Infectious Diseases Watch

August 2023

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General Infectious Diseases

Hospital Physicians' Stethoscopes: Bacterial Contamination After a Simple Cleaning Protocol Cureus 2023; 15(4): e37061

DOI: 10.7759/cureus.37061

The authors investigated bacterial contamination of stethoscopes at baseline, after simple cleaning, and after examining one patient. They surveyed 30 hospital providers on stethoscope cleaning practices and then measured bacterial contamination of stethoscope diaphragm surfaces before cleaning, after cleaning with alcohol-based hand sanitizer, and after use in examining one patient.

Only 20% of providers reported cleaning stethoscopes regularly. Before cleaning, 50% of stethoscopes were contaminated with bacteria, compared with 0% after cleaning ($p<0.001$) and 36.7% after examining one patient ($p=0.002$). Among providers who reported not cleaning stethoscopes regularly, 58% had bacterial-contaminated stethoscopes compared with 17% who did report cleaning regularly ($p=0.068$).

Comment: Clinician stethoscopes had a high probability of bacterial contamination at baseline and after examining one patient. I would recommend decontamination with alcohol swab immediately after each patient examination. I personally carry alcohol swabs with for the purpose of disinfecting my stethoscope after each patient contact. This study did not look at if a contaminated stethoscope actually transmitted pathogens to other patients.

Vaccine Effectiveness of JYNNEOS against Mpox Disease in the United States N Engl J Med 2023; 388:2434-43.

DOI: 10.1056/NEJMoa2215201

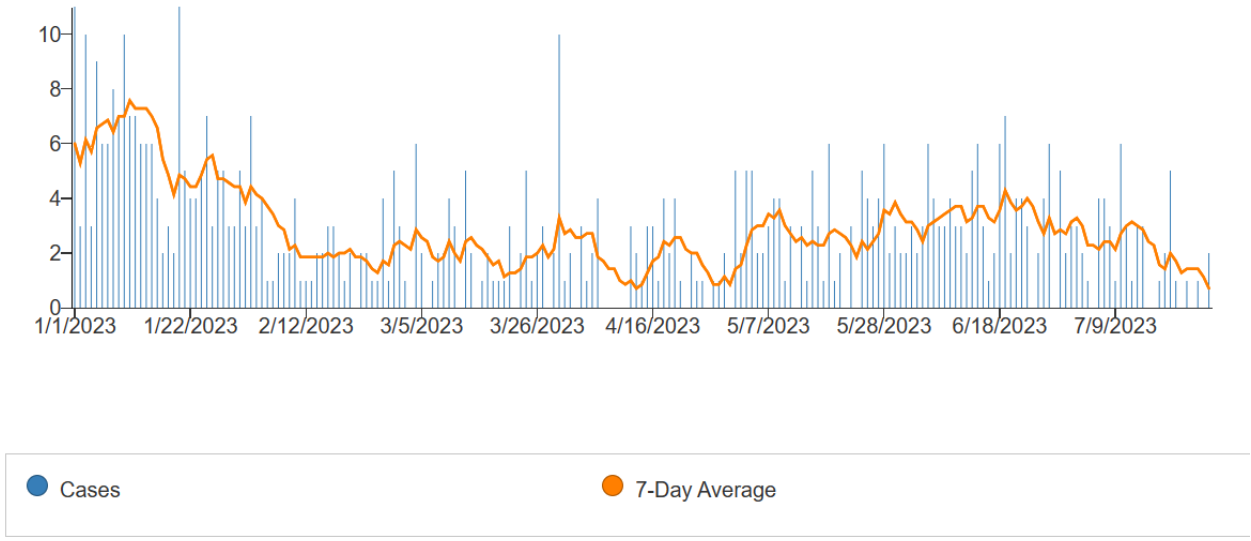
The investigators conducted a case–control study based on data from Cosmos, a nationwide Epic EHR database, to assess the effectiveness of JYNNEOS vaccination in preventing medically attended mpox disease among adults. Case patients had an mpox diagnosis code or positive orthopoxvirus or mpox virus laboratory result, and control patients had an incident diagnosis of HIV infection or a new or refill order for preexposure prophylaxis against HIV infection between August 15, 2022, and November 19, 2022. Odds ratios and 95% confidence

intervals were estimated from conditional logistic regression models, adjusted for confounders. They examined several covariates, including demographic characteristics, patient medical conditions (e.g., immunocompromising conditions, including HIV, identified on the basis of EHR documentation of ICD10th revision, diagnostic codes or prescriptions for immunosuppressive medications in the previous 6 months, characteristics of health care use (e.g., the number of in-person encounters during the year before the index event), and characteristics associated with the index event (e.g., hospitalization).

Overall, 89.2% of the patients identified as men, 9.1% as women, 1.0% as transgender women or men, and 0.7% as another gender identity. Case patients were younger than control patients, and more case patients were non-Hispanic Black or Hispanic. During the study period, more case patients than control patients had HIV and had a CD4 cell count of less than 200 in the previous 6 months (9.4% vs. 2.9%), but fewer case patients than control patients had a new HIV diagnosis (7.8% vs. 16.3%).

Among 2193 case patients and 8319 control patients, 25 case patients and 335 control patients received two doses (full vaccination), among whom the estimated adjusted vaccine effectiveness was 66.0% (95% confidence interval [CI], 47.4 to 78.1), and 146 case patients and 1000 control patients received one dose (partial vaccination), among whom the estimated adjusted vaccine effectiveness was 35.8% (95% CI, 22.1 to 47.1).

Comment: Mpox were less likely to have received either one or two doses of JYNNEOS vaccine than control patients, with two-dose series provided greater protection. These findings are consistent with other studies examining the effectiveness of JYNNEOS vaccine against mpox disease. This was an observational study, and therefore it does not provide definitive evidence of causality. Because information regarding sexual orientation and behavior are not consistently documented in the Cosmos database, the investigators had to rely on clinical encounter and diagnostic information to select control patients with characteristics that were consistent with characteristics outlined in the Mpox National Vaccine Strategy, which included patients receiving HIV PrEP or with a new HIV diagnosis. Sporadic cases of mpox. In the US over 30,000 cases have been reported. See below



WHO Warns of Dengue Risk

The WHO announced that cases of dengue fever could reach close to record highs this year, partly due to global warming benefiting mosquitoes that spread it. Dengue rates are rising globally, with reported cases since 2000 up eight-fold to 4.2 million in 2022.
In January, WHO warned that dengue is the world's fastest-spreading tropical disease and represents a "pandemic threat". About half of the world's population is now at risk according to the WHO.

Comment: Reported cases to WHO hit an all-time high in 2019 with 5.2 million cases in 129 countries. This year the world is on track for "4 million plus" cases, depending mostly on the Asian monsoon season. Already, close to 3 million cases have been reported in the Americas. There is concern about the southern spread to Bolivia, Paraguay and Peru. Argentina, which has faced one of its worst outbreaks of dengue in recent years, is sterilizing mosquitoes using radiation that alters their DNA before releasing them into the wild. A warmer climate is thought to help the mosquitoes multiply faster and enable the virus to multiply. In April 2023 ID Watch reviewed how climate change is spreading malaria. Like the *Anopheles* mosquito models predict that increased global temperatures will further expand the range of *Ae. aegypti* and Dengue risk.

Evaluating the PEN-FAST Clinical Decision-making Tool to Enhance Penicillin Allergy Delabeling JAMA Intern Med published online June 20, 2023.

doi:10.1001/jamainternmed.2023.1572

More than 90% of patients who are labeled as penicillin allergic have no true allergy. Avoiding penicillins in these patients often leads to adverse outcomes, including nosocomial and perioperative infections and more expensive and longer hospital stays. The previously described PEN-FAST decision tool is a simple and safe way to remove penicillin allergy labels without skin testing [*JAMA Intern Med* 2020; 180:745]. PEN-FAST scores allergy risk as follows:

- An allergy event ≤5 years ago (2 points)
- Anaphylaxis/angioedema or severe cutaneous adverse reaction (2 points)
- Treatment required for allergy episode (1 point)

To further validate PEN-FAST, investigators conducted a 2-year retrospective review of 120 patients from a US academic allergy clinic. All 88 patients with scores of 2 or lower were able to tolerate penicillin. Of the 32 patients with scores of 3 or higher, 2 patients had positive skin tests, and 2 had negative skin tests but positive oral challenges.

Comment: A PEN-FAST score of ≤2 had a negative predictive value of 100%! This should reassure physicians that most penicillin allergy patients can be delabeled safely by giving patients with PEN-FAST score of ≤2 a single dose of amoxicillin and observe for 1-2 hours. Select allergy to piperacillin has been reported but rare.

A Statewide Quality Initiative to Reduce Unnecessary Antibiotic Treatment of Asymptomatic Bacteriuria JAMA Intern Med published online July 10, 2023

doi:10.1001/jamainternmed.2023.2749

Evidence clearly shows that antibiotics are unnecessary for most patients with asymptomatic bacteriuria (ASB), but many patients get treated anyway, particularly if they are older or have indwelling catheters. Positive urine cultures often occur in the absence of true infection and are a major reason for inappropriate antibiotics which in turn leads to adverse events and acceleration of antimicrobial resistance.

The investigators conducted a quality improvement initiative across 46 hospitals in the state of Michigan from 2017 to 2020 to address the problem of inappropriate antibiotic use for ASB. They prospectively collected data on the prevalence of ASB at each hospital, shared data for benchmarking, shared best practices in antimicrobial and diagnostic stewardship, and, in 2018, selected treatment of ASB as a pay-for-performance metric. Hospitals then made individual decisions on how to best improve their practice. A total of 14 572 patients with a positive urine culture were included and 28.4% (n = 4134) of these patients had ASB. Patients were excluded if immunocompromised and have anatomic anomalies that might justify treatment in the absence of symptoms. In 2017, ASB accounted for 29.1% of antibiotic use in this population. The proportion of antibiotic use due to ASB declined to 22.5% of this population by 2020. During the study period, the percentage of patients with ASB who were treated remained unchanged at almost 80%, but the percentage of those with ASB in the entire cohort fell significantly, from 34% in 2017 to 22% in 2020. These patterns suggest that “diagnostic stewardship” (i.e., limiting cultures) is more effective than antimicrobial stewardship (ASP).

Comment: In this study the estimated effect on the ASB metric was predominantly achieved by reducing inappropriate testing (diagnostic stewardship), not by changing clinician antibiotic prescribing practices (antimicrobial stewardship). These findings nicely showcase 2 key underlying premises of diagnostic stewardship: (1) that misdiagnosis often results from excessive and unnecessary culturing and (2) holding back treatment of positive cultures is very difficult for clinicians. A number of diagnostic stewardship interventions have been studied. [Clin Infect Dis. 2022; 75:382-389] In my opinion and others the best interventions include requiring appropriate indication for urine culture ordering and only performing urine cultures if the urine sample has pyuria. Many have implemented reflex culture based on pyuria, but few have actually required an indication for the urine up front, since ~50% of ABU can have pyuria. Once a positive culture has been reported, clinicians have a hard time ignoring it. Not ordering a culture in the first place is an effective diagnostic stewardship intervention and this study adds evidence supporting this option. The National Quality Forum has endorsed a measure on inappropriate diagnosis of UTI in hospitalized patients. In an editorial they point out “diagnostic stewardship tends to make hardwired changes to testing and diagnosis, while antimicrobial stewardship tends to focus on communication with clinicians around treatment choices after a diagnosis.” In this study, diagnostic stewardship appears to have a greater influence on test-based diagnoses like UTI, where test positivity is a major driver for treatment decisions. Many of you have heard me preach that appropriate antibiotic prescribing requires using both diagnostic and antimicrobial stewardship. It has been more than 15 years since the initial IDSA ASB guideline was published and updated in 2019 [Clin Infect Dis. 2019;68: e83-e110] and yet clinicians still frequently prescribe antibiotics for ASB at alarming rates leading to unintended consequences. Many of you use EPIC and earlier this year in Am J Infect Control 2023; 51: 461-465 the investigators reduced urine cultures by building an indication screen. In the 2022

Compendium update for preventing UTIs, they added as an essential practice to standardize urine culturing by adapting an institutional protocol for appropriate indications for urine culture in patients with or without indwelling catheter. [in press] In July's ID Watch I reviewed an article on the utility of urine cultures during febrile neutropenia in HSCT without symptoms [OFID May 3, 2023]. The results support not doing routine urine cultures in patients with febrile neutropenia without urinary symptoms. The time has come to integrate diagnostic and antimicrobial stewardship practices across the continuum of care. This study and others suggest that diagnostic stewardship (reducing cultures) is more effective than antimicrobial stewardship (discouraging antimicrobial prescribing) for reducing unnecessary antimicrobial therapy in patients with asymptomatic bacteriuria. We should work with IT to build an indication screen for ordering urine cultures now.

Short-Course Therapy for Urinary Tract Infections in Children The SCOUT Randomized Clinical Trial JAMA Pediatr published online June 26, 2023

doi:10.1001/jamapediatrics.2023.1979

This was a multisite trial, in which investigators randomized 664 children (age range, 2 months–10 years) with UTIs (diagnosed based on typical symptoms and lab tests) who were improving after 5 days of antibiotics to 5 additional days of antibiotics or placebo. Subjects received one of five common antibiotics (i.e., amoxicillin-clavulanate, cefixime, cefdinir, cephalexin, or trimethoprim-sulfamethoxazole). Exclusion criteria included mixed or antibiotic-resistant flora, hospitalization, and urinary tract abnormalities.

The primary outcome, treatment failure, was defined as symptomatic UTI at or before the first follow-up visit (day 11 to 14). Secondary outcomes included UTI after the first follow-up visit, asymptomatic bacteriuria, positive urine culture, and gastrointestinal colonization with resistant organisms.

Analysis for the primary outcome included 664 randomized children (639 female [96%]; median age, 4 years). Among children evaluable for the primary outcome, 2 of 328 assigned to standard-course (0.6%) and 14 of 336 assigned to short-course (4.2%) had a treatment failure (absolute difference of 3.6% with upper bound 95% CI of 5.5.%). Children receiving short-course therapy were more likely to have asymptomatic bacteriuria or a positive urine culture at or by the first follow-up visit. There were no differences between groups in rates of UTI after the first follow-up visit, incidence of adverse events, or incidence of gastrointestinal colonization with resistant organisms.

