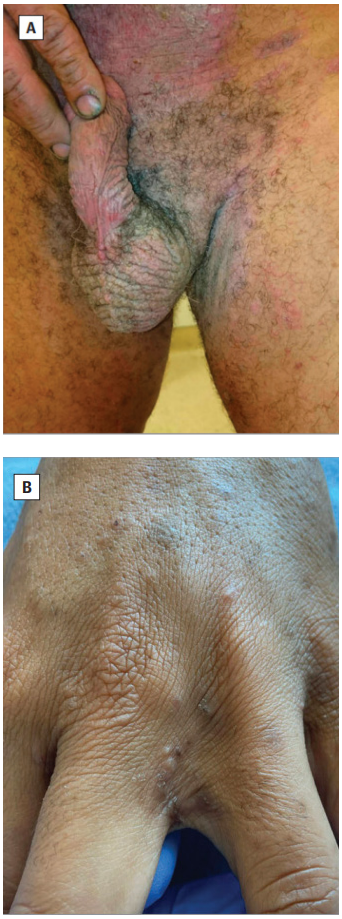
Scabies, Bedbug, and Body Lice Infestations A Review

JAMA published online September 9, 2024
DOI: 10.1001/jama.2024.13896

Scabies

Scabies is caused by mites (Sarcoptes scabiei) that burrow into the epidermis. Transmission primarily occurs from prolonged skin-to-skin contact with an individual who has an infestation. Scabies is caused by infestation by the mite Sarcoptes scabiei var hominis, which lives its entire approximately 14-day life cycle in the human epidermis. Female adult mites lay eggs in the uppermost layer of the skin that hatch in 3 to 4 days before developing into adult mites over 1 to 2 weeks. Subsequent skin hypersensitivity reaction occurs 4 to 6 weeks later and results in the cutaneous manifestations of scabies. Mite transmission typically requires at least 15 to 20 minutes of direct skin-to-skin contact and occurs in conditions of overcrowding, shared living spaces, bed sharing, sexual contact, and caregiving in shelters and long-term care facilities. Common scabies is characterized by excoriated pruritic papules, plaques, and pathognomonic burrows on finger/toe web spaces, volar wrists, ankles, axillae, buttocks, male genitalia, and areolae. Permethrin cream and oral ivermectin are first-line treatments for adults, with similar clearance rates by week 2 (74% with permethrin vs 68% with ivermectin; relative risk, 0.91; 95% CI, 0.76-1.08). Treatment failure can occur with oral ivermectin (11.8%; 95% CI, 8.4%-15.4%) and topical permethrin (10.8%; 95% CI, 7.5%-14.5%). A confirmed diagnosis can be made with (1) visualization of mites, eggs, or feces on light microscopy.

Clincal presentations of **scabies** infestation

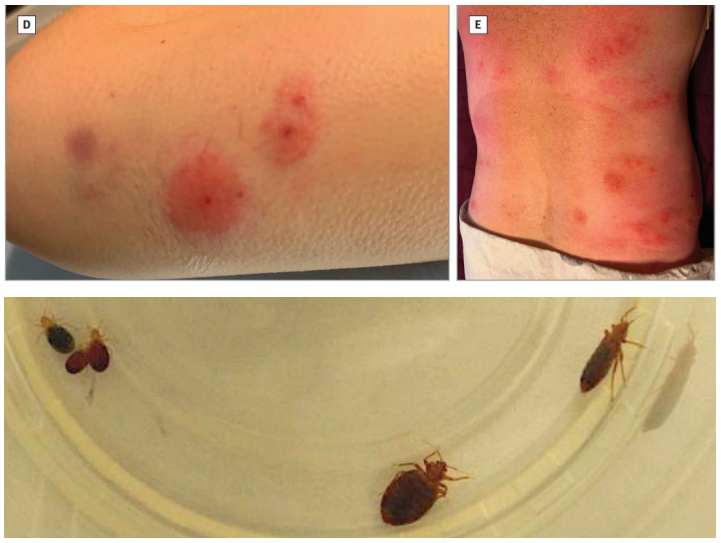


Bedbugs (*Cimex lectularius*, *Cimex hemipterus*)

Bedbugs (Cimex lectularius, Cimex hemipterus) are insects that live on mattresses and furniture and feed on blood nocturnally, causing linear pruritic erythematous papules. New skin lesions on waking, cohabitants with similar symptoms, and recently residing in a high-occupancy setting should raise suspicion. Bedbugs undergo 5 nymphal stages that each require a blood meal to transition to the adult form. They are flat, approximately 5-mm ovoid wingless insects that are visible to the unaided eye.

Bedbugs are nocturnal and are attracted to a host's body temperature and carbon dioxide exhalation. Skin reactions to most bites resolve after 1 week without treatment; symptomatic treatment with midpotency

Clincal presentations of **bedbug** infestation

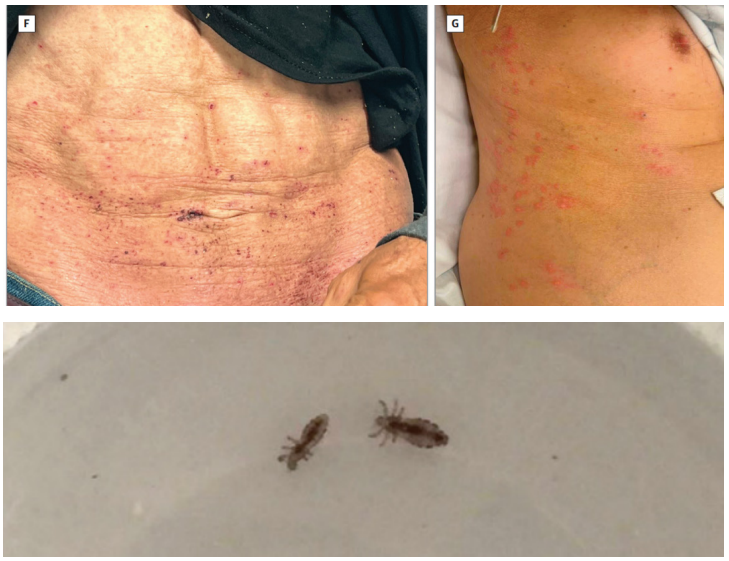


topical corticosteroids and oral antipruritics (eg, oral antihistamines, gabapentinoids) can be used as needed. Treatment requires eradication with pest management. Eradication is best performed by pest management professionals, who often use an integrated strategy that combines interventions, which may include temperature. extremes (heating or freezing), laundering, vacuuming, and insecticides.

Body lice (*Pediculus humanus humanus*)

Body lice (Pediculus humanus humanus) are insects found on clothing that travel to the skin for blood meals. Body lice bites cause pruritic excoriated macules/papules and hyperpigmentation in areas where clothing seams contact skin. Treatment and prevention require at least once-weekly bathing and laundering of clothing and bedding. First-line treatment and prevention is bathing and laundering clothing and bedding at least once a week; clothing and bedding should be machine washed in water heated to at least 130 °F and dried using the high-heat cycle; if laundering is not available, clothing and bedding can be sealed in a plastic bag and stored for 2 weeks. Symptomatic treatment with midpotency topical corticosteroids and oral antipruritics (e.g., oral antihistamines, gabapentinoids) can be used as needed.

Clincal presentations of **body lice** infestation



Body lice infestation may cause systemic complications. In a cross-sectional study of 27 hospitalized patients with body lice and 81 hospitalized patients without body lice matched on age, sex, and housing status, body lice infestation was associated with a 2.5-g/dL lower hemoglobin level (95% CI, 1.4-3.5 g/dL;P < .001), and a higher proportion of patients with body lice infestation had anemia (70.4% [95% CI, 50%-85%] vs 46.9% [95% CI, 36.2%-57.9%]; P = .03).[JAMA Dermatol. 2022;158(6):691-693] Secondary bacterial infection (impetigo, cellulitis, abscess) can be observed. Body lice are also a vector for Bartonella quintana, Borrelia recurrentis, and Rickettsia prowazekii. B quintana infection can have variable clinical presentations including asymptomatic bacteremia, endocarditis, and relapsing fevers [Clin Infect Dis. 2000;31:131-135] and has been documented in populations with poor access to clean water and inadequate housing. [J Infect Dis. 2022;226(suppl 3): S315-S321]

BOTTOM LINE

Scabies, bedbugs, and body lice infestations are common. Accurate diagnosis requires taking a history, including social drivers of health (e.g., housing status, living environment), and physical examination. This is an excellent review worth reading.

15

Oropouche Virus Disease Among U.S. Travelers — United States, 2024

MMWR Vol. 73 No. 35 published online August 27, 2024

Beginning in late 2023, Oropouche virus was identified as the cause of large outbreaks in Amazon region with known endemic transmission and in new areas in South America and the Caribbean. The virus is spread to humans by infected biting midges(fleas) and some mosquito species. Although infection typically causes a self-limited febrile illness, reports of two deaths in patients with Oropouche virus infection and vertical transmission associated with adverse pregnancy outcomes have raised concerns about the threat of this virus to human health. In addition to approximately 8,000 locally acquired cases in the Americas, travel-associated Oropouche virus disease cases have recently been identified in European travelers returning from Cuba and Brazil. As of August 16, 2024, a total of 21 Oropouche virus disease cases were identified among US travelers returning from Cuba. Most patients

initially experienced fever, myalgia, and headache, often with other symptoms including arthralgia, diarrhea, nausea or vomiting, and rash. At least three patients had recurrent symptoms after the initial illness, a common characteristic of Oropouche virus disease. Among the US patients, fever (95%), myalgia (86%), headache (76%), fatigue or malaise (62%) and arthralgia (57%) were the most common symptoms, with a combination of fever and myalgia with or without other symptoms (81%), a combination of fever and headache (71%) or a combination of all three (62%) also common among them.

Symptoms of the virus start 3 to 10 days after being bitten and are similar to other arboviruses, including headache, fever, muscle and joint aches, nausea, vomiting, chills and sensitivity to light. There is no specific treatment, but most people recover without long-term effects within about a week.

Dr. Septimus's Annotations

Oropouche virus (Simbu serogroup, genus Orthobunyavirus) is endemic to the Amazon region and was previously identified as a cause of human disease in several countries in South and Central America and the Caribbean. The virus circulates in a sylvatic cycle, possibly involving certain vertebrate hosts (e.g., sloths, nonhuman primates, and birds) and mosquitoes, and an urban cycle in which humans serve as amplifying hosts with known vectors being biting midges (Culicoides paraensis) and possibly mosquitoes (e.g., Culex quinquefasciatus).

BOTTOM LINE

Clinicians and public health jurisdictions should be aware of the occurrence of Oropouche virus disease in US travelers and request testing for suspected cases. Travelers should prevent insect bites when traveling, and pregnant persons should consider deferring travel to areas experiencing outbreaks of Oropouche virus disease.

