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Infectious Diseases Watch

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VII Editorial: Clinicians of the Future

A recent survey by Elsevier Health predicts that up to 75% of healthcare workers (HCWs) will leave the profession by 2025. And a 2020 study conducted by the Association of American Medical Colleges (AAMC) projected a shortfall of up to 139,000 physicians by 2033. The physician workforce is aging, with close to a quarter of the physicians in the US are 65 and over.

Stressors, like spending time on charts, pharmacy requests, and making sure all of the Medicare and Medicaid and insurance compliance issues are met, may compel some younger doctors to consider carving out a second career or fast-track younger physicians toward retirement. Burnout during the pandemic has accelerated physicians and other HCWs leaving the medical profession.

For starters, the country needs more physicians trained now — but it will take years to replace the baby boomer doctors ready to retire. The over-65 population is expected to grow by 45.1%, leaving a specialty care gap because older people generally have more complicated health cases that require specialists. In addition, physician burnout may lead more physicians under 65 to retire much earlier than expected. ID Watch has highlighted the concern in attracting physicians into infectious diseases. The shortage of ID clinicians is distressing today and expected to reach crisis levels in the next several years. It is critical that we focus on ways to support physician wellness, reduce burnout, which will allow physicians to remain active in the field longer. Physicians want a more balanced lifestyle even if that means reduced income. Physicians who find things they enjoy generally work to a later age and are more productive even if they are working less. Older physicians who remain physically and mentally fit can continue to contribute in many ways even if they work part-time. Han and colleagues concluded that approximately $4.6 billion in costs related to physician turnover and reduced clinical hours in the US each year in part due attributed to burnout. [Ann Intern Med 2019; 170:784-790] Meanwhile, the researchers estimated the annual cost associated with burnout related to turnover and reduced clinical hours, at an organizational level, to be approximately $7,600 per employed physician each year.

On the nursing front, hospitals have been rushing to fill nursing and other HCW vacancies during the pandemic. The staffing crunch combined with increased costs of traveling nursing, turnover, and inflation challenge health care systems to rethink training and reorganization of how we deliver health care. Currently opening for nurses and other HCWs are growing twice as fast as the overall US job market. The annual turnover for RNs is ~22.5% with the cost of turnover estimated at $52,000! About 40% of the nursing workforce is at or near retirement and projections forecast a shortage of over 2 million nurses by 2025.

Bottom line there is a national health care workforce crisis involving physicians, nurses, and other HCWs. We need to explore options for how we increase and attract the brightest and best into medicine.

General Infectious Diseases

Intravenous to Oral Antibiotic Switch Therapy among Patients Hospitalized with Community-Acquired Pneumonia Clin Infect Dis published online April 3, 2023

DOI: 10.1093/cid/ciad196

The investigators analyzed data on adults admitted with CAP and initially treated with IV antibiotics at 642 US hospitals from 2010 through 2015. Patients who were switched from IV to oral antibiotics without interruption of therapy by hospital day 3 were considered early switchers. The main outcomes of interest were hospital length of stay (LOS), in-hospital 14-day mortality, late intensive care unit (ICU) admission, and hospital costs.

Of 378,041 CAP patients, 21,784 (5.8%) were switched from IV to oral antibiotics by day 3, and 116,118 (30.7%) were switched before discharge. Early switching was more common in large hospitals, teaching hospitals, and urban hospitals. Patients switched early had shorter LOS and lower hospitalization costs, as well as fewer days of IV antibiotic therapy and shorter duration of inpatient antibiotic treatment. There were no significant differences in 14-day in-hospital mortality or late ICU admission between early switchers and others.

Patients with lower predicted risk of mortality were more likely to be switched, but even in hospitals with relatively high switch rates, fewer than 15% of very low-risk patients were switched early.

Comment: The study authors say the findings suggest clinicians remain wary of switching CAP patients from IV to oral antibiotics, despite evidence of safety and recommendations from several medical organizations to do so when patients are clinically stable.

The study suggests early switching appears safe but underused in patients with CAP. Their data suggests hospitals can reduce the burden of antibiotics delivered for CAP by encouraging clinicians to follow evidence-based recommendations to switch therapy in clinically stable patients. IDSA guidelines advocate for a prompt transition from intravenous to oral antibiotics in pneumonia patients as soon as they are clinically stable. We see this trend switching to oral antibiotics for other common clinical syndromes. More recent clinical data show that some serious infections (i.e., osteomyelitis, infective endocarditis, bacteremia from a urinary source) can be successfully managed with a step-down to a highly bioavailable oral agent. [N Engl J Med 2019;380:425–36; JAMA Netw Open 2020;3: e2020166] This study did not capture readmissions.

Effects of patient beliefs regarding the need for antibiotics and prescribing outcomes on patient satisfaction in urgent-care settings. Antimicrob Steward Healthcare Epidemiol published online April 26, 2023

doi: 10.1017/ash.2023.161

The investigators studied how patient beliefs regarding the need for antibiotics, as measured by expectation scores, and antibiotic prescribing outcome affect patient satisfaction using data from 2,710 urgent-care visits. For the survey, patients and guardians of pediatric patients at 27 UCCs and 5 pediatric UCCS in Colorado, Florida, Georgia, New Jersey, and Texas were asked to complete an anonymous questionnaire that asked about their demographics, expectation for antibiotics (expectation score), treatment plan, and level of satisfaction with their care (satisfaction score). The expectation score and satisfaction score were measured using a 5-point Likert scale, with 5 representing the highest belief in the need for antibiotics and the highest level of satisfaction. A total of 2,279 questionnaires from general UCCs and 431 from pediatric UCCs were included in the analysis.

The median expectation score was 3.37 among adults and 3.26 among guardians of pediatric patients. Expectation scores did not differ by age, ethnicity, race, or education level for general UCCs, while guardians aged 30 to 49 years had the highest expectation scores at pediatric UCCs. The median satisfaction score was 4.23 for adults and 4.18 for guardians of pediatric patients, with similar scores across sex, age group, ethnicity, and education level.

Antibiotics were prescribed for 53.4% of adult patients and 36.0% of pediatric patients. Logistic regression analysis found that antibiotic prescription had no effect on patient satisfaction among adult patients reporting low expectation scores, but medium-to-very-high expectation scores were associated with higher levels of satisfaction upon receiving antibiotics and with lower levels of satisfaction when antibiotics were not prescribed. No statistically significant association was found for pediatric visits.

Comment: These findings suggest that decreasing urgent-care patient expectations and beliefs regarding the need for antibiotics (e.g., thoroughly educating patients on the clinical applicability and risks of antibiotic use) may decrease unnecessary prescriptions without negatively impacting patient satisfaction. Previous studies have also shown that providers often incorrectly assume their patient's expectations for receiving antibiotics. In last month's ID Watch, I reported that shorter visits were associated with a higher likelihood of inappropriate antibiotics. [JAMA Health Forum 2023;4:e230052] Older studies have shown that if the providers take the time to explain why a patient does not need antibiotics, patient satisfaction remains high.

Sulbactam-durlobactam

The FDA's Antimicrobial Drug Advisory Committee (AMDAC) voted unanimously to support approval of the investigational antibiotic candidate sulbactam-durlobactam for the treatment of patients with hospital-related bacterial pneumonia caused by *Acinetobacter.*

Comment: Phase 3 trial results released in 2021 showed that sulbactam-durlobactam was statistically non-inferior to colistin in patients with hospital-acquired and ventilator-associated pneumonia caused by carbapenem-resistant *A baumannii (*CRAB) and exhibited a favorable safety profile. This drug meets the urgent need for new treatment options for patients with serious and life-threatening infections caused by CRAB. The FDA will make a final decision on May 29th.

