Infectious Diseases Watch

February 2023

Ed Septimus, MD

General Infectious Diseases

29 physician specialties ranked by 2022 burnout rates.

Across the board, physician burnout has jumped 11 percentage points from 2018, when 42 percent of physicians said they were burned out. The "Medscape Physician Burnout & Depression Report 2023 is based on survey responses from more than 9,100 physicians across 29 specialties, which were collected between June and October 2022. At least one third of respondents in all specialties said they were burned out. Below are the top 10:

1. Emergency medicine — 65 percent of physicians reported burnout

2. Internal medicine — 60 percent

3. Pediatrics — 59 percent

4. Obstetrics and gynecology — 58 percent

Infectious diseases — 58 percent

5. Family medicine — 57 percent

6. Neurology — 55 percent
Critical care — 55 percent
Anesthesiology — 55 percent

7. Pulmonary medicine — 54 percent
Radiology — 54 percent

8. Oncology — 52 percent
Gastroenterology — 52 percent

9. General surgery — 51 percent
Diabetes and endocrinology — 51 percent

10. Rheumatology — 50 percent

Comment: As ID Watch reported in the January 1, 2023, issue, ID is not filling fellowship slots. As this survey demonstrates ID is tied for 4th in terms of burnout. IDSA has been sounding the alarm about this important issue.

Piperacillin Nephrotoxicity Is Driven by Elevated Serum Trough Concentrations. J Antimicrob Chemother published online December 21, 2022

doi.org/10.1093/jac/dkac416.

Beta-lactams such as piperacillin have been associated with acute kidney injury (AKI), especially when given with vancomycin. Determining the etiology of drug-induced AKI is challenging especially in critically illness patients. The investigators evaluated piperacillin exposure in critically ill children and young adults to determine pharmacokinetic and clinical features associated with AKI. Repeated measurements of free piperacillin serum concentration were applied to a statistical pharmacokinetic model to estimate area under the curve exposure in the first 24 hours (AUC24), highest peak concentration in the first 24 hours ($C_{max}24$), and highest trough concentration in the first 24 hours ($C_{min}24$). Piperacillin AKI was adjudicated if kidney disease guideline staging indicated that severe AKI was present 1 to 7 days after the first dose of piperacillin/tazobactam. Clinical and pharmacokinetic predictors of AKI were determined with regression analysis.

Among 107 patients (age range, 1 month–33 years) 15% were rated as having possible or probable piperacillin AKI. Estimated AUC24 was higher in patients with AKI than without AKI (2042 vs. 1445 mg×hour/L; P=0.03). Maximum $C_{min}24$ was higher in those with AKI (50.1 vs. 10.7 mg/L; P<0.001). Logistic regression indicated that age and higher $C_{min}24$ were independent predictors of AKI.

Comment: In this retrospective cohort study, renal toxicity of piperacillin was related to AUC and highest C_{min} within the first 24 hours of therapy. This is typical for many nephrotic drugs followed by age. The rate of nephrotoxicity was surprisingly high given the younger age of this cohort. This study was too small to examine the impact of other possible other renal toxic drugs and/or conditions. Nonetheless this article and others have alerted us to the relationship of increased nephrotoxicity and dosing of piperacillin and vancomycin in high-risk patients.

Going Back in Time: Increasing Penicillin Susceptibility among Methicillin-Susceptible Staphylococcus aureus Osteoarticular Infections in Children

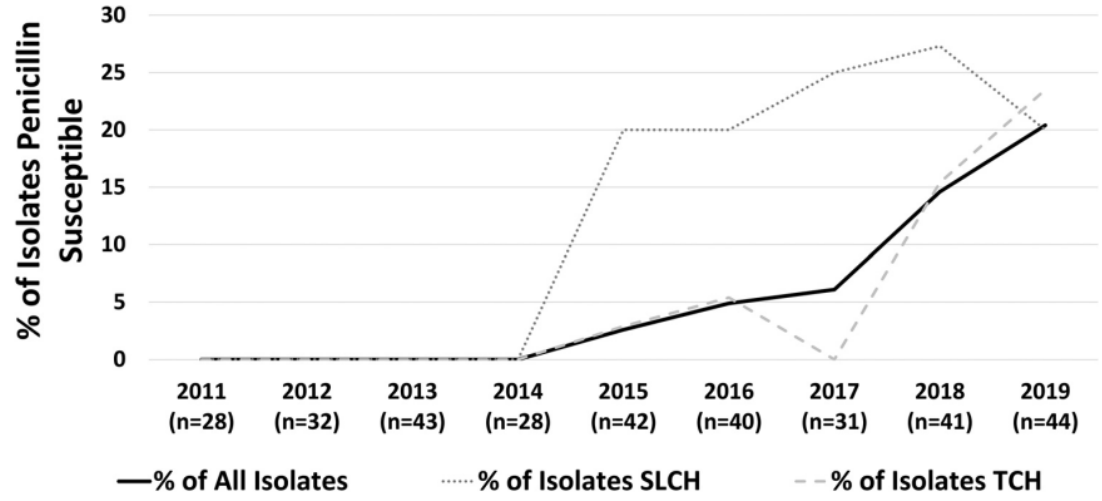
Antimicrob Agents Chemother 2023; 67:1-8

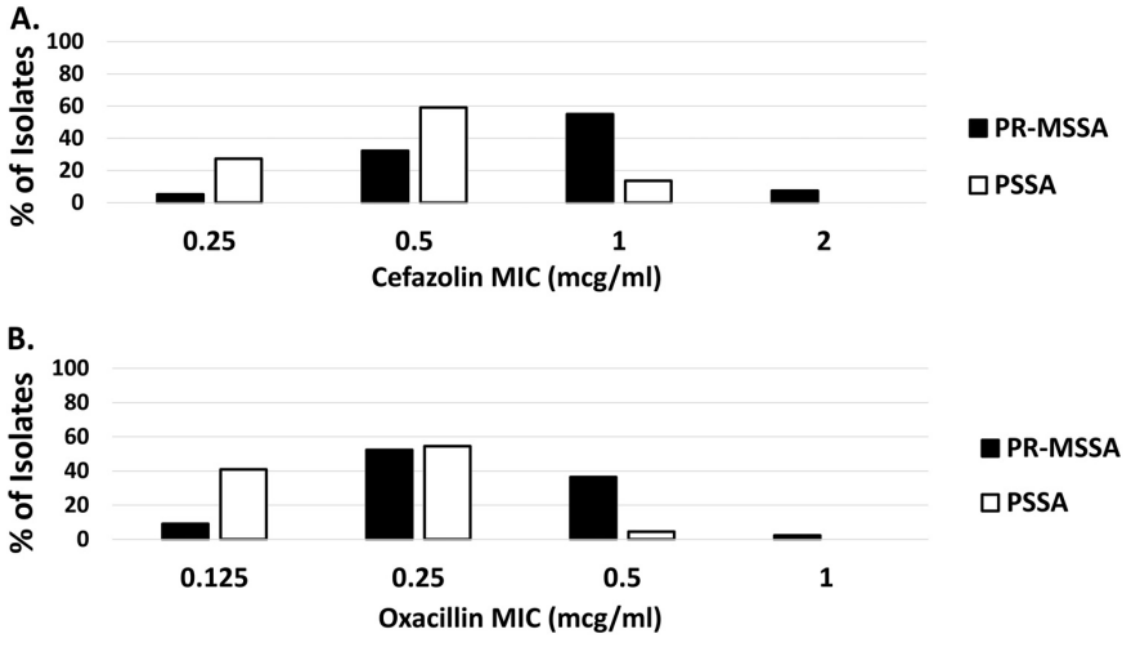
Doi:10.1128/aac.01196-22

Recently, some centers have described an increase in the proportion of methicillin susceptible S. aureus (MSSA) which are also susceptible to penicillin (PSSA). The investigators studied the prevalence of penicillin susceptibility among pediatric MSSA acute hematogenous osteoarticular infection (OAI) isolates. MSSA OAI isolates were obtained through surveillance studies at Texas Children's and St. Louis Children's Hospitals from January 2011 to December 2019. All isolates underwent PCR for blaZ b-lactamase, PVL genes and agr group. All blaZ negative isolates then underwent penicillin MIC determination. blaZ negative isolates with penicillin MIC ≤ 0.125 mg/mL were considered PSSA. Multilocus sequence typing (MLST) was conducted on a subset

of isolates. A total of 329 unique isolates were included in the study. The median patient age was 9.2 years (IQR:5.1 to 12.2).

Overall, 6.7% of isolates were penicillin susceptible. No PSSA were detected prior to 2015 but increased yearly thereafter. By the final study year, 20.4% of isolates were PSSA (P = 0.001). PSSA were similar to penicillin-resistant MSSA (PR-MSSA) isolates in terms agr group and PVL carriage as well as clinical presentation and outcomes. PSSA were of distinct sequence types compared to PR-MSSA. PSSA appears to be increasing among OAI in U.S. children. Overall, PSSA isolates are associated with a similar clinical presentation as penicillin-resistant isolates.





Comment: Cases of PSSA and PR-MSSA OAI were similar with respect to clinical presentation and epidemiology, making it impossible to distinguish between these based on clinical risk factors alone. This study did not capture data on preceding antimicrobial use, and thus, it is unclear how antibiotic pressure may have impacted penicillin susceptibility. They observed very low penicillin and ampicillin MICs among PSSA, much lower than for oxacillin or cefazolin. According to current CLSI guidance, susceptibility to penicillinase-labile penicillin's as a group (e.g., ampicillin) in S. aureus can be inferred from susceptibility to penicillin assuming the penicillin MIC ≤0.125 mg/mL and tests for β-lactamase are negative. The precise impact that penicillin-susceptibility in-and-of-itself has on clinical outcomes in S. aureus is unclear. In previous retrospective studies in both Canada and Sweden, there were no differences in mortality between adult patients with bacteremia caused by PSSA versus PR-MSSA after adjusting for confounders (Am J Med. 2016; 129:1331–1333; Infect Dis. 2017; 49:454–460). The investigators in this publication observed a numerically higher rate of orthopedic complications associated with PSSA isolates, although this did not achieve statistical significance. Given the overall relatively small number of PSSA isolates, this study was underpowered to detect subtle differences in clinical presentation between PSSA and PR-MSSA. IV penicillin requires every 4-to-6-hour dosing and can be costly compared to cefazolin.

On a different note, some have suggested increased PSSA may be driven by increasing use of daptomycin. [Ann NY Acad Sci 2013; 1277:139]. Another publication reported the deletion of blaZ-plasmid from PRSA was also associated with increased MIC to daptomycin. [Microbiol Resour Announ 2020;9:e01515] I think microbiology laboratories should consider nitrocefin assays to determine absence of β-lactamases in PSSA. However, the potential for use of penicillin treatment in PSSA OAI and other infections warrants further study.

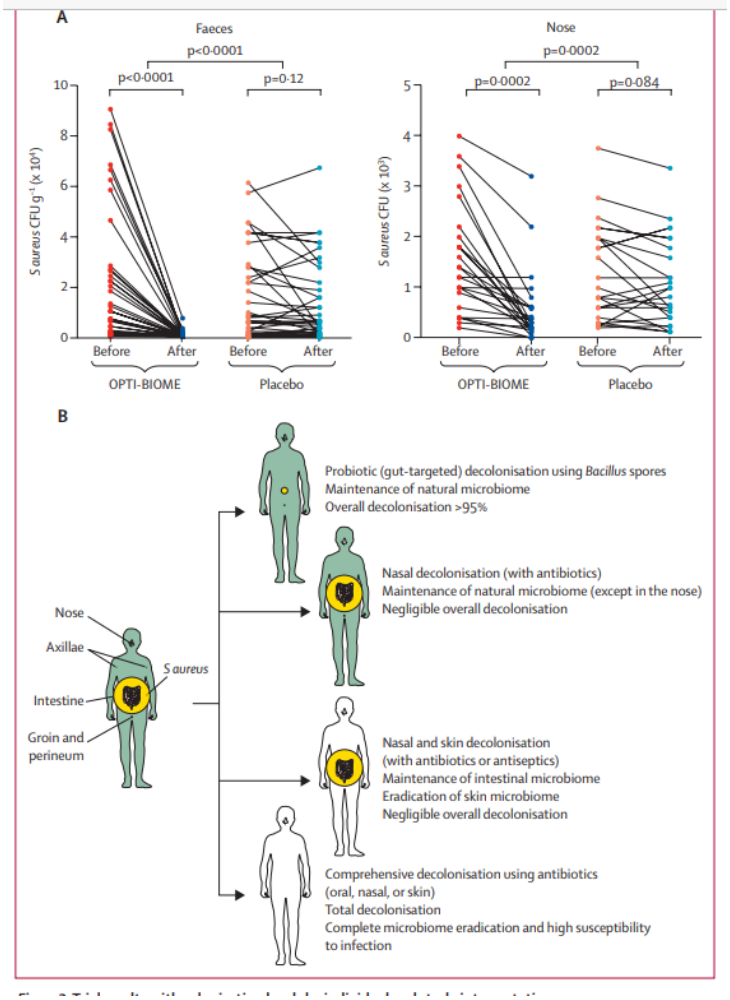
Probiotic for pathogen-specific Staphylococcus aureus decolonisation in Thailand: a phase 2, double-blind, randomised, placebo-controlled trial. Lancet Microbe published online January 13, 2023

https://doi.org/10.1016/ S2666-5247(22)00322-6

This is a single-center, phase 2, double-blind, randomized, placebo-controlled trial in adults who were colonized by S aureus. Eligible participants were adults (aged ≥18 years) without history of intestinal disease, antibiotic treatment, or hospital admission within the previous 90 days. Participants were excluded if they were pregnant, breastfeeding, taking probiotics, or had diarrhea. Participants were allocated (1:1) to groups by computer randomization in blocks of four, and research coordinators were masked to group allocation. Participants received 250 mg of probiotic B subtilis MB40 or placebo once per day for 30 days and S aureus colonization was determined after the last dose was received. The primary outcome was colonization by S aureus (continuous, mean decrease in colony-forming-unit count) in the intestine (by fecal counts) and nares (by nasal swabs) after intervention (30-day regimen of B subtilis probiotic). The research was conducted by researchers at the NIH.