Absence of Cerebrospinal Fluid Pleocytosis in Encephalitis

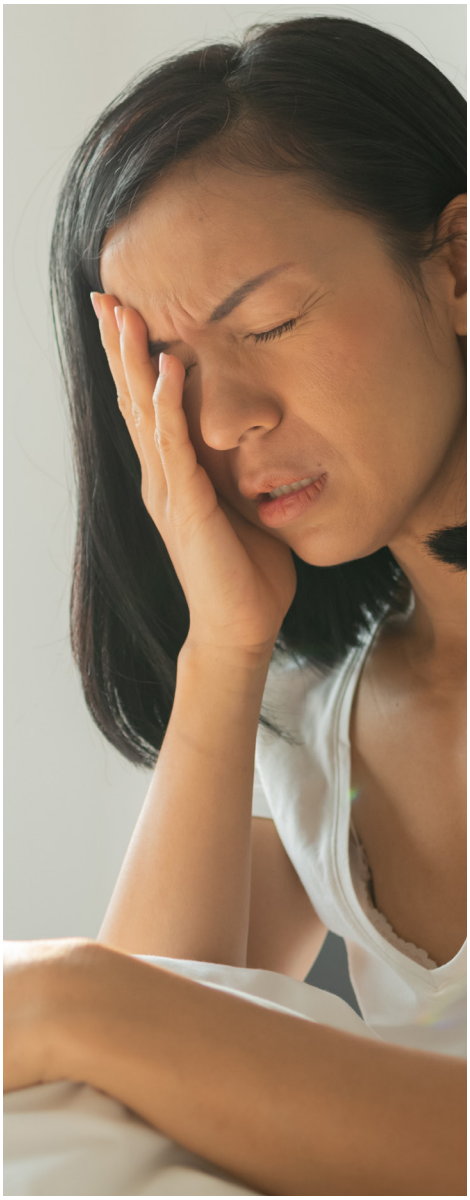
Clinical Infectious Diseases published online August 3, 2024
DOI: 10.1093/cid/ciae391

This retrospective study compared initial CSF profiles in 597 adult patients with all-cause encephalitis. Of the 597 patients, 446 (74.7%) had CSF pleocytosis while 151 (25.3%) did not. CSF pleocytosis occurred more commonly in infectious cases (200/446, 44.8%), along with 59 (13.2%) autoimmune cases, comprised chiefly of anti–N-methylD-aspartate receptor (anti-NMDAR) encephalitis (37/59, 62.7%). [NMDAR=autoimmune encephalitis after acute demyelinating encephalitis] Notably, the group without pleocytosis comprised similar proportions of infectious (47/151, 31.1%) and autoimmune (38/151, 25.92%; P > .05) encephalitis. Among those with infectious encephalitis, 47/247 (19%) had an absence of pleocytosis, including 18/76 (23.7%) with HSV-1 encephalitis. The absence of pleocytosis was associated with a decreased rate of acyclovir administration (47.7% in patients without pleocytosis vs 71.1% in patients with pleocytosis; P < .001). Despite pleocytosis being associated with some measures of clinical severity at admission such as a Full Outline of UnResponsiveness (FOUR) score ≤14, it was not associated with mortality or prolonged hospitalization.

Dr. Septimus's Annotations

Cerebrospinal fluid pleocytosis is an established biomarker for inflammation in the central nervous system. This study, which included almost 600 adult patients hospitalized at 2 geographically diverse urban settings between 2005 and 2023 reported an absence of pleocytosis in 19% of encephalitis cases due to an infectious cause, 39%

of autoimmune encephalitis cases, and 26% of encephalitis cases without an identified cause. Most strikingly, almost a quarter of patients with herpes simplex virus 1 (HSV-1) encephalitis (HSE) had normocellular CSF. Encephalitis denotes inflammation of brain parenchyma, whereas meningitis is inflammation of the meninges. In many cases, there is an overlap syndrome (meningoencephalitis). However, when infection is restricted to the brain, the CSF characteristics may not reflect encephalitis. International encephalitis consortium includes CSF pleocytosis as only 1 of 6 minor criteria, underscoring that this is an imperfect surrogate marker for pure brain infection. [Clin Infect Dis 2013; 57:1114–28] The absence of pleocytosis has been well documented for encephalitis due to West Nile virus [Neurology 2006; 66:361–5], tickborne encephalitis virus [BMC Infect Dis 2014; 14:614], and, increasingly, HSV-1 disease. The HSV PCR result can be negative early, so in patients with a clinical syndrome consistent with HSV encephalitis the lumbar puncture should be repeated at 48 hours — and acyclovir continued pending results — even if the first CSF examination did not show pleocytosis or HSV. False negative HSV PCR tests are well documented in HSE, particularly early in infection. [Clin Infect Dis 2002; 34:1154–7] The current study also reported 20% of HSE patients had a normal MRI scan, rising to 40% among the subset without pleocytosis.



Cost for inappropriate test utilization has led some health systems to restrict the use of multiplex molecular assays for meningoencephalitis to patients with CSF pleocytosis. [J Clin Microbiol 2020; 58: e00311-20] The current study challenges the wisdom of this approach to diagnostic stewardship. Limiting testing to only those with ≥5 WBC/mm3, almost a quarter of HSE cases would have gone undiagnosed.

Based on the current study they recommend HSV-1 PCR be performed on CSF regardless of WBC count, repeating testing on a second CSF sample collected 3–7 days later (if initial PCR negative) should be considered despite an initial negative test, even when classic findings like fever or temporal lobe focality are absent in patients with clinical encephalitis. A final point, namely 42% of cases presenting with encephalitis remain undiagnosed despite current diagnostic testing.

BOTTOM LINE

This study provides an important reminder that CSF pleocytosis is not required for diagnosing pure encephalitis. CSF pleocytosis has been an important criterion for encephalitis diagnosis, yet 25.3% of patients with all-cause encephalitis and 23.7% of those with HSV-1 encephalitis did not have pleocytosis on initial LP.

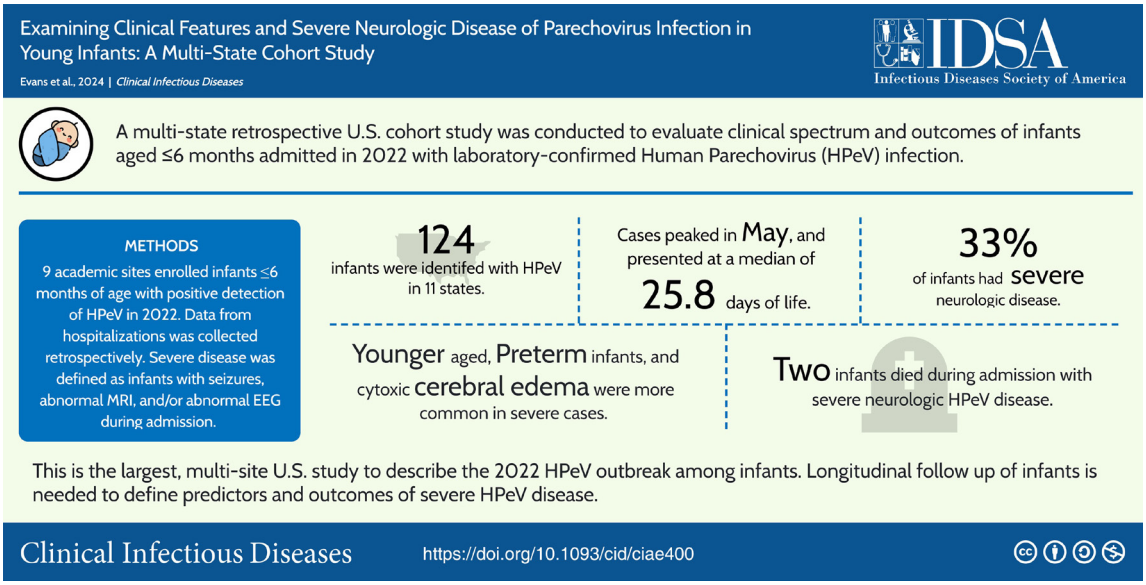
17

Examining Clinical Features and Severe Neurologic Disease of Parechovirus Infection in Young Infants: A Multi-State Cohort Study.

Clinical Infectious Disease published online August 2, 2024
DOI: 10.1093/cid/ciae400

This was a multi-state retrospective cohort study conducted to evaluate hospitalizations and outcomes of infants aged ~6 months admitted in 2022 with laboratory-confirmed human parechovirus (HPeV) infection. Infants with severe disease defined as having clinical seizures, or abnormalities on MRI or EEG during admission. Infants with severe vs non-severe disease were compared using descriptive statistics.

124 U.S. infants were identified with HPeV in 11 states. Cases of HPeV peaked in May and presented at a median of 25.8 days of life (0-194 d) with fever, fussiness, and poor feeding. Bacterial and other viral co-infections were rare. Four (3% of 157) blood cultures from three subjects were deemed true infections (MSSA, S epidermidis, and Enterococcus faecalis). Five (4% of 117) urine cultures were positive and treated as true infections (identifying E coli, Enterobacter aerogenes, K pneumoniae, and MRSA in 5 unique subjects) 33 (27%) of infants had severe neurologic disease, were more likely to present at an earlier age (13.9 vs 30 days of life, p<0,01) have preterm gestation (12% vs. 1%, p = 0.02) and present with respiratory symptoms (26% vs. 8%, p = 0.01) or apnea (41% vs. 1%, p <0.001). Subcortical white matter cytoxic cerebral edema was common in severe cases. Findings on MRI demonstrated supratentorial white matter involvement with branching T2 hyperintensity and T1 hyperintensity. The early and frequent involvement of the frontal lobe white matter, external capsule and sparing of the basal ganglia can help differentiate HPeV meningoencephalitis from damage due to neonatal hypoxic ischemic injury 19. The sparing of the posterior fossa, brainstem and the basal ganglia helps to distinguish infection from amino acidurias, uremia and mitochondrial diseases20,21Two infants with HPeV died during admission with severe neurologic HPeV disease; no infant with mild HPeV disease died.. CSF analysis was conducted on 97% of infants, with a total of 120 out of 124 infants undergoing lumbar puncture. Most infants had a normal CSF white blood cell count for age, with only 9 (7.2%) with a count >25 cells/mm3 (median CSF WBC 150 cells/mm3, IQR 57-238 cells/mm3). Of these, most had evidence of a traumatic lumbar puncture. Only one infant had severe hypoglycorrhachia (CSF glucose <40 mg/dL). Eighteen infants (14.5%) had elevated CSF protein (>100 mg/dL).



Dr. Septimus's Annotations

Human parechovirus (HPeV) can cause severe disease, including meningoencephalitis, in neonates and young infants . HPeV has previously been noted to circulate in a biannual pattern in the U.S., except during 2020- 2021 due to Covid-related home isolation and masking measures6 . After the mitigating measures used to prevent Covid-19 were discontinued, a large wave of HPeV was seen throughout the US as part of a respiratory viral infection resurgence in children. This comprehensive, multi-state study provides insights into the clinical presentation and management of severe HPeV infections in infants and highlights the specific patterns of HPeV brain injury found on brain MRI.

BOTTOM LINE

A resurgence of HPeV marked by a high incidence of severe neurologic disease in infants was seen in 2022 in the US. Continual surveillance of HPeV and research on long-term outcomes is needed, particularly in young infants who may be at risk for severe disease.

18

RSV Vaccine Effectiveness Against Hospitalization Among US Adults 60 Years and Older.