Comment: The difference in treatment failure between short and standard therapy was small. In addition, assessing treatment failure at 11-14 days just a few days after the 10-day group stopped antibiotics could incorrectly favor standard therapy since the follow-up interval is shorter than for the 5-day group. Unfortunately, the investigators did not distinguish children with cystitis and pyelonephritis in their primary outcome analysis. The inclusion of multiple oral agents with differing degrees of bioavailability complicates the interpretation of findings. The low failure rate in children receiving short-course therapy suggests that it could be considered as a reasonable treatment option for older children who were improving and without fever. [pyelo less

likely] The benefits of a short course of antibiotic therapy for UTIs are several, including improved patient convenience and compliance, lower costs, and a decreased likelihood of adverse events. However, one needs to consider the potential long-term complications of inadequately treated pyelonephritis and the results of the current trial demonstrating a potentially higher likelihood of treatment failure in the short-course group, therefore I would be favor treatment courses closer to 10 days for the treatment of pyelonephritis.

Characteristics, costs, and outcomes associated with central-line– associated bloodstream infection and hospital-onset bacteremia and fungemia in US hospitals

Infect Control Hosp Epidemiol published online July 10, 2023

doi:10.1017/ice.2023.132

The investigators set out to compare characteristics and outcomes associated with central-line–associated bloodstream infections (CLABSIs) and electronic health record–determined hospital-onset bacteremia and fungemia (HOB) cases in hospitalized US adults. They conducted a retrospective observational study of patients in 41 acute-care hospitals. CLABSI cases were defined as those reported to NHSN. HOB was defined as a positive blood culture with an eligible bloodstream organism collected during the hospital-onset period (i.e., on or after day 4). Only the first positive blood cultures were considered eligible for HOB designation. They evaluated patient characteristics, other positive cultures (urine, respiratory, or skin and soft tissue), and microorganisms in a cross-sectional analysis cohort. They adjusted patient outcomes [length of stay (LOS), hospital cost, and mortality] in a 1:5 case-matched cohort.

Their analysis included 403 patients with NHSN-reportable CLABSIs and 1,574 with non-CLABSI HOB. A positive non-bloodstream culture with the same microorganism as in the bloodstream was reported in 9.2% of CLABSI patients and 32.0% of non-CLABSI HOB patients, most commonly urine or respiratory cultures. CoNS and Enterobacteriaceae were the most common microorganisms in CLABSI and non-CLABSI HOB cases, respectively. In case-matched analyses, CLABSIs and non-CLABSI HOB, separately or combined, were associated with significantly longer LOS [difference, 12.1–17.4 days depending on intensive care unit (ICU) status], higher costs (by $25,207–$55,001 per admission), and a >3.5-fold increased risk of mortality in patients with an ICU encounter.

Comment: The results of this study confirm a study published in 2021 [Cin Infect Dis 2021; 73:1013–9] using the CDC's Adult Sepsis Event (ASE) definition. In the current study encompassing almost 800,000 hospitalized adult patients, there were ~4 times as many non-CLABSI HOB cases as CLABSI cases (1,574 vs 403). Batelle (NQF) just endorsed a new CDC, NHSN Hospital-Onset Bacteremia & Fungemia Outcome Measure. The CDC's own study found only 66% of HOB had central lines. Some hospitals have started putting in more midlines to avoid CLABSIs. We also know that PIVs can also be a source of HOB. This study highlights 2 key points: (1) the extra cost of care required for CLABSI and non-CLABSI HOB cases and (2) the hospital stay, mortality burden, and readmission risk related to both. Significant increases in 30-day readmission rates compared with controls were observed for patients who did not have an ICU encounter, but not those with ICU admissions, perhaps suggesting that the complexity of managing HOB may impact the stability of patients at the time of discharge from a non-ICU unit. They provided insights into non-CLABSI HOB and the additional burden of BSI cases not captured by reportable CLABSI events. It should be noted that only first positive blood cultures

were considered eligible for HOB designation, so HOB prevalence may have been underestimated. Sources of HOB were assigned to categories that could only be extracted from EHR. For example, quantification of secondary HOBs associated with peripheral IV lines was beyond the scope of this analysis. Future studies will be needed to delineate a more granular source attribution list for HOB to facilitate infection preventionist efforts to mitigate HOB events.

Reliability of Admission Procalcitonin Testing for Capturing Bacteremia Across the Sepsis Spectrum: Real-World Utilization and Performance Characteristics, 65 U.S. Hospitals, 2008–2017 Crit Care Med published online July 3, 2023

DOI: 10.1097/CCM.0000000000005968

The investigators sought to characterize the real-world utilization and performance of serum procalcitonin (PCT) testing in patients presenting with suspected bloodstream infections (BSIs). Testing frequency of PCT was determined. Sensitivity of PCT-on-admission for detecting BSI due to different pathogens was calculated. Area under the receiver operating characteristic curve (AUC) was calculated to assess discrimination by PCT-on-admission for BSI in patients with and without fever/hypothermia, ICU admission and sepsis defined by CDC Adult Sepsis Event criteria. AUCs were compared using Wald test and p values were adjusted for multiple comparisons.

At 65 procalcitonin-reporting hospitals, 74,958 of 739,130 patients (10.1%) who had admission blood cultures also had admission PCT testing. Most patients (83%) who had admission day PCT testing did not have a repeat procalcitonin test. Median procalcitonin varied considerably by pathogen, BSI source, and acute illness severity. At a greater than or equal to 0.5ng/mL cutoff, sensitivity for BSI detection was 68.2% overall, ranging between 58.0% for enterococcal BSI without sepsis and 96.4% for pneumococcal sepsis. PCT-on-admission displayed moderate discrimination at best for overall BSI (AUC, 0.73; 95% CI, 0.72–0.73) and showed no additional utility in key subgroups. Applying a PCT cutoff of 0.5ng/mL produced a sensitivity, specificity, PPV, and NPV, respectively, of 62.3%, 69.9%, 20.2%, and 93.8%, respectively, in patients without sepsis, 79.7%, 45.9%, 29.7%, and 88.8%, respectively, in patients with bacteremic sepsis without shock, and 86.5%, 34.1%, 32.7%, and 87.2%, respectively, in those with BSI with septic shock. Empiric antibiotic use proportions were not different between blood culture sampled patients with a positive PCT (39.7%) and negative procalcitonin (38.4%) at admission.

Operating Characteristics	Cutoff for Procalcitonin Positivity Applied (ng/mL)			
	≥ 0.5	≥ 1	≥ 0.25	≥ 0.1
Sensitivity	68.2%	59.4%	77.0%	87.8%
Specificity	65.6%	75.1%	53.6%	32.7%
Positive predictive value	23.1%	26.6%	20.1%	16.5%
Negative predictive value	93.2%	92.4%	93.9%	94.7%

Comment: In this retrospective cohort study of 74,958 patients with suspected BSI at 65 US hospitals, serum PCT was seldom trended beyond hospital admission day and its performance characteristics for identifying BSIs at admission were moderate to poor across a range of host and microbial factors. However, the NPV was excellent across the subgroups analyzed.(see above) PCT drawn at admission could allow clinicians to assess procalcitonin trends, which have prognostic utility and may facilitate earlier antibiotic discontinuation. [Clin Chem Lab Med 2019; 57:1308–1318] However, even though approximately one in every 10 study patients presenting with suspected BSI had PCT tested at admission, in over three-quarters of these patients, the test was never repeated. They were unable to analyze symptomatology, relying only on the presence or absence of fever or hypothermia when looking at patient characteristics. In real-world practice, observable symptoms that make a patient appear severely ill, such as tachypnea or altered mental status, influence antimicrobial treatment and workup for infection including the ordering of PCT, which may have confounded their results. They were unable to determine if antibiotics were ordered before or after a PCT result or administered pre-blood culture, increasing their false negative rate, and reducing the calculated sensitivity of PCT. However, given the limited accuracy of PCT in identifying patients with BSI on admission raises concerns about its reliability in helping guide empiric antibiotic decisions. In this real-world experience PCT had limited value in predicting BSI with ~1/3 would have been missed at a threshold of 0.5 ng/mL. In addition, PCT levels did not influence empiric antimicrobial prescribing. This study and others highlight that PCT testing practices represent an opportunity for improving diagnostic stewardship.

Real-life Assessment of BioFire FilmArray Pneumonia Panel in Adults Hospitalized With Respiratory Illness J Infect Dis published online June 27, 2023

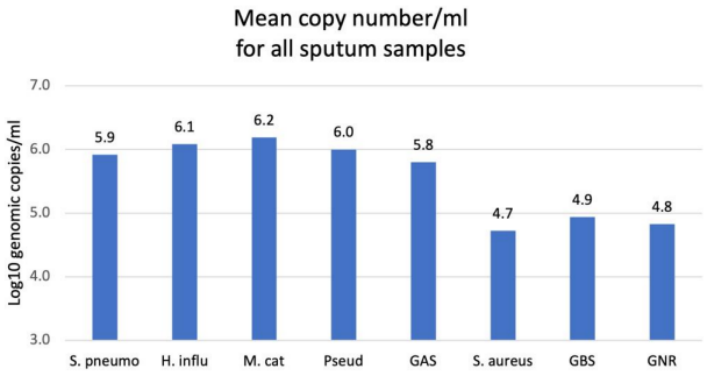
doi.org/10.1093/infdis/jiad221

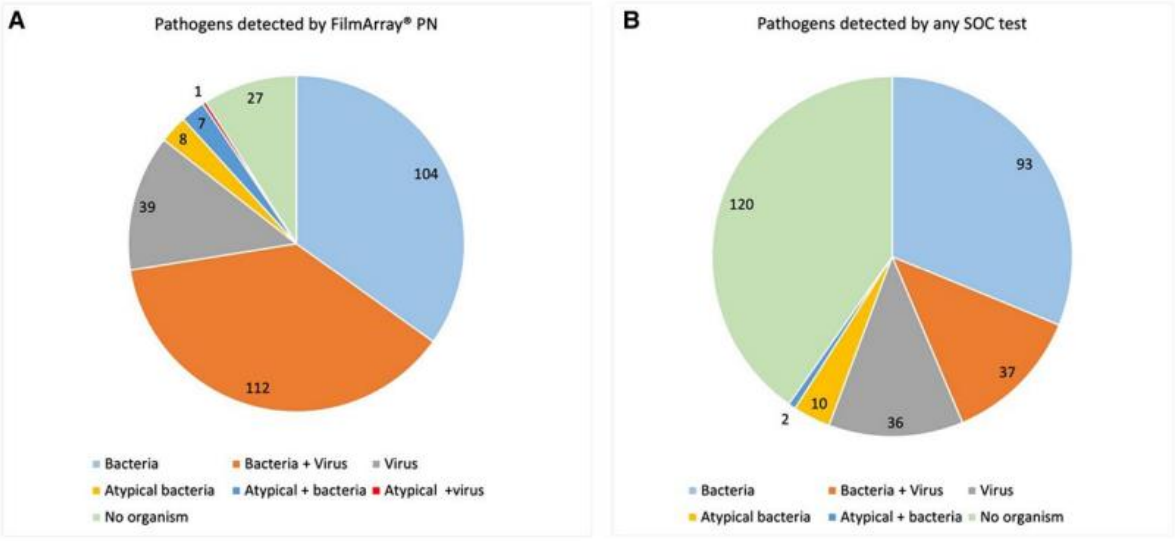
Acute respiratory infection is caused by a wide range of pathogens, and an etiologic diagnosis is established in only about 50% of cases by traditional means. As a result, broad-spectrum antibiotics are often prescribed empirically and continued in the absence of identifying the pathogen. The BioFire Pneumonia Panel (BioFire PN) is a commercial multiplex PCR assay directed against 33 targets, including viruses, bacteria, and a number of antibiotic resistance

genes. In critically ill patients, BioFire PN results have shown a high level of agreement with culture results when tracheal aspirates (TA) or bronchoalveolar lavage fluid were sampled.

In this study hospitalized adults with respiratory illness were recruited; sputa and clinical/laboratory data were collected. Sputa were cultured for bacteria and tested with BioFire PN. Microbial etiology was adjudicated by 4 physicians. Bacterial PCR was compared with culture and clinical adjudication.

They compared 298 samples (286 expectorated sputum and only 12 from TA) deemed of good or moderate quality obtained from hospitalized [community onset] adult patients with acute respiratory or cardiopulmonary illness. BioFire PN detected a total of 1.23 bacterial pathogens per sample. *Hemophilus influenzae* was detected most often (33.0%), followed by *Streptococcus pneumoniae* and *Staphylococcus aureus* (20.5% for both), gram-negative bacilli (18.5%), and *Moraxella catarrhalis* (12.4%). Standard bacterial culture detected only 0.48 organisms per sample (compared with BioFire PN; *P*<0.001). BioFire PN correctly identified a bacterial pathogen in 95 of 100 cases deemed bacterial based on clinical adjudication; the negative predictive value of BioFire PN was >90%. Viral pathogens were detected in 51% of samples. Based on adjudication, the specificity of BioFire PN was only 45.0%. This was attributed to the greater number of potential pathogens identified compared with standard culture. Cases were adjudicated as viral (n = 58) and bacterial (n = 100). PCR detected bacteria in 55% of viral cases and 95% of bacterial (P < .0001). High serum procalcitonin and bacterial adjudication were more often associated with sputa with 10^6 or 10^7 copies detected. [BioFire PN is a semi-quantitative assay for bacteria]





Comment: Multiplex PCR testing of sputa for bacteria is useful to rule out bacterial infection with added value to detect viruses and atypical bacteria, however, how the results are reported and will the clinician understand the results will need extensive education. They were unable to collect sputum samples on all patients, and frequent administration of antibiotics prior to sputum collection hampered direct comparisons of BioFire PN and culture. In addition, their study population was limited to those who could provide informed consent. An important aspect of this study is that only good quality samples were evaluated, which in my experience is an uncommon practice. Despite some imitations, BioFire PN testing yielded significantly more potential pathogens than culture and was less affected by prior antibiotics in hospitalized patients with a variety of community acquired LRTIs. The NPV for sputa of good and moderate quality was excellent, and with increased viral detections, BioFire PN offers a tool that could reduce unnecessary or overly broad antibiotic use.