FDA approves Seres Therapeutics SEP-109 (Vowst)

This past week, the FDA approved SEP-109(Vowst) for treating 18 years and older for recurrent C. diff (rCDI). SER-109, an investigational, oral microbiome therapeutic composed of purified Firmicutes spores. The capsules are made by purifying fecal matter derived from healthy people, while fecal transplants (FMT) are donated by healthy volunteers and are not purified. Treatment is four pills taken once a day for 3 consecutive days. The company expects the product to be available by June.

Comment: *C diff* is one of the nation's most common healthcare-associated infections and with recurrence rates ~20% leading to 15,000 to 30,000 deaths each year. The efficacy and safety data from several trials reinforce advantages of using a microbiome therapeutic composed of purified Firmicutes spores for the treatment of rCDI. The use of Firmicutes spores (1) achieves efficient drug delivery within the acidic environment of the stomach; (2) enables a low pill burden because spores can germinate, multiply, and replicate into metabolically active bacteria within the gastrointestinal tract; and (3) allows for specific inactivation of nonspore microorganisms during manufacturing, mitigating risks to patients. Spore-forming Firmicutes are thought to restore epithelial barrier integrity, decrease colonic inflammation, and modulate bile acid concentrations important to colonization resistance. Common side effects included abdominal bloating, constipation, and diarrhea. The FDA warned in a release that the drug “may carry a risk of transmitting infectious agents. It is also possible for Vowst(SEP-109) to contain food allergens.”

SEP-109 is the second pharmaceutical product approved for rCDI. In November 2022 Ferring Pharmaceuticals (Rebyota) was given FDA approval. This product must be delivered via the rectum. Both products provide much-needed new treatment that offers hope to the thousands of people who suffer from rCDI each year. See next review

VE303, a Defined Bacterial Consortium, for Prevention of Recurrent *Clostridioides difficile* Infection A Randomized Clinical Trial. JAMA. 2023; 329:1356-1366.

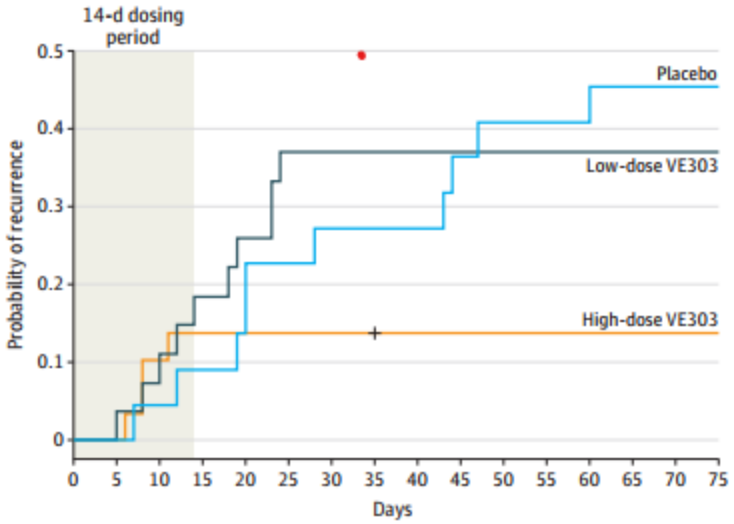
doi:10.1001/jama.2023.4314

VE303 is a defined bacterial consortium composed of 8 well-characterized, nonpathogenic, nontoxigenic, commensal strains of Clostridia derived from healthy human stool samples and manufactured from clonal cell banks. The primary objective of this study was to evaluate VE303 at 2 different doses in adults at high risk for recurrent CDI to determine recommendations for a phase 3 regimen.

This trial(phase 2) was a randomized, double-blind, placebo-controlled, dose-ranging study conducted from February 2019 to September 2021 at 27 sites in the US and Canada. Participants were randomly assigned to high-dose VE303 (10 capsules 8.0 × 109 colony-

forming units [CFUs]) (n = 30), low-dose VE303 (2 capsules 1.6 × 109 CFUs) (n = 27), or placebo capsules (n = 22) orally once daily for 14 days. The study included 79 participants aged 18 years or older who were diagnosed with laboratory-confirmed CDI with 1 or more prior CDI episodes in the last 6 months and those with primary CDI at high risk for recurrence (defined as aged ≥75 years or ≥65 years with ≥1 risk factors: creatinine clearance <60 mL/min/1.73 m2, proton pump inhibitor use, remote [>6 months earlier] CDI history). The primary efficacy end point was the proportion of participants with CDI recurrence at 8 weeks using a combined clinical and laboratory definition. The primary efficacy end point was analyzed in 3 prespecified analyses, using successively broader definitions for an on-study CDI recurrence: (1) diarrhea consistent with CDI plus a toxin-positive stool sample; (2) diarrhea consistent with CDI plus a toxin-positive, polymerase chain reaction–positive, or toxigenic culture–positive stool sample; and (3) diarrhea consistent with CDI plus laboratory confirmation or (in the absence of a stool sample) treatment with a CDI-targeted antibiotic. Fecal samples were collected at screening, after treatment for the qualifying CDI episode, and longitudinally through week 24. Metagenomic sequencing was performed to determine VE303 strain colonization and changes in microbiome diversity.

The participants' median age was 63.5 years (range, 24-96); 70.5% were female; and 1.3% were Asian, 1.3% Black, 2.6% Hispanic, and 96.2% White. CDI recurrence rates through week 8 (using the efficacy analysis 3 definition) were 13.8% (4/29) for high-dose VE303, 37.0% (10/27) for low-dose VE303, and 45.5% (10/22) for placebo (P = .006, high-dose VE303 vs placebo). .Most participants experienced sustained cure through week 24, suggesting that VE303 has a durable effect given high-dose. Most participants (76/79 [96.2%]) experienced 1 or more treatment-emergent AEs (TEAEs), which were generally of mild or moderate intensity and were mainly gastrointestinal . There were no reported grade 4 TEAEs and no deaths. Treatment-related TEAEs were reported by more participants in the high-dose VE303 group (16/30 [53.3%]) than in the low-dose VE303 group (8/27 [29.6%]) or the placebo group (7/22 [31.8%]). Serious TEAEs were reported in 7 participants (8.9%) across treatment groups (total of 11 serious TEAEs). At the end of study treatment on day 14, VE303 fecal colonization, as measured by the number of consortium strains detected and the sum of the strain relative abundances, was significantly increased (P < .001, Wilcoxon rank-sum test) in the VE303-dosed groups compared with the placebo group. VE303 detection was significantly increased in the high-dose VE303 vs low-dose VE303 group (P < .05, Wilcoxon test). Likewise, total VE303 relative abundance in the high-dose VE303 group (5.2%) was greater than in the low-dose VE303 group (0.8%) (P = .09, Wilcoxon rank-sum test), indicating a dose-exposure effect. In this study, 72% of participants were treated with vancomycin 4 times daily and 21% with fidaxomicin for the qualifying CDI episode.



Comment: Among adults with laboratory-confirmed CDI with 1 or more prior CDI episodes in the last 6 months and those with primary CDI at high risk for recurrence, high-dose VE303 prevented recurrent CDI compared with placebo or low dose VE303. The efficacy analysis included 2 participants whose recurrences were diagnosed clinically, without confirmation by positive laboratory testing. The numbers enrolled were low since study enrollment were hindered by the Covid-19 pandemic and other factors, including availability of open label fecal microbial transplant in many areas, which negatively affected the sample size goal. In addition, the study was predominantly white population may limit the generalizability of these findings. A larger, phase 3 study is needed to confirm these findings. See next review.