JAMA published online September 4, 2024.
DOI: 10.1001/jama.2024.15775

Investigators at the CDC and Vanderbilt University conducted interviews and examined the electronic medical records of 2,978 adults aged 60 and older hospitalized with an acute respiratory illness at 24 centers in 19 states participating in a surveillance network from October 2023 to March 2024.

Overall, 367 patients tested positive for RSV, while the 2,611 control patients tested negative for RSV, Covid-19, and influenza. The median age was 72 years, the median Charlson Comorbidity Index score was 5, and 24.2% were immunocompromised. The study investigators noted that the prelicensure trials weren't powered to evaluate effectiveness against RSV hospitalization, didn't include immunocompromised patients, and underrepresented other populations at high risk for severe illness, including those aged 75 and older.

In total, 2.5% of RSV patients and 9.8% of controls were vaccinated against RSV a median of 84 days before respiratory illness onset. Of the 288 RSV patients with known viral subtype, 72.9% had RSV B. VE against RSV-associated hospitalization was 75% (95% confidence interval [CI], 50% to 87%) and didn't differ when estimated with inverse probability of vaccination weighting (79% [95% CI, 56% to 90%]) or among adults 60 to 74 years old (75% [95% CI, 31% to 91%]) or 75 and older (76% [95% CI, 40% to 91%]).

Relative to unvaccinated patients, vaccinated participants tended to be older (median age, 75 vs 72 years) and White (82.6% vs 60.7%). They were also more likely to be immunocompromised (31.7% vs 23.4%), to have had outpatient visits in the past year (95.9% vs 90.1%), and to live in communities with a lower Social Vulnerability Index score (median, 0.37 vs 0.58). VE against RSV-associated hospitalization was 75% (95% confidence interval [CI], 50% to 87%) and didn't differ when estimated with inverse probability of vaccination weighting (79% [95% CI, 56% to 90%]) or among adults 60 to 74 years old (75% [95% CI, 31% to 91%]) or 75 and older (76% [95% CI, 40% to 91%]).

Dr. Septimus's *Annotations*

In June 2023 the CDC recommended that all adults aged 60 and older receive the RSV vaccine based on the high vaccine effectiveness (VE) against RSV lower respiratory disease seen in prelicensure randomized trials. In a June 2024 update, the CDC recommended the vaccine for all adults aged 75 years and older and those 60 to 74 at high risk for severe RSV. An estimated 60,000 to 160,000 RSV hospital admissions occur each year among US adults aged 65 years and older.

BOTTOM LINE

The findings expand on prelicensure trial results by providing real-world evidence of vaccine protection against RSV hospitalization and demonstrating protection in a population at high risk for severe RSV, including adults aged 75 years and older and those who are immunocompromised.

19

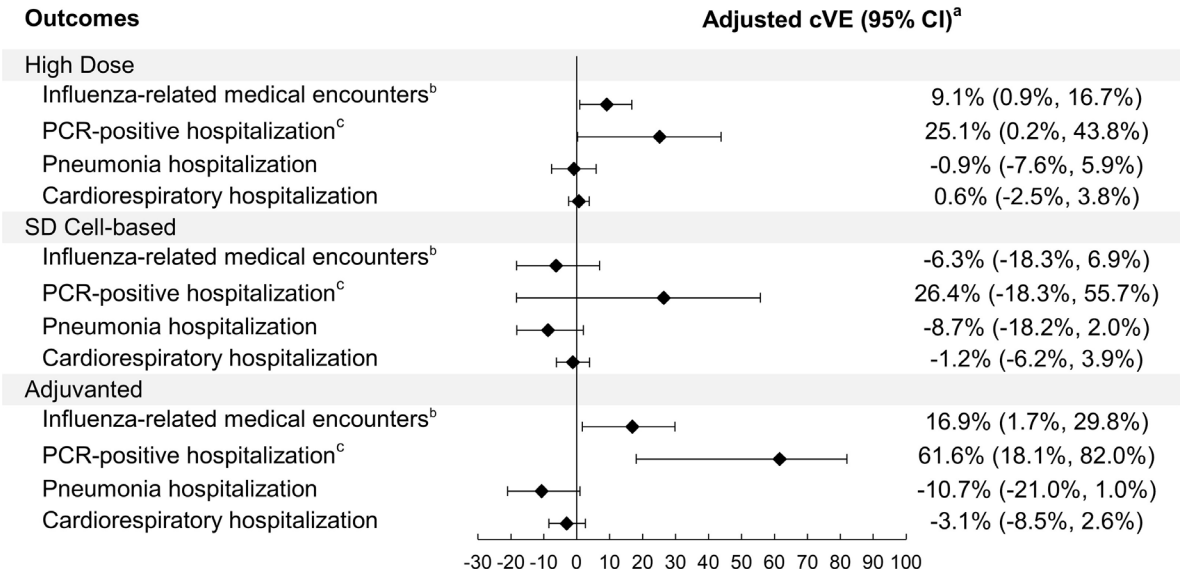
Comparative Effectiveness of Licensed Influenza Vaccines in Preventing Influenza-related Medical Encounters and Hospitalizations in the 2022–2023 Influenza Season Among Adults ≥65 Years of Age.

Clinical Infectious Diseases published online August 21, 2024
DOI: 10.1093/cid/ciae375

The investigators conducted a retrospective cohort study to evaluate comparative vaccine effectiveness (cVE) of high-dose (HD), adjuvanted, and standard-dose (SD) cell-based influenza vaccines, relative to the SD egg-based vaccine. They included adults aged ≥65 years who received an influenza vaccine between 1 August 2022 and 31 December 2022, with follow-up up to 20 May 2023. Primary outcomes were: (1) influenza-related medical encounters and (2) polymerase chain reaction (PCR)-confirmed influenza-related hospitalization.

The study population (n = 495 119) was 54.9% female, 46.3% non-Hispanic White, with a median age of 73 years (interquartile range [IQR] 69–79). Characteristics of all groups were well balanced after IPTW (inverse probability of treatment weighting). Adjusted cVEs against influenza-related medical encounters in the HD, adjuvanted, and SD cell-based vaccine groups were 9.1% (95% confidence interval [CI]: .9, 16.7), 16.9% (95% CI: 1.7, 29.8), and −6.3 (95% CI: −18.3, 6.9), respectively. Adjusted cVEs against PCR confirmed hospitalization in the HD, adjuvanted, and SD cell-based groups were 25.1% (95% CI: .2, 43.8), 61.6% (95% CI: 18.1, 82.0), and 26.4% (95% CI: −18.3, 55.7), respectively. Compared to the other groups, the adjuvanted group also tended to have higher comorbidity burden (mean 2.26 Charlson comorbidity score), was more likely to receive the vaccine earlier (84.2% during August-September 2022) and was more likely to receive a coronavirus disease 2019 (Covid-19) vaccine (90.4%) in the year prior.

Forest plot: adjusted cVE for high-dose, adjuvanted, and SD cell-based influenza vaccines, compared to SD egg-based vaccine.



Dr. Septimus's Annotations

The preferentially recommended HD and adjuvanted influenza vaccines conferred additional protection for older individuals against influenza-related medical encounters and PCR-confirmed influenza hospitalizations; cVEs were insignificant for SD cell-based vaccine, which is not preferentially recommended in this age group. cVEs remained

insignificant and low for all vaccine types against pneumonia hospitalization and cardiorespiratory hospitalization. Data from immunogenicity studies comparing trivalent SD egg-based vaccine to trivalent HD vaccine in US adults aged ≥65 years demonstrated higher antibody levels with HD vaccine. In a randomized efficacy trial, trivalent HD vaccine induced significantly higher antibody responses and was 24% more efficacious in preventing laboratory-confirmed influenza than SD egg-based vaccine.[N Engl J Med 2014; 371:635–45] In a study in Medicare beneficiaries (≥65 years) during the 2019–2020 season reported a cVE of 13.3% (95% CI: 7.4, 18.9) for recombinant vaccine, 8.2% (95% CI: 4.2, 12.0) for adjuvanted vaccine, and 6.8% (95% CI: 3.3, 10.1) for HD vaccine against influenza-related hospital encounters, compared to SD egg-based vaccine. [Clin Infect Dis 2021; 73: e4251–9] These findings were similar to the current study- HD and adjuvanted vaccines conferred better protection against influenza-related outcomes. Although the comparison and reference groups were well balanced after IPTW, there could be unmeasured confounding (e.g. masking, distancing, handwashing, congregate settings).

BOTTOM LINE

The investigators demonstrated that the preferentially recommended high dose and adjuvanted influenza vaccines conferred additional protection for older adults against influenza-related medical encounters and PCR-confirmed influenza hospitalizations, compared to standard dose egg-based vaccines.

20

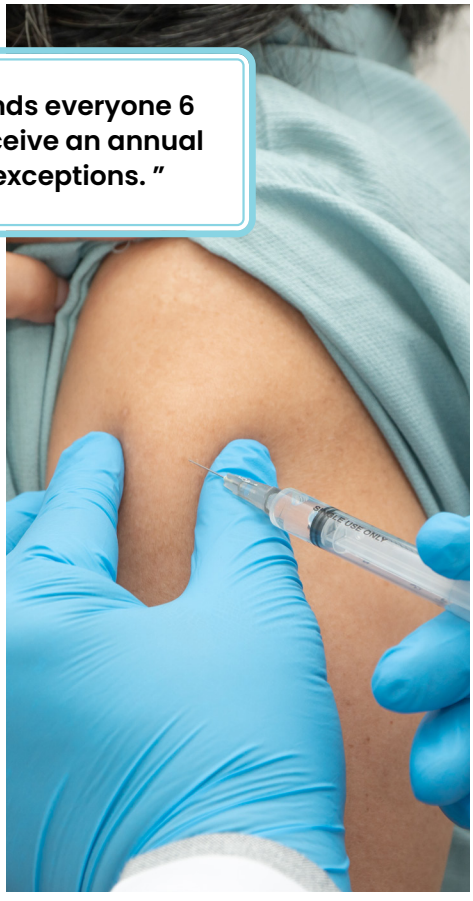
Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024–25 Influenza Season

MMWR Vol. 73 No. 5 published August 29, 2024

The CDC has updated annual flu shot recommendations for the 2024-25 season, noting two key changes: A return to trivalent vaccines, and two vaccines now considered acceptable options for adult solid organ transplant recipients.

The CDC recommends everyone 6 months and older receive an annual flu shot, with rare exceptions.

"The CDC recommends everyone 6 months and older receive an annual flu shot, with rare exceptions. "



Here are two primary updates the CDC shared in its recommendations for this flu season:

1. This year's vaccines do not include an Influenza B/Yamagata component, marking a return to trivalent vaccines after more than a decade of quadrivalent formulations. There have been no confirmed detections of infections caused by B/Yamagata lineage viruses globally since March 2020, suggesting it may have been eliminated. All vaccines available this year will target three strains, including two influenza A viruses — H1N1 and H3N2 and an influenza B/victoria virus.
2. Vaccination recommendations for adult solid organ transplant recipients aged 18 to 64 who are on immunosuppressive medications now include the use of HD-IIV3(high dose) and aIIV3 vaccines(adjuvant). These vaccines are now considered acceptable options without preference over other similar vaccines. They are designed to boost the immune response of older adults.