FDA Approves Nirsevimab Antibody Injection To Protect Babies And Toddlers From RSV

FDA approved nirsevimab injection, developed by Sanofi and AstraZeneca, for infants and children up to 2 years old who face increased risk of severe RSV. FDA officials approved the drug based on three studies showing nirsevimab reduced the risk of RSV infection between 70% and 75% among infants and children 2 and younger. The drug is a laboratory-made version of an antibody that helps the immune system fight off RSV. Based on the FDA approval, infants can receive a single injection to protect against their first season of RSV, which typically lasts about five months. [has been less predictable during the pandemic] Additionally, children up to age 2 can receive another dose to protect them during their second season facing the virus.

Comment: The drug, which is already approved in Canada, Europe and the UK, will be marketed in the US by Sanofi. CDC advisers will meet early next month to recommend exactly who should get the drug. The FDA is also looking at a vaccine given to pregnant women to reduce the risk of RSV. See next review.

Seasonality in Respiratory Syncytial Virus Hospitalizations and Immunoprophylaxis JAMA Health Forum 2023;4(6): e231582.

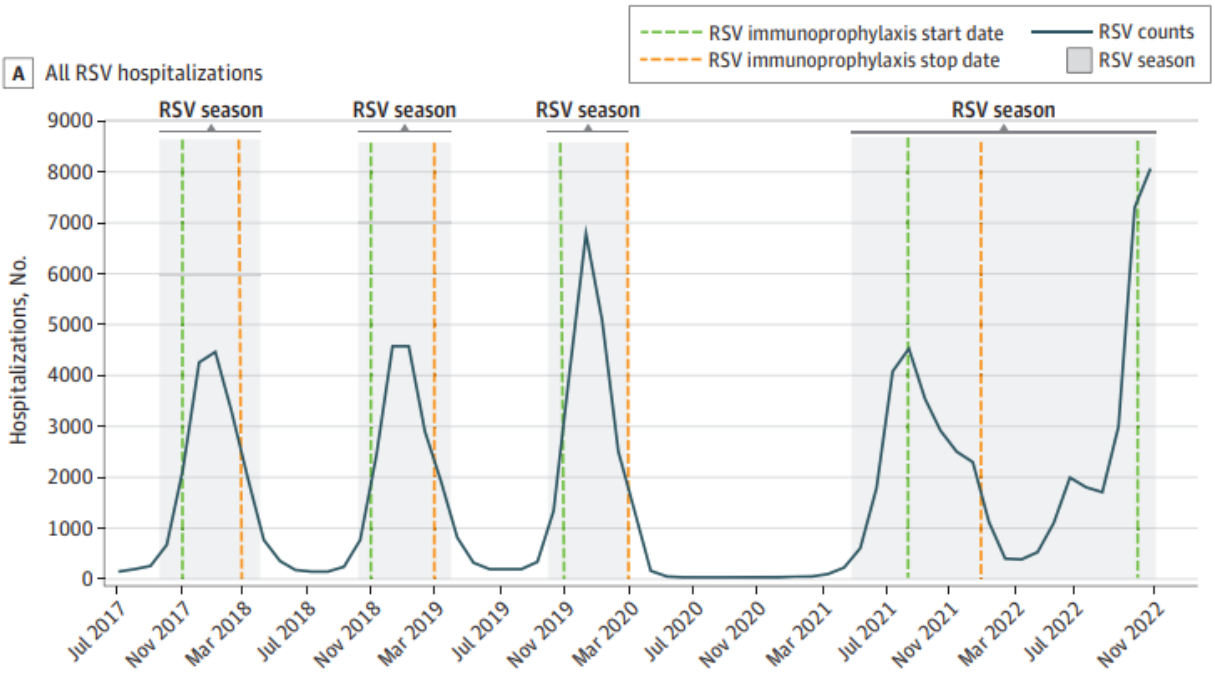
doi:10.1001/jamahealthforum.2023.1582

This is a retrospective cross-sectional study identifying children younger than 2 years who were hospitalized for RSV between July 2017 and November 2022 using the Pediatric Health Information System (PHIS). ICD-10 Clinical Modification diagnosis codes were used to identify RSV-related hospitalizations and children with RSV-immunoprophylaxis eligibility. They defined RSV seasons as months during which RSV-related hospitalizations exceeded by 3 SDs mean monthly hospitalization counts.

They identified 4 RSV seasons with 109,185 RSV-related hospitalizations [see below] among 104,898 children (median [IQR] age, 4.7 [2.0-10.6] months; 45,931 girls [43.8%], 58,947 boys [56.2%]). Seasonal spikes between 2017 and 2019 began in October. High-risk children represented a larger proportion of hospitalizations during interseasons. Children with public insurance constituted the largest proportion of hospitalizations, and even larger during interseasons.

Seasonal hospitalization pattern from 2017 to 2019 (starting in November, ending in March) aligned with RSV immunoprophylaxis availability. However, the 2021 RSV season started in May (579 hospitalizations per month). Public and commercial insurance in most states did not approve RSV immunoprophylaxis until September or later. Although RSV immunoprophylaxis ended between January and March 2022 and restarted in October or November 2022, RSV season was continuous, with monthly hospitalizations larger than the interseasonal threshold.

The 2021 to 2022 RSV season consisted of 45% of all hospitalizations over the study period.



Comment: RSV frequently causes hospitalization, particularly among children with significant congenital heart disease, chronic lung disease, or prematurity (<29 weeks gestation). Immunoprophylaxis administration to high-risk children during active RSV circulation periods is beneficial and cost-effective. [Pediatrics. 2019;143: e20184064]. AAP guidelines recommended that high-risk children receive RSV immunoprophylaxis with monoclonal antibodies. [Pediatrics. 2014;134: 415-420] Insurers typically cover RSV immunoprophylaxis annually (November-March) in accordance with RSV seasonality. Since the Covid-19 pandemic, RSV has been characterized by unexpected interseasonal spikes. To maximize benefits of RSV immunoprophylaxis, preventing hospitalization and death among high-risk children, policies must be responsive to atypical epidemiological patterns. Public health–hospital relationships and data infrastructure should be utilized for real-time pediatric surveillance to guide RSV immunoprophylaxis initiation and cessation. Additionally, insurers should establish flexible models that are responsive to timely regional RSV epidemiological data.

Multipathogen Respiratory Virus Testing Among Primary and Secondary School Students and Staff Members in a Large Metropolitan School District — Missouri, November 2, 2022– April 19, 2023 MMWR 2023; 72:772-4

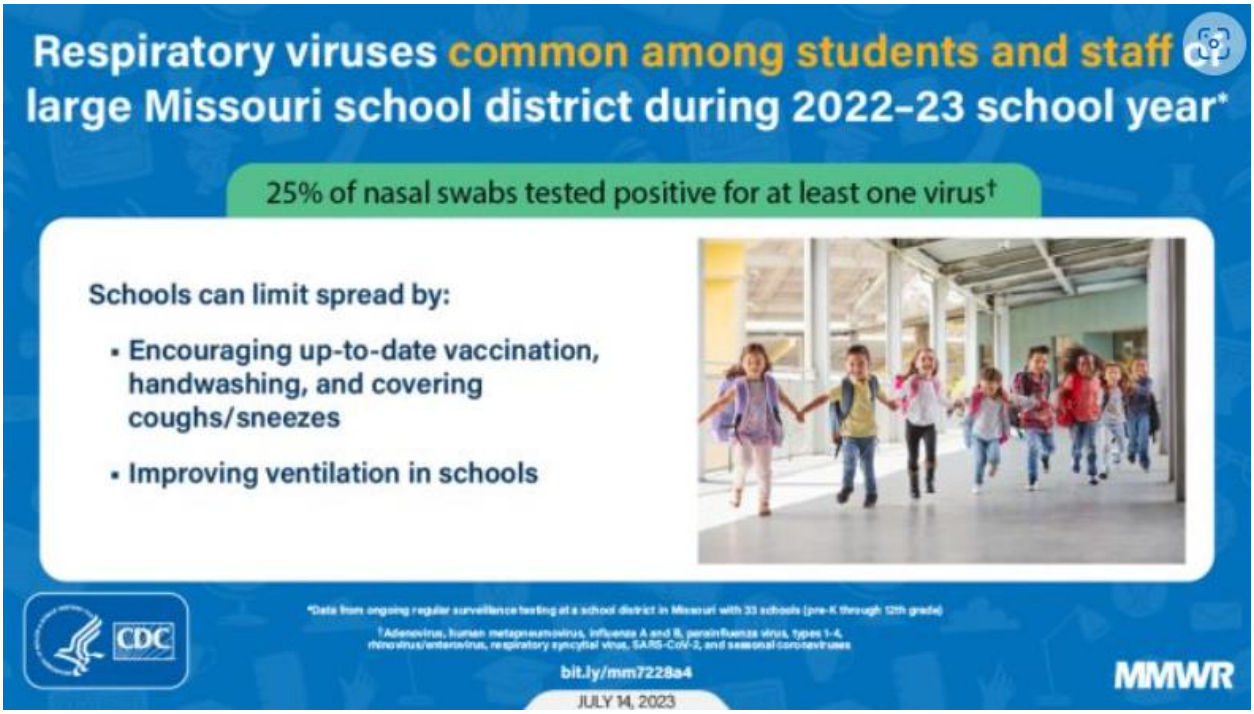
To determine the prevalence of respiratory viruses in school students and staff members, prospective surveillance was implemented in a large metropolitan school district in Kansas City, Missouri with 33 pre-Kindergarten (pre-K)–grade 12 schools during the 2022–23 school year. All district students and staff members were eligible to enroll in opt-in respiratory virus testing and symptom surveys irrespective of the presence of symptoms; enrollment information was sent by the school district using existing communication channels. Self-collected anterior nasal swabs were obtained monthly and tested using multiplex viral polymerase chain reaction. Thirty-six

hours before each scheduled monthly test, an electronic survey was sent to enrolled participants (or their parent or guardian) inquiring about respiratory virus infection symptoms during the preceding 7 days.

Among the 894 total participants, 639 (71.5%) were students (representing 3.0% of total district enrollment of 21,419), and 255 (28.5%) were staff members (representing 7.1% of the total 3,577 district full-time staff members). Demographic characteristics of participants were similar to those reported districtwide, except that the proportion of female participants was higher (60.7%) than that from districtwide estimates (51.1%), and the proportion of students qualifying for free or reduced-price meals was lower (31.3% versus 38.0%). A total of 3,232 surveillance specimens were tested, including 872 (27.0%) from staff members and 2,360 (73.0%) from students. Student specimens included 90 (2.8%) from pre-K students, 1,413 (43.7%) from elementary school students, 479 (14.8%) from middle school students, and 378 (11.7%) from high school students.

Overall, 805 (24.9%) specimens tested positive for any virus (95% CI = 23.4%–26.4%). A substantially higher percentage of pre-K specimens tested positive (40.0%) compared with staff member specimens (14.1%) ($p<0.001$) Overall, rhinovirus/enterovirus (RV/EV) was detected most frequently (392; 12.1%), followed by all seasonal coronaviruses including NL63, HKU1, OC43, and 229E (181; 5.6%). Among specimens from pre-K and elementary school students, RV/EV (14.4% and 17.1%, respectively), adenovirus (12.2% and 3.3%, respectively), seasonal coronaviruses (6.7% and 8.1%, respectively) and human metapneumovirus (4.4% and 3.7%, respectively) were frequently detected. Among staff member specimens, RV/EV (4.8%), seasonal coronaviruses (3.8%), and SARS-CoV-2 (3.3%) were frequently detected. Influenza and RSV were infrequently detected from surveillance specimens, possibly because testing commenced after the occurrence of early seasonal peaks. More than one virus was detected in 81 (2.5%) specimens. Pre-K students had the highest prevalence of reporting one or more symptoms (41.1%) compared with high school students, among whom prevalence of symptoms was lowest (14.0%) ($p<0.001$).

	School level, no. of specimens (% of total)									
	Pre-K n = 90 (2.8)		Elementary school n = 1,413 (43.7)		Middle school n = 479 (14.8)		High school n = 378 (11.7)		Staff members n = 872 (27.0)	
Virus detected, no. (%)	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**	**No.**	**% (95% CI)**
Any virus detection, 805 (24.9)*	**36**	**40.0 (26.4–45.2)**	**466**	**33.0 (29.6–36.7)**	**117**	**24.4 (18.1–29.2)**	**63**	**16.7 (12.9–20.5)**	**123**	**14.1 (10.9–16.5)**
Rhinovirus/Enterovirus, 392 (12.1)	13	14.4 (3.2–29.8)	241	17.1 (14.5–20.0)	65	13.6 (7.9–17.6)	31	8.2 (6.0–10.3)	42	4.8 (3.2–6.5)
Adenovirus, 70 (2.2)	11	12.2 (7.6–21.0)	46	3.3 (2.2–4.5)	7	1.5 (0.8–3.8)	3	0.8 (0.4–2.5)	3	0.3 (0.1–0.8)
Seasonal coronavirus, 181 (5.6)	6	6.7 (2.9–8.8)	114	8.1 (6.7–9.3)	17	3.5 (1.1–5.8)	11	2.9 (1.2–4.9)	33	3.8 (2.7–5.0)
Human metapneumovirus, 93 (2.9)	4	4.4 (2.4–11.9)	52	3.7 (2.6–5.0)	13	2.7 (1.0–4.2)	7	1.9 (1.2–3.2)	17	1.9 (0.9–3.2)
SARS-CoV-2, 77 (2.4)	2	2.2 (1.5–4.2)	29	2.1 (1.3–2.9)	9	1.9 (0.7–3.8)	8	2.1 (0.7–4.8)	29	3.3 (2.0–5.2)
Parainfluenza virus, 29 (0.9)	2	2.2 (1.0–8.5)	13	0.9 (0.5–1.3)	5	1.0 (0.3–2.5)	4	1.1 (0.6–3.3)	5	0.6 (0.2–1.3)
RSV,† 23 (0.7)	1	1.1 (0.6–2.8)	11	0.8 (0.3–1.4)	5	1.0 (0.5–2.8)	4	1.1 (0.3–3.0)	2	0.2 (0.1–0.6)
Influenza A,† 21 (0.6)	0	—	11	0.8 (0.4–1.2)	5	1.0 (0.4–2.5)	2	0.5 (0.2–1.1)	3	0.3 (0.1–0.7)
Influenza B, 2 (0.1)	0	—	0	—	1	0.2 (0.1–1.2)	0	—	1	0.1 (0.1–0.1)
Reported symptoms during previous 7 days, no.										
Asymptomatic, 1,628	28	31.1 (18.0–41.6)	657	46.5 (42.0–51.2)	246	51.4 (37.8–57.2)	220	58.2 (46.9–65.4)	477	54.7 (49.0–60.7)
One or more symptoms, 765	37	41.1 (32.3–65.0)	343	24.3 (21.3–27.5)	111	23.2 (18.0–33.6)	53	14.0 (6.8–18.6)	221	25.3 (21.3–29.6)
Survey not completed, 839	25	27.8 (3.1–40.2)	413	29.2 (24.1–34.1)	122	25.5 (18.6–36.4)	105	27.8 (19.9–45.8)	174	20.0 (15.5–24.6)



Comment: The pandemic highlighted the gap in knowledge related to the prevalence and symptoms of respiratory viruses among children and in schools. The data reported here are important to improve understanding of the epidemiology of respiratory viruses in a school setting, including but not limited to SARS-CoV-2. To support healthy learning environments for all, it is important to prevent and reduce the spread of infectious diseases, including staying up to date with recommended vaccinations, practicing good hand hygiene and respiratory etiquette, staying home when sick, and improving indoor ventilation. We need to remember that participation in this program was voluntary; therefore, participants who opt in might not be representative of the full school population. In addition, all nasal swabs were collected by participants, and approximately 25% of specimens did not have known symptomatology because of lack of survey response. Lastly, the normal pattern of respiratory viruses was impacted by the pandemic.