Fecal microbiota transplantation for the treatment of recurrent *Clostridioides dfficile* (*Clostridium difficile*). Cochrane Database of Systematic Reviews 2023, Issue 4. Art. No.: CD013871.

DOI: 10.1002/14651858.CD013871.p

The authors used the standard, extensive Cochrane search methods. considered randomized trials of adults or children with rCDI for inclusion. Eligible interventions must have met the definition of FMT, which is the administration of fecal material containing distal gut microbiota from a healthy donor to the gastrointestinal tract of a person with rCDI. The comparison group included participants who did not receive FMT and were given placebo, autologous FMT, no intervention, or antibiotics with activity against *C difficile*. Their primary outcomes were 1. proportion of participants with resolution of rCDI and 2. serious adverse events. Our secondary outcomes were 3. treatment failure, 4. all-cause mortality, 5. withdrawal from study, 6. rate of new CDI infection after a successful FMT, 7. any adverse event, 8. quality of life, and 9. colectomy. We used the GRADE criteria to assess certainty of evidence for each outcome.

They included six studies with 320 participants. Four were single-center and two were multicenter studies. All studies included only adults. Five studies excluded people who were severely immunocompromised, with only one study including 10 participants who were receiving

immunosuppressive therapy out of the 64 enrolled; these were similarly distributed between the FMT arm (4/24 or 17%) and comparison arms (6/40 or 15%). The route of administration was the upper gastrointestinal tract via a nasoduodenal tube in one study, two studies used enema only, two used colonoscopic only delivery, and one used either nasojejunal or colonoscopic delivery, depending on a clinical determination of whether the recipient could tolerate a colonoscopy. Five studies had at least one comparison group that received vancomycin. The risk of bias (RoB2) assessments did not find an overall high risk of bias for any outcome. All six studies assessed the efficacy and safety of FMT for the treatment of rCDI.

Pooled results from six studies showed that the use of FMT in immunocompetent participants with rCDI likely leads to a significant increase in resolution of rCDI in the FMT group compared to control (risk ratio (RR) 1.92, 95% confidence interval (CI) 1.36 to 2.71; P = 0.02, I^2 = 63%; 6 studies, 320 participants; number needed to treat for an additional beneficial outcome (NNTB) 3; moderate-certainty evidence). Fecal microbiota transplantation probably results in a slight reduction in serious adverse events; however, the CIs around the summary estimate were wide (RR 0.73, 95% CI 0.38 to 1.41; P = 0.24, I^2 = 26%; 6 studies, 320 participants; NNTB 12; moderate-certainty evidence). Fecal microbiota transplantation may result in a reduction in all-cause mortality; however, the number of events was small, and the CIs of the summary estimate were wide (RR 0.57, 95% CI 0.22 to 1.45; P = 0.48, I^2 = 0%; 6 studies, 320 participants; NNTB 20; low-certainty evidence). None of the included studies reported colectomy rates.

Comment: In immunocompetent adults with rCDI, FMT likely leads to a large increase in the resolution of rCDIs compared to alternative treatments such as antibiotics. There was no conclusive evidence regarding the safety of FMT for the treatment of rCDI as the number of events was small for serious adverse events and all-cause mortality. They suggest and I agree data from large national registry databases might be very helpful to assess any short-term or long-term risks with using FMT for the treatment of rCDI.

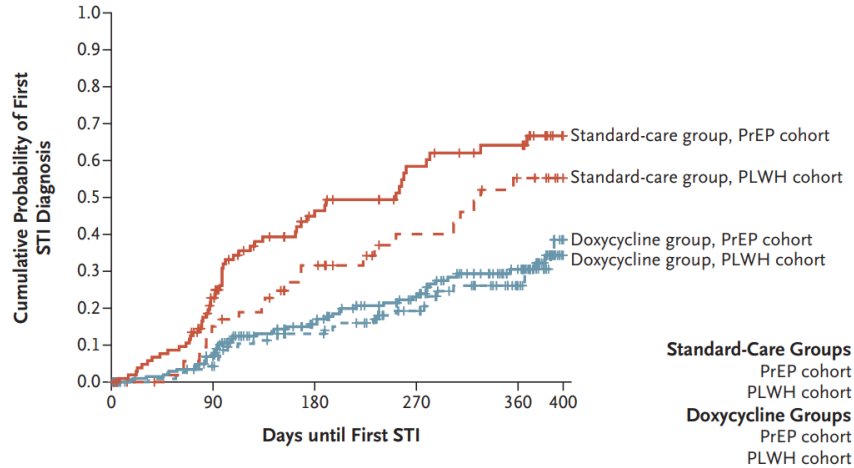
In 2021 IDSA/SHEA published an updated clinical guideline on treatment of CDI [Clin Infect Dis. 2021, 73: e1029–e1044]. They recommend patients with first episode of rCDI use fidaxomicin (standard or extended-pulsed regimen) rather than a standard course of vancomycin (conditional recommendation, low certainty evidence. FMT was only recommended for patients with multiple rCDI who have failed appropriate antibiotic treatments and where appropriate screening of donor and donor fecal specimens has been performed, in accordance with these newer FDA recommendations. The IDSA/SHEA guideline specifically mentioned 3 separate safety alerts had been published by the FDA since June of 2019, which outline adverse events or potential adverse events among recipients of FMT. Two alerts document transmission of pathogenic *E coli* from donor to FMT recipients, some of whom became ill and some of whom died. On the other hand, the ACG guidelines also published in 2021 recommended for second or further CDI recurrences treatment with antibiotics followed by FMT is preferred. (Strong recommendation; moderate-quality evidence). [Am J Gastroenterol. 2021;116(6):1124-1147]

Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. N Engl J Med 2023; 388:1296-1306

DOI: 10.1056/NEJMoa2211934

This study is an open-label, randomized study involving MSM and transgender women who were taking preexposure prophylaxis (PrEP) against HIV infection (PrEP cohort) or living with HIV infection (persons living with HIV infection [PLWH] cohort) and who had had *Neisseria gonorrhoeae* (gonorrhea), *Chlamydia trachomatis* (chlamydia), or syphilis in the past year. Participants were randomly assigned in a 2:1 ratio to take 200 mg of doxycycline within 72 hours after condomless sex (doxycycline postexposure prophylaxis-PEP) or receive standard of (SOC) care without doxycycline. STI testing was performed quarterly. The primary end point was the incidence of at least one STI per follow-up quarter.

Within the PrEP group, an STI was diagnosed in 61 of 570 quarterly visits (11%) for those receiving DOXY versus 82 of 257 visits (32%) for SOC. A significant 66% reduction was seen for the three STIs, including a 55% reduction in gonorrhea incidence. For the PLWH group, a new STI was diagnosed in 36 of 305 quarterly visits (12%) in the doxycycline arm compared with 39 of 128 visits (30%) in the SOC arm. The reduction in new STI diagnoses for the PLWH group was 62% (also significant) for those receiving doxycycline, including a 57% reduction in new gonorrhea diagnoses. Doxycycline resistance was seen in 4 of 15 gonorrhea cases (27%) at baseline and 5 of 14 cases (38%) in the doxycycline group versus 2 of 16 (12%) in the SOC group. Five grade 3 adverse events and no serious adverse events were attributed to doxycycline.