ACIP still recommends that adults aged ≥65 years preferentially receive any one of the following higher dose or adjuvanted influenza vaccines: trivalent high-dose inactivated influenza vaccine (HD-IIV3), trivalent recombinant influenza vaccine (RIV3), or trivalent adjuvanted inactivated influenza vaccine (aIIV3).

Dr. Septimus's Annotations

During each of the six influenza seasons from 2010–11 through 2015–16, influenza vaccination prevented an estimated 1.6–6.7 million illnesses, 790,000–3.1 million outpatient medical visits, 39,000–87,000 hospitalizations, and 3,000–10,000 respiratory and circulatory deaths each season in the US. [Influenza Other Respir Viruses 2018; 12:132–7] During the severe 2017–18 season, higher rates of outpatient visits and hospitalizations compared with recent seasons, vaccination prevented an estimated 7.1 million illnesses, 3.7 million medical visits, 109,000 hospitalizations, and 8,000 deaths, despite an overall estimated vaccine effectiveness of 38% (62% against influenza A[H1N1]pdm09 viruses, 22% against influenza A[H3N2] viruses, and 50% against influenza B viruses).[Clin Infect Dis 2019;69:1845–53]

BOTTOM LINE

Vaccination is still the best protection against influenza. Individuals should be vaccinated ideally in October.

21

Timing of influenza antiviral therapy and risk of death in adults hospitalized with influenza-associated pneumonia, flusurv-NET, 2012-2019.

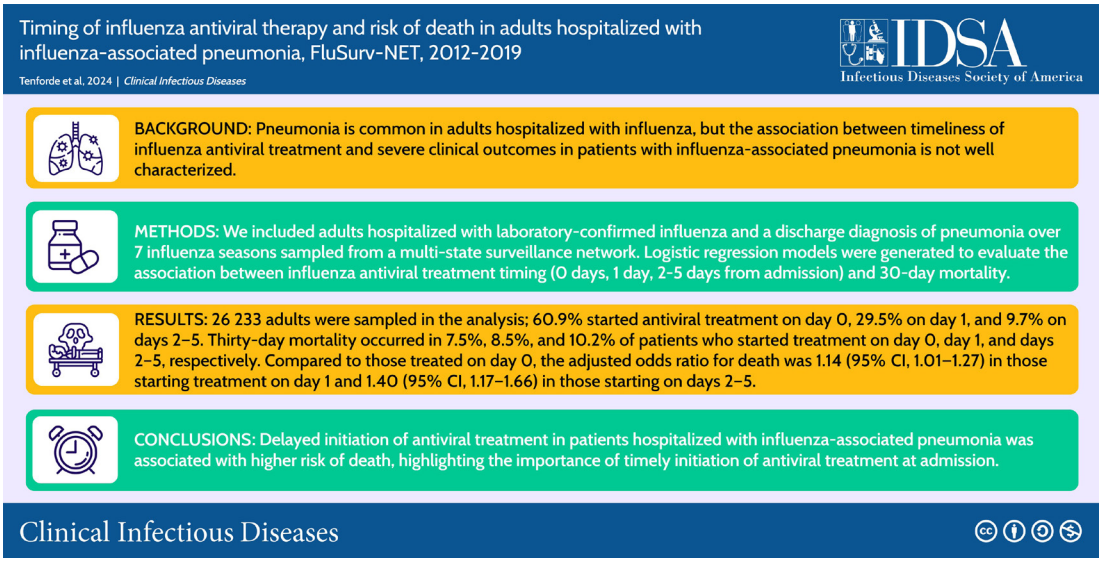
Clinical Infectious Diseases published online August 22, 2024
DOI: 10.1093/cid/ciae427

The association between timeliness of influenza antiviral treatment and severe clinical outcomes in patients with influenza-associated pneumonia is not well characterized. The investigators included adults aged ≥18 years hospitalized with laboratory-confirmed influenza and a discharge diagnosis of pneumonia over 7 influenza seasons (2012-2019) sampled from a multi-state population-based surveillance network. They evaluated 3 treatment groups based on timing of influenza antiviral initiation relative to admission date (day 0, day 1, days 2-5). Baseline characteristics and clinical outcomes were compared across groups using unweighted counts and weighted percentages accounting for the complex survey design. Logistic regression models were generated to evaluate the association between delayed treatment and 30-day all-cause mortality.

26,233 adults were included in the analysis. The median age was 71 years and most (92.2%) had ≥1 non-immunocompromising condition and over half of patients had 3 or more categories of underlying medical conditions. Overall, 60.9% started antiviral treatment on day 0, 29.5% on day 1, and 9.7% on days 2-5 (median 2 days). Baseline characteristics were similar across groups. More than one-third of patients had a diagnosis of pneumonia by ICD-9 or ICD-10 discharge code or discharge summary. Thirty-day mortality occurred in 7.5%, 8.5%, and 10.2% of patients who started treatment on day 0, day 1, and days 2-5, respectively. Compared to those treated on day 0, adjusted OR for death was 1.14 (95%CI: 1.01-1.27) in those starting treatment on day 1 and 1.40 (95%CI: 1.17-1.66) in those starting on days 2-5.

Dr. Septimus's Annotations

Infectious Disease Society of America (IDSA) Guidelines recommend that adults hospitalized with suspected or confirmed influenza start treatment with influenza antiviral therapy as soon as possible. [Clin Infect Dis 2019; 68(6): e1-e47] While most US adults hospitalized with laboratory-



confirmed influenza receive antiviral treatment, timing of initiation vary based on when a patient seeks care after illness onset, availability of influenza test results, and clinical suspicion for influenza. [Open Forum Infect Dis 2023; 10(1): ofac681] Pneumonia is the most common acute diagnosis among patients hospitalized with influenza [JAMA Netw Open 2020; 3(3): e201323], but there are limited data from clinical trials on the efficacy of antiviral treatment of influenza-associated pneumonia and trials have not been sufficiently powered to evaluate critical outcomes such as death.[Clinical Infectious Diseases 2018; 67: 736-42] Observational studies of adults hospitalized with influenza, with or without pneumonia, suggest that early antiviral treatment initiation improves several clinical outcomes, such as decreased length of stay or decreased likelihood of ICU admission.[Lancet Respir Med 2014; 2(5): 395-404; Clin Infect Dis 2019; 69: 1896-902] The current study found a strong association between timing of influenza antiviral therapy and odds of all-cause death. Compared to patients treated on the day of admission, those who started antiviral treatment 2-5 days after admission had 40% higher odds of dying within 30 days of hospital admission. These findings support the recommendation by the CDC and the IDSA guidelines to initiate antiviral treatment with oseltamivir as soon as possible to maximize benefit for patients being hospitalized with suspected or confirmed influenza, ideally with treatment started in the outpatient setting or emergency department. This analysis did not account for duration of illness prior to hospitalization as information on illness onset was captured through medical chart abstraction and subject to imperfect recall and/or inconsistent documentation in medical charts. They did not evaluate clinical outcomes stratified by influenza A virus subtype, which may be associated with differences in influenza severity or antiviral treatment effectiveness.

BOTTOM LINE

Delayed initiation of antiviral treatment in patients hospitalized with influenza-associated pneumonia was associated with higher risk of death, highlighting the importance of timely initiation of antiviral treatment at admission.

22 Antivirals for post-exposure prophylaxis of influenza: a systematic review and network meta-analysis.

The Lancet published online August 24, 2024, Volume 404, Issue 10454

The investigators systematically searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Global Health, Epistemonikos, and ClinicalTrials.gov for randomized controlled trials published up to Sept 20, 2023, that evaluated the efficacy and safety of antivirals compared with another antiviral or placebo or standard care for prevention of influenza. Pairs of reviewers independently screened studies, extracted data, and assessed the risk of bias. They performed network meta-analyses with frequentist random effects model and assessed the certainty of evidence using the GRADE (Grading of Recommendations Assessment,

Development and Evaluation) approach. The outcomes of interest were symptomatic or asymptomatic infection, admission to hospital, all-cause mortality, adverse events related to antivirals, and serious adverse events.

Of 11,845 records identified by their search, 33 trials of six antivirals (zanamivir, oseltamivir, laninamivir, baloxavir, amantadine, and rimantadine) that enrolled 19,096 individuals (mean age 6·75–81·15 years) were included in this systematic review and network meta-analysis. Most of the studies were rated as having a low risk of bias. Zanamivir, oseltamivir, laninamivir, and baloxavir probably achieve important reductions in symptomatic influenza in individuals at high risk of severe disease (zanamivir: risk ratio 0·35, 95% CI 0·25–0·50; oseltamivir: 0·40, 0·26–0·62; laninamivir: 0·43, 0·30–0·63; baloxavir: 0·43, 0·23–0·79; moderate certainty) when given promptly (e.g., within 48 h) after exposure to seasonal influenza. These antivirals probably did not achieve important reductions in symptomatic influenza in individuals at low risk of severe disease when given promptly after exposure to seasonal influenza (moderate certainty). Zanamivir, oseltamivir, laninamivir, and baloxavir might achieve important reductions in symptomatic zoonotic influenza in individuals exposed to novel influenza A viruses associated with severe disease in infected humans when given promptly after exposure (low certainty). Oseltamivir, laninamivir, baloxavir, and amantadine probably decrease the risk of all influenza (symptomatic and asymptomatic infection; moderate certainty). Zanamivir, oseltamivir, laninamivir, and baloxavir probably have little or no effect on prevention of asymptomatic influenza virus infection or all-cause mortality (high or moderate certainty). Oseltamivir probably has little or no effect on admission to hospital (moderate certainty). All six antivirals do not significantly increase the incidence of drug-related adverse events or serious adverse events, although the certainty of evidence varies.

This analysis discovered that "post-exposure prophylaxis (PEP) with a range of antivirals probably decreased risk of severe disease in high-risk individuals after exposure to seasonal influenza viruses and may have also reduced the risk of zoonotic infection after exposure to novel influenza A viruses. The Infectious Diseases Society of America (IDSA) only recommends PEP "for severely immunocompromised asymptomatic adults and children ages 3 months or older who are at very high risk of developing complications from influenza and for whom influenza vaccination is contraindicated or unavailable after household exposure to influenza. [Clin Infect Dis 2019; 68(6): e1-e47]

BOTTOM LINE

Post-exposure prophylaxis with zanamivir, oseltamivir, laninamivir, or baloxavir probably decreases the risk of symptomatic seasonal influenza in individuals at high risk for severe disease after exposure to seasonal influenza viruses.

23

Antivirals for treatment of severe influenza: a systematic review and network meta-analysis of randomised controlled trials.

The Lancet published online August 24, 2024, Volume 404, Issue 10454

The investigators systematically searched MEDLINE, Embase, Cochrane Central Register of Controlled Trials, Cumulative Index to Nursing and Allied Health Literature, Global Health, Epistemonikos, and ClinicalTrials.gov for randomized controlled trials published up to September 2023, that enrolled hospitalized patients with suspected or laboratory confirmed influenza and compared direct-acting influenza antivirals against placebo, standard care, or another antiviral. Pairs of coauthors independently extracted data on study characteristics, patient characteristics, antiviral characteristics, and outcomes, with discrepancies resolved by discussion or by a third coauthor. Key outcomes of interest were time to alleviation of symptoms, duration of hospitalization, admission to ICU, progression to invasive mechanical ventilation, duration of mechanical ventilation, mortality, hospital discharge destination, emergence of antiviral resistance, adverse events, adverse events related to treatments, and serious adverse events. They conducted frequentist network meta-analyses to summarize the evidence and evaluated

the certainty of evidence using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach.