115 participants were colonized by S aureus, either in the intestine (n=84), nose (n=50), or both (n=19), and were randomly assigned to treatment (n=55) and placebo groups (n=60). Oral

probiotic B subtilis resulted in significant reduction of S aureus in stool (96·8%; p <0.0001) and nose (65·4%; p=0·0002). There were no differences in adverse effects or significant microbiome changes between the intervention and placebo groups.



Comment: The probiotic used did not kill S. aureus, but it specifically and strongly diminishes its capacity to colonize. In prior studies, the same group discovered an S. aureus sensing system needed for S. aureus to grow in the gut. They also found that fengycins, Bacillus lipopeptides that are part peptide and part lipid, prevent the S. aureus sensing system from functioning, thereby eliminating the bacteria. [Nature 2018; 562:532–537] In this recent study B subtilis probiotic eliminated more than 95% of the total S aureus colonizing the human body without altering the microbiota. This probiotic strategy offers some advantages over presently used decolonization strategies especially for potential use in people with chronic or long-term risk of S aureus infection. The researchers also found that levels of S. aureus bacteria in the gut far exceeded S. aureus in the nose, which for decades has been the focus of staph infection prevention research. Furthermore, by establishing a defining role of the intestinal colonization site, their findings call for revisiting fundamental notions about S aureus colonization. Among the non-intestinal S aureus colonization sites, they only analyzed the nose. The intervention group also had somewhat higher average baseline fecal and nasal CFUs than the placebo groups. However, the differences were not significant. This approach requires further study but may be a viable alternative to current practice.

FDA panel recommends rezafungin as new Candida treatment.

The FDA antimicrobial drugs advisory committee yesterday recommended the approval of rezafungin for the treatment of candidemia and invasive candidiasis in adults, the first new drug to treat the conditions in over a decade.

The FDA committee's recommendation passed by a 14-to-1 vote. The committee's vote isn't binding, but the FDA often accepts the recommendations of its advisory groups when making its approval decisions.

The FDA panel based its recommendation on encouraging phase 3 and phase 2 trials, along with extensive nonclinical findings. When given once-weekly to patients, rezafungin demonstrated statistical noninferiority when compared to caspofungin, the current standard of care that is given once daily. The results of the studies met the primary end points defined by the FDA and the European Medicines Agency.

Comment: Rezafungin in vitro has activity against *C. auris* including some echinocandin resistant strains (higher MICs vs *FKS1* mutations).

2 days versus 5 days of postoperative antibiotics for complex appendicitis: a pragmatic, open-label, multicentre, noninferiority randomised trial Lancet published online January 17, 2023

doi.org/10.1016/S0140-6736(22)02588-0

This is a pragmatic, open-label, non-inferiority trial involving 15 hospitals in the Netherlands. Patients with complex appendicitis (aged ≥8 years) were randomly assigned (1:1) to receive 2 days or 5 days of intravenous antibiotics after appendectomy. Randomization was stratified by center, and treating physicians and patients were not masked to treatment allocation. The primary endpoint was a composite endpoint of infectious complications and mortality within 90 days. The main outcome was the absolute risk difference (95% CI) in the primary endpoint, adjusted for age and severity of appendicitis, with a non-inferiority margin of 7.5%. Outcome assessment was based on electronic patient records and a telephone consultation 90 days after appendectomy. Efficacy was analyzed in the intention-to-treat and per-protocol populations. Safety outcomes were analyzed in the intention-to-treat population.

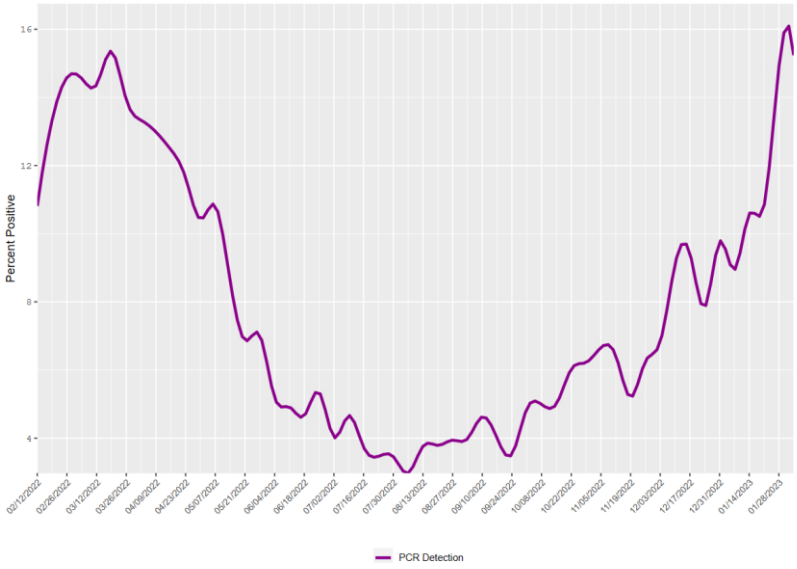
13,267 patients were screened and 1066 were randomly assigned, 533 to each group. Appendectomy was done laparoscopically in 955 (95%) of 1005 patients. The telephone follow-up was completed in 664 (66%) of 1005 patients. The primary endpoint occurred in 51 (10%) of 502 patients analyzed in the 2-day group and 41 (8%) of 503 patients analyzed in the 5-day group (adjusted absolute risk difference 2.0%, 95% CI -1.6 to 5.6). Rates of complications and re-interventions were similar between trial groups. Fewer patients had adverse effects of antibiotics in the 2-day group (45 [9%] of 502 patients) than in the 5-day group (112 [22%] of 503 patients; odds ratio [OR] 0.344, 95% CI 0.237 to 0.498). Re-admission to hospital was more frequent in the 2-day group (58 [12%] of 502 patients) than in the 5-day group (29 [6%] of 503 patients; OR 2.135, 1.342 to 3.396). There were no treatment-related deaths.

	2-day group (n=502)	5-day group (n=503)
(Continues from previous page)		
Laparoscopic procedure	480 (96%)	475 (94%)
Operating time (min)	47 (36–59)	46 (36–58)
Missing	3 (<1%)	11 (2%)
Classification of appendicitis†		
Gangrenous	264 (53%)	283 (56%)
Perforated	365 (73%)	365 (73%)
Periappendiceal abscess	75 (15%)	61 (12%)
Pus or peritonitis present	421 (84%)	440 (87%)
Diffuse peritonitis	51 (10%)	45 (9%)
Drain placement	8 (2%)	13 (3%)
Histopathological examination‡		
Appendicitis	485 (97%)	491 (98%)
Malignant or premalignant lesion	12 (2%)	8 (2%)
Missing	4 (1%)	5 (1%)

Comment: This is the first adequately powered level I randomized controlled trial that evaluates the safety and efficacy of postoperative antibiotics restricted to 2 days for complex appendicitis. This study indicates that no more than 2 days of postoperative antibiotics for complex appendicitis is needed after adequate source control. These recommendations are valid for laparoscopic appendectomy in a well-resourced health-care setting. [95% of patients underwent laparoscopic surgery which suggests a health system that facilitates earlier patient presentation, better preoperative capacity to diagnose, and the ability to identify and treat postoperative complications] They did not report ethnicity data. Such data remains challenging to collect, as current classification systems are inadequate and approval to collect such data is challenging to obtain. After open appendectomy, patients might benefit from an extended regimen of antibiotics. Whether 2 days of antibiotics is safe for patients who are immunocompromised or pregnant is unknown. The relatively high losses to follow-up were equal across trial arms, which should reduce the chance of bias. Follow-up was primarily conducted using electronic patient records, in which some events might not be recorded, introducing the potential for detection and recall bias.

Norovirus National Trends-CDC February 9, 2023

Participating U.S. laboratories report the total number of norovirus tests performed that week, and the number of those tests that were positive to CDC weekly.



Comment: Each point on the trend graph below displays the average percent of tests that were positive from three adjacent weeks: the specified week, and the weeks preceding and following it. [3 week moving average] In the US, cases of norovirus occur most frequently during late fall, winter, and early spring. The rate of norovirus tests coming back positive, averaged over three weeks, exceeded 15% at the end of last week, the highest recorded since late March 2022. The Midwest had the highest average test positivity rate for norovirus at over 19%.

Outbreak of Extensively Drug-resistant *Pseudomonas aeruginosa* Associated with Artificial Tears. HAN February 1, 2023

The CDC is issuing this Health Alert Network (HAN) Health Advisory about infections with an extensively drug-resistant strain of Verona Integron-mediated Metallo-β-lactamase (VIM) and Guiana-Extended Spectrum-β-Lactamase (GES)-producing carbapenem-resistant *Pseudomonas aeruginosa* (VIM-GES-CRPA) in 12 states. Most patients reported using artificial tears. Patients reported more than 10 different brands of artificial tears, and some patients used multiple brands. The majority of patients who used artificial tears reported using EzriCare Artificial Tears, a preservative-free, over-the-counter product packaged in multidose bottles. CDC laboratory testing identified the presence of the outbreak strain in opened EzriCare bottles with different lot numbers collected from two states.

Recommendations for Healthcare Providers

- Immediately discontinue using EzriCare Artificial Tears pending additional guidance from CDC and FDA.
- Advise patients who used EzriCare Artificial Tears to monitor for signs and symptoms of infection. Perform culture and antimicrobial susceptibility testing when clinically indicated.
- Healthcare providers treating patients for keratitis or endophthalmitis should ask patients if they have used EzriCare Artificial Tears. Providers should consider performing culture and antimicrobial susceptibility testing to help guide therapy if patients report use of this product.
- Healthcare providers treating VIM-GES-CRPA infections should consult with a specialist knowledgeable in the treatment of antibiotic-resistant bacteria to determine the best treatment option. VIM-GES-CRPA isolates associated with this outbreak are extensively drug-resistant. Isolates that underwent susceptibility testing at public health laboratories were not susceptible to cefepime, ceftazidime, piperacillin-tazobactam, aztreonam, carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, fluoroquinolones, polymyxins, amikacin, gentamicin, and tobramycin. A subset of 3 isolates that underwent antimicrobial susceptibility testing for cefiderocol at clinical laboratories or CDC were susceptible to this agent.
- Place patients infected or colonized with VIM-GES-CRPA and admitted to acute care settings in isolation and use Contact Precautions. For residents of skilled nursing facilities who are infected or colonized with VIM-GES-CRPA, use Enhanced Barrier Precautions if the resident does not have an indication for Contact Precautions.
- At this time, CDC does not recommend testing patients who have used this product and who are not experiencing any signs or symptoms of infection.

Comparing complication rates of midline catheter vs. Peripherally inserted central catheter (PICC). A systematic review and meta-analysis OFID published online January 18, 2023

DOI: 10.1093/ofid/ofad024

The investigators conducted a systematic review and meta-analysis of RCTs and observational trials. The primary outcomes were catheter-related bloodstream infection (CRBSI) and thrombosis. Secondary outcomes evaluated included mortality, failure to complete therapy, catheter occlusion, phlebitis, and catheter fracture. The certainty of evidence was assessed using the GRADE approach.

Of 8,368 citations identified, 20 studies met eligibility criteria, including one RCT and nineteen observational studies. Midline use was associated with fewer patients with CRBSI compared to PICC (OR: 0.24; 95% CI: 0.15 to 0.38). This association was not observed when we evaluated risk per catheter. No significant association was found between catheters when evaluating risk of localized thrombosis and pulmonary embolism. A subgroup analysis based on location of thrombosis showed higher rates of superficial venous thrombosis in patients using midline (OR: 2.30; 95% CI: 1.48 to 3.57). We did not identify any significant difference between midline and PICC for the secondary outcomes.