E-11 infections in newborns

Following reports in May of enterovirus-echovirus 11 (E-11) neonatal sepsis cases in France, five more countries in Europe have reported similar cases. In its initial report, the WHO said the French cases involved a recombinant enterovirus (echovirus 11 [E-11]) that hadn't been detected in France before and were unusual due to extremely rapid health deterioration and a high case-fatality rate. Also, the proportion of infections seen in twins was much higher than expected.

Since then and as of June 26, five more countries have reported 17 cases, including Croatia (1), Italy (7), Spain (2), Sweden (5), and the United Kingdom (2). Most of the cases were from 2023,

but some of Sweden's were reported from 2022, as were some of France's cases. France's cases remain at nine, which includes seven deaths.

Comment: With no systemwide Enterovirus surveillance in place in Europe, it's hard to gauge the extent of the severe cases and the background rates for E-11 circulation in the general population. Viruses isolated from some of Italy's cases belong to the same genetic cluster as those isolated from France and are part of a new divergent lineage. Nonpolio enterovirus infection is not a notifiable disease in most countries, so other severe cases may have gone undiagnosed or unreported.

Potential for Maternally Administered Vaccine for Infant Group B Streptococcus

N Engl J Med 2023;389:215-27.

DOI: 10.1056/NEJMoa2116045

A hexavalent CPS–cross-reactive material 197 glycoconjugate vaccine (GBS6) is being developed as a maternal vaccine to prevent invasive group B streptococcus in young infants. The investigators evaluated the safety and antibody levels in infants after their mothers received one dose of different formulations of Pfizer's hexavalent (six-strain) GBS6 vaccine or a placebo in the second or third trimester of pregnancy.

A total of 17,752 women were included. Over the same period (March 2019 to June 2020), the team also assessed which antibody concentrations were tied to a lower risk of invasive strep infection in infants up to 89 days old. Twenty-eight infants developed streptococcal disease and were studied in combination with a group of 90 infants with invasive disease retrospectively enrolled.

Naturally acquired anti-CPS IgG concentrations were associated with a reduced risk of disease among infants in the seroepidemiologic study. IgG thresholds that were determined to be associated with 75 to 95% reductions in the risk of disease were 0.184 to 0.827 µg per milliliter. No GBS6-associated safety signals were observed among the mothers or infants.

Comment: GBS6 elicited anti-CPS antibodies against group B streptococcus in pregnant women that were transferred to infants at levels associated with a reduced risk of invasive group B streptococcal disease. In an editorial Dr. Baker pointed out there are some limitations. Dr. Baker wrote: **"**The results were derived from a single study in which only 17% had group B streptococcal disease due to four of the six CPS serotypes in the vaccine; they were obtained with a limited number of matched infant controls to case patients (e.g., 0.63:1 in prospective study); they apply only to a South African pregnant population with a high disease burden among infants; and they require corroboration in future studies."

The impact of influenza and pneumococcal vaccination on antibiotic use: an updated systematic review and meta-analysis Antimicrobial Resistance & Infection Control (2023) 12:70 published online July 14, 2023

doi.org/10.1186/s13756-023-01272-6

Investigators reviewed literature published from 1998 through 2021, from the Netherlands Institute for Health Services Research included 29 randomized controlled trials (RCTs) and 69 observational studies in their meta-analysis. Most studies were performed in high-income countries in Europe and the Americas, and outcome measures included the proportion of people receiving antibiotics, the number of antibiotic courses or prescriptions per person, and days of antibiotic use. Results were stratified by global region and age-group. They included studies present data for different outcome measures: (1) the proportion of people receiving antibiotics, (2) the number of antimicrobial courses or prescriptions per person, and (3) the days of antibiotic use. They combined the outcome measures (2) and (3) for the purpose of the meta-analysis.

The RCTs showed that the effect of influenza vaccination on the number of antibiotic prescriptions or days of antibiotic use (ratio of means [RoM], 0.71; 95% confidence interval [CI], 0.62 to 0.83) is stronger compared to the effect of pneumococcal vaccination (RoM, 0.92; 95% CI, 0.85 to 1.00) and confirmed a reduction in the proportion of people receiving antibiotics after flu vaccination (risk ratio [RR], 0.63; 95% CI 0.51 to 0.79). The effect of influenza vaccination in Europe and the Americas ranged from 0.63 and 0.87 RoM to 0.70 and 0.66 RR, respectively. The evidence from observational studies supported these findings but presented a less consistent picture.

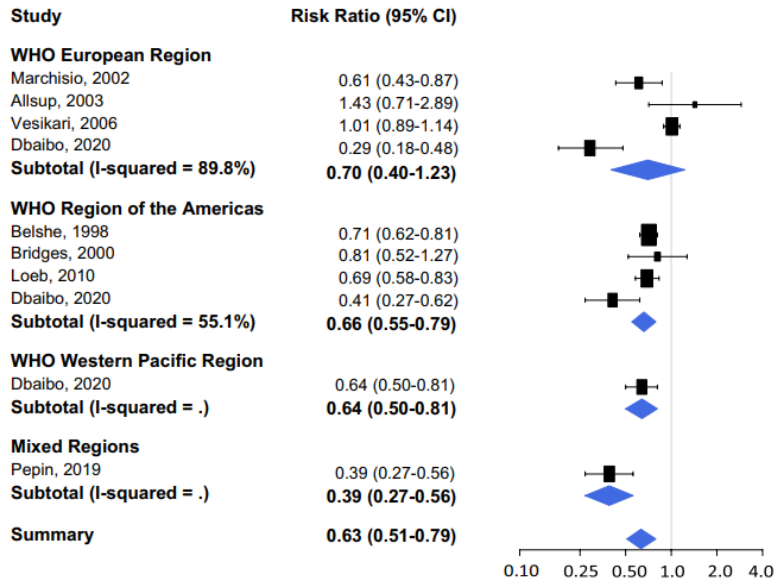


Fig. 3 Number of antimicrobial prescriptions or days of antibiotic use after influenza vaccination

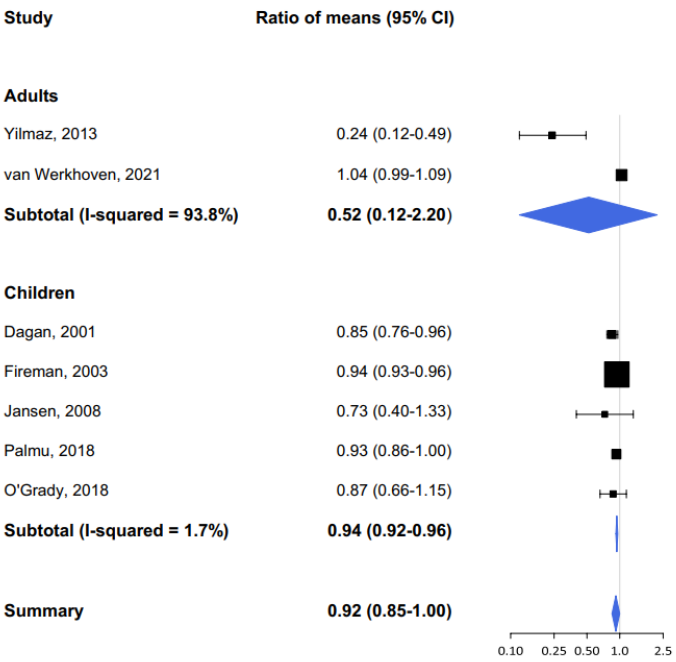


Fig. 4 Number of antimicrobial prescriptions or days of antibiotic use after pneumococcal vaccination

Comment: The stronger effect of the flu vaccine on antibiotic use is surprising to me, given that influenza should not be treated with antibiotics (except for some with oseltamivir) and that the vaccine effectiveness (VE) of pneumococcal vaccines is considerably higher than the VE of influenza vaccines. There were no clear regional patterns that were found due to the high heterogeneity between studies. The quality of evidence of most of the studies was low or moderate and the type of antibiotics were often not reported. Despite this finding both vaccines should be used as a public health intervention to reduce unnecessary antimicrobial use and antimicrobial resistance.

Estimating the cost of inappropriate antibiotic prophylaxis prior to dental procedures Infect Control Hosp Epidemiol published online July 10, 2023

doi: 10.1017/ice.2023.126

Since 2007, the American Heart Association, with input from the American Dental Association, has limited the target populations for antibiotic prophylaxis prior to dental procedures for the prevention of infective endocarditis to only those with cardiac conditions at highest risk. The most recent guideline recommends prophylaxis only prior to dental procedures that involve manipulation of gingival tissue or the periapical region of teeth or perforation of the oral mucosa in patients with valvular heart disease; patients with selected congenital heart conditions; and patients with previous, relapsed, or recurrent infective endocarditis. [Circulation 2021;143: E963–E978] Several analyses have shown that ~5 of every 6 dental prophylactic prescriptions are inconsistent with guidelines. [Am J Prev Med 2022; 62:943–948]

Based on 2018 census data, the investigators modeled adults aged ≥18 years in the US who had a dental visit with an antibiotic prescribed over a 1-year period and based on published data from large cohorts, ~83.1% of these prescriptions are considered inappropriate. They considered only amoxicillin, cephalexin, and clindamycin because they account for 94% of the prescribed drugs in the dental setting.

They calculated that inappropriate dental antibiotic prescriptions to prevent infective endocarditis in the US results in ~$31 million in excess costs to the healthcare system and patients. This includes out-of-pocket costs ($20.5 million), drug costs ($2.69 million) and adverse event costs (e.g., Clostridioides difficile and hypersensitivity) of $5.82 million (amoxicillin), $1.99 million (clindamycin), and $380,849 (cephalexin).

Comment: Dentists account for 6%–10% of all antibiotic prescriptions in the US, [Infect Control Hosp Epidemiol 2022;43:1565–1574] resulting in a substantial burden of preventable adverse events. More antimicrobial stewardship efforts need to be focused on dentistry and dermatology. This study helps focus on the substantial opportunity for improvement in dentistry. The datasets used to assess inappropriate antibiotic prescribing did not include the uninsured. Estimates did not contain costs associated with antibiotics not included in their analysis; indirect costs associated with adverse events; pharmacist time spent filling the drug and counseling a patient; patient time lost to pick up a prescription; or the impact of unnecessary antibiotic use promoting community antibiotic resistance.

Determinants of worldwide antibiotic resistance dynamics across drug-bacterium pairs: a multivariable spatial-temporal analysis using ATLAS Lancet Planet Health 2023; 7: e547–557

Doi.org/10.1016/S2542-5196(23)00127-4

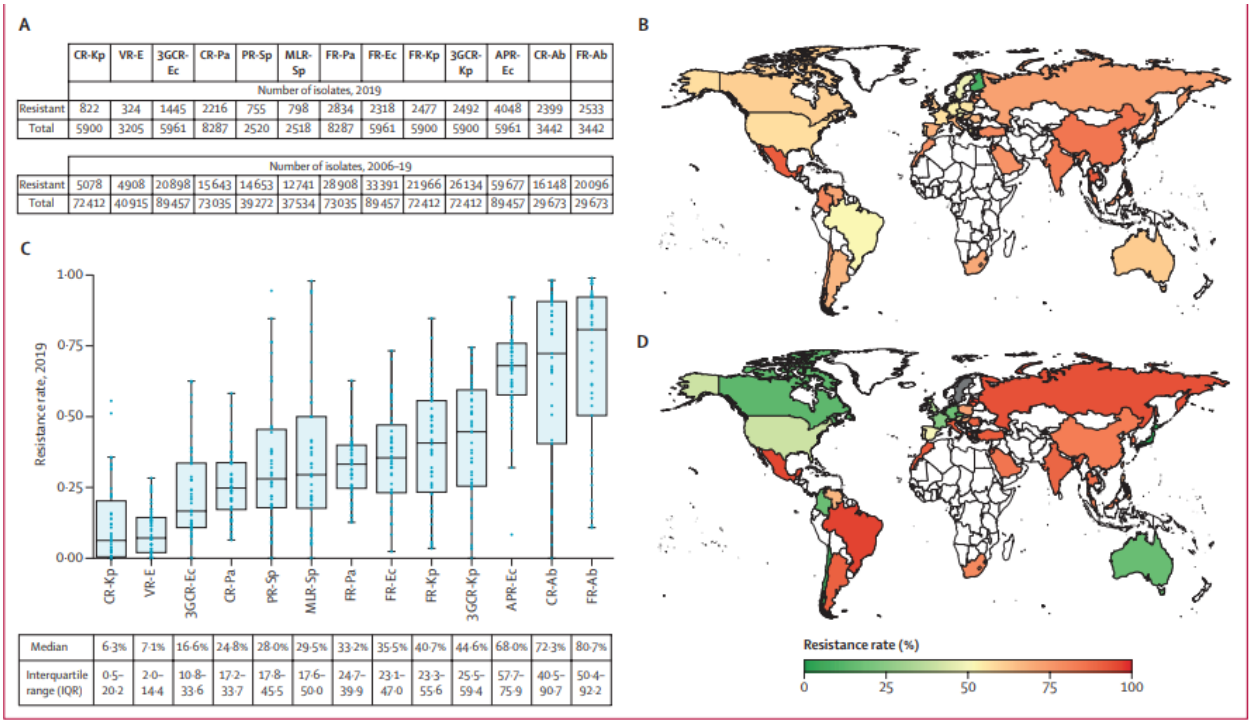
The investigators analyzed count data of clinical isolates from 51 countries over 2006–19 for thirteen drug-bacterium pairs taken from the ATLAS (Antimicrobial Testing Leadership and Surveillance) database. They characterized AR (antimicrobial resistance) spatial and temporal patterns and used a mixed-effect negative binomial model, accounting for country-year dependences with random effects, to investigate associations with potential drivers, including antibiotic sales, economic and health indicators, meteorological data, population density, and tourism.