No. at Risk					
Standard-care groups					
PrEP cohort	107	72	37	23	17
PLWH cohort	55	45	30	20	13
Doxycycline groups					
PrEP cohort	220	179	122	93	57
PLWH cohort	119	111	91	64	36

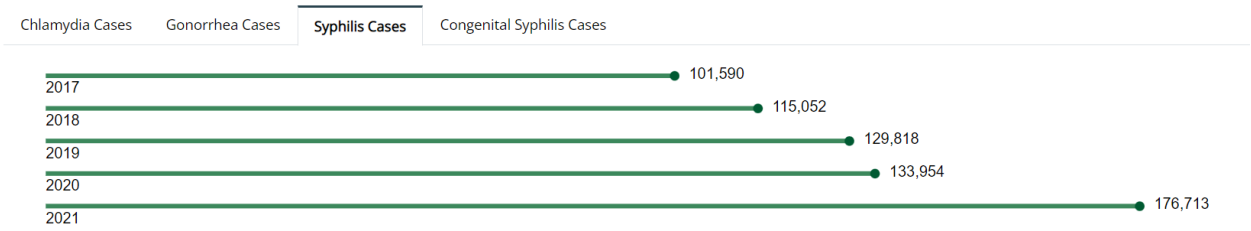
Comment: The investigators concluded that doxycycline PEP represents an effective strategy for reducing bacterial STIs in this high-risk population. Measuring adherence to doxycycline-PEP was limited by the challenges of accurately ascertaining condomless sex and event-driven PEP use. Quarterly computer assisted surveys recorded sexual activity and doxycycline use; however, these are limited by recall. Tetracycline susceptibility results were available in only 17% of gonorrhea end points, because only half the participants with incident gonorrhea

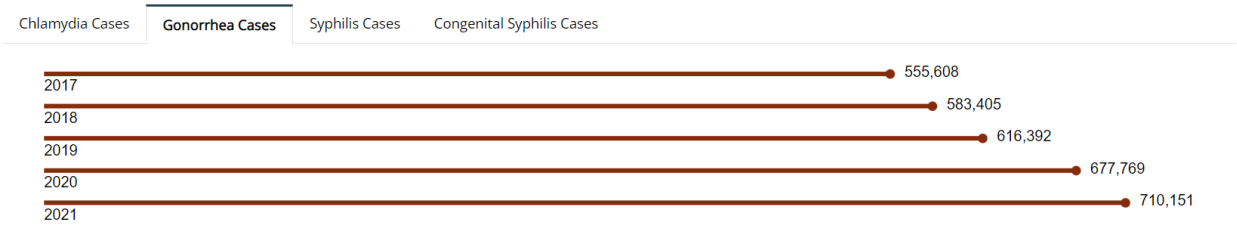
infections during follow-up had *N. gonorrhoeae* culture obtained before treatment and because of lower cultivability from extragenital infections.

In a prior study PEP with doxycycline after condomless sex was shown to be beneficial against syphilis and chlamydia but not gonorrhea. [Lancet Infect Dis 2018; 18:308-317] Two studies were recently presented at the 2023 Conference on Retroviruses and Opportunistic Infections. The ANRS DOXYVAC study was stopped early after a 65% reduction in bacterial STDs were observed in the doxycycline group including a 50% reduction in new gonorrhea infections. A second study was presented involving only women on PrEP. In this study doxycycline PEP was not effective. How do we interpret the current science? Taken together these studies support the use of doxycycline PEP for at-risk MSM and transgender women, but for now not cisgender women. See next review.

STDs are on the rise. -new CDC report April 12, 2023

More than 2.5 million cases of chlamydia, gonorrhea, and syphilis were reported in 2021. In 2021, chlamydia, gonorrhea, and syphilis continued to increase in the US. Syphilis and GC showed the greatest increases. Sadly, with the increase in syphilis cases in adults we have also seen a marked increase in congenital syphilis.



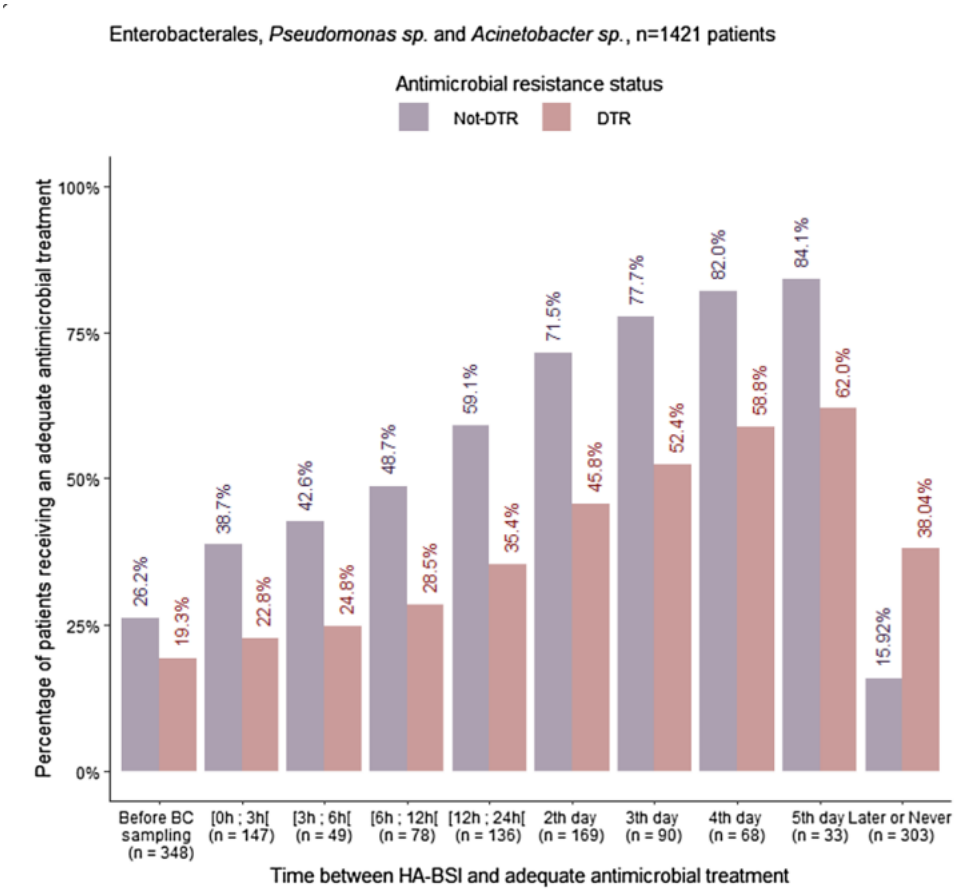


Comment: Disruptions in STD-related prevention and care services due to the Covid-19 pandemic likely continued in 2021, but the impact was most acute in 2020. Covid-19 exposed shortcomings in our public health system. Penicillin G benzathine, was recently added to the FDA drug shortage list this past week. . Pfizer has limited supply of the drug because of increased demand, according to the agency, and the situation may persist into September. I hope the nation's response offers lessons learned that could help reverse rising STD trends.