Comment: The findings suggest that patients who use midline might experience fewer CRBSI than those who use PICC. It is important to note that CLABSI rates being higher in PICC is largely being driven by one study [JAMA Intern Med 2022; 182: 50-8] A prior meta-analysis found no difference in rates of CRBSI between PICC and midline (RR: 0.77; 95% CI: 0.50 to 1.17).[Nursing Open 2021; 8:1292-300] However, the use of midline catheter was associated with greater risk of superficial vein thrombosis. These findings can help guide future cost-benefit analyses and direct comparative RCTs to further characterize efficacy and risks of PICC versus midline catheters. Most of the data came from observational studies and only one small RCT (n=54) at high risk of bias, which ultimately accounted for overall very low certainty in the evidence. Inclusion of head-to-head prospective studies was limited. Further head-to-head RCTs in patients who are candidates to receive either PICC or midline are needed. For NHSN reporting midlines are not considered central lines.

High Dose Cefepime Versus Carbapenems for Bacteremia Caused by Enterobacterales with Moderate to High Risk of Clinically Significant ampC β-lactamase Production. OFID published online January 25, 2023

https://doi.org/10.1093/ofid/ofad034

Studies suggest that serious infections caused by Enterobacterales with a moderate to high risk of clinically significant AmpC production can be successfully treated with cefepime if the cefepime minimum inhibitory concentration (MIC) is ≤2 µg/mL. However, isolates with a cefepime susceptible dose-dependent (SDD) MIC of 4-8 µg/mL should receive a carbapenem due to target attainment and extended-spectrum β-lactamase (ESBL) concerns. Several Enterobacterales spp. contain chromosomally encoded and inducible ampC genes, with E. cloacae, K. aerogenes, and C. freundii demonstrating a moderate to high risk for clinically significant inducible AmpC production (AmpC-E). Exposure of these bacteria to certain β-lactam antibiotics, even if they demonstrate initial in vitro susceptibility, can induce ampC gene expression, which may lead to clinical failure.

The investigators conducted a retrospective cohort study of hospitalized patients with E. cloacae, K. aerogenes or C. freundii BSIs from January 2015 to March 2022 receiving high dose cefepime or a carbapenem. High dose cefepime was defined as 2 g every 8 hours, while meropenem and ertapenem were dosed 1-2 g every 8 hours and 1 g every 24 hours, respectively. Cox regression models were used with incorporation of inverse probability of treatment weighting (IPTW) and time-varying covariates.

Of the 315 patients included, 169 received cefepime and 146 received a carbapenem (ertapenem n=90, meropenem n=56). Cefepime was not associated with an increased risk of 30- day mortality compared to carbapenem therapy (adjusted hazard ratio [aHR] 1.45; 95% confidence interval [CI] 0.79-2.14), which was consistent for patients with cefepime SDD isolates (aHR 1.19; 95% CI 0.52-1.77). Multivariable weighted Cox models identified Pitt Bacteremia score >4 (aHR 1.41; 95% CI 1.04-1.92), deep infection (aHR 2.27; 95% CI 1.21-4.32), and ceftriaxone-resistant AmpC-E (aHR 1.32; 95% CI 1.03-1.59) to be independent predictors associated with increased mortality risk, while receipt of prolonged infusion β-lactam was protective (aHR 0.67; 95% CI 0.40-0.89).

Comment: Among patients with bacteremia caused by Enterobacterales with moderate to high risk of clinically significant AmpC production, these data demonstrate similar risk of 30-day mortality for high dose cefepime or a carbapenem as definitive β-lactam therapy. IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-negative Infections suggests that infections caused by AmpC-E can be successfully treated with cefepime with the caveat that cefepime SDD AmpC-E isolates have a higher likelihood of being an ESBL- producer and thus, should preferentially be treated with a carbapenem since cefepime is considered suboptimal. [Clin Infect Dis 2022; 74:2089–2114]. Another controversial topic regarding AmpC-E is whether carbapenems are necessary for infections caused by all ceftriaxone-resistant Enterobacterales spp. In the current study, ceftriaxone resistant isolates were independently associated with 30-day mortality in multivariable Cox regression analysis. According to the IDSA Guidance, carbapenems are the preferred drugs for moderate to severe infections caused by ESBL-producing E. coli, K. pneumoniae, K. oxytoca, or P. mirabilis of which a ceftriaxone MIC of ≥2 µg/mL can be used as a proxy for ESBL production. While most E. coli, K. pneumoniae, K. oxytoca, or P. mirabilis producing ESBLs have ceftriaxone MIC ≥2 µg/mL, data evaluating ceftriaxone-resistance and ESBL production in other AmpC-E is limited. The current study also demonstrated that receipt of prolonged infusion β-lactam (e.g., cefepime or meropenem) was associated with a protective effect in patients with AmpC-E bacteremia compared to those receiving an intermittent infusion. AmpC-E isolate genotyping was not conducted to confirm that the same organism was recovered and that AmpC production had in fact significantly increased. Thus, I cannot eliminate the possible presence of ESBL-producing isolates harboring and expressing β-lactamase genes other than CTX-M. SHV has previously been identified in 33% of ESBL-producing E. cloacae isolates and current molecular panels do not identify SHV.

Azithromycin to Prevent Sepsis or Death in Women Planning a Vaginal Birth N Engl J Med published online February 9, 2023

DOI: 10.1056/NEJMoa2212111

This is a multicountry, placebo-controlled, randomized trial. The study involved eight sites in seven countries: Bangladesh, Democratic Republic of the Congo, Guatemala, India, Kenya, Pakistan, and Zambia). They assigned women who were in labor at 28 weeks' gestation or more and who were planning a vaginal delivery to receive a single 2-g oral dose of azithromycin or placebo. The two primary outcomes were a composite of maternal sepsis or death and a composite of stillbirth or neonatal death or sepsis.

A total of 29,278 women underwent randomization. The incidence of maternal sepsis or death was lower in the azithromycin group than in the placebo group (1.6% vs. 2.4%), with a relative risk of 0.67 (95% confidence interval [CI], 0.56 to 0.79; P<0.001), but the incidence of stillbirth or neonatal death or sepsis was similar (10.5% vs. 10.3%), with a relative risk of 1.02 (95% CI, 0.95 to 1.09; P=0.56). The difference in the maternal primary outcome appeared to be driven mainly by the incidence of sepsis (1.5% in the azithromycin group and 2.3% in the placebo group), with a relative risk of 0.65 (95% CI, 0.55 to 0.77); the incidence of death from any cause was 0.1% in the two groups (relative risk, 1.23; 95% CI, 0.51 to 2.97). Neonatal sepsis occurred in 9.8% and 9.6% of the infants, respectively (relative risk, 1.03; 95% CI, 0.96 to 1.10). The incidence of stillbirth was 0.4% in the two groups; neonatal death within 4 weeks after birth

occurred in 1.5% in both groups. Azithromycin was not associated with a higher incidence in adverse events. During an interim analysis, the data and safety monitoring committee recommended stopping the trial for maternal benefit.

Comment: The results are consistent with findings from a large US trial and other studies involving the use of azithromycin in women who had undergone a c-section delivery and received usual antibiotics. In the US trial, the use of azithromycin resulted in a lower incidence of maternal infections (including a 50% lower risk of endometritis and wound infections) than the use of placebo and was associated with fewer readmissions or unscheduled care visits but did not affect newborn outcome. [N Engl J Med 2016; 375:1231-41] The frequencies of prophylactic use of antibiotics (which may reflect increased screening for group B streptococcus) and c-section birth varied according to site and were particularly high in several non-African sites. The use of azithromycin is postulated to reduce infections because of its broad antimicrobial coverage, including for ureaplasma, mycoplasmas and some anaerobes that may not be covered by other commonly prescribed antibiotics. However, the investigators did not perform cultures for these specific microorganisms. Will this study be sufficient to change clinical practice? More long-term data are needed to inform the association between the routine use of oral azithromycin prophylaxis for vaginal delivery, macrolide resistance patterns, and subsequent effects on the microbiome.

Respiratory Viruses

Worst Avian Flu in U.S. History Is Hitting Poultry, Wild Birds, Even Bears WSJ 1.23.23

The worst avian-influenza outbreak in US history is continuing to decimate poultry flocks across the Midwest and Colorado. While it rarely affects humans, the disease is mostly fatal for domestic birds. It can also infect other animals. Recently Montana wildlife officials said three young grizzly bears had contracted bird flu during the fall and were euthanized, the first known cases of grizzlies getting the disease. The bears likely contracted the virus from eating infected birds, according to Montana Fish, Wildlife and Parks officials. To keep bird flu from spreading, entire poultry flocks must be destroyed after an infection is confirmed. The outbreak has caused the deaths of nearly 58 million poultry in 47 states, according to US Department of Agriculture data.

Comment: This is affecting the nation's egg prices and supply. If the virus were to mutate to infect mammals and spillover into humans, we may have another public health crisis. See next article.

Bird Flu Has Begun to Spread in Mammals— Here's What's Important to Know JAMA published online February 8, 2023. suggested by Cesar Arias

doi:10.1001/jama.2023.1317

A highly pathogenic avian influenza (HPAI) A(H5N1) virus spread between farmed mink in Spain last October. The virus also may have been transmitted between seals in coastal New England last summer. The events mark the first large H5N1 outbreaks potentially driven by mammal-to-mammal transmission.

There is also ongoing transmission in wild birds and poultry the virus' ongoing transmission in wild birds and poultry. The current avian influenza outbreak is now the largest on record in Europe and North America. The outbreak is being driven by H5N1 clade 2.3.4.4b viruses. The exposure to other animals is high including mammals. In addition to minks and seals, the list of mammals with confirmed infections in Europe and the Americas now includes black bear, bobcat, coyote, dolphin, ferret, fisher cat, fox, leopard, lynx, opossum, otter, pig, polecat, porpoise, raccoon, raccoon dog, skunk, and now bears. Mammals probably have become infected with H5N1 while eating sick or dead birds with high virus loads.

During the past 20 years, fewer than 900 confirmed human cases of H5N1 have been reported to the WHO. Human cases have generally been "dead-end" infections. Although there has been some evidence of human-to-human transmission between close contacts in previous H5N1 outbreaks, those cases were extremely rare. Most human infections have been among people who have had direct contact with infected poultry. Mutations will be necessary for H5N1 to develop the capability for human-to-human transmission. So far this has not been identified.

Comment: This report reminds us that Covid-19 is not the only threat we need to worry about. We need a universal influenza vaccine which continues to be developed. In addition to vaccine development, we need to increase our zoonotic disease surveillance.

Codetections of Other Respiratory Viruses Among Children Hospitalized With COVID-19. Pediatrics 2023; 151:e2022059037

During March 2020 to February 2022, the US COVID-19- Associated Hospitalization Surveillance Network (COVID-NET) identified 4372 children hospitalized with SARS-CoV-2 infection admitted primarily for fever, respiratory illness, or presumed Covid-19. They compared demographics, clinical features, and outcomes between those with and without codetections who had any non-SARS-CoV-2 virus testing. Among a subgroup of 1670 children with complete additional viral testing, they described the association between presence of codetections and severe respiratory illness using age-stratified multivariable logistic regression models.

Among 4372 children hospitalized, 62% had non-SARS-CoV-2 respiratory virus testing, of which 21% had a codetection. Children with codetections were more likely to be < 5 years old, receive increased oxygen support, or be admitted to the ICU (P < .001). Among children <5 yo having any viral codetection (< 2 yo: adjusted odds ratio [aOR] 2.1 [95% confidence interval [CI] 1.5–3.0]; 2–4 yo: aOR 1.9 [95% CI 1.2–3.1]) or rhinovirus/enterovirus codetection (<2yo aOR 2.4 [95% CI 1.6–3.7]; 2-4: aOR 2.4 [95% CI 1.2–4.6]) was significantly associated with severe illness. Among children <2yo RSV codetections were also significantly associated with severe illness (aOR 1.9 [95% CI 1.3–2.9]). No significant associations were seen among children ≥5 yo.