Of 11,878 records identified by their search, eight trials with 1424 participants (mean age 36–60 years for trials that reported mean or median age; 43–78% male patients) were included in this systematic review, of which six were included in the network meta-analysis. The effects of oseltamivir, peramivir, or zanamivir on mortality compared with placebo or standard care without placebo for seasonal and zoonotic influenza were of very low certainty. Compared with placebo or standard care, they found low certainty evidence that duration of hospitalization for seasonal influenza was reduced with oseltamivir (mean difference −1·63 days, 95% CI −2·81 to −0·45) and peramivir (−1·73 days, −3·33 to −0·13). Compared with standard care, there was little or no difference in time to alleviation of symptoms with oseltamivir (0·34 days, −0·86 to 1·54; low certainty evidence) or peramivir (−0·05 days, −0·69 to 0·59; low certainty evidence). There were no differences in adverse events or serious adverse events with oseltamivir, peramivir, and zanamivir (very low certainty evidence). Uncertainty remains about the effects of antivirals on other outcomes for patients with severe influenza. Due to the small number of eligible trials, they could not test for publication bias.

Dr. Septimus's Annotations

This systematic review and network meta-analysis to evaluate the efficacy and safety of different antivirals for treatment of severe influenza. They focused on evidence for approved antivirals from randomized controlled trials, assessed the certainty of evidence using the GRADE approach, and presented absolute effects for outcomes. Due to limited data from the small number of randomized controlled trials of antivirals for treatment of patients with severe seasonal influenza and a lack of randomized controlled trials for treatment of severe zoonotic influenza, the current level of evidence for antiviral treatment of severe seasonal or zoonotic influenza is of low certainty However, this study provides evidence that oseltamivir and peramivir, relative to placebo or standard care, might reduce the duration of hospitalization for patients with severe seasonal influenza. These findings primarily highlight the uncertainty regarding effects of antivirals for treatment of patients with severe influenza but do provide some justification for their use.

BOTTOM LINE

Treatment of severe influenza with oseltamivir (Tamiflu) and peramivir (Rapivab) appeared to reduce the length of hospital stays, but overall, the effects of antivirals on key clinical outcomes – such as mortality – remained questionable. More clinical trials of antivirals are needed to inform the clinical benefit, safety, and effects on antiviral resistance in patients with severe influenza.

24

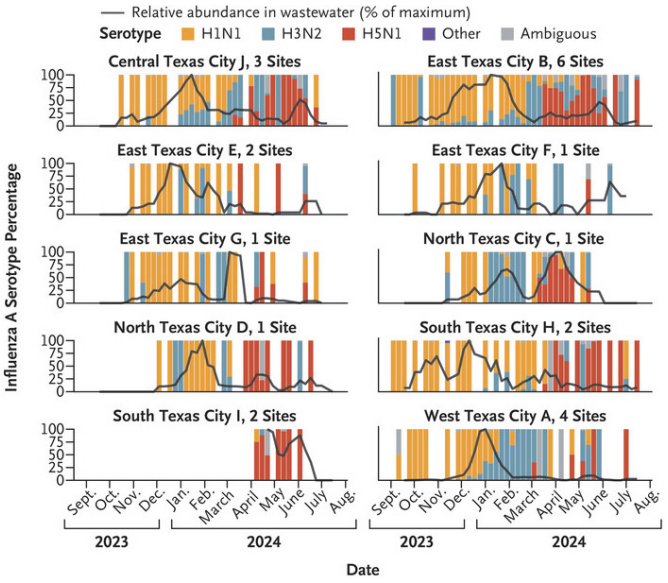
Sequencing-Based Detection of Avian Influenza A(H5N1) Virus in Wastewater in Ten Cities.

The New England Journal of Medicine published online September 11, 2024
DOI: 10.1056/NEJMc2405937

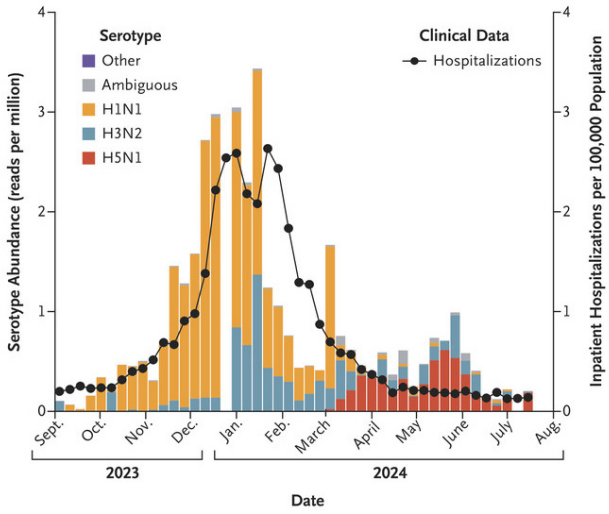
Since May 2022, the Texas Epidemic Public Health Institute has been using hybrid-capture sequencing to test weekly wastewater samples in mostly urban areas in cities throughout Texas and has detected over 400 human and animal viruses to date, several of which (e.g., SARS-CoV-2, influenza virus, and mpox virus) correlate with clinical case data.5 Seasonal influenza virus serotypes H3N2 and H1N1 are routinely detected in Texas Epidemic Public Health Institute wastewater samples, and levels in wastewater have corresponded to clinical caseloads from May 2022 through the beginning of March 2024, but serotype H5N1 had not been detected.

However, in samples from March 4 through July 15, 2024, H5N1 was detected in 10 of 10 cities, 22 of 23 sites, and 100 of 399 samples, however, the presence of H5N1 sequences identified did not correlated with influenza-related hospitalizations, which in fact declined in Texas during the spring of 2024. All sequencing reads best match H5N1 genomes from birds and mammals.

Relative Abundance of Influenza A in Wastewater Samples



Abundance of Influenza A Virus in Texas Wastewater and Hospitalizations



Dr. Septimus's Annotations

On March 25, 2024, H5N1 2.3.4.4b was detected in dairy cattle herds in Texas concomitantly with herds in Michigan and Kansas. The first case in humans in 2024 was detected shortly in Texas on March 28, 2024 in a person with exposure to symptomatic cattle. As of July 28, 2024, H5N1 had been detected in 14 human infections in 3 US states (4 cattle-associated and 10 poultry-associated), 171 dairy herds across 13 states, and 94 poultry flocks across 26 states. [https://www.aphis.usda.gov/livestock-poultry-disease/avian/ avian influenza/hpai-detections/hpai-confirmed-cases-livestock] The widespread detection of influenza A(H5N1) virus in wastewater from 10 US cities is worrisome. Wastewater monitoring should be considered as a sentinel surveillance tool that augments our detection of evolutionary adaptations of concern.

BOTTOM LINE

Although the detection of influenza A(H5N1) virus in wastewater from 10 US cities is troubling the risk to human health without direct contact with infected cattle remains low.

25

Effectiveness of pneumococcal vaccination in adults with common immune-mediated inflammatory diseases in the UK: a case–control study

The Lancet Rheumatology Volume 6, Issue 9, September 2024
DOI: 10.1016/ S2665-9913(24)00128-0

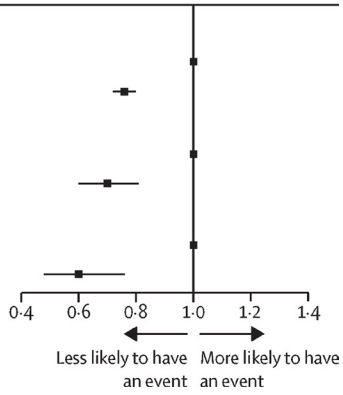
Investigators in the UK probed a large clinical database for rates of respiratory infection among 90,000 people with rheumatoid arthritis, inflammatory bowel disease (IBD), spondyloarthritis, or systemic lupus erythematosus between 1997

and 2019 who were receiving long-term non–glucocorticoid-based immunosuppression (methotrexate, azathioprine, 5-mercaptopurine, sulfasalazine, 5-aminosalicylate, mycophenolate, leflunomide, ciclosporin, tacrolimus, or sirolimus). Outcomes were hospitalization due to pneumonia, death due to pneumonia, or primary care consultation for lower respiratory tract infection requiring antibiotics. We defined hospital admission for pneumonia using hospital discharge diagnoses, death due to pneumonia using death certification data, and lower respiratory tract infection as present when primary-care consultation and antibiotic prescription occurred on the same date. They used multivariable, unconditional, logistical regression and constructed three models to examine the association between pneumococcal vaccination as an exposure and each of the three outcomes.

Three nested case-control analyses showed that receipt of pneumococcal vaccination was associated with a 20% to 40% lower risk for three separate outcomes: respiratory infection requiring outpatient antibiotics; hospitalization for pneumonia, and death from pneumonia. These results were unaffected by sex, age, and presence of comorbidities. Neither specific immunosuppressant regimen nor specific rheumatologic diagnosis generally affected results, although reduction in risk for fatal pneumonia was considerably less apparent in vaccinated individuals with IBD than those with other diagnoses.

Effectiveness of pneumococcal vaccination in patients with immune-mediated inflammatory diseases

	Cases (n [%])	Controls (n [%])	Model 1 (OR [95% CI])	Model 2 (OR [95% CI])	Model 3 (OR [95% CI])
Primary-care consultation for lower respiratory tract infection requiring antibiotics					
Unvaccinated	5299 (50·2)	22 035 (50·1)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	5250 (49·8)	21 946 (49·9)	0·94 (0·90–0·99)	0·73 (0·70–0·77)	0·76 (0·72–0·80)
Hospitalisation due to pneumonia					
Unvaccinated	639 (33·9)	4182 (39·9)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	1245 (66·1)	6294 (60·1)	1·09 (0·98–1·23)	0·71 (0·62–0·82)	0·70 (0·60–0·81)
Death due to pneumonia					
Unvaccinated	200 (25·6)	1168 (25·7)	1 (ref)	1 (ref)	1 (ref)
Vaccinated	581 (74·4)	3372 (74·3)	0·86 (0·72–1·03)	0·64 (0·51–0·81)	0·60 (0·48–0·76)



Dr. Septimus's Annotations

These data come with the usual concern that residual confounding might have affected results. Still, the results give clinicians a reasonably clear-cut message to transmit to patients about benefits of vaccination. Because the 23-valent unconjugated vaccine (Pneumovax) still is the only vaccine recommended for adults in the UK, I assume that patterns in the UK also apply to the range of vaccine products now available in the US including the newly approved conjugated 21 valent vaccine. In addition, due to the limited specific microbial causes of pneumonia, they were unable to ascertain vaccine efficacy on pneumococcal pneumonia.

BOTTOM LINE

Pneumococcal vaccination prevents morbidity and mortality associated with pneumonia in people with common immune-mediated inflammatory diseases. These findings should be used to promote pneumococcal vaccination in this at-risk patient group.