A total of 808,774 isolates from all infection sources were analyzed. For 2019, median AR rates ranged from 6.3% for carbapenem-resistant *K pneumoniae* to 80.7% for fluoroquinolone-resistant *A baumannii,* with variations across countries. The only resistance trend observed from 2006 to 2019 was for drug-bacterium pairs associated with carbapenem resistance, which increased in more than 60% of investigated countries.

Key factors associated with AR rates varied greatly among drug-bacterium pairs. Multivariable analyses identified significant associations of AR with country-level antibiotic sales, but only in fluoroquinolone-resistant *E coli,* fluoroquinolone-resistant *P aeruginosa,* and carbapenem-resistant *A baumannii.* There was also a correlation between temperature and resistance in Enterobacteriaceae, between carbapenem-resistant *A baumannii* and gross domestic product, and with health system quality for all drug-bacterium pairs except Enterococci and *S pneumoniae* pairs.

	FR-Ec	APR-Ec	3GCR-Ec	FR-Kp	3GCR-Kp	CR-Kp	FR-Pa	CR-Pa	FR-Ab	CR-Ab	VR-E	PR-Sp	MLR-Sp
Significant covariables in final multivariable models	• Quinolones sales • GHS index • Extreme events • Temperature	• GHS index • Extreme events • Temperature • Tourist departures	• GHS index • Extreme events • Temperature	• GHS index	• GHS index	• GHS index • Temperature	• Quinolones sales • GHS index • GDP	• GHS index • Tourist departures	• GHS index • Rainfall	• Carbapenem sales • Global antibiotic sales • GHS index • GDP	..	• Global antibiotic sales • Relative humidity	• Global antibiotic sales • GDP • Extreme events

Figure 3: **Significant covariables associated with each drug-bacterium pair, from final multivariable models**
Summary of significant covariables in multivariable models for each drug–bacterium pair. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. ABR=antibiotic resistance. APR-Ec=aminopenicillin-resistant *E coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A baumannii*. FR-Ec=fluoroquinolone-resistant *E coli*. FR-Kp=fluoroquinolone-resistant *K pneumoniae*. FR-Pa=fluoroquinolone-resistant *P aeruginosa*. GDP=Gross Domestic Product. GHS=Global Health Security index. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. PR-Sp=penicillin-non-susceptible *S pneumoniae*. VR-E=vancomycin-resistant Enterococci.



	CR-Kp	VR-E	3GCR-Ec	CR-Pa	PR-Sp	MLR-Sp	FR-Pa	FR-Ec	FR-Kp	3GCR-Kp	APR-Ec	CR-Ab	FR-Ab
	Number of isolates, 2019												
Resistant	822	324	1445	2216	755	798	2834	2318	2477	2492	4048	2399	2533
Total	5900	3205	5961	8287	2520	2518	8287	5961	5900	5900	5961	3442	3442
	Number of isolates, 2006–19												
Resistant	5078	4908	20898	15643	14653	12741	28908	33391	21966	26134	59677	16148	20096
Total	72412	40915	89457	73035	39272	37534	73035	89457	72412	72412	89457	29673	29673
Median	6·3%	7·1%	16·6%	24·8%	28·0%	29·5%	33·2%	35·5%	40·7%	44·6%	68·0%	72·3%	80·7%
Interquartile range (IQR)	0·5–20·2	2·0–14·4	10·8–33·6	17·2–33·7	17·8–45·5	17·6–50·0	24·7–39·9	23·1–47·0	23·3–55·6	25·5–59·4	57·7–75·9	40·5–90·7	50·4–92·2

Figure 1: **Worldwide ABR rates distribution in 2019 according to ATLAS**
ABR rates are reported in proportions or percentages of resistant isolates over total number of tested isolates per country for each drug–bacterium pair. (A) Sample sizes (number of resistant and total isolates) for each drug–bacterium pair, for the year 2019 and for the whole study period (2006–19). (C) Median (IQR) ABR rates across countries for all drug–bacterium pairs. Maps of worldwide ABR rates for APR-*Ec* (B) and CR-*Ab* (D), two pairs exhibiting high median rates in 2019; grey countries indicate missing value for 2019. White countries are not included in the analysis. 3GCR-Ec=third generation cephalosporin-resistant *Escherichia coli*. 3GCR-Kp=third generation cephalosporin-resistant *Klebsiella pneumoniae*. ABR=antibiotic resistance. APR-Ec=aminopenicillin-resistant *E coli*. CR-Ab=carbapenem-resistant *Acinetobacter baumannii*. CR-Kp=carbapenem-resistant *K pneumoniae*. CR-Pa=carbapenem-resistant *Pseudomonas aeruginosa*. FR-Ab=fluoroquinolone-resistant *A baumannii*. FR-Ec=fluoroquinolone-resistant *E coli*. FR-Kp=fluoroquinolone-resistant *K pneumoniae*. FR-Pa=fluoroquinolone-resistant *P aeruginosa*. MLR-Sp=macrolide-resistant *Streptococcus pneumoniae*. PR-Sp=penicillin-non-susceptible *S pneumoniae*. VR-E=vancomycin-resistant Enterococci.

Comment: Using longitudinal data provided by ATLAS, they analyzed spatial and temporal patterns of AR and determinants of AR for thirteen drug–bacterium pairs of clinical relevance. Their results confirmed that worldwide AR dynamics were highly drug–bacterium pair dependent, both spatially and temporally. They found that key factors varied greatly between drug–bacterium pairs, but some similarities existed between bacteria of the same species. However, after hypothesis driven investigation of factors, high unexplained country-level variance remained in most of the drug–bacterium pairs. High GHS index, used as a proxy for health system quality, was significantly associated with decreased AR rates in most drug–bacterium pairs. This result highlights the crucial role of infection prevention measures for containing resistance, especially in hospitals. The study findings show that AR is a worldwide threat. Despite differences across pathogens, we know resistances are driven by both individual behaviors and global environmental mechanisms setting AR in a One Health framework. Therefore, strategies to tackle worldwide antibiotic resistance should be tailored accounting for the species, the resistance, and the epidemiological settings. In addition, these findings reflect the diversity of mechanisms driving global AR across pathogens and stress the need for tailored interventions to tackle bacterial resistance.

This study has a few limitations. The sampling protocol was based on clinical isolates from hospitals, ABR rates reported in ATLAS might not be fully representative of true resistance prevalence at the country level. Isolates from severe infections could present more resistance because going to the hospital is the last option after unsuccessful community treatment. This would lead to over-estimations of AR rates globally in ATLAS. Within a country, distribution of

retail versus hospital sales were not available, nor information about heterogeneity in use in different populations. Lastly, tourism was measured here by the total numbers of tourists entering and leaving a country. This metric possibly missed important information, such as destination country.

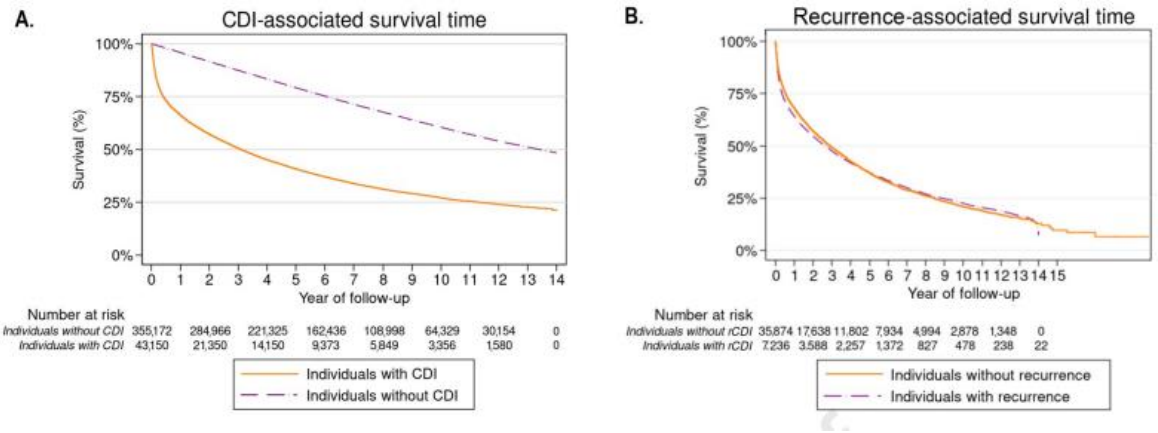
Clostridioides difficile infection-associated cause-specific and all-cause mortality: A population-based cohort study Clin Microbiol Infect published online July 18, 2023

doi.org/10.1016/j.cmi.2023.07.008

The investigators aimed to examine the association between CDI and all-cause and cause-specific mortality. They additionally explored contributing causes of mortality, including recurrent CDI (rCDI), hospital- or community-acquired CDI, chronic comorbidities, and age.

The investigators did a nationwide population-based cohort study (from 2006–2019) comparing individuals with CDI to the entire Swedish background population using standardized mortality ratios (SMRs). Additionally, a matched cohort design (1:10), utilizing multivariable Poisson regression models, providing incidence rate ratios (IRRs) with 95% Cis.

This study included 43,150 individuals with CDI and 355,172 controls. In total, 69.7% were ≥65 years, and 54.9% were female. CDI was associated with a 3 to 7-fold increased mortality rate (IRR=3.5, 95% CI: 3.3-3.6; SMR=6.8, 95% CI:6.7- 40 6.9) compared to the matched controls and Swedish background population, respectively. Mortality rates were highest for hospital-acquired CDI (IRR=2.4, 95% CI: 1.9- 42 3.2) and during the first CDI episode (IRR=0. 2, 95% CI: 0.2-0.3 for recurrent versus first CDI). Individuals with CDI had more chronic comorbidities than controls, yet mortality remained higher among CDI cases even after adjustment and stratification for comorbidity; CDI was associated with increased mortality (IRR=6.1, 95% CI: 5.5- 46 6.8), particularly among those without any chronic comorbidities.



Comment: CDI was associated with elevated all-cause and cause-specific mortality, despite adjusting for comorbidities. Mortality rates were consistently increased across both sexes, all age groups, and comorbidity groups. The Patient Registry captures 85-95% of all inpatient

care diagnoses, and 80% of all hospital-based outpatient healthcare. However, since CDI-reporting is not mandatory in Sweden, CDI may remain un-diagnosed, particularly milder cases may be missed. Community-acquired CDI could also be underrepresented in this study, since they lacked information whether individuals were diagnosed with CDI within three days after in-hospital admission, classifying those as having hospital-acquired CDI. The registry had no clinical data on CDI-severity, applied diagnostic tests or clinical practices regarding CDI diagnosis. Comorbidities were associated with CDI and higher mortality making it difficult to distinguish if CDI is a main or contributing cause if it actually affected survival.

In conclusion, survival bias and underlying comorbidities may play a role. Although they adjusted for chronic comorbidities, residual confounding by comorbidities may still impact results. Mortality risks were, however, still significantly increased when they restricted their analyses to those without comorbidities.

Management of Pediatric Pneumonia: A Decade After the PIDS/IDSA Guideline.

Clin Infect Dis published online June 24, 2023

doi.org/10.1093/cid/ciad385

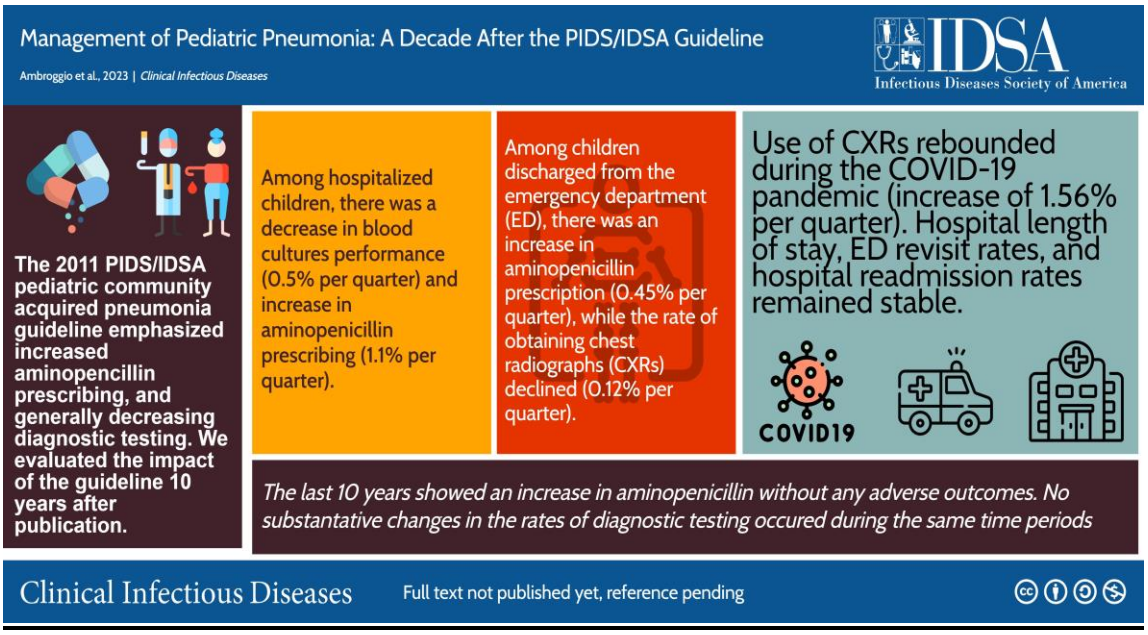
This is a quasi-experimental study which queried a national administrative database of children's hospitals to identify children 3 months-18 years with CAP who visited one of 28 participating hospitals from 2009-2021. PIDS/IDSA pediatric CAP guideline recommendations regarding antibiotic therapy, diagnostic testing, and imaging were evaluated. Segmented regression interrupted time series was used to measure guideline concordant practices with interruptions for guideline publication and the Covid-19 pandemic. Children were excluded if they had a chronic complex condition, were transferred from an outside hospital, or had a prior diagnosis of CAP within the past 30 days. Billing data were used to assess rates of performance of diagnostic testing, including blood culture, CBC, CXR, and acute phase reactants, including ESR, CRP, and procalcitonin (PCT).