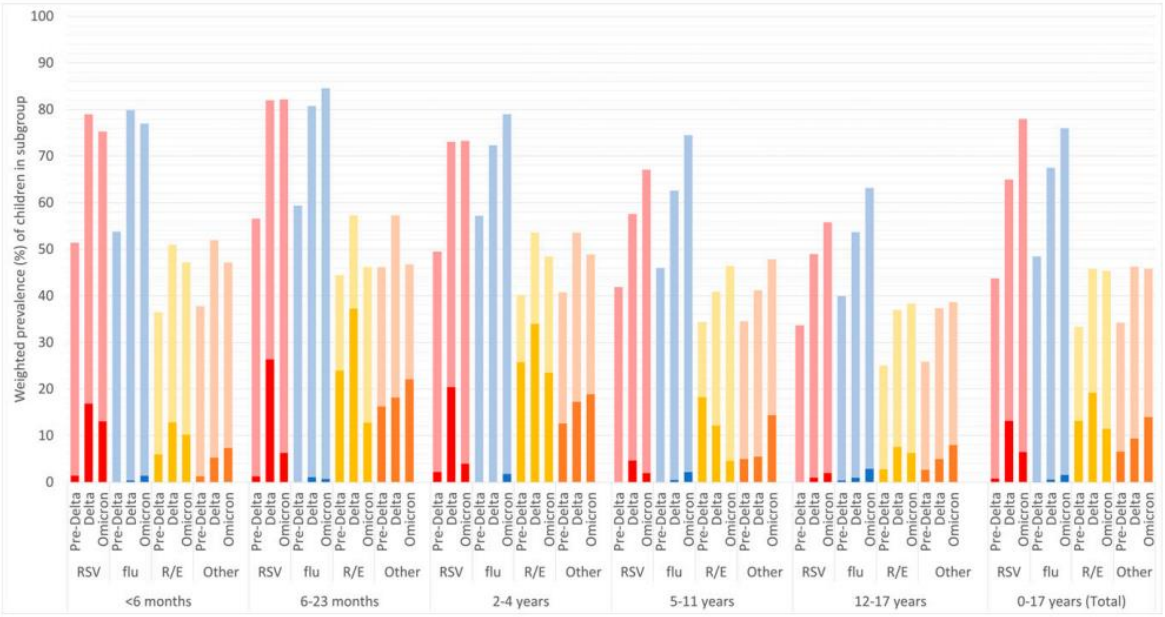


FIGURE 2

Weighted prevalence of children hospitalized ($n = 4658$) who had any non-SARS-CoV-2 virus testing and codetections stratified by virus type, age, and admission period. Each column (solid color plus shaded color) represents the weighted prevalence of children who had a test done for RSV (red), influenza (blue), rhinovirus or enterovirus ("R/E"; yellow), or "Other" viruses (orange; includes adenovirus, parainfluenza, human coronaviruses, or human metapneumovirus) in that age and time period subgroup. The bottom solid color of each column represents the prevalence of all children in the subgroup who had a codetection of that virus or group of viruses; the top shaded area represents the prevalence of children in the subgroup who had a negative test done for that virus or group of viruses. The denominator for all prevalence includes all hospitalized children in the subgroup, ie, those who were tested and those who were not tested for the virus or virus groups.

Comment: This study suggests respiratory virus codetections, including RSV and rhinovirus/enterovirus, may increase illness severity among children <5 yo. The higher frequency of viral codetections among children ages <5 yo is consistent with prepandemic data on viral codetections among hospitalized children. [N Engl J Med. 2015;372(9):835–845] Children with codetections were also more likely to have respiratory-related diagnoses and complications and more likely to receive systemic steroids than those with Covid-19 alone. Although systemic steroids are recommended for children hospitalized with Covid-19 who require high-flow oxygen or greater respiratory support, they are often not recommended for uncomplicated respiratory illness caused by other respiratory viruses, such as RSV-associated bronchiolitis. Increased use of steroids among those with codetections, compared with those with only SARS-CoV-2 infection, may be related to increased overall disease severity. Furthermore, the findings demonstrate the impact of reemerging non-SARS-CoV-2 pathogens on pediatric hospitalizations like recent RSV. Continued surveillance of circulation of SARS-CoV-2 and other viruses is critical to predict future increases in hospital utilization.

A Pragmatic Randomized Feasibility Trial of Influenza Vaccines NEJM Evidence published online January 23, 2023

DOI: 10.1056/EVIDoa2200206

The investigators conducted a pragmatic, open-label, active-controlled, randomized feasibility trial in Danish citizens aged 65 to 79 years during the 2021–2022 influenza season. Participants were randomly assigned 1:1 to receive QIV-HD or QIV-SD. Randomization was integrated into routine vaccination practice, and the trial relied solely on nationwide administrative health registries for data collection. Outcomes consisted of a feasibility assessment and descriptive rVE estimates.

A total of 12,477 randomly assigned participants were included in the final analyses. Mean (–SD) age was 71.7–3.9 years, and 5877 (47.1%) were women. Registry-based data collection was feasible, with complete follow-up data for 99.9% of participants. Baseline characteristics were comparable to those of the overall Danish population aged 65 to 79 years. The incidence of hospitalization for influenza or pneumonia was 10 (0.2%) of 6245 in the QIV-HD group and 28 (0.4%) of 6232 in the QIV-SD group (rVE, 64.4%; 95% confidence interval, 24.4 to 84.6). All-cause death occurred in 21 (0.3%) and 41 (0.7%) participants in the QIV-HD and QIV-SD groups, respectively (rVE, 48.9%; 95% confidence interval, 11.5 to 71.3).

Comment: Although the trial was not fully powered to assess clinical outcomes, receipt of the high-dose vaccine was associated with significantly lower likelihood of hospitalization for influenza or pneumonia (0.2% vs. 0.4%) and significantly lower all-cause mortality (0.3% vs. 0.7%). Incidence of other postvaccine clinical events were similar between groups, as were vaccine-associated adverse events. Previous trials invariably end by concluding we need a larger trial. This trial also calls for larger trials, but despite imperfect data, this and other trials favor HD vaccine.

HHS Weekly Report (Influenza/RSV)

Influenza

- Seasonal flu activity continues to decline across the country. CDC estimates that as of January 28, 2023, there have been at least 25 million flu illnesses, 280,000 hospitalizations, and 17,000 deaths from flu this season.
- There were 2,671 flu hospitalizations reported nationally last week. This is a decrease from the 4,028 hospitalizations reported the week prior.
- There were six reported flu pediatric deaths this past week for a total of 97 flu pediatric deaths this season.

RSV

- Overall, national trends in RSV activity continue to indicate the peak of seasonal activity has passed in all HHS Regions.

- RSV activity remains elevated in some regions but is decreasing or stable across all regions. As of January 21, 2023, preliminary data show test positivity decreased by ≥1% in 4 of 10 HHS Regions (Regions 2, 5, 8, and 10) and increase of >1% in Region 3.
- RSV-associated hospitalizations and ED visits among people of all ages have peaked, continue to decrease, and are nearing more typical winter-season levels.
- As typically seen throughout the year, children ages 4 years and younger, especially those aged <6 months, have the highest RSV-associated hospitalization rates currently. Compared to previous years, there are also more RSV-associated ED visits and hospitalizations among older children.
- In preliminary analyses among hospitalized children, there continue to be no indications of increased severity of disease among children who tested positive for RSV this year compared to the 4 pre-pandemic seasons, even when accounting for co-infections. See article above on codetection

The Influence of Rapid Influenza Diagnostic Testing on Clinician Decision-making for Patients with Acute Respiratory Infection in Urgent Care. Clin Infect Dis published online February 1, 2023

DOI: 10.1093/cid/ciad038

This study compared patients with acute respiratory infection (ARI) symptoms who received an RIDT(rapid influenza diagnostic test) and patients who did not at two urgent care facilities. Primary analysis using one-to-one exact matching resulted in 1145 matched pairs to which McNemar's 2x2 tests were used to assess association between the likelihood of prescribing, imaging or laboratory ordering, and RIDT use. Secondary analysis compared the same outcomes using logistic regression among the RIDT-tested population between participants who tested negative [RIDT(-)] and positive [RIDT(+)].

Primary analysis identified that compared to patients without RIDT testing, RIDT(+) patients were more likely to be prescribed antivirals (OR:10.23; 95% CI:5.78-19.72) and less likely to be prescribed antibiotics (OR:0.15; 95% CI:0.08-0.27). Comparing all RIDT-tested participants to all non-RIDT-tested participants, RIDT use increased antiviral prescribing odds (OR:3.07; 95% CI:2.25-4.26) and reduced antibiotic prescribing odds (OR:0.52; 95% CI:0.43- 0.63). The secondary analysis identified an increased odds of prescribing antivirals (OR:28.21; 95% CI:18.15-43.86; *P* <0.0001) and a decreased odds of prescribing antibiotics (OR:0.20; 95% CI:0.13-0.30; *P* <0.0001) for RIDT(+) participants compared to RIDT(-).

Comment: Utilization of RIDTs in patients presenting to urgent care with ARI symptoms influences clinician diagnostic and treatment decision-making, which could lead to improved patient outcomes, population-level reductions in influenza burden, and a decreased threat of antibiotic resistance. while this was a large-scale study, participants came from only two urgent care clinics in the same mid-sized midwestern city. Prescribing and diagnostic test ordering patterns are known to differ regionally. Future research should replicate this study design in different or more widespread areas. Third, baseline clinical characteristics related to underlying comorbid conditions were not collected as part of this study and could have affected the diagnostic and prescribing behaviors observed by clinicians. clinicians were acutely aware of the presence of the RIDT results in the RIDT-tested population which, as identified, resulted in differences in prescribing behaviors. This is both a finding and a source of bias (Hawthorne

effect), however clinicians were unaware of the future comparison to non-RIDT-tested individuals. Lastly, while our study mimics a randomized trial setup with the one-to-one matching, it was not truly a randomized trial, and, thus, results are not necessarily causal. If an accurate diagnosis of influenza through RIDT use is achieved and antivirals are subsequently prescribed, then studies have shown patients are more likely to have reduced severity and duration of illness [JAMA 2016; 315:1864–1873. Journal of the Pediatric Infectious Diseases Society 2015; 4:297–304] which could decrease the spread of influenza at a population level. [Pediatrics 2019; 143:e20181056] This research suggests implementation of RIDTs could provide clinicians information to improve their diagnostic and prescribing practice, benefit patients by reducing the burden of unnecessary testing, increase efficiency and reduce costs for urgent care centers, assist in mitigating the burden of influenza at the population level, and help confront the spread of antibiotic resistance. However, due to the limited sensitivities (sensitivities of RIDTs are generally approximately 50-70%), negative results of RIDTs do not exclude influenza virus infection in patients with signs and symptoms suggestive of influenza. Therefore, if clinically indicated, antiviral treatment should not be withheld from patients with suspected influenza, even if they test negative by RIDT. For hospitalized patients PCR is preferred.

COVID-19

US Plans to End Public Health Emergency for Covid-19 in May

The Biden administration plans to let the Covid-19 public health emergency expire in May, a sign that federal officials believe the pandemic has moved into a new phase.

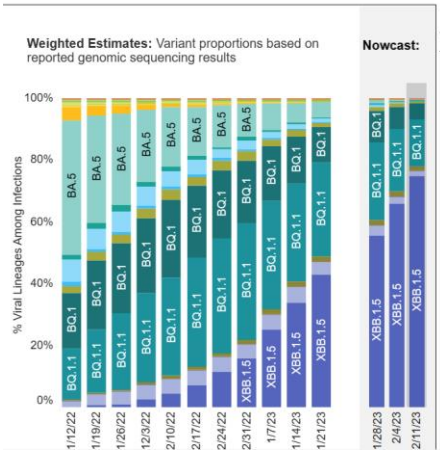
Millions of Americans have received free Covid tests, treatments, and vaccines during the pandemic, and not all of that will continue to be free once the emergency is over. The White House wants to keep the emergency in place for several more months so hospitals, health care providers and health officials can prepare for a host of changes when it ends, officials said.

Comment: Ending the emergency will prompt complex changes in the cost of Covid-19 tests and treatments that Americans are getting for free. Any charges they face will vary depending on whether they have private insurance, Medicare coverage, Medicaid coverage or no health insurance. What state they live in could also be a factor. And while vaccines will continue to be covered for people with private insurance or Medicare or Medicaid coverage, the end of the emergency will mean that some Americans may have to pay out of pocket for Covid-19 treatments, such as Paxlovid. Hospitals will also no longer receive higher Medicare payment rates for treating Covid-19 patients.