26 The CDC says COVID-19 is endemic

U.S. health officials now say Covid-19 is an endemic disease. That means it's here to stay – circulating regularly like the flu. Even though that changes how public health officials think about managing the virus, they say it doesn't mean being less cautious or vigilant during surges, like the current one this summer. Covid-19 still poses significant risks for older individuals and those with underlying conditions — and anyone who gets Covid-19 is at risk of developing long Covid.

27 Uptake of COVID-19 vaccines and association with hospitalisation due to COVID-19 in pregnancy: Retrospective cohort study

Vaccine published online August 13, 2024
DOI: 10.1016/j.vaccine.2024.126214

This is a retrospective cohort study including all pregnancies ending between 18 June 2021 and 22 August 2022, among adult women registered in a London general practice. Statistical analyses were mixed effects multiple logistic regression models. They conducted a nested case-control analysis to quantify the relationship between vaccine uptake by end of pregnancy and hospitalization for COVID-19 during pregnancy.

This study included 47,046 pregnancies among 39,213 women. In 26,724 (57%) pregnancies, women had at least one dose of vaccine by the end of pregnancy. Uptake was lowest in pregnant women aged 18–24 (33%; reference group), Black women compared with White (37%; OR 0.55, 95% CI: 0.51 to 0.60), and women in lower economic areas (50%; reference group). Women with chronic conditions were more likely to receive the vaccine than women without (Asthma OR 1.21, 95% CI: 1.13 to 1.29). The most common of the five risk factors studied was asthma (9.9%), and chronic heart disease was the least common (0.68%).

Patterns were similar for the second dose. Women admitted to hospital were much less likely to be vaccinated (22%) than those not admitted (57%, OR 0.22, 95% CI: 0.15 to 0.31). Pregnant women were at higher risk of Covid-19 complications such as hospitalization, intensive care unit admission, invasive mechanical ventilation, and death. They were also at increased risk of pregnancy-related complications such as preeclampsia and emergency cesarean delivery, and their infants are at higher risk of being preterm or stillborn. A conditional logistic regression model suggested a five-fold decrease in the chances of Covid-19 hospitalization in vaccinated women, compared with their unvaccinated peers (odds ratio [OR], 0.22).

Dr. Septimus's Annotations

Pregnant women are at increased risk of severe adverse outcomes from Covid-19. In this study women who received the Covid -19 vaccine were less likely to be hospitalized for Covid-19 during pregnancy. However, Covid-19 vaccine uptake among pregnant women was suboptimal. These results were similar to another report in the UK and a US report which found uptake lowest among Black pregnant and highest among Asian pregnant women. [Am J Obstet Gynecol 2022;226(2); MMWR 2021;70(24):895–9]

The investigators did not include admissions where the primary diagnosis related to obstetric complications, which may have resulted in results being conservative, due to such complications resulting from Covid-19 infection. While they accounted for a range of demographic and health-related risk factors in their analysis, there were no available data on other factors that may impact uptake, for instance, political opinions, family medical history, and more general behavior and lifestyle factors.

BOTTOM LINE

Covid-19 vaccine uptake among pregnant women was suboptimal, particularly in younger women, Black women, and women in lower socioeconomic area. Interventions should focus on increasing uptake in these groups to improve health outcomes and reduce health inequalities. Future vaccination programs should engage pregnant women earlier and communicate with them clearly.

28

Characterizing Long COVID in Children and Adolescents

JAMA published online August 21, 2024
DOI: 10.1001/jama.2024.12747

The objective of this study was to identify the most common prolonged symptoms experienced by children (aged 6 to 17 years) after SARS-CoV-2 infection, how these symptoms differ by age (school-age [6-11 years] vs adolescents [12-17 years]), how they cluster into distinct phenotypes, and what symptoms in combination could be used as an empirically derived index to assist researchers to study the likely presence of postacute sequelae of SARS-CoV-2 infection (PASC).

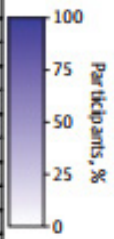
This study was a multicenter longitudinal observational cohort study with participants recruited from more than 60 US health care and community settings between March 2022 and December 2023, including school-age children and adolescents with and without SARS-CoV-2. PASC and 89 prolonged symptoms across 9 symptom domains were measured.

A total of 898 school-age children (751 with previous SARS-CoV-2 infection [referred to as infected] and 147 without [referred to as uninfected]; mean age, 8.6 years; 49% female; 11% were Black or African American, 34% were Hispanic, Latino, or Spanish, and 60% were White) and 4469 adolescents (3109 infected and 1360 uninfected; mean age, 14.8 years; 48% female; 13% were Black or African American, 21% were Hispanic, Latino, or Spanish, and 73% were White) were included. The median time between first infection and symptom survey was 506 days for school-age children and 556 days for adolescents. In models adjusted for sex and race and ethnicity, 14 symptoms in both school-age children and adolescents were more common in those with SARS-CoV-2 infection history compared with those without infection history, with 4 additional symptoms in school-age children only and 3 in adolescents only. These symptoms affected almost every organ system. Combinations of symptoms most associated with infection history were identified to form a PASC research index for each age group; these indices correlated with poorer overall health and quality of life. The index emphasizes neurocognitive, pain, and gastrointestinal symptoms in school-age children but change or loss in smell or taste, pain, and fatigue/malaise–related symptoms in adolescents. Clustering analyses identified 4 PASC symptom phenotypes in school-age children and 3 in adolescents.

"This study identified separate [postacute sequelae of SARS-CoV-2 infection] research indices for school-age children and adolescents based on symptoms most likely to differentiate between those with and without an infection history."

Figure 4. Frequency of Prolonged Symptoms Among School-Age Children and Adolescents Stratified by Infection and PASC Status

School-age children (6-11 y)			Symptom	Adolescents (12-17 y)		
5	4	49	Daytime tiredness, sleepiness, or low energy	80	7	8
8	6	47	Feeling anxious	47	12	12
4	3	57	Headache	55	6	6
3	2	51	Body, muscle, or joint pain	60	3	4
3	3	44	Trouble sleeping	47	6	5
1	0	44	Trouble with memory or focusing	47	3	4
3	2	35	Feeling depressed	38	9	10
2	1	38	Tired after walking	42	0	1
5	5	34	Stuffy nose	27	4	4
1	1	43	Stomach pain	27	2	3
1	0	31	Back or neck pain	41	2	2
1	1	26	Feeling lightheaded or dizzy	39	2	2
1	0	34	Nausea or vomiting	30	2	2
2	1	28	Poor appetite	30	2	3
2	3	30	Itchy skin or skin rash	15	3	4
4	5	23	Dry cough	20	2	2
1	1	17	Change or loss in smell or taste	36	0	0
3	2	24	Dark circles	19	2	2
1	1	22	Fear of crowds or enclosed spaces	22	3	4
2	2	26	Fear about specific things	17	2	2
1	2	21	Palpitation during exercise	24	1	1
3	4	20	Chapped lips	18	3	3
0	1	19	Muscle weakness	27	1	1
0	1	19	Palpitation at rest	24	1	1
0	1	18	Light hurts eyes	24	1	1
4	2	18	Constipation	17	2	2
1	1	23	Refusing to go to school	16	2	2
0	1	20	Trouble with walking, running, or stairs	20	0	1
5	3	20	Refusing to follow rules	9	2	3
3	2	23	Nightmares	11	1	2
1	1	14	Hot cold spells	24	0	1
2	1	17	Increased thirst	18	1	1
1	0	18	Chest pain	17	1	1
1	2	15	Sore throat	17	1	1
5	4	18	Hyperactive	6	1	2
1	1	15	Watery or red eyes	15	1	1
1	1	15	Diarrhea	13	1	1
3	2	14	Gained weight	10	1	2
1	2	13	Blurry vision	13	1	2
1	1	12	Excess sweat	15	1	1
1	1	15	Fear of other children/adults	11	1	2
2	2	12	Increased appetite	10	1	2
1	1	11	Tingling	15	0	1
2	2	11	Wet cough	10	1	1
			Panic attack	22	2	3
0	1	16	Repeating thoughts after traumatic event	8	0	1
1	0	11	Trouble breathing	13	0	0
1	0	9	Tremors	13	0	1
1	1	7	Lost weight	12	1	1
1	2	10	Barking cough	8	0	1
1	0	10	Ringing ears	10	0	1
0	0	11	Problems with talking	8	0	0
0	1	9	Fever	9	0	0
1	0	9	Breathing pain	9	0	0
2	1	7	Serious behavior problems	4	1	1
0	0	9	Problem with teeth/gums	4	0	1
0	1	6	Dry mouth	6	0	0
0	0	5	Hair problems	8	0	1
0	1	8	Frequent urination	4	0	0
0	0	5	Problems with swallowing	6	0	0
1	0	6	Hallucinations	5	0	0
1	1	3	Dry eyes	6	1	1
0	0	9	Hearing changed	2	0	0
0	0	7	Skin color change	4	1	0
1	0	6	Rocking back and forth	3	0	0
0	0	3	Loss of voice	5	0	1
0	0	4	Color change in fingers/toes	4	0	0
0	0	3	Nail problems	3	0	0
0	0	5	Urination pain	2	0	0
1	0	1	Lost height	3	0	0
0	0	3	Unable to move body	2	0	0
Uninfected (n = 147)	Infected, PASC-unspecified (n = 599)	Infected, PASC-probable (n = 152)		Infected, PASC-probable (n = 445)	Infected, PASC-unspecified (n = 2664)	Uninfected (n = 1369)



Dr. Septimus's Annotations

In this large-scale study, children with probable PASC experienced prolonged symptoms in almost every organ system, with the majority having multisystem involvement. Most prior pediatric studies have relied on electronic health records. The current study had the advantage of comprehensively assessing reported symptoms across every organ system, examining them in combination, and comparing them directly to an uninfected seronegative control group. This study identified separate PASC research indices for school-age children and adolescents based on symptoms most likely to differentiate between those with and without an infection history. Higher indices were correlated with worse functional outcomes. The strongest differentiators of infection history in adults (RECOVER-Adult study) and adolescents overlapped considerably. [JAMA.2023;329:1934-1946] There was less overlap between adults and school-age children. These findings underscore the need for separate assessments in different age groups. Four symptom clusters in school-age children and 3 in adolescents were identified. In both age groups, there was a single cluster with high symptom burden (as in adults) and a cluster predominated by fatigue and pain symptoms. Other clusters differed by age. School-age children had a cluster with neuropsychological and sleep impacts and another with gastrointestinal predominance. Adolescents had a cluster that was primarily loss of taste and smell, similar to that found in adults, which was not noted in the school-age clusters.

The research index is not intended for use in clinical practice to diagnose PASC. Rather it can be considered with clinical judgement because children may have PASC without meeting the index threshold. There are also many prolonged symptoms that differ between those previously infected and uninfected with SARS-CoV-2 that are not part of this index. It remains unknown how many children with other diagnoses would have similar prolonged symptoms. Since the symptoms were caregiver-reported, recall bias is possible. Future analyses will examine PASC symptoms in early childhood (birth to 5 years) and the effects of SARS-CoV-2 on worsening underlying conditions and increasing new conditions, such as diabetes, autoimmune diseases, neurocognitive disorders, and postinfectious syndromes.