Epidemiology and outcomes of hospital-acquired bloodstream infections in intensive care unit patients: the EUROBACT-2 international cohort study
Intensive Care Med 2023. 49:178–190

doi.org/10.1007/s00134-022-06944-2

The investigators carried out a prospective international cohort study of adult patients (≥18) with HA-BSI treated in ICUs between June 2019 and February 2021. 2600 patients from 333 ICUs in 52 countries were included. 78% HA-BSI were ICU-acquired. Median SOFA) score was 8 [IQR 5; 11] at HA-BSI diagnosis. Most HA-BSIs were monomicrobial (89%). Most frequent sources of infection included pneumonia (26.7%) and intravascular catheters (26.4%). Most frequent pathogens were Gram-negative bacteria (59.0%), predominantly Klebsiella spp. (27.9%), Acinetobacter spp. (20.3%), E coli (15.8%), and Pseudomonas spp. (14.3%). Carbapenem resistance was present in 37.8%, 84.6%, 7.4%, and 33.2%, respectively. Difficult-to-treat resistance (DTR) [DTR was defined as resistance to all first line antimicrobials, and pan-drug-resistance (PDR) as resistance to all tested antimicrobial] was present in 23.5% and pan-drug resistance in 1.5%. Gram-positive bacteria made up 31% of pathogens (Enterococcus spp. 35%, coagulase negative Staphylococcus 30%, S. aureus 28%), and fungi comprised 8%. Antimicrobial therapy was deemed adequate within 24 h for 51.5%. Meropenem, piperacillin/tazobactam, and vancomycin were administered empirically most often. Antimicrobial resistance was associated with longer delays to adequate antimicrobial therapy. More than half (53%) of patients required source control, performed successfully in 82% within a median 25 hours. Mortality was 37.1%, and only 16.1% had been discharged alive from hospital by day-28.



Comment: The prevalence of MDROs, especially gram-negative pathogens, is alarming. Measures in preventing HA-BSIs should remain a priority as well as prevention of antimicrobial resistance and focusing on adequate antimicrobial therapy and source control are important to optimize patient management and outcomes. The investigators started data collection before and continued during the first year of the Covid-19 pandemic. This likely influenced the patient population, microorganism distribution, antimicrobial resistance, and mortality. Pathogen identification and antimicrobial susceptibility testing relied on each laboratory, with possible differences in interpretation leading to inconsistencies. In April's ID Watch I reported on the changing epidemiology of carbapenemases among carbapenem-resistant Enterobacterales from US hospitals. The investigators do not mention the use of molecular diagnostics. I think the handwriting is on the wall, we need to double down on optimal infection prevention, diagnostic and antimicrobial stewardship.

Epidemiology, Resistance Profiles, and Outcomes of Bloodstream Infections in Community-Onset Sepsis in the United States Crit Care Med published online April 3, 2023

DOI: 10.1097/CCM.0000000000005870

This is a retrospective cohort study involving two hundred one US hospitals from 2016 to 2020 using the Premier Healthcare Database. The study included adult patients (age ≥ 18 yr)

hospitalized with community-onset sepsis from hospitals that reported laboratory and microbiology data during the study period. Patients transferred from outside hospitals and skilled nursing facilities were excluded. The Premier database includes patient demographics, admission type (elective vs nonelective), hospital characteristics, patient-specific date-stamped billing logs, and ICD, 10th Revision, Diagnosis and Procedure codes. Microbiology data including source of specimens and isolated organisms with their susceptibility results were collected using Safety Surveillor web-based tracking tool in each hospital. They defined sepsis using the CDC Adult Sepsis Event Surveillance criteria [https://www.cdc.gov/sepsis/pdfs/Sepsis-Surveillance-Toolkit-Mar-2018_508]. Patients had concurrent evidence of presumed serious infection, defined as having a blood culture drawn and exposure to new antibiotics within 2 days of hospital admission for a duration of at least 4 consecutive days. Criteria for the presence of organ dysfunction included one of the following: initiation of vasopressors, initiation of mechanical ventilation, lactate level greater than or equal to 2.0 mmol/L, two-fold increase in baseline creatinine level or greater than or equal to 50% decrease in estimated glomerular filtration rate, two-fold increase in total bilirubin level to greater than or equal to 2.0 mg/dL, or greater than or equal to 50% decrease in platelet count from baseline and platelet count less than 100,000/μL for patients with baseline plate count greater than 100,000/μL. In order to restrict community-onset sepsis, patients had to have blood cultures, initial antibiotic administration, and organ dysfunction documented within 2 days of hospital admission.

They identified 147,061 patients with community-onset sepsis. The number of blood culture-positive sepsis episodes was 21,167 (14%) and the number of nonblood culture-positive sepsis episodes was 20,326 (14%). Among patients with blood culture-positive sepsis, Gram-negative bacteria were isolated in 55% of patients, Gram-positive cocci were isolated in 47%. Of those, MRSA was 11%, ceftriaxone-resistant *Enterobacterales*/ESBLs was 7%, and carbapenem-resistant *Enterobacterales* was 1.3%. The crude in-hospital mortality was 17% for culture-negative sepsis, 13% for nonblood culture-positive sepsis, and 17% for blood culture-positive sepsis. In multilevel logistic regression models, compared with culture-negative sepsis, blood culture-positive sepsis (adjusted odds ratio [aOR], 0.89; 95% CI, 0.85–0.94) and nonblood culture-positive sepsis (aOR, 0.82; 95% CI, 0.78–0.87) were associated with lower odds of in-hospital mortality. *Acinetobacter* species, *Pseudomonas aeruginosa*, MSSA, and MRSA were associated with higher in-hospital mortality, whereas *Escherichia coli*, *Klebsiella* species, *Proteus* species, and *Streptococcus* species were associated with lower in-hospital mortality.

Comment: In patients hospitalized with community-onset sepsis, the prevalence of blood culture-positive sepsis was 14% with 55% for GNBs and 47% for GPCs. Among positive blood culture sepsis resistant organisms were infrequent which is in sharp contrast to hospital onset infections as reported above and in the last issue of ID Watch. Although 201 US hospitals were analyzed in this study, this sample may not be representative of all US hospitals, and therefore the findings might not be generalizable to other hospitals. Information on prior hospital admission, source control, and baseline laboratory results prior to hospital admission was unavailable in this dataset. However, the investigators were able to include variables related to severity as well as comorbidities in regression models that might mitigate the influences of unmeasured confounding. The Premier database did not allow investigators to control the timing of antibiotic administration relative to cultures if both occur on the same day. Lastly, this study only goes to 2020 so may not have captured the full impact of the pandemic on antimicrobial resistance. The high rate of culture-negative CO-sepsis reported in this analysis is remarkable especially since it was associated with worse outcomes (? inadequate antibiotic therapy).

Incidence, complications, and costs of peripheral venous catheter-related bacteraemia: a retrospective, single-centre study J Hosp Infect published online March 12, 2023

doi.org/10.1016/j.jhin.2023.02.012

Occurrence of (peripheral venous catheters) PVC-related bloodstream infections (BSIs) has been associated with increased duration of hospital stay, mortality, and costs [Ann Intern Med 1991;114:845e54] In the 2012-point prevalence survey of HAIs and antimicrobial use in European acute care hospitals conducted by the European Centre for Disease Prevention and Control, 6% of HA- BSIs were reported to be PVC-related. [Available at: https://data.europa.eu/doi/10.2900/86011]

This was an observational, retrospective, single-center study a 956-bed acute care hospital located in France. Adult ED has 50,000 visits per year on average. Approximately 30% of patients require hospitalization, more than half of them in a medical ward, generally after insertion of a PVC. The aim of the present study was to estimate the current incidence, complications, and costs of BSI attributable to PVC inserted in patients visiting their ED and requiring hospital admission in a medical ward, a hospital using an institutional protocol for PVC insertion, and maintenance based on all the current recommendations for PVC care. For the study, all adult (18 years) patients of both sexes visiting the ED from January 1, 2018, to March 31, 2020 (before the COVID-19 pandemic) were included, and requiring a PVC followed by hospital admission in a medical ward. Patients requiring transfer to a surgical ward or to the ICU before the diagnosis of PVC related BSI were excluded. The primary endpoint was to estimate the incidence of PVC related BSI, which was defined as a combination of (all items required): (i) fever (body temperature 38.5 C) or hypothermia (body temperature 36.5 C), chills or hypotension (systolic blood pressure <90 mmHg); (ii) one or more positive peripheral blood cultures drawn 48 h before or after catheter withdrawal; (iii) isolation of the same organism (same species and same antibiotic susceptibility testing profile) from the colonized catheter or from the catheter insertion site culture (in the absence of culture, the presence of infectious signs (such as redness, phlebitis or purulent discharge) at catheter insertion site was required); and (iv) no other source of infection. Secondary endpoints were: (1) To describe the characteristics, type of causative micro-organisms and consequences of PVC-related BSI in patients requiring admission to a medical ward after visiting an adult ED and (2) To estimate PVC-related BSI costs.