Covid-19 by the Numbers

Weighted and Nowcast Estimates in United States for Weeks of 11/6/2022 – 2/11/2023

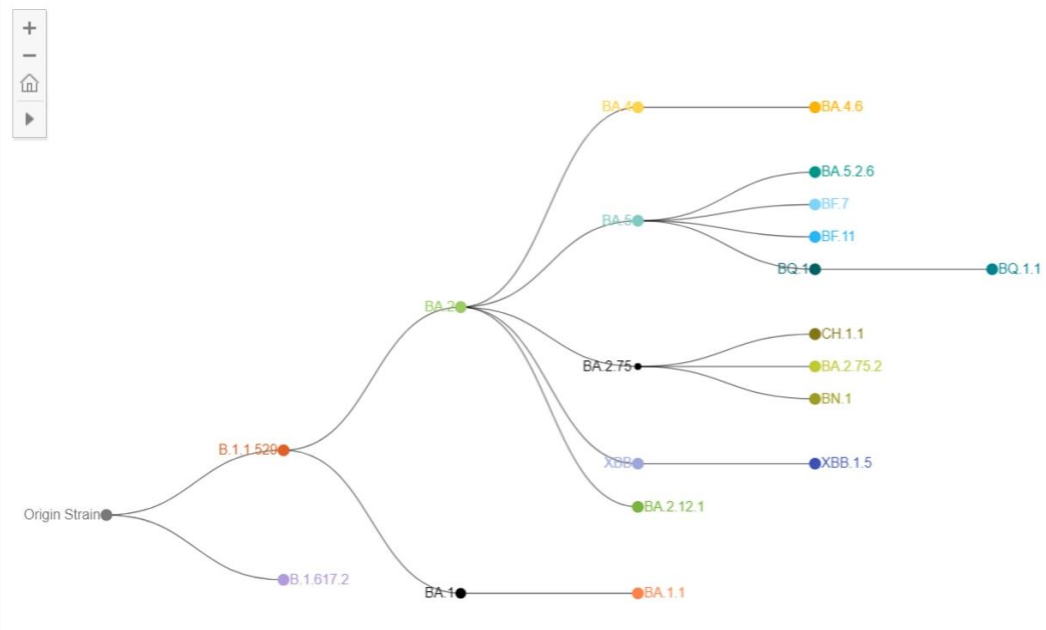
Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



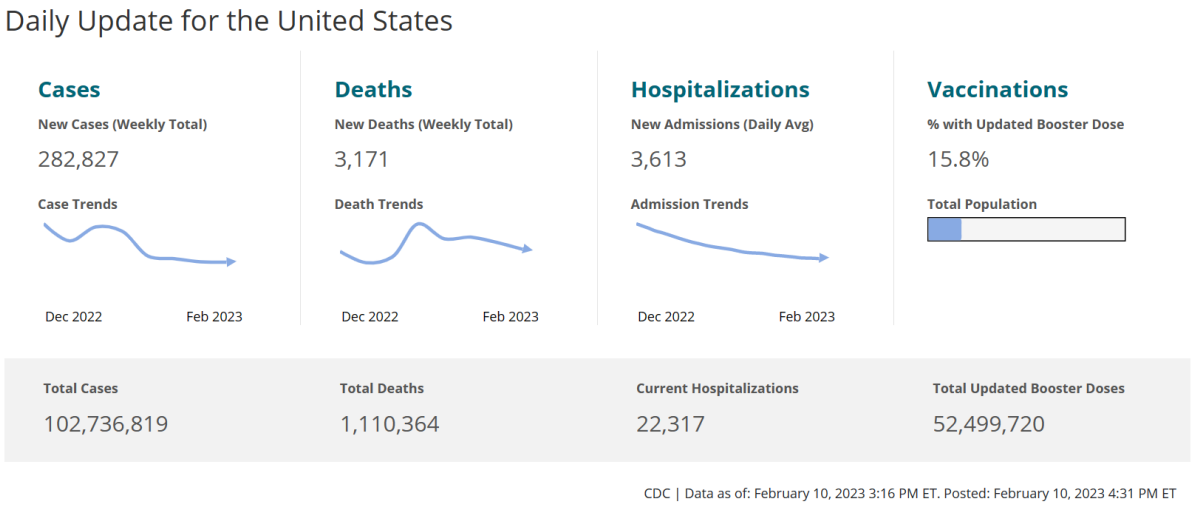
Nowcast Estimates in United States for 2/5/2023 – 2/11/2023

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	74.7%	67.0-81.2%
	BQ.1.1	VOC	15.3%	11.4-20.2%
	BQ.1	VOC	5.1%	3.7-6.8%
	XBB	VOC	1.9%	1.4-2.5%
	CH.1.1	VOC	1.3%	0.9-1.9%
	BN.1	VOC	0.8%	0.5-1.1%
	BA.5	VOC	0.3%	0.2-0.5%
	BF.7	VOC	0.3%	0.2-0.4%
	BA.5.2.6	VOC	0.1%	0.1-0.2%
	BA.2	VOC	0.1%	0.0-0.1%
	BF.11	VOC	0.0%	0.0-0.1%
	BA.2.75	VOC	0.0%	0.0-0.0%
	BA.2.75.2	VOC	0.0%	0.0-0.0%
	BA.4.6	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.4	VOC	0.0%	0.0-0.0%



In the last CDC report, the CDC said the more transmissible XBB.1.5 subvariant makes up an estimated 74.7% of cases, up from 66.4% last week. The only area where the subvariant isn't dominant is in the far northwestern region, which includes Alaska, Idaho, Oregon, and Washington.

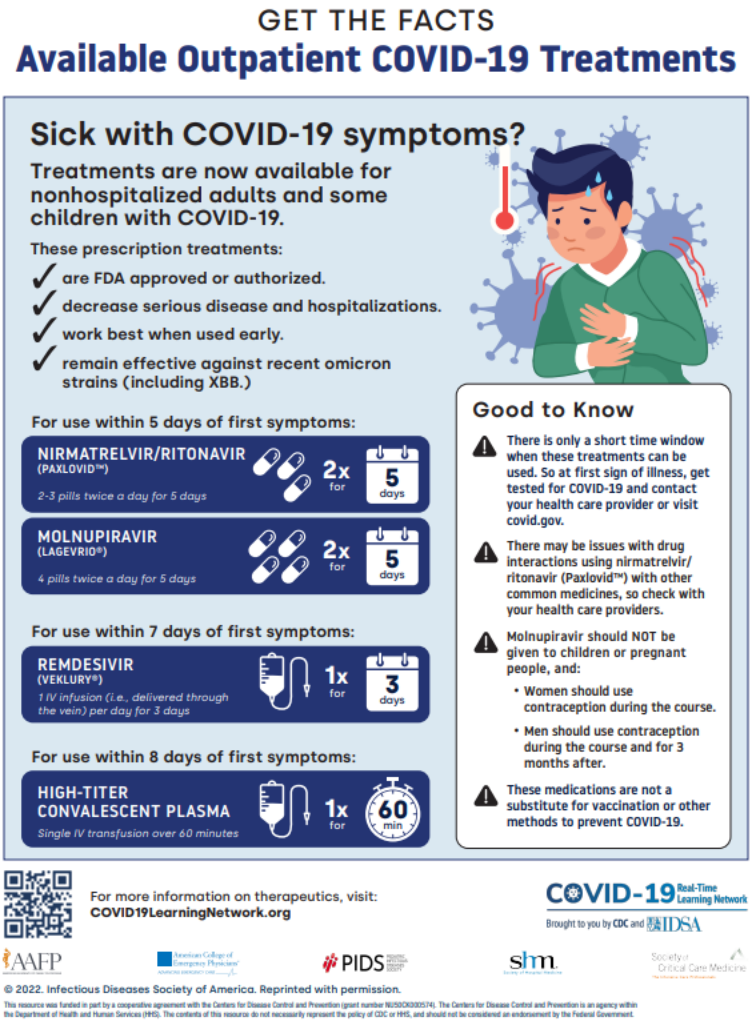


The CDC said the 7-day average for new daily cases is 40,404, down 1% compared to a week ago. For comparison, the decline in the 7-day average last week was 6%. Meanwhile, the 7-day average for new COVID-19 hospitalizations declined 6.2% last week. For deaths, the country averaged 453 new fatalities each day last week, down 9.7% compared to the previous week.

FDA Removes Positive COVID-19 Test Requirement for Antiviral Treatments

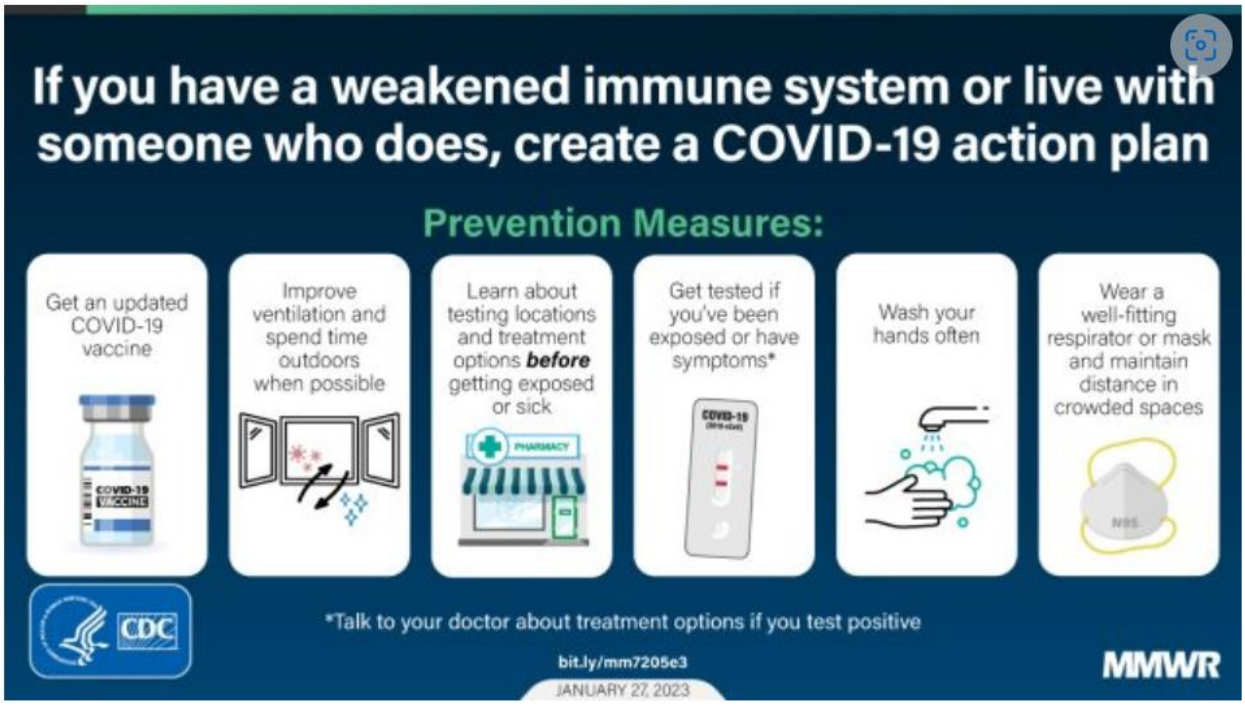
On February 1st, the FDA “removed the need for a positive test for Covid-19 treatments with nirmatrelvir/ritonavir or molnupiravir. The FDA still says the patients should have a current diagnosis of mild-to-moderate COVID infection Nirmatrelvir/ritonavir (Paxlovid) and Merck’s molnupiravir (Lagevrio) were given EUA in Dec. 2021 for patients with mild-to-moderate Covid-19 who tested positive for the virus, and who were at risk of progressing to severe COVID.

Comment: I am not sure the rationale for dropping a positive test since both antivirals have side effects and drug interactions which need to be considered before prescribing. Other viral illnesses may mimic Covid-19 and in terms of influenza an alternative antiviral is available. See article above on RIDT



Comment: This is an excellent resource put together by the Covid-19 Learning Network. As discussed in recent ID Watch, there is renewed interest on the use of high-titer CP especially given loss of monoclonal antibody treatment and prophylaxis. See reviews below.

Information for Persons Who Are Immunocompromised Regarding Prevention and Treatment of SARS-CoV-2 Infection in the Context of Currently Circulating Omicron Sublineages — United States, January 2023 MMWR 2023; 72;128–131



Comment: Given loss of monoclonals, we need to have a plan to protect our most vulnerable. Among persons with immunocompromise and their household members and close contacts, prevention measures including wearing a high-quality and well-fitting mask, maintaining physical distance from others (≥6 ft [1.8 m]), improving indoor ventilation, practicing frequent handwashing, and developing a care plan, should be considered in addition to receipt of a bivalent booster dose. It is important to wear a mask and maintain physical distance from others if it is not possible to avoid crowded indoor spaces. In addition, simple interventions should be used to improve ventilation in buildings and decrease SARS-CoV-2 transmission by improving air flow. In-duct ultraviolet germicidal irradiation lights can also be added to home heating ventilation and air conditioning systems to inactivate SARS-CoV-2 as air passes through the system. Frequent handwashing with soap and water is the best way to eliminate germs in most situations. If soap and water are not readily available, an alcohol-based hand sanitizer containing ≥60% alcohol is a good alternative. Also, it is important for persons who are immunocompromised to develop a care plan in consultation with their physician if they develop Covid-19.

FDA withdraws EUA for **Tixagevimab/Cilgavimab**

The FDA has withdrawn EUA for tixagevimab/cilgavimab (Evusheld) as the treatment because Evusheld has poor neutralizing activity new variants including the currently dominant XBB.1.5 subvariant of Omicron.