BOTTOM LINE

This study developed research indices for characterizing pediatric PASC (postacute sequelae of SARS-CoV-2 infection). Symptom patterns were similar but distinguishable between school-age children and adolescents, highlighting the importance of characterizing PASC separately in different age groups.

Long-Term Prognosis of Patients With Myocarditis Attributed to COVID-19 mRNA Vaccination, SARS-CoV-2 Infection, or Conventional Etiologies

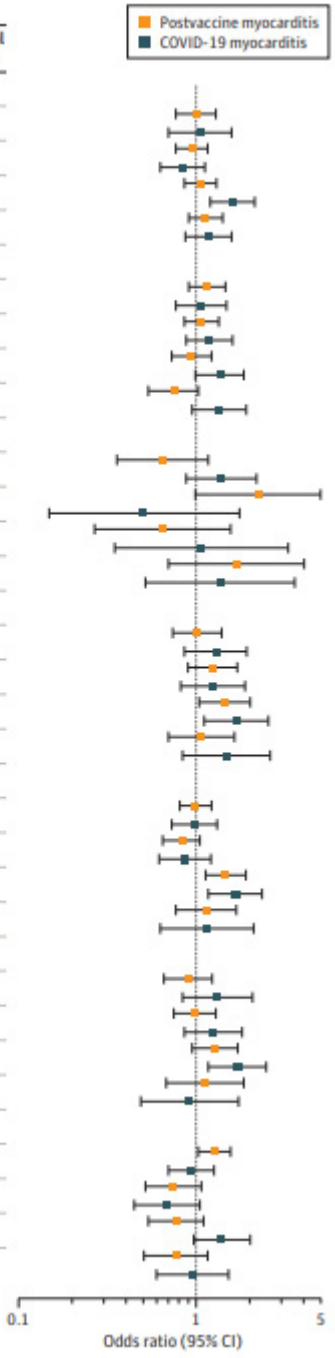
JAMA published online August 26, 2024
DOI: 10.1001/jama.2024.16380

The purpose of this study was to examine the cardiovascular complications of post–Covid-19 mRNA vaccination myocarditis and other types of myocarditis during an 18-month follow-up. Investigators mined data from the French National Health Data System on 4,635 residents aged 12 to 49 years hospitalized for myocarditis from December 2020 to June 2022.

In total, 4635 individuals were hospitalized for myocarditis: 558 with postvaccine myocarditis, 298 with post–Covid-19 myocarditis, and 3779 with conventional myocarditis. Patients with postvaccine myocarditis were younger than those with post–Covid-19 and conventional myocarditis (mean [SD] age of 25.9 [8.6], 31.0 [10.9], and 28.3 [9.4] years,

respectively) and were more frequently men (84%, 67%, and 79%). Patients with postvaccine myocarditis had a lower standardized incidence of the composite clinical outcome than those with conventional myocarditis (32/558 vs 497/3779 events; weighted hazard ratio, 0.55 [95% CI, 0.36-0.86]), whereas individuals with post–Covid-19 myocarditis had similar results (36/298 events; weighted hazard ratio, 1.04 [95% CI, 0.70-1.52]). Two thirds of cases of postvaccine myocarditis occurred after a second Covid-19 vaccine dose. The standardized frequency of medical procedures and drugs prescribed in patients with postvaccine myocarditis or post–Covid-19 myocarditis followed a similar trend in the 18 months following hospital discharge to that of patients with conventional myocarditis. After standardization, postvaccination myocarditis was tied to lower rates of hospital readmission for myopericarditis, other cardiovascular problems, all-cause death, and a composite of all three outcomes than those with the conventional type, while those with post-infection myocarditis had comparable outcomes as patients with conventional myocarditis (wHR, 1.04).

Outcome	No. of events (%)		
	Postvaccine myocarditis	COVID-19 myocarditis	Conventional myocarditis
Cardiac medical imaging procedure			
<3 mo	460 (82)	253 (86)	3148 (84)
3 to <6 mo	288 (51)	133 (45)	1970 (52)
6 to <12 mo	258 (46)	161 (54)	1696 (45)
12 to <18 mo	170 (30)	99 (34)	1112 (30)
Cardiovascular treatment[a]			
<3 mo	431 (77)	217 (73)	2867 (76)
3 to <6 mo	192 (34)	122 (41)	1330 (35)
6 to <12 mo	120 (21)	98 (33)	986 (26)
12 to <18 mo	67 (12)	71 (24)	664 (18)
Coronary network examination[b]			
<3 mo	22 (3.9)	30 (10)	284 (8)
3 to <6 mo	9 (1.6)	3 (1.0)	45 (1)
6 to <12 mo	6 (1.0)	5 (1.7)	63 (2)
12 to <18 mo	8 (1.4)	5 (1.7)	44 (1)
Holter monitor			
<3 mo	67 (12)	47 (15)	498 (13)
3 to <6 mo	71 (12)	36 (12)	440 (12)
6 to <12 mo	67 (12)	38 (12)	339 (9)
12 to <18 mo	30 (5.3)	20 (6.8)	198 (5)
Magnetic resonance imaging			
<3 mo	237 (42)	113 (38)	1569 (42)
3 to <6 mo	114 (20)	58 (19)	833 (22)
6 to <12 mo	112 (20)	60 (20)	590 (16)
12 to <18 mo	38 (6.8)	18 (6.1)	246 (7)
Stress test			
<3 mo	57 (10)	33 (11)	375 (10)
3 to <6 mo	92 (16)	50 (17)	623 (17)
6 to <12 mo	85 (15)	54 (18)	485 (13)
12 to <18 mo	30 (5.3)	15 (5.1)	204 (5)
Troponin assay			
<3 mo	223 (39)	111 (37)	1435 (38)
3 to <6 mo	51 (9.1)	34 (11)	530 (14)
6 to <12 mo	57 (10)	55 (18)	570 (15)
12 to <18 mo	42 (7.5)	31 (10)	387 (10)



Dr. Septimus's Annotations

Several studies have reported reassuring results for the prognosis of patients with postvaccine myocarditis at discharge, with a low likelihood of cardiac dysfunction at presentation and generally rapid recovery. [Vaccine. 2023;42: 522-528] In this cohort study including 4635 patients hospitalized for myocarditis in France during the first 1.5 years after Covid-19 vaccination, the 558 individuals with postvaccine myocarditis had less severe cardiovascular events than those with myocarditis of other origins at 18 months of follow-up. However, affected patients, mainly healthy young men, may require medical management up to several months after hospital discharge. In a previous study the risk of myocarditis and vaccination was found, reaching a 30-fold–higher risk for the second dose of the RNA1273 vaccine and an 8-fold–higher risk for the second dose of the BNT162b2 vaccine. [Nat Commun. 2022; 13:3633] The current study only focused on cases of myocarditis requiring hospitalization. Patients who did not seek medical attention for an acute illness, such as simple chest pain, were not included.

BOTTOM LINE

Patients with post–Covid-19 mRNA vaccination myocarditis, contrary to those with post–Covid-19 myocarditis, showed a lower frequency of cardiovascular complications than those with conventional myocarditis at 18 months.

30

A systematic review of nirmatrelvir/ritonavir and molnupiravir for the treatment of COVID-19

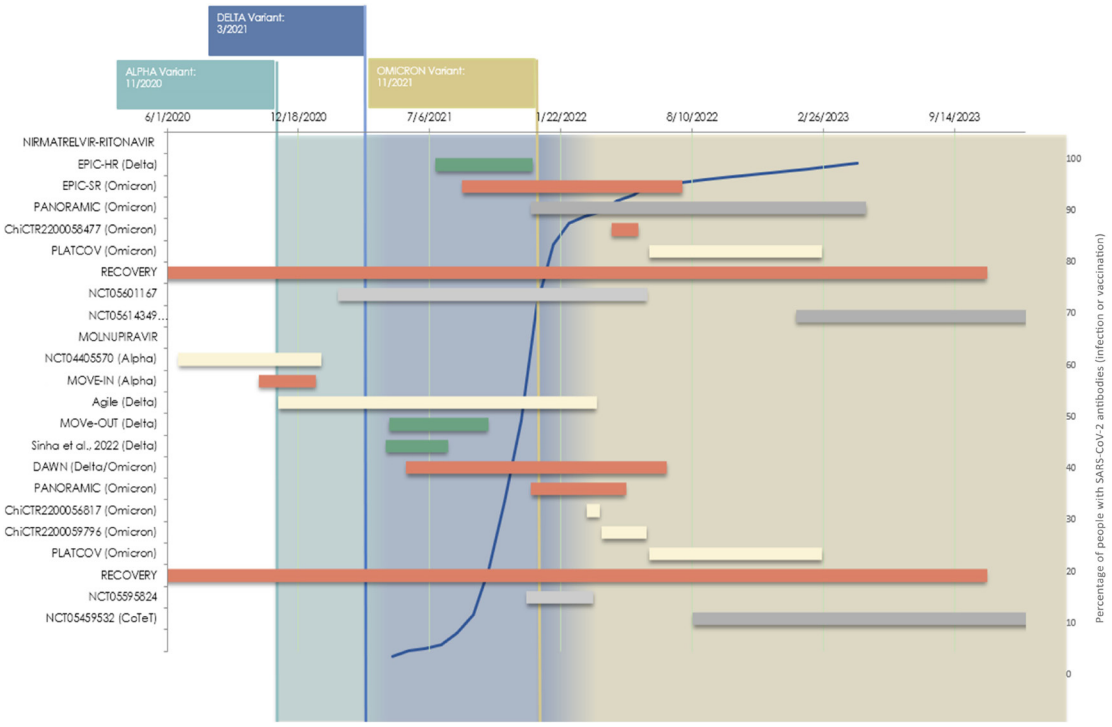
Open Forum Infectious Diseases publishes online September 7, 2024; article provided by Josh Septimus
DOI: 10.1093/ofid/ofae497

The evolving strains of the SARS-CoV-2 virus and increasing population immunity, either through vaccination or infection, may result in changing effectiveness of the approved drugs. The investigators sought to systematically search all randomized trial data on FDA approved oral drug therapies in treating mild to moderate Covid-19, including nirmatrelvir/ritonavir and molnupiravir. They searched PubMed using the search terms (nirmatrelvir and ritonavir) OR paxlovid AND covid. They searched Embase using the terms, ((‘nirmatrelvir’/exp OR nirmatrelvir) AND (‘ritonavir’/exp OR ritonavir) OR ‘paxlovid’/exp OR paxlovid) AND (‘covid’/exp OR covid). They also searched Web of Science using the search terms (NIRMATRELVIR and RITONAVIR) OR paxlovid AND covid AND randomized). In addition they searched Embase using (‘molnupiravir’/exp OR molnupiravir) AND (‘covid’/exp OR covid). They searched Web of Science using molnupiravir AND covid AND randomized. They included all interventional studies testing nirmatrelvir/ritonavir or molnupiravir for Covid-19, including long Covid-19, and the study population could include either hospitalized or non-hospitalized patients.

Of the 23 studies found, 11 tested nirmatrelvir/ritonavir, 10 tested molnupiravir, and two tested both agents. The pooled estimate in reducing deaths and hospitalization for molnupiravir was 0.62 (95% CI: 0.15 to 2.53), and the pooled estimate for nirmatrelvir/ritonavir was 0.33 (95%CI: 0.03 to 3.35). The one nirmatrelvir/ritonavir trial that reported significant improvements tested people who were predominantly infected with earlier Covid-19 variants, whereas the two null trials were tested in people infected with more recent variants. The two positive molnupiravir trials included participants primarily with the delta variant, whereas the null trials were tested later, against more recent variants.