From January 1, 2018, to March 31, 2020, a total of 9833 out of 113,068 patients visiting the ED (9%) were hospitalized in a medical ward after insertion of a PVC. Among them, 581 (6%) had at least one positive blood culture. Twenty-five (4%) of these were judged as having a PVC-related BSI. Staphylococci were the micro-organisms responsible for 90% of infections, with S aureus accounting for three-quarters of the staphylococci involved. Catheters inserted in the emergency department were involved in almost half of cases. The median time from hospital admission to onset of infection was 7 (4-12) days. Major complications were noted in nine patients including severe sepsis requiring admission to ICU for eleven days followed by thoracic spondylodiscitis, mitral valve endocarditis, and pre-sacral abscess. Median (interquartile range)

hospital stay costs were €11,597 (8,479-23,759) for cases and €6,789 (4,019-10,764) for controls, leading to median additional costs of €5,587.

Comment: PVCs are the most widely used invasive medical device in hospitals. Up to 90% of hospitalized patients require a PVC. Each year, two billion catheters are sold worldwide. In this study, although the risk of developing PVC-related BSI in patients admitted to medical wards may seem low, the complications of PVC-related BSI may be severe, and associated mortality remains high. Catheters placed in the ED were involved in half of the cases. PVC insertion in the ED is a well-known risk factor for infection [Infect Control Hosp Epidemiol 2011; 32:579e83.] S aureus was the most common microorganism involved in PVC-related BSI, which is consistent with other studies. [J Hosp Infect 2017; 97:260e6] The study design is retrospective and the study was conducted in a single hospital. The impact of infection on death and of antibiotic use on bacterial resistance could not be studied. Several years ago, investigators demonstrated that PVC-associated SAB is a common cause of HO SAB that results in significant morbidity. [OFID 2019; doi.org/10.1093/ofid/ofz111] CLABSIs account for a minority of HO-BSIs. The CDC is now recommending reporting all cause HO-BSI which will capture PVC BSIs.

Utility of Differential Time to Positivity in Diagnosing Central Line Associated Bloodstream Infections: A Systematic Review and Meta-Analysis

Clin Infect Dis published online April 17, 2023

doi.org/10.1093/cid/ciad225

Differential time to positivity (DTP), typically defined as pathogen growth at least two hours earlier from catheter vs paired peripheral blood cultures, is sometimes used to diagnose central line associated bloodstream infections (CLABSIs). The authors state that prior studies have been small, providing conflicting results. Therefore, they conducted a systematic review of the diagnostic characteristics of DTP for CLABSI, using MEDLINE, Embase, Web of Science, CINAHL, LILACS, AMED and the Cochrane database. Studies were eligible for inclusion if they reported sensitivities, specificities, predictive values, likelihood ratios, or 2x2 tables of DTP for diagnosing CLABSI. Extracted data were analyzed by creating forest plots, performing bivariate model meta-analysis, and assessing quality using QUADAS-2.

Their search identified 274 records of which 23 met criteria for meta-analysis. Among 2,526 suspected CLABSIs, DTP demonstrated a summary sensitivity of 81.3% (95% CI 72.8- 87.7%), specificity of 91.8% (95% CI 84.5-95.8%), positive likelihood ratio of 9.89 (95% CI 5.14-19.00), and negative likelihood ratio of 0.20 (95% CI 0.14-0.30). Covariate analysis based on catheter duration, study design, and patient immune status demonstrated no significant differences. However, DTP performed worse for S aureus (low sensitivity but high specificity) and Candida (high sensitivity but low specificity) compared to other organisms.

Comment: DTP performs well in ruling CLABSIs in or out. The current review has several methodological differences that make it more reliable. A possible explanation for the findings relating to S aureus is that S. aureus has several virulence factors that allow it to quickly disseminate systemically. The quick dissemination into systemic circulation would raise the bacterial load and decrease the time to positivity in peripheral blood cultures leading to a lower DTP and more false negatives. In addition, studies with small sample sizes support the idea that

DTP may have inferior performance in Candida compared to other organisms. Although diagnostic characteristics of DTP may be suboptimal in Candida fungemia, many believe all lines should be removed in Candida fungemia regardless of the source.

The systematic design in this publication allowed a reproducible and less biased search of available literature. This review also gathered additional study details allowing for the assessment of heterogeneity. Finally, the publication of new studies since the last review has allowed for the inclusion of many more articles. The largest limitation of this systematic review and meta-analysis is the poor quality of included studies. However, obtaining paired catheter and peripheral blood cultures for DTP when the infectious source is unclear may prevent unnecessary line removal and diagnostic tests, although this needs to be balanced against potentially higher contamination rates from catheter cultures. One last item-to be accurate equal volumes must be obtained for each bottle.

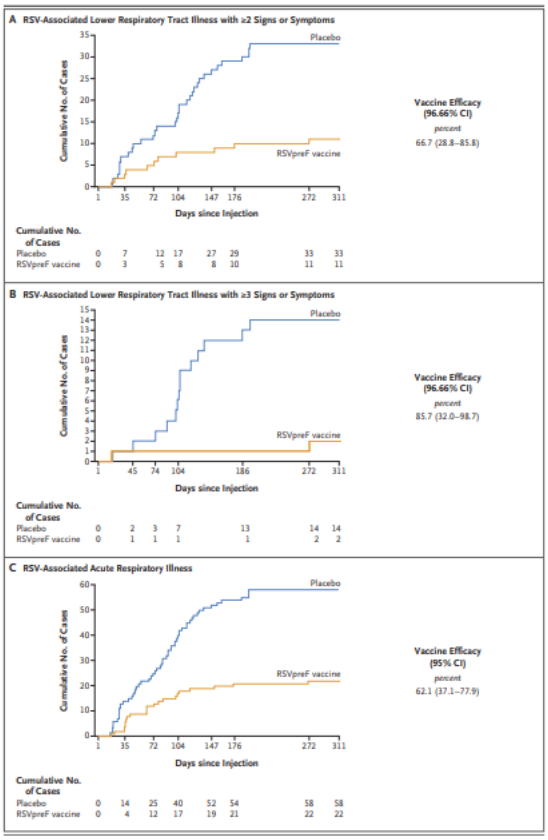
Efficacy and Safety of a Bivalent RSV Prefusion F Vaccine in Older Adults N Engl J Med published 2023;388:1465-1477