Of 315,384 children with CAP, 71,804 (22.8%) were hospitalized. Among hospitalized children, there was a decrease in blood cultures performance (0.5% per quarter) and increase in aminopenicillin prescribing (1.1% per quarter). Among children discharged from ED, there was an increase in aminopenicillin prescription (0.45% per quarter), while the rate of obtaining CXRs declined (0.12% per quarter). However, use of CXRs rebounded during the Covid-19 pandemic (increase of 1.56% per quarter). Hospital length of stay, ED revisit rates, and hospital readmission rates remained stable. There was no change in rates of performance of CBC or acute phase reactants among hospitalized children relative to guideline publication.

Comment: CAP is the fifth most prevalent and second most costly reason for hospitalization among children. Additionally, CAP accounts for the most antibiotic days of therapy for children who are hospitalized. [Infect Control Hosp Epidemiol. 2013;34(12):1252-1258] Prior to 2011, there was wide variability in the use of diagnostic testing, antibiotic choice, and hospitalization rates among children with CAP. To standardize care, PIDS and IDSA jointly published a guideline in 2011 for the management of otherwise healthy children with suspected CAP. [Clin Infect Dis. 2011;53: e25-76] In general, the guideline recommends less overall diagnostic testing for children with CAP unless it will directly impact management. The guideline strongly recommends narrow spectrum antibiotic use for uncomplicated CAP as first-line therapy for

children without penicillin allergy, specifically amoxicillin for children treated in the outpatient setting and amoxicillin or ampicillin for children treated in the ED or inpatient setting. In fact, the most noticeable change since guideline publication is the increased use of aminopenicillins. The PIDS/IDSA guideline also strongly recommends obtaining a CXR for children who are hospitalized with moderate to severe CAP; however, the guideline recommends against performance of CXR in children with CAP who are well enough to be managed as outpatients. In this study, 81% of children discharged from the ED received a CXR. Since the guideline was published, studies have shown that CXR performance in children managed as outpatients does not change overall diagnosis or antibiotic prescribing. [Pediatrics. 2020;145(3)] Although blood culture is not routinely recommended in children with CAP, they were obtained in 7.9% of children with CAP in the ED and 44.6% of children hospitalized with CAP. Blood cultures are, however, recommended in children requiring hospitalization for presumed bacterial CAP that is moderate to severe. In two separate studies, blood cultures were positive in only 2.2%-2.5% of cultures with *Streptococcus pneumoniae* being the most common pathogen detected. [Pediatrics. 2019;144(1); Pediatrics. 2017;140(3)] It is unknown whether illness severity has changed over time, impacting the utilization of the ED or hospitalization among children diagnosed with CAP. Although the recommendations are to reduce diagnostic testing for children with suspected CAP, there may be other diagnoses as part of the differential, therefore it is difficult using administrative data to determine the intent of ordering the specific diagnostic test or medication. Vaccine history and/or immunization status was not available.

Overall, they observed that the PIDS/IDSA guideline published in 2011 was associated with a meaningful reduction in broad-spectrum antibiotic prescribing among children with pneumonia, without adverse outcomes. However, rates of diagnostic testing including the use of CXR in the ED setting was not substantially changed. Future guidelines should incorporate both diagnostic and antimicrobial stewardship to improve patient safety and outcomes. See “A Statewide Quality Initiative to Reduce Unnecessary Antibiotic Treatment of Asymptomatic Bacteriuria” on page 3.



Periprosthetic Joint Infection: Current Clinical Challenges Clin Infect Dis published online July 12, 2023

doi.org/10.1093/cid/ciad360

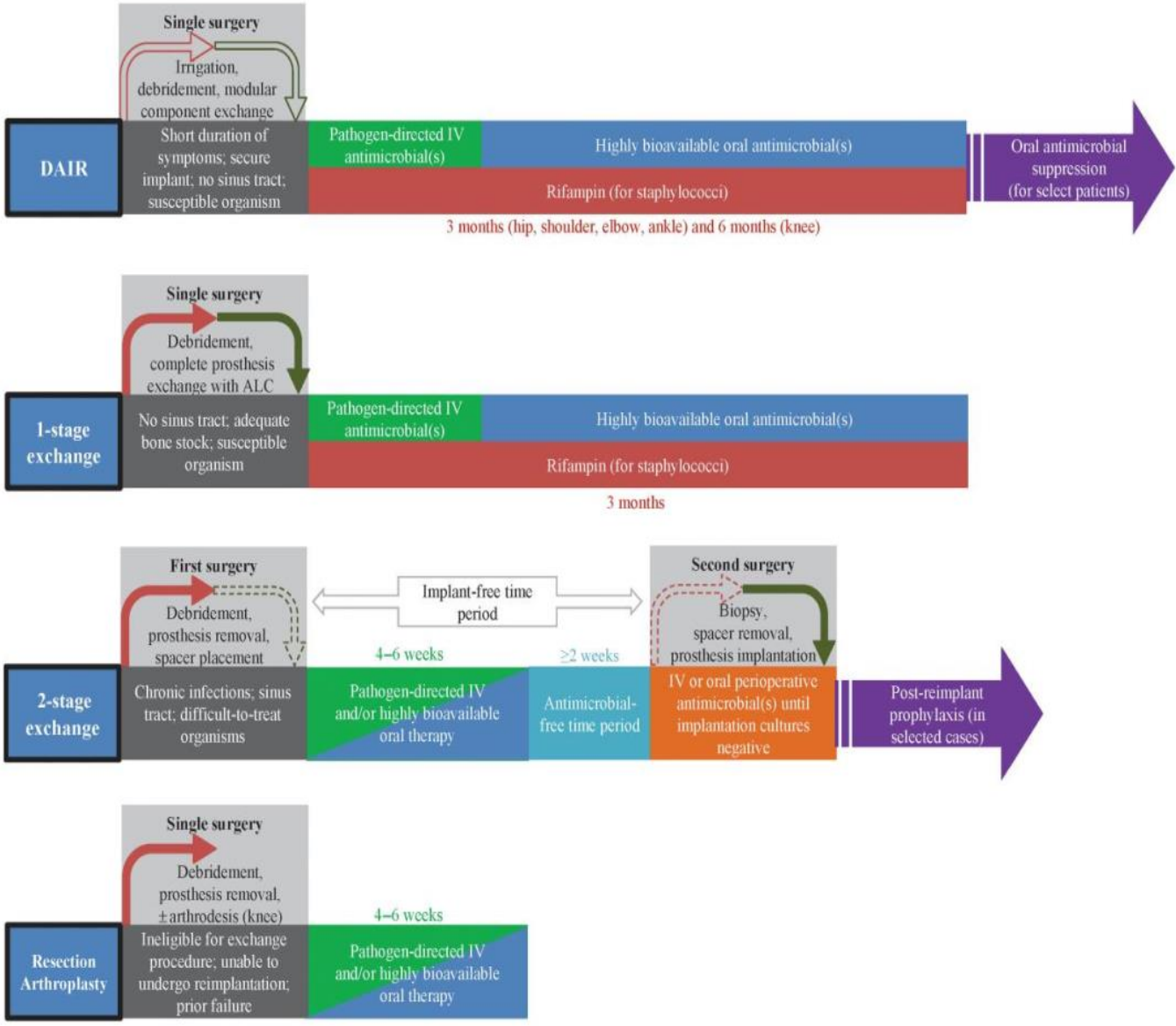
Highlights

- The last several decades have seen important advances in diagnostic approaches and surgical and antimicrobial treatments, significant gaps in our understanding remain. Treatment has become more nuanced over time.
- Overall, periprosthetic joint infection (PJI) impacts more than 2% of arthroplasty patients. Given the growth in arthroplasty procedures, the incidence of PJI will continue to rise.
- A single positive culture for pathogenic organisms, such as *Staphylococcus aureus*, is highly likely to represent a true infection, while positive cultures for organisms such as *Cutibacterium acnes* and/or coagulase-negative Staphylococci (CoNS), may be true positives or represent contamination.
- When confirmation of infection is not achieved through initial synovial fluid testing, additional synovial fluid biomarkers, such as alpha-defensin, synovial CRP, and calprotectin, may be used. Of these, alpha-defensin has been the most widely adopted. Alpha-defensin is an antimicrobial peptide released by neutrophils activated in the presence of pathogens and has a high reported sensitivity (96%) and specificity (95%) when measured in synovial fluid for PJI. [Int Orthop 2017; 414:2447-2455]
- imaging studies have limited utility in confirming PJI diagnosis, though imaging is still useful in evaluating noninfectious causes of pain and in informing surgical decision making. Plain films are an important tool to assess loosening, subsidence, and periprosthetic fracture but are neither sensitive nor specific for PJI.

- PJI due to organisms such as MRSA, *P aeruginosa*, and *Candida* species is more difficult to eradicate, and their preoperative identification should be weighed among other factors in surgical decision-making.
- Culture yield is improved when antibiotics are withheld at least 14 days prior to sampling, by including incubation in blood culture bottles and via prolonged (14 days) culture incubation.
- Culture-negative PJI, reported in 5%–42% of cases [J Arthroplasty 2019; 34:S339-350].
- When organisms do not grow in conventional culture, sonication and molecular methods, including 16S ribosomal RNA PCR and sequencing can be considered. The FDA recently approved synovial fluid multiplex PCR panel (BioFire), which may provide additional information, but importantly, the BioFire PJI panel does not include *C. acnes* or any CoNS other than *S lugdunensis.*
- The most commonly used surgical procedures include debridement, antibiotics, and implant retention (DAIR) and 1-stage and 2-stage exchange procedures.
- For acute and hematogenous infections, the first line of treatment is typically a DAIR procedure for short duration of symptoms.
- DAIR procedures are less successful compared with exchange procedures, estimated at 60%–67% in several recent meta-analyses. [J Infect 2018; 77:479-488]
- In general, the 2-stage provides best infection control outcomes.
- The choice of surgical procedure hinges on the duration of symptoms, the offending microorganism, and patient comorbidities and considers trade-offs between surgical morbidity and the likelihood of successful infection control.
- Decisions about antibiotic duration hinge on whether all components of the arthroplasty are resected or retained.
    - A treatment duration of minimum 4–6 weeks of antimicrobial therapy following resection arthroplasty (either as part of a 2-stage exchange or as definitive management), 1-stage exchange, or DAIR was advised.
    - For patients undergoing DAIR or 1-stage exchange with staphylococcal infection, recommendations differed according to the joint involved. For hip PJI, 3 months of rifampin-based combination therapy was recommended. For knee PJI, 3 months of such therapy was recommended when 1-stage exchange was performed, and 6 months when the patient underwent DAIR. No consensus about need for chronic suppression afterwards.
    - The recent Duration of Antibiotic Treatment in Prosthetic Joint Infection (DATIPO) trial was conducted to provide clarity around duration of PJI therapy. Patients who underwent surgical treatment of PJI were randomized to receive either 6 or 12 weeks of antimicrobial therapy [N Engl J Med 2021; 384:1991-2001]. The primary outcome, persistent infection within 2 years, occurred in 18.1% of the 6-week group and 9.4% of the 12-week group, failing to meet the prespecified noninferiority level. However, most failure events occurred among those who underwent DAIR, supporting current clinical practice of extending antibiotic treatment beyond 6 weeks for PJI treated with DAIR.
    - Findings among those with knee PJI treated with DAIR were particularly notable (38.2% failure, 6-week arm vs 13.5%, 12-week arm). This emphasizes the high failure rates for knee PJI treated with DAIR and suggests that such patients should receive courses of at least 12 weeks and/or be considered for oral suppression.
    - Among patients undergoing 1-stage exchange, 12 weeks of therapy is supported by guideline documents and large studies. In the DATIPO study, among those undergoing 1-stage exchange, 6 weeks was noninferior to 12 weeks, although it was underpowered to detect a difference within this subgroup.

- For patients undergoing a 2-stage procedure, the historical standard has been a 6-week treatment course following resection, then an antibiotic-free period prior to reimplantation. In the DATIPO trial, among those who underwent 2-stage exchange, a 10.1% risk difference between the 2 treatment groups favored the 12-week arm. However, in the centers where this study was performed, 1-stage exchange is the standard for most patients with chronic PJI, and 2-stage exchange is reserved for those at a higher risk of failure. Therefore, accumulated experience supports a 6-week antimicrobial duration for most patients who undergo 2-stage exchange. However, there may be a subgroup of patients at higher risk of failure who would benefit from a longer duration of antibiotic therapy.
- In the last 2 decades, there has been growing practical experience and evidence for oral therapy in the management of bone and joint infection. The decision to use oral antimicrobials involves several factors. First, the organism must be susceptible to highly bioavailable oral agents, and ideally the planned regimen should be one studied for use in bone and joint infection.
- Most clinical studies suggest significant benefits of rifampin-based combination therapy in staphylococcal PJI due to bioflim. Given the consistent association with improved outcomes and the magnitude of benefit in other studies, the authors of this review use rifampin for staphylococcal PJI following DAIR or 1-stage exchange. When treating staphylococcal PJI, the authors recommend a 6-month course of rifampin for knee infections and a 3-month course of rifampin for other arthroplasty infections following DAIR.
- Long-term suppression should be targeted to those at highest risk for failure and/or those for whom recurrence would be most devastating.

Comment: This is an excellent review on current knowledge and challenges. In the end a collaborative approach and shared decision making is important in deciding on the best treatment plan. Lastly prevention is essential in reducing the risk for a PJI which include screening for MSSA and MRSA, decolonization of colonized patients, appropriate surgical prophylaxis, preoperative bathing, glucose control, normothermia, chlorhexidine alcohol surgical prep, limit traffic in the OR, etc.