Dr. Septimus's Annotations

Based on randomized data showing reduced hospitalization/death, nirmatrelvir/ritonavir was given emergency Use Authorization (EUA) on December 22,



Timeline of trials testing nirmatrelvir/ritonavir and/or molnupiravir in patients with coronavirus disease 2019.

Red indicates negative results for hospitalization and death; green indicates positive results for hospitalization and death; yellow indicates softer outcomes (e.g., viral clearance) and gray indicates no published results.

2021 (fully approved on May 25, 2023), and molnupiravir was given EUA on December 23, 2021. The early approvals were based on trials that excluded participants who were vaccinated (EPIC-HR), had not been previously infected with the SARS-CoV-2 virus (EPIC-HR), and/or were tested during earlier strains of the SARS-Co-V2 virus (e.g., delta) that are no longer circulating (EPIC-HR and EPIC-SR).[N Engl J Med. 2024;390:1186-1195; N Engl J Med. 2022;386:1397-1408] Since then, other trials have been planned and initiated (e.g., RECOVERY).[medRxiv. May 24, 2024. doi:10.1101/2024.05.23.24307731] These trials have been tested against more contemporary strains of the virus and have included patients who have been vaccinated and/or acquired immunity through natural infection.

This review found 23 studies assessing nirmatrelvir/ritonavir and/or molnupiravir. Fourteen of these studies had published results, and two of these trials reported favorable results for nirmatrelvir/ritonavir and six trials reported favorable results for molnupiravir (4 based on viral clearance). Many of the primary outcomes were based on viral clearance, rather than patient centered outcomes, such as hospitalization or death, and most positive trials were tested against unvaccinated populations and/or earlier strains of SARS-CoV-2. A notable finding from this study is the lack of benefit for hospitalization and death in the pooled analysis. The only study that reported improvements in these outcomes was the EPIC-HR study, which is unique in that it included unvaccinated and non-hospitalized individuals. Similarly, the MOVE-OUT trial reported improvements in hospitalizations and deaths in unvaccinated, nonhospitalized patients. Positive trials were also the only trials in the pooled analysis to be tested when the Delta variant was the most common variant. 39% of studies evaluating these therapies have yet to report results. Results for the EPIC-SR study, that failed to find benefit with nirmatrelvir/ritonavir, are only available as press-release data. Furthermore, the Panoramic study tested both nirmatrelvir/ritonavir and molnupiravir but has only published data on molnupiravir.

Several large observational studies have been performed, assessing the association between receipt of nirmatrelvir or molnupiravir and Covid-19 during the omicron wave. Their findings indicate a reduction in deaths and hospitalization, suggesting possible efficacy. However, because of the observational nature of these studies, they may not have accounted for confounders, which is most evident by the almost immediate separation of the survival curves between those who received nirmatrelvir or molnupiravir and those who did not. [Ann Intern Med. 2023; 176:77-84] The randomized studies done during the omicron wave have failed to corroborate any hospitalization or mortality benefit. [medRxiv. May 24, 2024. doi:10.1101/2024.05.23.24307731; Lancet. 2023;401(10373):281-293] To be clear these treatments still may be beneficial to patients who are immunocompromised or significant risk factors for progression to severe disease.

This analysis focused on hospitalization and death outcomes, rather than virus clearance, so these results may not reflect the findings at-large or earlier studies. While they did include these studies in their analysis, they instead wanted to focus on outcomes they felt were most important to the health of patients and the population. Lastly, the incompleteness of the study publications may affect the generalizability of our findings.

BOTTOM LINE

The early data of nirmatrelvir/ritonavir and molnupiravir for the treatment of Covid-19 was encouraging, but trials during later strains of the SARS-CoV-2 virus have failed to show clinical benefit, in terms of hospitalization and death. Against the backdrop of the evolving strains of virus and increasing population immunity, current available treatments for Covid-19 may need to be re-evaluated. However, treatments still may be beneficial to patients who are immunocompromised or significant risk factors for progression to severe disease.

31 FDA approves season's updated mRNA and Novavax COVID-19 vaccines

The FDA announced its approval of the updated 2024-25 monovalent (single-strain) mRNA Covid-19 vaccines for people aged 12 and older and granted emergency use authorization for those aged 6 months to 11 years. The updated vaccines are called 2024-2025 Pfizer Covid-19 Vaccine and Moderna Covid-19 Vaccine (2024-2025 Formula) for those aged 6 months through 11 years and by Pfizer and by Moderna for those 12 years and older.

The vaccine, intended as a single dose for those 5 years and older previously vaccinated at least 2 months earlier, is adapted to the currently circulating Omicron KP.2 strain of the JN.1 SARS-CoV-2 lineage to better protect against hospitalization and death.

Unvaccinated children aged 6 months to 4 years are eligible to receive three doses of the Pfizer vaccine or two doses of the Moderna vaccine. Vaccinated children in this age-group can receive one or two doses of the Moderna or Pfizer vaccine, depending on the timing and number of previous doses received. People with weakened immune systems and those who haven't completed a three-dose series with previous formulations may be eligible for more than one dose

The FDA also announced that it has granted emergency use authorization for Novavax's updated Covid-19 vaccine. The Novavax vaccine targets JN.1, the parent of KP.2. Novavax's updated vaccine is authorized for people ages 12 and older.

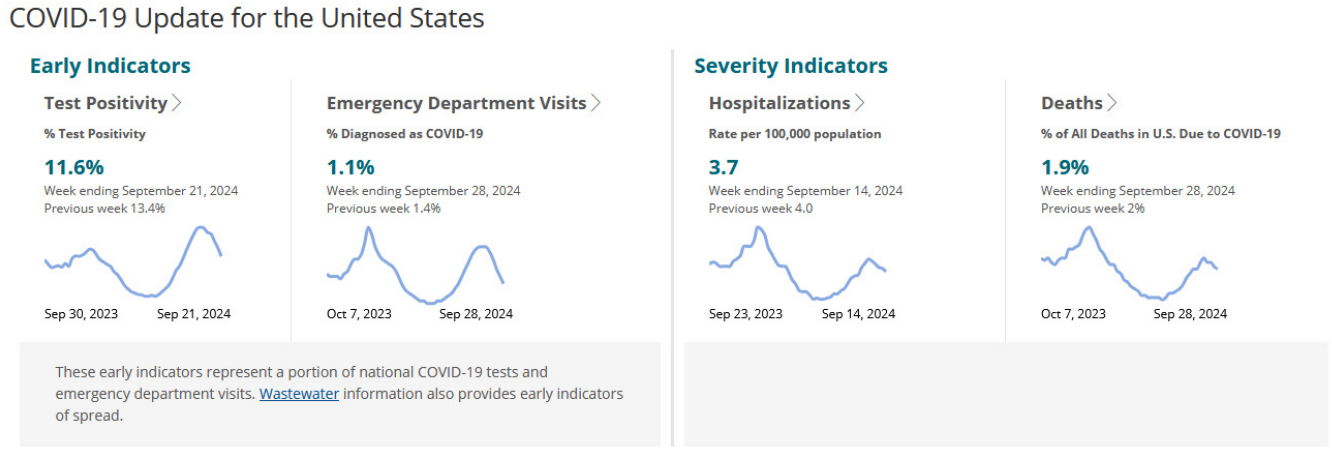
Unvaccinated children aged 6 months to 4 years are eligible to receive three doses of the Pfizer vaccine or two doses of the Moderna vaccine. Vaccinated children in this age-group can receive one or two doses of the Moderna or Pfizer vaccine, depending on the timing and number of previous doses received. People with weakened immune systems and those who haven't completed a three-dose series with previous formulations may be eligible for more than one dose.

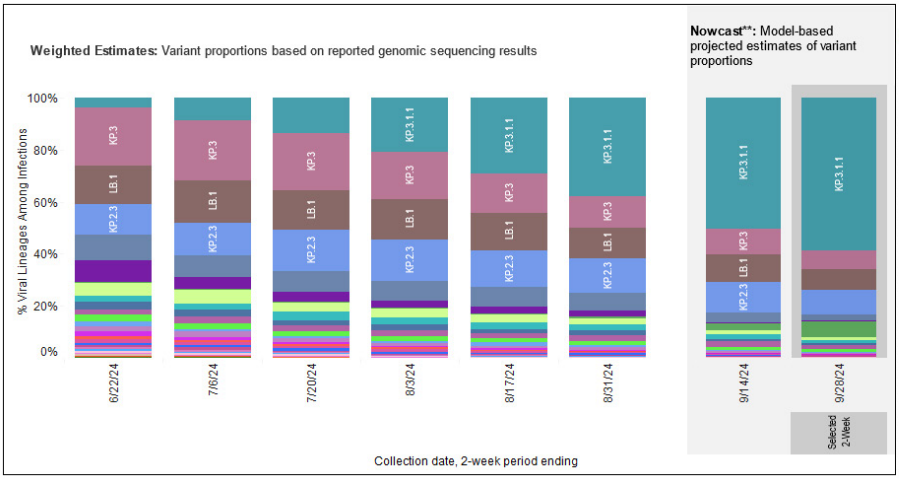
Dr. Septimus's *Annotations*

Vaccination continues to be the cornerstone of Covid-19 prevention. Given waning immunity of the population from previous exposure to the virus and/or from prior vaccination, I encourage those who are eligible to consider receiving an updated Covid-19 vaccine when available to provide better protection against currently circulating variants.

32 Covid-19 by the Numbers

Covid-19 infections remained elevated across the US, with wastewater SARS-CoV-2 detections highest in the West, where levels are trending upward again. However, other indicators showed declines, including test positivity, which was at 14.9% during the week ending September 7th, down 1.6% from the previous week. KP.3.1.1 variant now accounts for over 50% of cases.





USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	KP.3.1.1	58.7%	54.4-62.9%	
	KP.2.3	9.4%	8.3-10.7%	
	LB.1	7.9%	6.6-9.4%	
	KP.3	7.1%	6.1-8.4%	
	XEC	6.0%	2.4-13.2%	
	KP.2	2.5%	1.9-3.5%	
	LP.1	1.7%	1.1-2.5%	
	KP.1.1.3	1.4%	1.0-2.0%	
	KP.1.1	1.1%	0.8-1.5%	
	JN.1.18	1.1%	0.5-2.4%	
	KS.1	0.6%	0.4-0.9%	
	JN.1.16.1	0.6%	0.4-0.8%	
	KP.2.15	0.4%	0.2-0.7%	
	LF.3.1	0.3%	0.2-0.4%	
	JN.1	0.2%	0.1-0.3%	
	JN.1.11.1	0.1%	0.1-0.3%	
	KP.4.1	0.1%	0.0-0.2%	
	XDV.1	0.0%	0.0-0.1%	
	KW.1.1	0.0%	0.0-0.0%	
	JN.1.7	0.0%	0.0-0.0%	
	JN.1.16	0.0%	0.0-0.0%	
	KQ.1	0.0%	0.0-0.0%