Comment: The NIH Panel now recommends against the use of tixagevimab plus cilgavimab as PrEP of COVID-19 (AIII)**.** See IDSA Update

IDSA Releases Updated Guideline for COVID-19 February 8, 2023

- Neutralizing Antibodies for Pre-Exposure Prophylaxis: This recommendation was retired and replaced with a statement mentioning that EUA was withdrawn by the US FDA for tixagevimab/cilgavimab (Evusheld)**,** the sole product that has been available for pre-exposure prophylaxis.
- Neutralizing Antibodies for Post-Exposure Prophylaxis: This recommendation was retired and replaced with a statement mentioning that EUA was withdrawn by the US FDA for both bamlanivimab/etesevimab and casirivimab/imdevimab, leaving no available neutralizing antibody product for use in the US for post-exposure prophylaxis.
- Neutralizing Antibodies for Treatment: This recommendation was retired and replaced with a statement mentioning that the US FDA withdrew EUA for bebtelovimab, leaving no available neutralizing antibody product in the US for treatment of COVID-19.

Comment: The above reflects the challenge that new variants have posed. The loss of neutralizing antibody treatment poses a serious threat especially for our immunosuppressed population. Fortunately, antivirals continue to be effective alternatives. We need better vaccines and additional therapeutics. The next article provides a promising addition, but will face FDA hurdles. See next article.

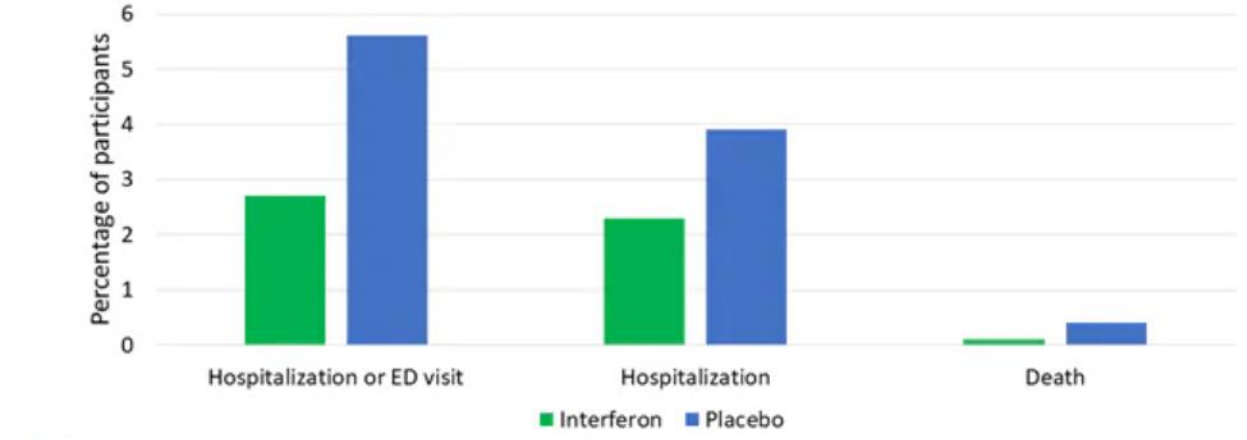
Early Treatment with Pegylated Interferon Lambda for Covid-19. N Engl J Med. 2023;388:518-28.

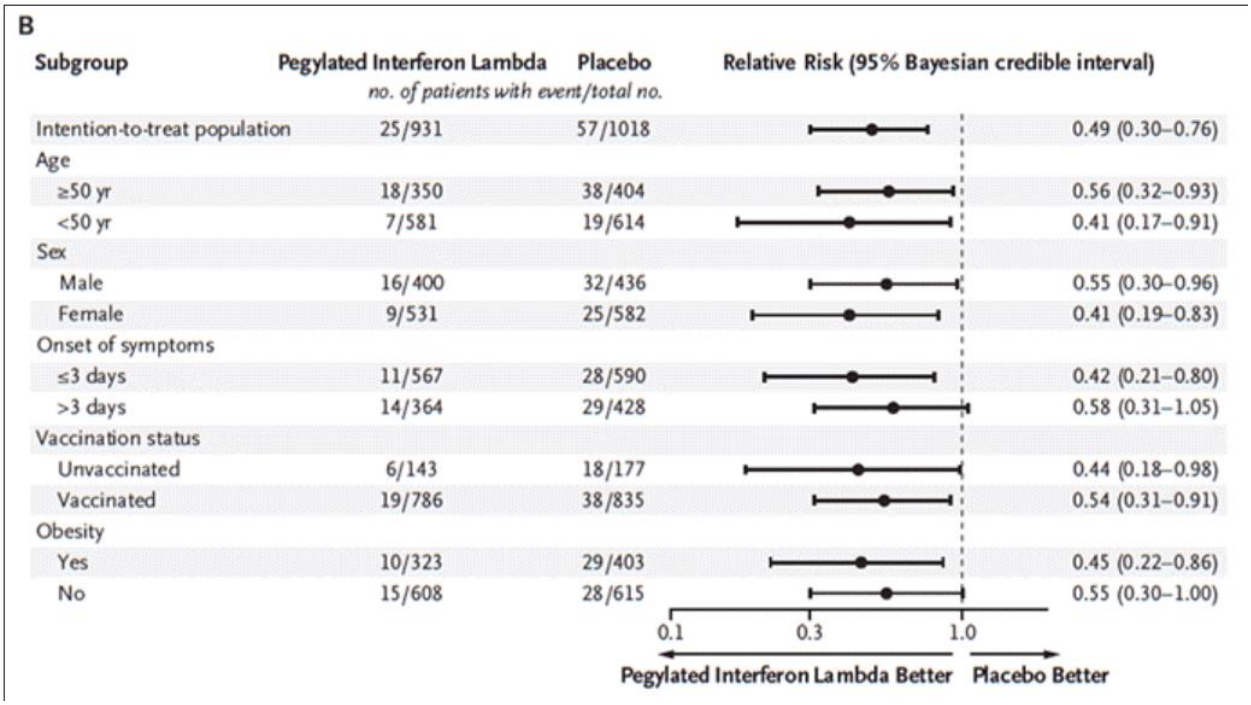
DOI: 10.1056/NEJMoa2209760

The investigators conducted a RCT trial involving mostly vaccinated adults with SARS-CoV-2 infection in Brazil and Canada. Outpatients who presented with an acute clinical condition consistent with Covid-19 within 7 days after the onset of symptoms received either pegylated interferon lambda (single subcutaneous injection, 180 µg) or placebo (single injection or oral). The primary composite outcome was hospitalization (or transfer to a tertiary hospital) or an ED visit (observation for >6 hours) due to Covid-19 within 28 days after randomization.

A total of 933 patients were assigned to receive pegylated interferon lambda and 1018 were assigned to receive placebo. Overall, 83% of the patients had been vaccinated, and during the trial, multiple SARS-CoV-2 variants emerged. A total of 25 of 931 patients (2.7%) in the interferon group had a primary-outcome event, as compared with 57 of 1018 (5.6%) in the

placebo group, a difference of 51% (relative risk, 0.49; 95% Bayesian credible interval 0.30 to 0.76; posterior probability of superiority to placebo, >99.9%). Results were generally consistent in analyses of secondary outcomes, including time to hospitalization for Covid-19 (hazard ratio, 0.57; 95% Bayesian credible interval, 0.33 to 0.95) and Covid-19–related hospitalization or death (hazard ratio, 0.59; 95% Bayesian credible interval, 0.35 to 0.97). The effects were consistent across dominant variants and independent of vaccination status. Among patients with a high viral load at baseline, those who received pegylated interferon lambda had lower viral loads by day 7 than those who received placebo. The incidence of adverse events was similar in the two groups.



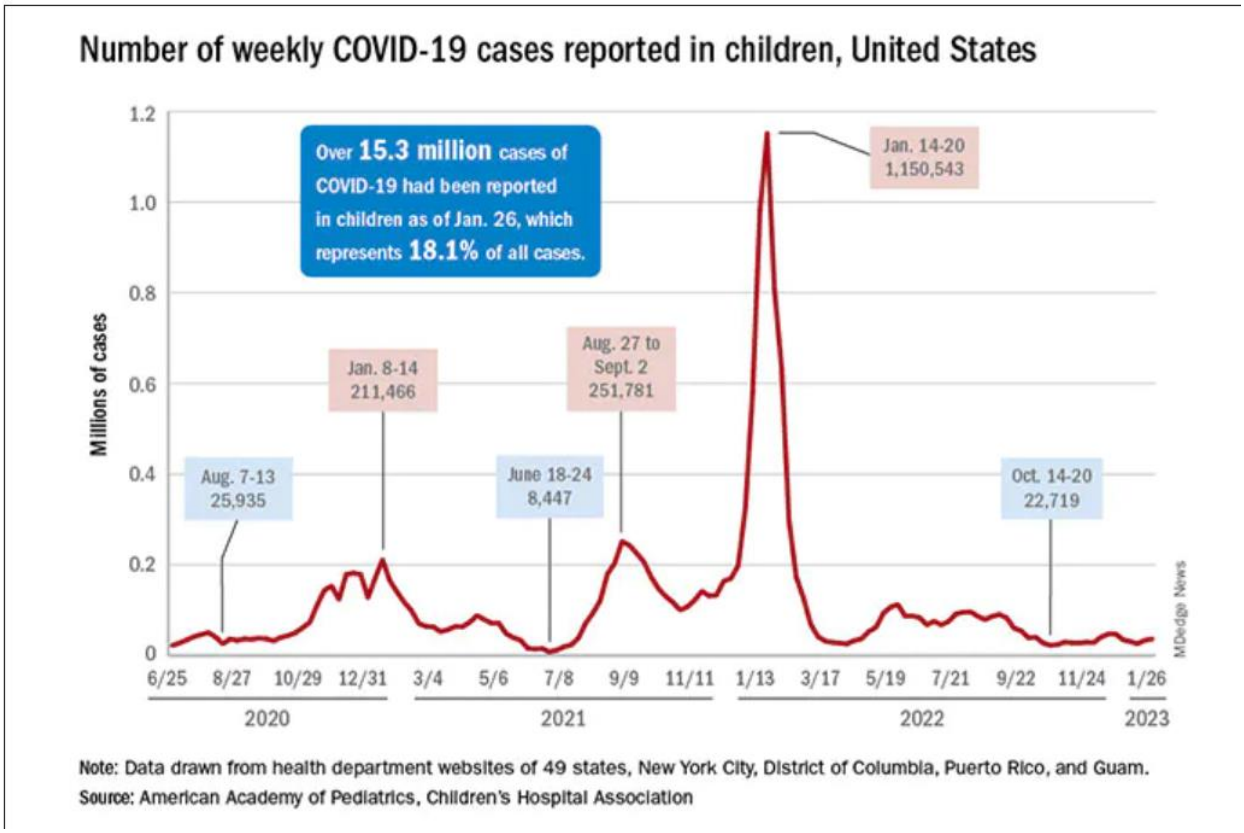


Comment: Bottom line-Interferon Lambda worked. The primary outcome — hospitalization or a prolonged emergency room visit for Covid-19 — was 50% lower in the interferon group. Secondary outcomes, including death from Covid-19, were lower in the interferon group as well.

Interferon also seemed to help those who were already vaccinated and those who were not vaccinated. It also appears that earlier treatment improves outcomes. Interferon lambda is not FDA approved and thus not even available in the US. The reason it has not been approved is that there has not been a large, well-conducted interferon lambda trial. Now there is. Will this study be enough to prompt an EUA? Last year the FDA told the manufacturer that they were not prepared to authorize EUA. The problem seemed to be that the clinical trial did not include a US site, but rather only sites in Brazil and Canada. The funders had no role in the design and conduct of the trial; the collection, management, analysis, and interpretation of the data; or the preparation and submission of the manuscript for publication. Pegylated interferon lambda was provided at no cost by Eiger BioPharmaceuticals, which was not made aware of any trial results before the completion of the trial. Of course, there is nirmatrelvir/ritonavir which at this point has a longer safety track record and, importantly, is oral, but interferon lambda is a single dose. I'd love to see a head-to-head trial. Since the completion of this trial, a polymorphism in the innate antiviral response gene OAS1 has been associated with clearance of SARS-CoV-2, and a common haplotype could be used to identify patients with an increased likelihood of response. [Nat Genet 2022; 54:1103-16] Evaluation of the prevalence of this haplotype seems warranted. I think we need more options.

Children and COVID: Weekly Cases May Have Increased in Early January

For the most recent week covered in the AAP/CHA weekly report, January 20-26, there were over 36,000 child COVID cases reported in the US, an increase of 8.8% from the week before (January 13-19). New cases for the first 2 weeks of the year – 31,000 for the week of December 30 to January 5 and 26,000 during January 6-12 – were consistent with the AAP/CHA assertion that weekly reported child cases have plateaued at an average of about 32,000 cases ... over the past 4 months.