Single surgery
Irrigation, debridement, modular component exchange
DAIR
Short duration of symptoms; secure implant; no sinus tract; susceptible organism
Pathogen-directed IV antimicrobial(s)
Highly bioavailable oral antimicrobial(s)
Rifampin (for staphylococci)
Oral antimicrobial suppression (for select patients)
3 months (hip, shoulder, elbow, ankle) and 6 months (knee)
Single surgery
Debridement, complete prosthesis exchange with ALC
1-stage exchange
No sinus tract; adequate bone stock; susceptible organism
Pathogen-directed IV antimicrobial(s)
Highly bioavailable oral antimicrobial(s)
Rifampin (for staphylococci)
3 months
First surgery
Debridement, prosthesis removal, spacer placement
Implant-free time period
Second surgery
Biopsy, spacer removal, prosthesis implantation
4–6 weeks
≥2 weeks
2-stage exchange
Chronic infections; sinus tract; difficult-to-treat organisms
Pathogen-directed IV and/or highly bioavailable oral therapy
Antimicrobial-free time period
IV or oral perioperative antimicrobial(s) until implantation cultures negative
Post-reimplant prophylaxis (in selected cases)
Single surgery
Debridement, prosthesis removal, ±arthrodesis (knee)
4–6 weeks
Resection Arthroplasty
Ineligible for exchange procedure; unable to undergo reimplantation; prior failure
Pathogen-directed IV and/or highly bioavailable oral therapy

A pathology-based case series of influenza- and COVID-19-associated pulmonary aspergillosis: the proof is in the tissue Am J Respir Crit Care Med published online June 13, 2023

doi.org/10.1164/rccm.202208-1570OC

Influenza-associated pulmonary aspergillosis (IAPA) has been established as a life-threatening infection, occurring early after intensive care unit (ICU) admission in up to 19-25% of critically ill influenza patients. [Lancet Respir Med 2018; 6: 782-792] Covid-19 associated pulmonary aspergillosis (CAPA) has similarly emerged as an important coinfection in critically ill Covid-19 patients. To better characterize viral-associated pulmonary aspergillosis (VAPA), investigators in Belgium retrospectively studied antemortem and autopsy data in 44 patients who died after being admitted to the intensive care unit (ICU) with severe influenza (21 patients) or COVID-19 (23 patients). Galactomannan (GM) testing, Aspergillus PCR and conventional mycological culture were performed.

Postmortem examination demonstrated invasive pulmonary aspergillosis in 12 patients (6 with influenza and 6 with COVID-19). In those diagnosed with VAPA at autopsy, sensitivity of bronchoalveolar lavage (BAL) Aspergillus galactomannan testing (GM) was 92% and specificity was 64%. BAL culture had a sensitivity of 58% with a specificity of 93%. Serum GM sensitivity was only 33%, with a specificity of 94%. Among all 44 patients, an antemortem diagnosis of VAPA was made in 21. Eleven of these cases were histologically proven after postmortem examination. Antemortem diagnosis was missed in one instance. Fungal tracheobronchitis was identified bronchoscopically in eight cases and histologically confirmed in six instances. Fungal tracheobronchitis was microscopically indistinguishable in influenza and COVID-19 cases, yet a more extensive disease severity was identified in IAPA cases.

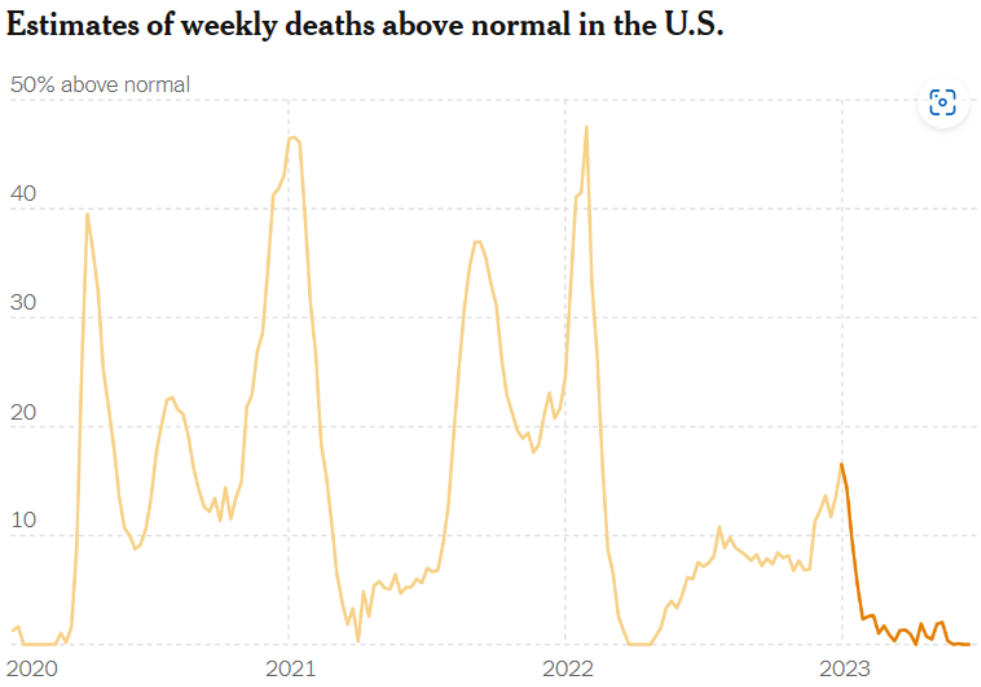
Comment: Histologically proven aspergillosis was found in >25% of cases with severe influenza or Covid-19 pneumonia. All cases but one was diagnosed prior to death, and antemortum BAL GM demonstrated high sensitivity. This study makes the argument that we should have a high index of suspicion with repeat bronchoscopic examinations for both GM testing and assessment for tracheobronchitis. Starting antifungal therapy should be prescribed for patients with severe influenza or Covid-19 pneumonia with a positive BAL GM or evidence of tracheobronchitis.

Due to the retrospective nature of the study, patient selection bias cannot be ruled out. Autopsy was routinely requested in patients who die in their ICU departments, yet the overall autopsy rate was only 35% due to capacity limitations of the pathology department. There were no statistical comparisons between influenza and Covid-19 patients, or between antemortem diagnostics and autopsy findings are reported due to sample size limitations and associated potential for irreproducibility of odds ratios for VAPA prediction. Lastly this study was based predominantly on autopsy material, therefore, association of diagnostic criteria with outcome is not possible.

COVID-19

COVID-19: Where are we now?

The Human Mortality Database now estimates that slightly fewer Americans than normal have died since March, and CDC put the excess-death number below 1 percent. The story is similar in many other countries. Below is the CDC data:



Comment: There are several factors contributing to this progress. (1) ~ ¾ of Americans have received at least one dose of vaccine; (2) more than three-quarters of Americans have been infected with Covid-19, providing natural immunity. (3) over 95 percent of adults fall into at least one of those first two categories; and (4) post-infection treatments like Paxlovid, which can reduce the severity of symptoms, became widely available last year.

To be clear, Covid-19 has not fallen to zero. The CDC's main Covid-19 webpage estimates that about 80 people per day have been dying from the virus in recent weeks, which is equal to about 1 percent of overall daily deaths. The official number is probably an exaggeration because it includes some people who had virus when they died even though it was not the underlying cause of death. Other CDC data suggests that almost one-third of official recent Covid-19 deaths have fallen into this category. Currently mortality is related to older age, immunosuppressed, and the unvaccinated.

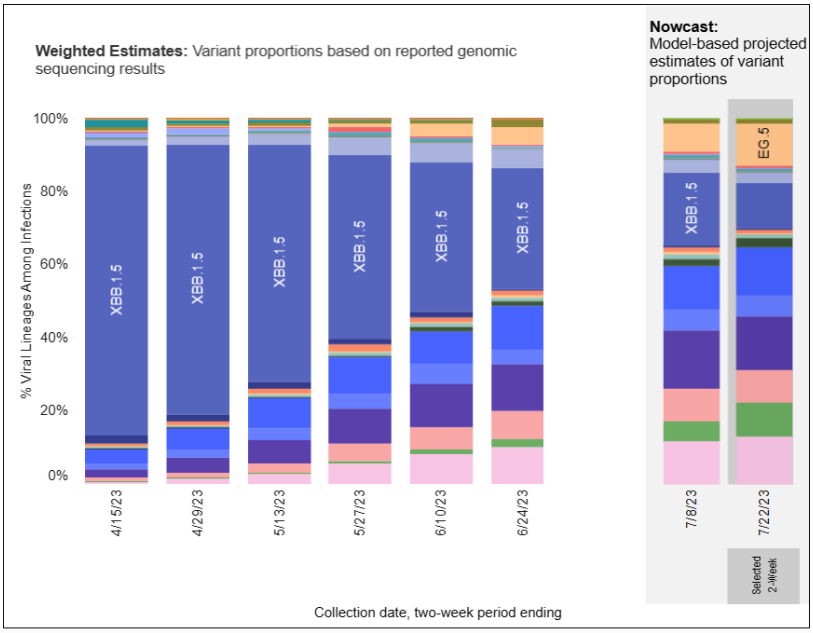
Omicron EG.5

WHO yesterday added EG.5 to the list of Omicron variants under monitoring (VUM), as most indicators for tracking COVID-19 activity declined. EG.5 is a descendant of XBB.1.9.2, with one extra spike mutation. Global prevalence has been rising since the end of May. The WHO now has seven VUMs. The number of variants of interest remains at two, including XBB.1.5, which is steadily declining, and XBB.1.16, which is holding steady at 20.7% of sequences.

The US is one of the countries seeing rising EG.5 proportions. The CDC said in its last estimates on July 22 that EG.5 made up 11.4% of samples. See below

Weighted and Nowcast Estimates in United States for 2-Week Periods in 4/2/2023 – 7/22/2023

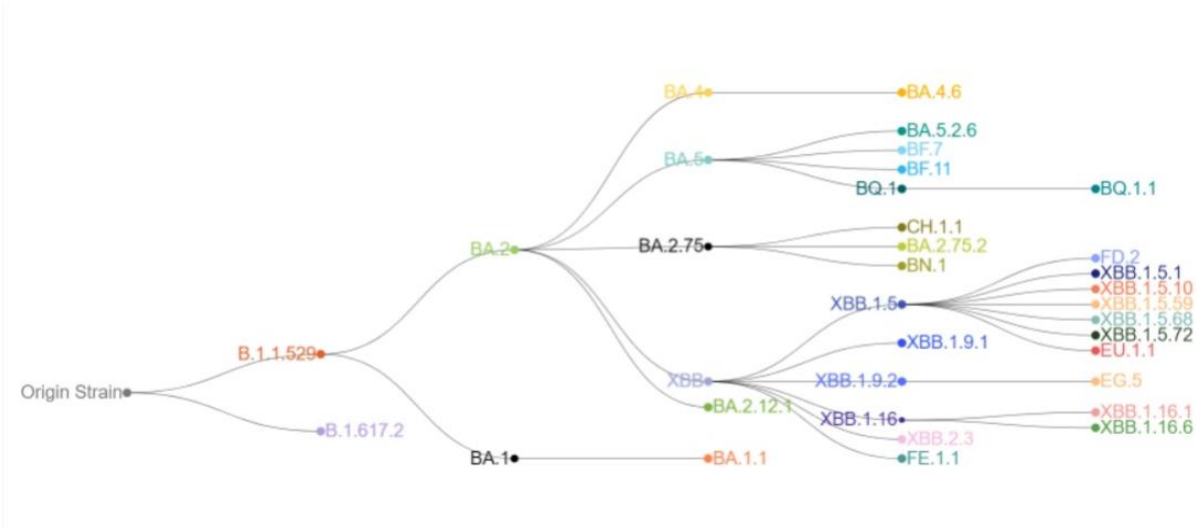
Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



Nowcast Estimates in United States for 7/9/2023 – 7/22/2023

USA

WHO label	Lineage #	%Total	95%PI
Omicron	XBB.1.16	14.8%	12.2-17.8%
	XBB.1.9.1	13.2%	8.3-20.3%
	XBB.2.3	13.0%	10.4-16.1%
	XBB.1.5	12.3%	10.2-14.7%
	EG.5	11.4%	8.3-15.3%
	XBB.1.16.6	9.3%	5.4-15.4%
	XBB.1.16.1	8.8%	7.4-10.4%
	XBB.1.9.2	5.6%	4.0-7.8%
	XBB	3.0%	1.8-4.9%
	XBB.1.5.72	2.2%	1.2-3.9%
	CH.1.1	1.7%	0.8-3.6%
	FE.1.1	1.1%	0.6-2.0%
	XBB.1.5.68	1.0%	0.6-1.7%
	XBB.1.5.10	1.0%	0.6-1.6%
	EU.1.1	0.6%	0.3-1.0%
	XBB.1.5.59	0.4%	0.2-1.0%
	XBB.1.5.1	0.3%	0.2-0.5%
	FD.2	0.0%	0.0-0.1%
	BA.2	0.0%	0.0-0.0%
	BN.1	0.0%	0.0-0.0%
	BQ.1.1	0.0%	0.0-0.0%
	BA.5	0.0%	0.0-0.0%
	BQ.1	0.0%	0.0-0.0%
	BA.2.75	0.0%	0.0-0.0%
Other	Other*	0.1%	0.0-0.1%



Comment: The WHO said so far there's no evidence that EG.5 is fueling any rises in cases or deaths or that infections involving the virus are more severe. The current increase is being driven by a mix of XBB variants. (See above) However, hospitalizations have increased in the US in the last week. (See above) Other than XBB.1.9.2 descendant lineages, no other VUMs are showing rising proportions. ED visits for Covid-19 rose 17.4% compared with the past week, with several states in the Southeast and Northeast showing substantial increases. Wastewater viral load is up 40% in the last week in the Midwest, but still lower than prior years. In fact measures of Covid-19 rates including virus levels in wastewater, ED visits, test positivity and hospital admissions are increasing nationally, according to the most recent CDC statistics. Several factors may be contributing to this rise. First the heat is sending people to indoor air-conditioned spaces, where Covid may be transmitted more easily compared with outside. Second, travel at an all-time high as people crowd into airports sharing respiratory pathogens from around the world. Third, most people have not received the latest booster and even if they have, neutralizing antibodies fade in 2-3 months meaning they can be reinfected but are unlikely to get severe disease due to T-cell immunity. In addition, we have learned that Covid-19 mutates faster than influenza, so it is changing more quickly and able to better evade our immunity from prior infections. To put all this into perspective, Covid-19 rates are still at historic lows since most people have immunity. Despite these trends, I do not think we need to panic, especially if you're young and healthy. But elderly people and those who are immunocompromised might want to keep a closer attention to the numbers and act more cautiously, including masking in crowded indoor spaces, if rates continue to rise.