DOI: 10.1056/NEJMoa2213836

In this ongoing, phase 3 trial, the investigators randomly assigned, in a 1:1 ratio, adults (≥60 years of age) to receive a single intramuscular injection of RSVpreF vaccine at a dose of 120 µg (RSV subgroups A and B, 60 µg each) or placebo.(RENOIR trial-RSV Vaccine Efficacy Study in Older Adults Immunized against RSV Disease) The two primary end points were vaccine efficacy against seasonal RSV-associated lower respiratory tract illness with at least two or at least three signs or symptoms. The secondary end point was vaccine efficacy against RSV-associated acute respiratory illness. The investigational bivalent RSV prefusion F protein based (RSVpreF) vaccine contains stabilized prefusion F glycoproteins from the two major cocirculating antigenic subgroups (RSV A and RSV B). In an RSV challenge study involving healthy persons who were 18 to 50 years of age, the vaccine efficacy was 87% (95% confidence interval [CI], 54 to 96) against symptomatic RSV infection confirmed by any detectable viral RNA on at least 2 consecutive days. [N Engl J Med 2022; 386:2377-86]

At the interim analysis (data-cutoff date, July 14, 2022), 34,284 participants had received RSVpreF vaccine (17,215 participants) or placebo (17,069 participants). RSV-associated lower respiratory tract illness with at least two signs or symptoms occurred in 11 participants in the vaccine group (1.19 cases per 1000 person-years of observation) and 33 participants in the placebo group (3.58 cases per 1000 person-years of observation) (vaccine efficacy, 66.7%; 96.66% confidence interval [CI], 28.8 to 85.8); 2 cases (0.22 cases per 1000 person-years of observation) and 14 cases (1.52 cases per 1000 person-years of observation), respectively, occurred with at least three signs or symptoms (vaccine efficacy, 85.7%; 96.66% CI, 32.0 to 98.7). RSV-associated acute respiratory illness occurred in 22 participants in the vaccine group (2.38 cases per 1000 person-years of observation) and 58 participants in the placebo group (6.30 cases per 1000 person-years of observation) (vaccine efficacy, 62.1%; 95% CI, 37.1 to 77.9). The incidence of local reactions was higher with vaccine (12%) than with placebo (7%); the incidences of systemic events were similar (27% and 26%, respectively). Similar rates of adverse events through 1 month after injection were reported (vaccine, 9.0%; placebo, 8.5%),

with 1.4% and 1.0%, respectively, considered by the investigators to be injection related. Severe or life-threatening adverse events were reported in 0.5% of vaccine recipients and 0.4% of placebo recipients. Serious adverse events were reported in 2.3% of participants in each group through the data-cutoff date.



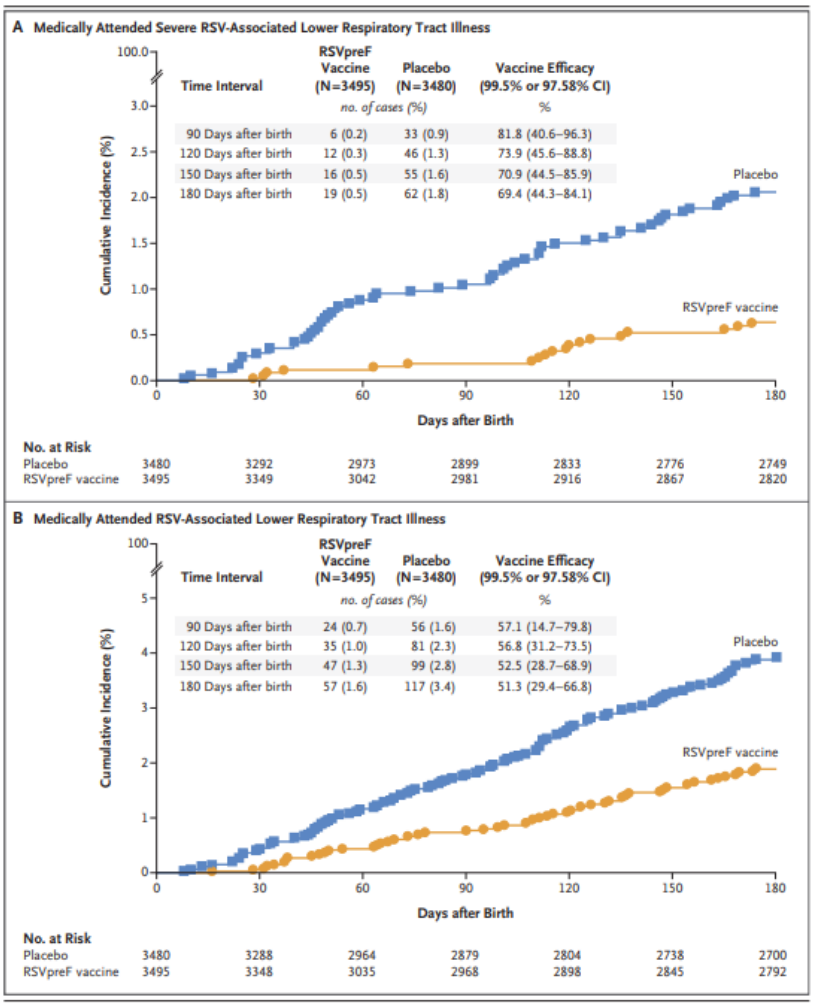
Comment: RSVpreF vaccine prevented RSV-associated lower respiratory tract illness and RSV associated acute respiratory illness in adults (≥60 years of age), without evident safety concerns. A limitation of this trial was the exclusion of immunocompromised persons. Furthermore, an insufficient number of cases of severe RSV-associated lower respiratory tract illness (hospitalization and illness warranting the use of oxygenation or mechanical ventilation) were enrolled for evaluation. Therefore, RSV-associated lower respiratory tract illness, which can progress to severe disease with substantial morbidity and mortality, has a considerable effect on this population and further study in this vulnerable population is warranted. See next review.

Bivalent Prefusion F Vaccine in Pregnancy to Prevent RSV Illness in Infants. N Engl J Med 2023;388:1451-64.

DOI: 10.1056/NEJMoa2216480

This is a double-blind trial conducted in 18 countries, randomly assigned, in a 1:1 ratio, pregnant women at 24 through 36 weeks' gestation to receive a single intramuscular injection of 120 µg of a bivalent RSV prefusion F protein–based (RSVpreF) vaccine or placebo. The two primary efficacy end points were medically attended severe RSV-associated lower respiratory tract illness and medically attended RSV-associated lower respiratory tract illness in infants within 90, 120, 150, and 180 days after birth. (MATTISE trial-Maternal Immunization Study for Safety and Efficacy)

Overall, 3682 maternal participants received vaccine and 3676 received placebo; 3570 and 3558 infants, respectively, were evaluated. Medically attended severe lower respiratory tract illness occurred within 90 days after birth in 6 infants of women in the vaccine group and 33 infants of women in the placebo group (vaccine efficacy, 81.8%; 99.5% CI, 40.6 to 96.3); 19 cases and 62 cases, respectively, occurred within 180 days after birth (vaccine efficacy, 69.4%; 97.58% CI, 44.3 to 84.1). Medically attended RSV-associated lower respiratory tract illness occurred within 90 days after birth in 24 infants of women in the vaccine group and 56 infants of women in the placebo group (vaccine efficacy, 57.1%; 99.5% CI, 14.7 to 79.8); these results did not meet the statistical success criterion. No safety signals were detected in maternal participants or in infants and toddlers up to 24 months of age. The incidences of adverse events reported within 1 month after injection or within 1 month after birth were similar in the vaccine group (13.8% of women and 37.1% of infants) and the placebo group (13.1% and 34.5%, respectively).