Comment: The CDC data, however, show that new cases doubled during the week of January 1-7 to over 65,000, compared with the end of December, and stayed at that level for January 8-14, and since CDC figures are subject to a 6-week reporting delay, the final numbers may even higher. ED visits, however, for January do not show a corresponding increase. ED visits among children aged 0-11 years with Covid-19, measured as a percentage of all ED visits, declined over the course of the month, as did visits for 16- and 17-year-olds, while those aged 12-15 started the month at 1.4% and were at 1.4% on Jan. 27, with a slight dip down to 1.2% in between, the CDC said on its Covid Data Tracker. Daily hospitalizations for children aged 0-17 also declined through mid-January and did not reflect the jump in new cases.
Meanwhile, vaccinated children are still in the minority: 57% of those under age 18 have received no Covid-19 vaccine yet. Just 7.4% of children under age 2 years had received at least one dose as of January 25, as had 10.1% of those aged 2-4 years, 39.6% of 5- to 11-year-olds and 71.8% of those 12-17 years old, according to the CDC, with corresponding figures for completion of the primary series at 3.5%, 5.3%, 32.5%, and 61.5%.

Assessment of Efficacy and Safety of mRNA COVID-19 Vaccines in Children Aged 5 to 11 Years A Systematic Review and Meta-analysis JAMA Pediatr published online January 23, 2023

doi:10.1001/jamapediatrics.2022.6243

In this systematic review and meta-analysis, the authors evaluated the safety and efficacy of 2 doses of the Pfizer vaccine in children aged 5 to 11 years during both the delta and omicron

waves of COVID-19. They included 17 published studies of 10,935,541 vaccinated and 2,635,251 unvaccinated children.

Two-dose Pfizer vaccination compared with no vaccination was associated with lower risks of SARS-CoV-2 infections with or without symptoms (OR, 0.47; 95% CI, 0.35-0.64), symptomatic SARS-CoV-2 infections (OR, 0.53; 95% CI, 0.41-0.70), hospitalizations (OR, 0.32; 95% CI, 0.15-0.68), and multisystem inflammatory syndrome in children[MIS-C] (OR, 0.05; 95% CI, 0.02-0.10). Two RCTs and 5 observational studies investigated AEs among vaccinated children. Most vaccinated children experienced at least 1 local AE following the first injection (32,494 of 55,959 [86.3%]) and second injection (28,135 of 46,447 [86.3%]). Vaccination was associated with a higher risk of any AEs compared with placebo (OR, 1.92; 95% CI, 1.26-2.91). The incidence of AEs that prevented normal daily activities was 8.8% (95% CI, 5.4%-14.2%) and that of myocarditis was estimated to be 1.8 per million (95% CI, 0.000%-0.001%) following the second injection.

Comment: In this systematic review and meta-analysis, COVID-19 mRNA vaccines among children aged 5 to 11 years were associated with measures of efficacy in preventing SARS-CoV-2 infection and severe Covid-19–related illnesses. While most children developed local AEs, severe AEs were rare, and most of AEs resolved within several days. Specifically, they found that the mRNA vaccine was effective at preventing SARS-CoV-2 infection, symptomatic infection, hospitalization, and MIS-C. This analysis offers 2 important advances over previous, smaller studies. First, during both the delta and omicron waves, mRNA vaccines consistently protected against serious illness, including MIS-C. Second, the risk of myocarditis was very low. The uptake of mRNA vaccines in children aged 5 to 11 years has been poor. While it is true that Covid-19 is far less devastating in children than older adults, children are still at risk of serious and rarely fatal infections.

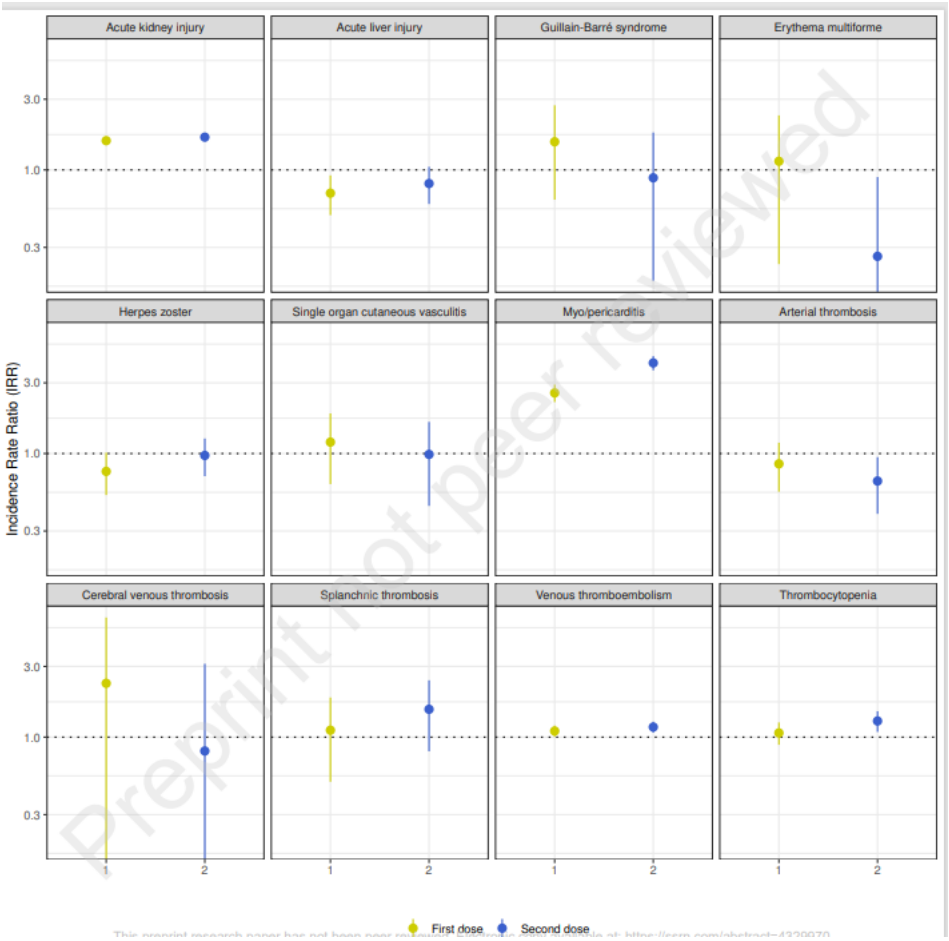
In editorial by Paul Offit, he concludes that “Parents should be both compelled and reassured by the following facts: (1) although the Covid-19 pandemic is ending, SARS-CoV-2 virus will be circulating for years, if not decades; (2) while some SARS-CoV-2 variants might have become less virulent, the virus is unlikely to evolve to avirulence; (3) about 3 to 4 million children will be born every year who will be susceptible to this virus; (4) the SARS-CoV-2 virus can cause severe and occasionally fatal disease in all age groups; (5) mRNA vaccines, which have now been given to more than 10 million children between 5 and 11 years of age, have been shown to be effective at preventing severe disease; and (6) myocarditis is an extremely rare consequence of mRNA vaccines in young children. Given the amount of information currently available to parents, the decision to vaccinate their children should be an easy one.” Remember the risk of myocarditis is primarily in older children and young males (12-35) usually after the second dose.

Adverse events following the BNT162b2 mRNA COVID-19 Vaccine (Pfizer-BioNTech) in Aotearoa New Zealand Lancet preprint January 2023

https://ssrn.com/abstract=4329970

Using national electronic health records, the observed rates of adverse events of special interest (AESIs) within a risk period (0- 21 days) following vaccination were compared to the expected rates based on background data (2014 - 2019). The incidence rate ratio (IRR) for each AESI was estimated with 95% confidence intervals (CI) and adjusted by age. The risk difference was calculated to estimate the excess number of events per 100,000 persons vaccinated.

As of February 10, 2022, 4,277,163 first and 4,114,364 second doses of Pfizer were administered to the eligible New Zealand population, aged ≥ 5 years. The observed rates of most AESIs post-vaccination were not statistically different than the expected rates. The IRR (95% CI) of myo/pericarditis following the first dose was 2.6 (2.2– 2.9) with a risk difference (95% CI) of 1.6 (1.1– 2.1) per 100,000 persons vaccinated and was 4.1 (3.7– 4.5) with a risk difference of 3.2 (2.6– 3.9) per 100,000 persons vaccinated following the second dose. The highest IRR was 25.8 (95% CI 15.6– 37.9) in the 5-19 years age group, following the second dose of the vaccine, with an estimated 5 additional myo/pericarditis cases per 100,000 persons vaccinated. An increased incidence of acute kidney injury (AKI) was observed following the first (1.6 (1.5– 1.6)) and second (1.7 (1.6– 1.7)) dose of Pfizer.



Comment: Although uncommon, a statistically significant association between Pfizer vaccination and myo/pericarditis and AKI was observed. The association between Pfizer and myo/pericarditis has been confirmed internationally in other studies primarily after the second dose and in young males. Unlike myo/pericarditis, AKI has not been identified as an adverse reaction to the Pfizer vaccine. They observed a statistically significant increased incidence of AKI following both doses of the vaccine. This increased incidence was seen in all age groups except the 5-19- year-olds. The majority of patients who reported AKI were older than 65 years, and more than 50% had underlying diseases that could contribute to AKI such as hypertension, diabetes, and chronic kidney disease. Therefore, further investigation is needed to understand this finding. only hospital discharge information was used to identify the outcomes of interest in the vaccinated and historical comparator cohorts. Although many of the AESI analyzed in this study result in hospitalization, less serious conditions are commonly treated in primary care settings. ICD-10-AM codes were used to identify outcomes of interest. There is potential for misclassification as clinical record assessments were not conducted to validate the diagnoses or codes used. Lastly, they were limited with the use of hospitalization data from the pre-pandemic years, 2014 to 2019, as their reference for the background incidence rates of AESI.

Novavax NVX-COV2373 triggers neutralization of Omicron sub-lineages Sc Rep 2023; 13:1222

doi.org/10.1038/s41598-023-27698-x

The SARS-CoV-2 Omicron (B.1.1.529) Variant of Concern (VOC) and its sub-lineages (including BA.2, BA.4, BA.5, BA.2.12.1) contain spike mutations that confer high level resistance to neutralizing antibodies induced by vaccination with ancestral spike or infection with previously circulating variants. The NVX-CoV2373 vaccine, a protein nanoparticle vaccine containing the ancestral spike sequence, has value in countries with constrained cold-chain requirements. Here they investigators report neutralizing titers following two or three doses of NVX-CoV2373.

They show that after two doses, Omicron sublineages BA.1 and BA.4/BA.5 were resistant to neutralization by 72% (21/29) and 59% (17/29) of samples respectively. However, after a third dose of NVX-CoV2373, they demonstrated high titers against Omicron BA.1 (GMT: 1,197) and BA.4/BA.5 (GMT: 582), with responses similar in magnitude to those triggered by three doses of an mRNA vaccine.

Comment: These data are of particular relevance as BA.4/BA.5 has dominated in multiple locations and highlight the potential utility of the NVX-CoV2373 vaccine as a booster in resource-limited environments. I think we have been primarily focused on the mRNA vaccines, but NVX-CoV2373 may offer an alternative. Studies need to be done against XBB strains.

Early Estimates of Bivalent mRNA Booster Dose Vaccine Effectiveness in Preventing Symptomatic SARS-CoV-2 Infection Attributable to Omicron BA.5– and XBB/XBB.1.5–Related Sublineages Among Immunocompetent Adults — Increasing Community Access to Testing Program, United States, December 2022–January 2023 MMWR early release January 25, 2023

Doi.org/10.15585/mmwr.mm7205e1

Data from the Increasing Community Access to Testing (ICATT) national pharmacy program for SARS-CoV-2 testing were analyzed to estimate VE of updated (bivalent) mRNA COVID-19 vaccines against symptomatic infection caused by BA.5-related and XBB/XBB.1.5-related sublineages among immunocompetent adults during December 1, 2022–January 13, 2023. Reduction or failure of spike gene (*S*-gene) amplification (SGTF) in RT-PCR was used as a proxy indicator of infection with likely BA.5-related sublineages and *S*-gene target presence (SGTP) of infection with likely XBB/XBB.1.5-related sublineages.

Among 29,175 NAATs with SGTF or SGTP results available from adults who had previously received 2–4 monovalent COVID-19 vaccine doses, the relative VE of a bivalent booster dose given 2–3 months earlier compared with no bivalent booster in persons aged 18–49 years was 52% against symptomatic BA.5 infection and 48% against symptomatic XBB/XBB.1.5 infection.