Performance of Rapid Antigen Tests to Detect Symptomatic and Asymptomatic SARS-CoV-2 Infection Ann Intern Med published online July 4, 2023

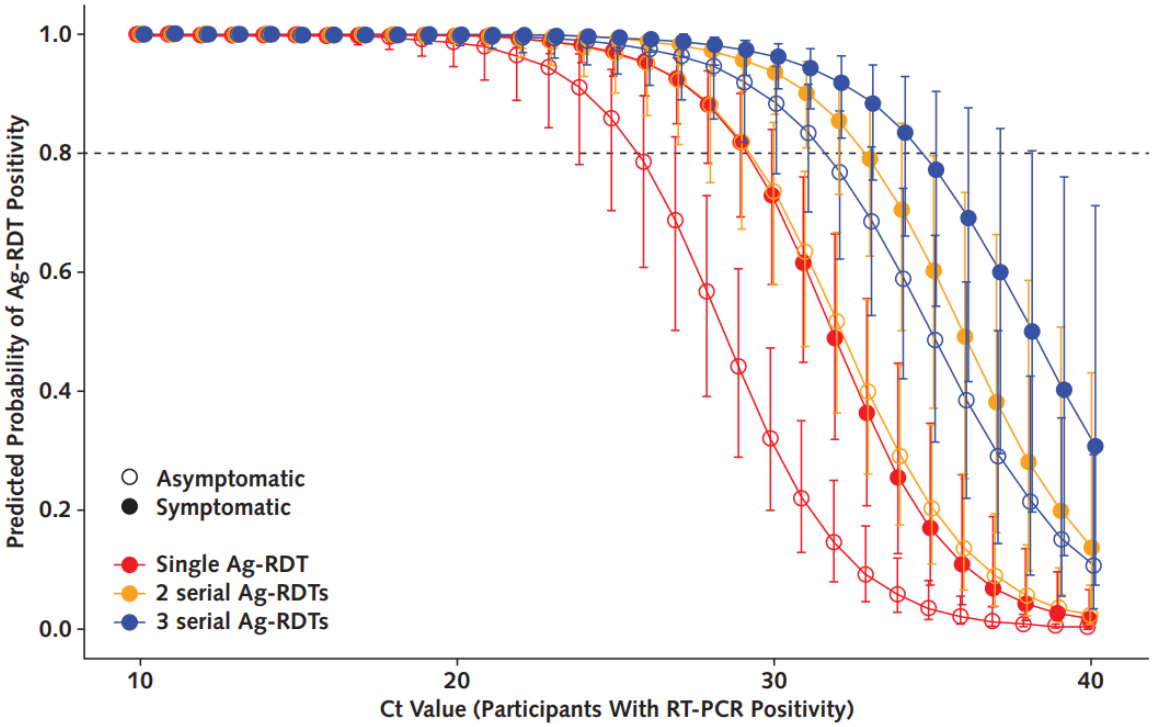
doi:10.7326/M23-0385

The investigators set out to evaluate the performance of Ag-RDTs for detection of SARS-CoV-2 among symptomatic and asymptomatic participants. This prospective cohort study enrolled participants between October 2021 and January 2022. Participants completed Ag-RDTs and PCR testing for SARS-CoV-2 every 48 hours for 15 days. Participants were enrolled digitally throughout the mainland US. They self-collected anterior nasal swabs for Ag-RDTs and PCR testing. Nasal swabs for PCR were shipped to a central laboratory, whereas Ag-RDTs were done at home. Enrolled participants were assigned to 1 of 3 types of AgRDT with EUA (Quidel QuickVue At-Home OTC COVID-19 Test, BinaxNOW COVID-19 Antigen Self-Test, or BD Veritor At-Home COVID-19 Test). Cycle threshold (Ct) values for the E gene from the PCR test were used as a measure to quantify viral load. To approximate real-world scenarios, where a person may not necessarily start testing with Ag-RDTs on the day of infection onset, they calculated performance separately on DPIPPs (days past index PCR positivity) 2, 4, 6, 8, and 10 to approximate scenarios where a person started serially testing with Ag-RDTs on those days.

Of 7361 participants in the study, 5353 who were asymptomatic and negative for SARS-CoV-2 on study day 1 were eligible. In total, 154 participants had at least 1 positive PCR result.

The sensitivity of Ag-RDTs was measured on the basis of testing once (same-day), twice (after 48 hours), and thrice (after a total of 96 hours). The analysis was repeated for different days past index PCR positivity (DPIPPs) to approximate real-world scenarios where testing initiation may not always coincide with DPIPP 0. Results were stratified by symptom status. The performance of Ag-RDTs among symptomatic and asymptomatic participants was evaluated by Ct value to analyze the performance by viral load. [higher CT lower viral load]

Among 154 participants who tested positive for SARS-CoV-2, 97 were asymptomatic and 57 had symptoms at infection onset. Serial testing with Ag-RDTs twice 48 hours apart resulted in an aggregated sensitivity of 93.4% (95% CI, 90.4% to 95.9%) among symptomatic participants on DPIPPs 0 to 6. When singleton positive results were excluded, the aggregated sensitivity on DPIPPs 0 to 6 for 2-time serial testing among asymptomatic participants was lower at 62.7% (CI, 57.0% to 70.5%), but it improved to 79.0% (CI, 70.1% to 87.4%) with testing 3 times at 48-hour intervals. The distribution of Ct values significantly differed between symptomatic and asymptomatic participants, with symptomatic participants having lower Ct values on average than asymptomatic participants at DPIPPs 0 and 2. On the day of index PCR positivity, more than 75% of asymptomatic persons had a Ct value of 30 or higher, whereas fewer than 33% of symptomatic persons had a Ct value of 30 or higher. At the end of 1 week from index PCR positivity (DPIPP 6), most of both asymptomatic and symptomatic persons had a Ct value lower than 30.



Comment: The performance of Ag-RDTs was optimized when asymptomatic participants tested 3 times at 48-hour intervals and when symptomatic participants tested 2 times separated by 48 hours. Their finding of higher Ct values associated with lower sensitivity is in line with results from a comprehensive meta-analysis encompassing data from 214 clinical studies and 112,323 samples, which demonstrated that the sensitivity of rapid antigen testing deteriorated with increasing Ct values. [PLoS Med. 2021;18:e1003735] They also observed that Ag-RDTs have higher sensitivity among symptomatic participants, regardless of Ct value. This study was done during the circulation of the Delta and Omicron variants, and future variants may warrant further investigation, especially as milder, less symptomatic variants emerge in an immune population. The public health implications of these findings are that people who initial testing for SARS-CoV-2 should exercise caution despite an initial negative result on an Ag-RDT and favor mask wearing and avoiding crowded places if they suspect they may be infected or have been exposed. Repeat Ag-RDT improves sensitivity, 2 tests within 48 hours for symptomatic and 3 tests in 48 hours for asymptomatic persons. I found this study to provide the clearest guidance to date on use of Ag-RDT to date. They conclude: “Dissemination of clear guidance for appropriate testing using Ag-RDTs based on data from this study may help preserve confidence in the performance of serial Ag-RDTs to detect SARS-CoV-2.”

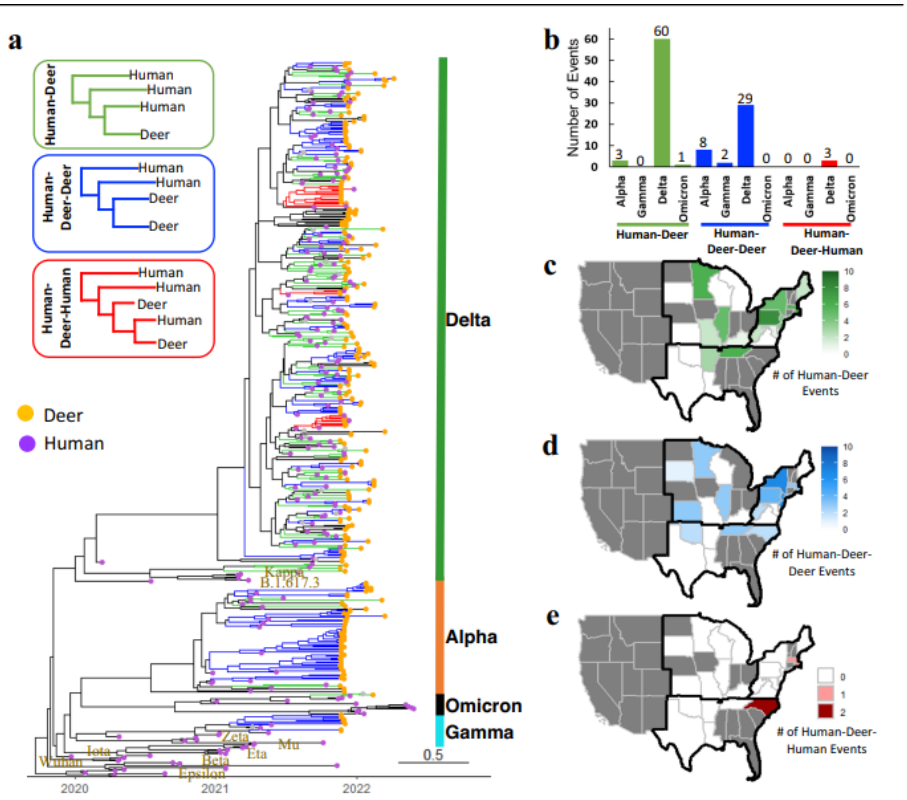
Transmission of SARS-CoV-2 in free-ranging white-tailed deer in the United States
Nat Comm published online July 10, 2023

doi.org/10.1038/s41467-023-39782-x

Transmission of SARS-CoV-2 from humans to free-ranging white-tailed deer (Odocoileus virginianus) poses a unique public health risk due to the potential for reservoir establishment where variants may persist and evolve. The investigators collected 8,830 respiratory samples from free-ranging white-tailed deer across Washington, DC and 26 states in the US between November 2021 and April 2022. They obtained 391 sequences and identified 34 Pango lineages including the Alpha, Gamma, Delta, and Omicron variants.

Evolutionary analyses showed these white-tailed deer viruses originated from at least 109 independent spillovers from humans, which resulted in 39 cases of subsequent local deer-to-deer transmission and three cases of potential spillover from white-tailed deer back to humans. Viruses repeatedly adapted to white-tailed deer with recurring amino acid substitutions across spike and other proteins.

Genetic association between SARS-CoV-2 viruses from humans and those from free-ranging white-tailed deer in the United States (November 2021- April 2022)



Comment: These studies show that SARS-CoV-2 is likely to have spread widely within the US white-tailed deer population. Additionally, their research shows that SARS-CoV-2 was transmitted from humans to deer, mutated, and was potentially transmitted back to humans. Despite these findings there is no evidence that animals play a significant role in spreading the virus to humans, however, this research is helping us understand if animals like the white-tailed deer, can act as a host or reservoir, meaning an animal host where the virus can survive and potentially mutate. This is another example where human, animal, and environmental health groups can collaborate when One Health questions arise.

FDA approved remdesivir for COVID-19 Patients with severe renal impairment.

FDA approval was based on the phase 1 and phase 3 REDPINE trials, which showed the pharmacokinetics and safety profile of the drug in patients with severe renal impairment. Updated prescribing information for remdesivir states dose adjustments are not required for renal-impaired patients and eGFR testing is not required before or during treatment, according to the release.

Comment: Patients with advanced [chronic kidney disease] CKD and end-stage kidney disease are at high risk for severe Covid-19 with hospitalization and mortality rates remaining high, even for those who are vaccinated. In the past, patients with renal insufficiency were not eligible to receive remdesivir. The drug is indicated for the treatment of Covid-19 in adults and pediatric patients in the US, who are either hospitalized or at high risk for progression to severe Covid-19.

A common allele of HLA is associated with asymptomatic SARS-CoV-2 infection

Nature published online July 19, 2023

doi.org/10.1038/s41586-023-06331-x

Studies have demonstrated that at least 20% of individuals infected with SARS-CoV-2 remain asymptomatic. [Ann. Intern. Med. 2020; 173: M20-3012] The investigators felt examining asymptomatic infection provides a unique opportunity to consider early immunological features that promote rapid viral clearance. Here, the investigators postulated that variation in the human leukocyte antigen (HLA) loci may underly processes mediating asymptomatic infection.

They enrolled 29,947 volunteer bone marrow donors, because high-quality genetic data was already available for this group. They asked volunteers to use their smartphones daily to track their own SARS-CoV-2 infections and resulting symptoms, including a runny nose, a scratchy throat, fever or chills. Participants were also asked to record if they had taken a Covid-19 test each week and note monthly whether they had been hospitalized.

During the nine-month study period, 1,428 unvaccinated individuals reported a positive Covid-19 test, and 136 of them had no symptoms. Among the asymptomatic participants, 20 percent carried a common HLA variant called HLA-B*15:01. People carrying two copies of this variant — one passed down from each parent — were more than eight times more likely to remain asymptomatic than those carrying other HLA variants.

The majority of the reactive T cells displayed a memory phenotype, were highly polyfunctional and were cross-reactive to a peptide derived from seasonal coronaviruses. The crystal structure of HLA-B*15:01–peptide complexes demonstrates that the peptides NQKLIANQF and NQKLIANAF (from OC43-CoV and HKU1-CoV) [common cold viruses] share a similar ability to be stabilized and presented by HLA-B*15:01. Finally, they show that the structural similarity of the peptides underpins T cell cross-reactivity of high-affinity public T cell receptors, providing the molecular basis for HLA-B*15:01-mediated pre-existing immunity. This suggests carriers exposed to seasonal cold viruses may have developed preexisting immunity to SARS-CoV-2.

Comment: Four strains of seasonal coronaviruses (229E-CoV, NL63-CoV, OC43-CoV and HKU1-CoV) represent 15% to 30% of all respiratory tract infections every year. Notably, previous studies have shown that T cells can cross-react to SARS-CoV-2 and seasonal coronavirus peptides, indicating that long-lasting T cell protective immunity can potentially limit the severity of Covid-19. [Immunity 2021; 54:1055–1065]. Although the results may explain why some asymptomatic infections occur, the study was limited to genetic data that already existed from prior work. Also, the study group was quite homogenous, with all participants self-identifying as White and 81 percent self-identifying as female.