Comment: As new SARS-CoV-2 variants emerge, continued VE monitoring is important. Bivalent vaccines appear to provide some additional protection against symptomatic BA.5-related sublineage and XBB/XBB.1.5-related sublineage infections in persons who had previously received 2, 3, or 4 monovalent vaccine doses. Underlying medical conditions were self-reported and might be subject to recall bias. Previous infection is likely underreported. Previous infection provides some protection against repeat infection; therefore, VE estimates in this study might be biased toward no effect. Lastly, bivalent booster dose coverage to date has been low (6%–39% among persons aged ≥18 years among different age groups as of January 14, 2023). See next article.

COVID-19 Incidence and Mortality Among Unvaccinated and Vaccinated Persons Aged ≥12 Years by Receipt of Bivalent Booster Doses and Time Since Vaccination — 24 U.S. Jurisdictions, October 3, 2021–December 24, 2022 MMWR 2023; 72:145-152

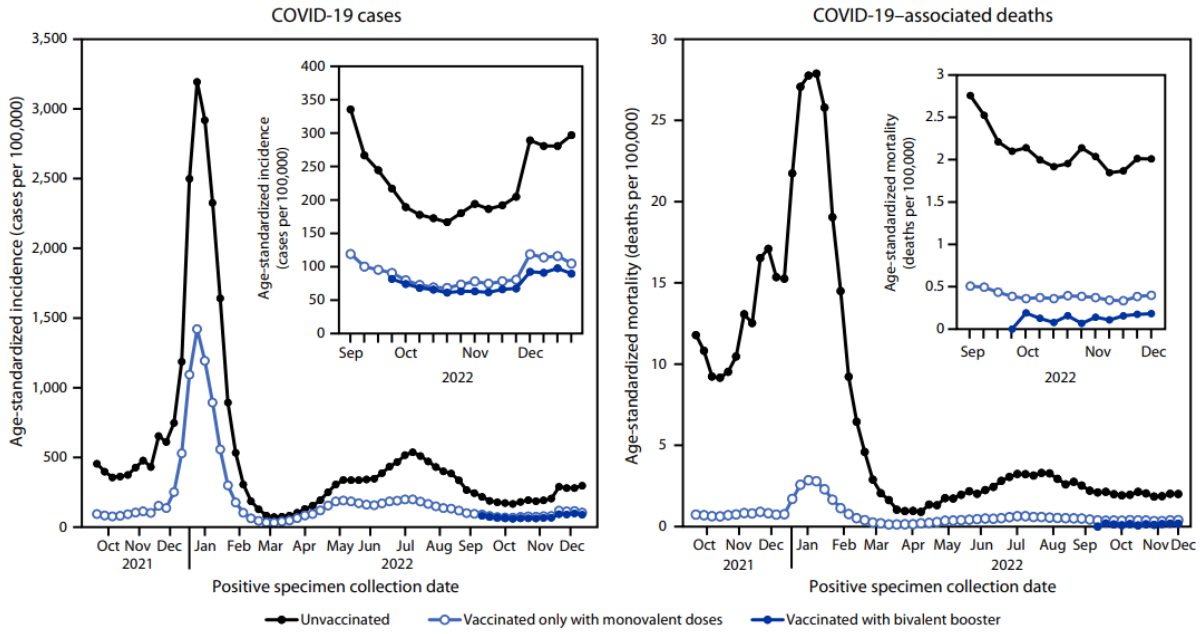
This is a CDC study of people aged 12 years and older in 24 US jurisdictions from October 3, 2021, to December 24, 2022. They used case-surveillance, vaccination, and death data to compare infection and death rates in vaccinated and unvaccinated people by receipt of and time since a monovalent or bivalent booster during the Delta variant era and late BA.4/BA.5 predominance.

A total of 21,296,326 Covid-19 cases and 115,078 related deaths were reported during the study period. Average weekly age-standardized incidence and death rates rose substantially during the Omicron BA.1 wave and, to a lesser extent, during the early BA.4/BA.5 period. In all periods, average weekly infection and death rates were higher among unvaccinated people (ranges, 216.1 to 1,256.0 and 1.6 to 15.8, respectively) than among monovalent booster-only

recipients (ranges, 86.4 to 487.7 and 0.3 to 1.4, respectively). Cases and deaths during the late BA.4/BA.5 period were lowest among bivalent booster recipients (78.5 and 0.1, respectively).

Overall, case rate ratios (RRs) for unvaccinated versus monovalent-only vaccine recipients decreased from 4.0 during Delta to 2.6 during BA.1 and 1.8 during BA.2 before climbing to 2.7 in early BA.4/BA.5. Case RRs for unvaccinated versus bivalent booster recipients were slightly higher (2.8) than those for monovalent-only vaccine recipients (2.5) during late BA.4/BA.5.

Average death RRs in monovalent-only vaccine recipients declined from Delta (16.2) to BA.1 (11.5) and then leveled off during BA.2 (5.3), early BA.4/BA.5 (5.3), and late BA.4/BA.5 (5.4). Death rates among unvaccinated people were 14.1 times those of bivalent vaccine recipients and 2.6 times higher among monovalent-only vaccine recipients than among bivalent vaccine recipients during late BA.4/BA.5. Relative to that of unvaccinated people, protection among bivalent booster recipients aged 65 to 79 years (RR, 23.7) and those 80 and older (RR,10.3) was significantly higher than that among monovalent booster recipients aged 65 to 79 (RR, 8.3) and 80 and older (RR, 4.2).



Comment: Bivalent booster recipients in 24 U.S. jurisdictions had slightly higher protection against infection and significantly higher protection against death than was observed for monovalent booster recipients or unvaccinated persons, especially among older adults. Specifically, recipients of the bivalent vaccine booster were 14 times less likely to die of Omicron BA.4/BA.5 infections than their unvaccinated peers and 5 times less likely to die than recipients of the monovalent booster, mostly among older people. The numbers for ages 12-17 were too small to make meaningful interpretation. The numbers were higher for ages 18-49, but with low vaccination rates it is not possible to determine the benefit of bivalent vs monovalent vaccine in terms of severe disease in this age group. Authorizations for monovalent and bivalent boosters were not concurrent; the median time after vaccination was longer for persons who received monovalent boosters than for those who received bivalent boosters, which limits direct comparability. The study could not adjust for important confounders that might contribute to rate differences, such as possible variations in infection-derived immunity, co-morbidities, and

testing or prevention behaviors by age and vaccination status. Only 17.5% of Americans aged 12 and older have received a bivalent booster. My takeaway restored protection was highest in older adults. Therefore, individuals over 65 or who have multiple high-risk underlying medical conditions should get 1 bivalent booster dose ≥3-4 months after their Covid-19 primary series or last monovalent booster dose, or natural infection. Once again, we see no mention of prior natural infection in any guidance. What do you do if you are healthy and under 50? Given the mildness of current variants along with high community immunity due to natural infection and/or vaccination we are rarely seeing younger healthy people get severe disease even though most have not received the bivalent booster. Recent CDC data does report the bivalent booster does offer slightly better protection against death than the original vaccine in younger people (small numbers), but the difference was less than 1 in a million. As with the original vaccine, the bivalent booster slightly increases the risk of myocarditis especially in males aged 12 to 35. As a result, some experts are hesitant to recommend more booster doses to this group. Bottom line: If you are healthy and young, you have already been vaccinated and boosted and probably had an infection or two in the past, I think you should be protected from severe disease for now. Therefore, for young, healthy people the decision of when to get a booster, or whether to get one at all, is an individual choice. Until more data is available, I would not require this group to get a bivalent vaccine at this time.

Protective effectiveness of previous SARS-CoV-2 infection and hybrid immunity against the omicron variant and severe disease: a systematic review and meta-regression Lancet Infect Dis published online January 18, 2023

doi.org/10.1016/ S1473-3099(22)00801-5

The authors searched MEDLINE (Ovid), Embase (Ovid), Web of Science (Core Collection), ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (Ovid), the WHO COVID-19 database, and Europe PubMed Central (limited to preprints) from January 1, 2020, to June 1, 2022, with keywords related to SARS-CoV-2, reinfection, protective effectiveness, previous infection, presence of antibodies, and hybrid immunity.

11 studies reporting the protective effectiveness of previous SARS-CoV-2 infection and 15 studies reporting the protective effectiveness of hybrid immunity were included. For previous infection, there were 97 estimates (27 with a moderate risk of bias and 70 with a serious risk of bias). The effectiveness of previous infection against hospital admission or severe disease was 74·6% (95% CI 63·1–83·5) at 12 months. The effectiveness of previous infection against reinfection waned to 24·7% (95% CI 16·4–35·5) at 12 months. For hybrid immunity, there were 153 estimates (78 with a moderate risk of bias and 75 with a serious risk of bias). The effectiveness of hybrid immunity against hospital admission or severe disease was 97·4% (95% CI 91·4–99·2) at 12 months with primary series vaccination and 95·3% (81·9–98·9) at 6 months with the first booster vaccination after the most recent infection or vaccination. Against reinfection, the effectiveness of hybrid immunity following primary series vaccination waned to 41·8% (95% CI 31·5–52·8) at 12 months, while the effectiveness of hybrid immunity following first booster vaccination waned to 46·5% (36·0–57·3) at 6 months.

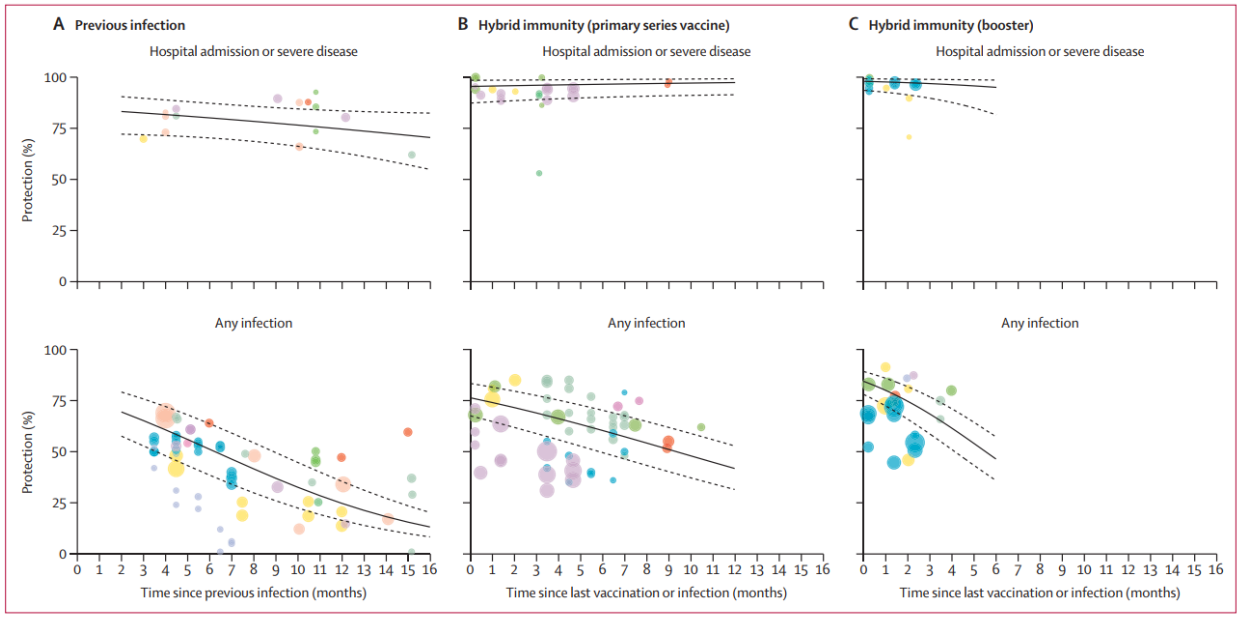


Figure 2: **Protection against omicron variant conferred by previous infection or hybrid immunity compared to immune-naive individuals over time**
This analysis uses a log-odds meta-regression model. Points of the same color represent estimates from the same study. The diameter of the circles varies with the sample size of the study. Dotted lines

Comment: As reported in other studies, all estimates of protection waned within months against reinfection but remained high and sustained for hospital admission or severe disease. Individuals with hybrid immunity had the highest magnitude and durability of protection, and as a result might be able to extend the period before booster vaccinations are needed compared to individuals who have never been infected. Public health officials (e.g., CDC/FDA) should consider including the use and timing of vaccinations based on the local extent of past infection, the protection conferred by previous infection or hybrid immunity, and the duration of this protection as key considerations to inform future recommendations. The observational studies they included assumed that all individuals had the same risk of exposure. Individual studies adjusted for some of these factors (e.g., calendar time, age, comorbidities, and testing frequency) and these adjustments were considered in the risk of bias assessment; however, not all studies reported these adjustments. Second, their analysis did not incorporate the sequence of and timing between vaccination and previous infection for hybrid immunity. Lastly, they were only able to examine protection conferred by pre-omicron SARS CoV-2 variants (i.e., the index virus through to the delta [B.1.617.2] variant). Future evidence will be needed to ascertain the protection conferred by the omicron variants against reinfection.