Comment: In this worldwide, phase 3 trial, maternal vaccination with RSVpreF was efficacious in preventing medically attended severe RSV-associated lower respiratory tract illness in infants, with vaccine efficacy of 81.8% (99.5% CI, 40.6 to 96.3) within 90 days after birth and 69.4% (97.58% CI, 44.3 to 84.1) within 180 days after birth. There are a few limitations of this trial. First was the exclusion of women with high-risk pregnancies such as those with a current risk of preterm birth, multiple pregnancy, or a previous infant with a clinically significant congenital anomaly. Offspring of these women could be at higher risk for severe RSV-associated illness. Another limitation of this trial includes limited data from low-income countries where the vaccine is likely to have the greatest effect. Lastly, the trial was insufficiently powered to assess differences in vaccine efficacy according to RSV antigen subgroup. In the US, substantial efforts are needed to increase the percentage of pregnant women who receive the RSVpreF vaccine above the 57 to 61% reported for influenza and tetanus–diphtheria–acellular pertussis vaccines. [MMWR 2020; 69:1391-7] See next review.

Reduced Respiratory Syncytial Virus Load, Symptoms, and Infections: a Human Challenge Trial of MVA-BN-RSV Vaccine. J Infect Dis published online April 20, 2023

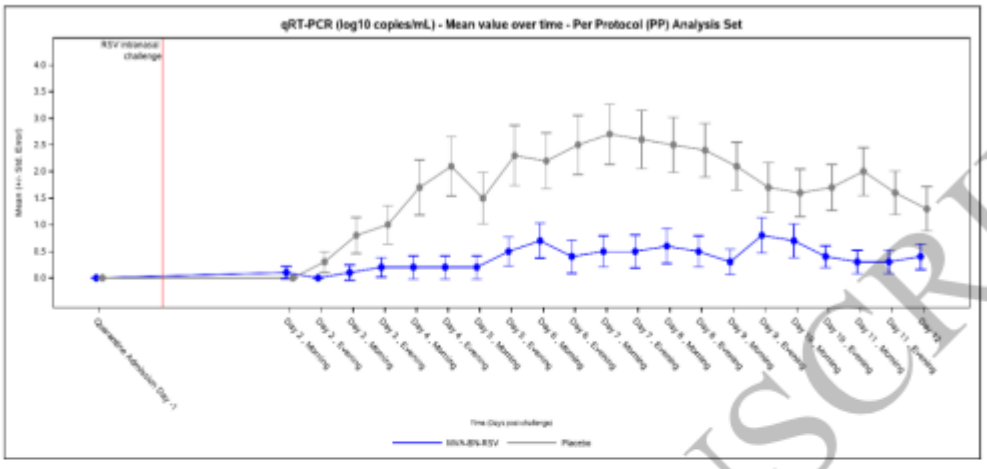
DOI: 10.1093/infdis/jiad108

This is phase 2a randomized double-blind, placebo-controlled trial. Healthy participants aged 18 to 50 years received MVA-BN-RSV or placebo, then were challenged 4 weeks later with RSV-A Memphis 37b. Viral load was assessed from nasal washes. RSV symptoms were collected. Antibody titers and cellular markers were assessed before and after vaccination and challenge.

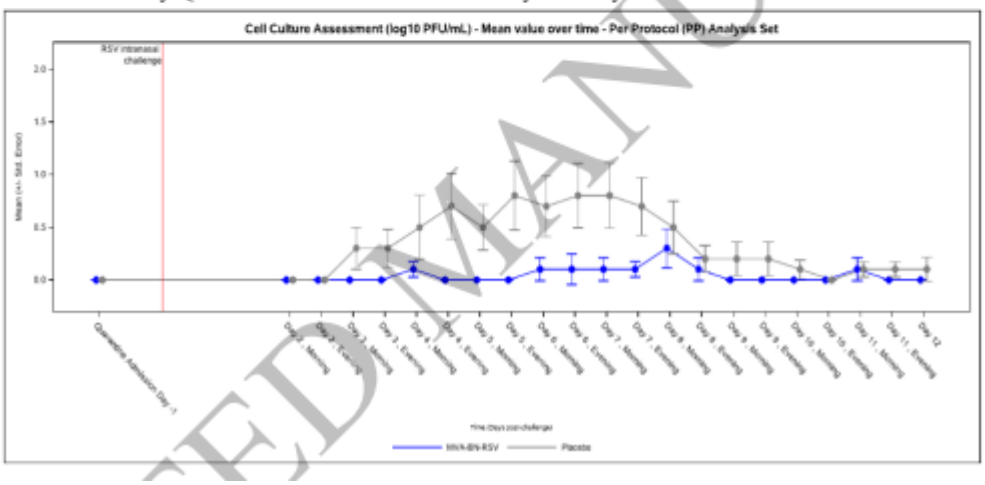
The MVA-BN-RSV recombinant vaccine encodes not only the F protein (expressed as both pre- and post-F) but also surface glycoproteins from the 2 RSV subtypes (G(A) and G(B)) that facilitate viral attachment to airway ciliated epithelial cells and 2 internal proteins (nucleoprotein (N) and transcription elongation factor (M2-1)). The F and G proteins are the main target of RSV nAbs, but this immune response to natural infection is not durable. The N and M2-1 proteins, highly conserved among different RSV subtypes, were included in the recombinant vaccine to promote cytotoxic T-cell responses. MVA-BN-RSV may have an advantage over other candidate vaccines that rely on nAbs to a single protein. The vaccine has induced humoral and cellular immune responses in animal models and in early clinical trials [Vaccine. 2020; 38:2608– 2619] without safety concerns.

After receiving MVA-BN-RSV or placebo, 31 and 32 participants, respectively, were challenged. Viral load AUC from nasal washes were lower ($p = 0.017$) for MVA-BN-RSV (median = 0.00) than placebo (median = 49.05). Total symptom scores also were lower (median = 2.50 and 27.00, respectively; $p = 0.004$). Vaccine efficacy (VE) against symptomatic, laboratory-confirmed or culture-confirmed infection was 79.3% to 88.5% ($p = 0.022$ and 0.013). Serum immunoglobulin A and G titers increased ∼4-fold after MVA-BN-RSV vaccination. Interferon-γ-producing cells increased 4- to 6-fold after MVA-BN-RSV in response to stimulation with the encoded RSV internal antigens. Injection site pain occurred more frequently with MVA-BN-RSV. No serious adverse events were attributed to vaccination.

A. Viral Load by qRT-PCR from Day 2 to Day 12



B. Viral Load by Quantitative Virus Culture from Day 2 to Day 12



Comment: MVA-BN-RSV vaccination resulted in significantly lower viral load AUC by qRT-PCR after challenge with RSV-A Memphis 37b compared to placebo. Vaccination also resulted in fewer infectious virus particles by culture, lower symptom scores, and vaccine efficacy in the range of 79.3% to 88.5% against infection after challenge confirmed by symptoms and quantifiable viral load measures or by positive culture The MVA-BN-RSV vaccine appears to represent a mode of action broader than other vaccine candidates focused on the production of neutralizing antibodies to the preF protein discussed in the two prior articles. The picture with infection prevention, used to measure vaccine efficacy, was more complex. The vaccine did not prevent detectable qRT-PCR confirmed infection alone, as there was little difference between the treatment groups in this regard. However, the importance of detectable RSV in the absence of symptoms or positive culture and whether it represents clinically relevant RSV infection is unclear, as qRT-PCR can detect RNA from non-replicating virus. Inherent in this study design, it is noteworthy that even in the placebo group, less than half of subjects had quantifiable virus by qRT-PCR, and less than a quarter had quantifiable culture results, despite eligibility criteria intended to select for susceptibility to RSV infection. This, along with a small sample size, made it more difficult to detect differences between the treatment groups, and vaccine efficacy

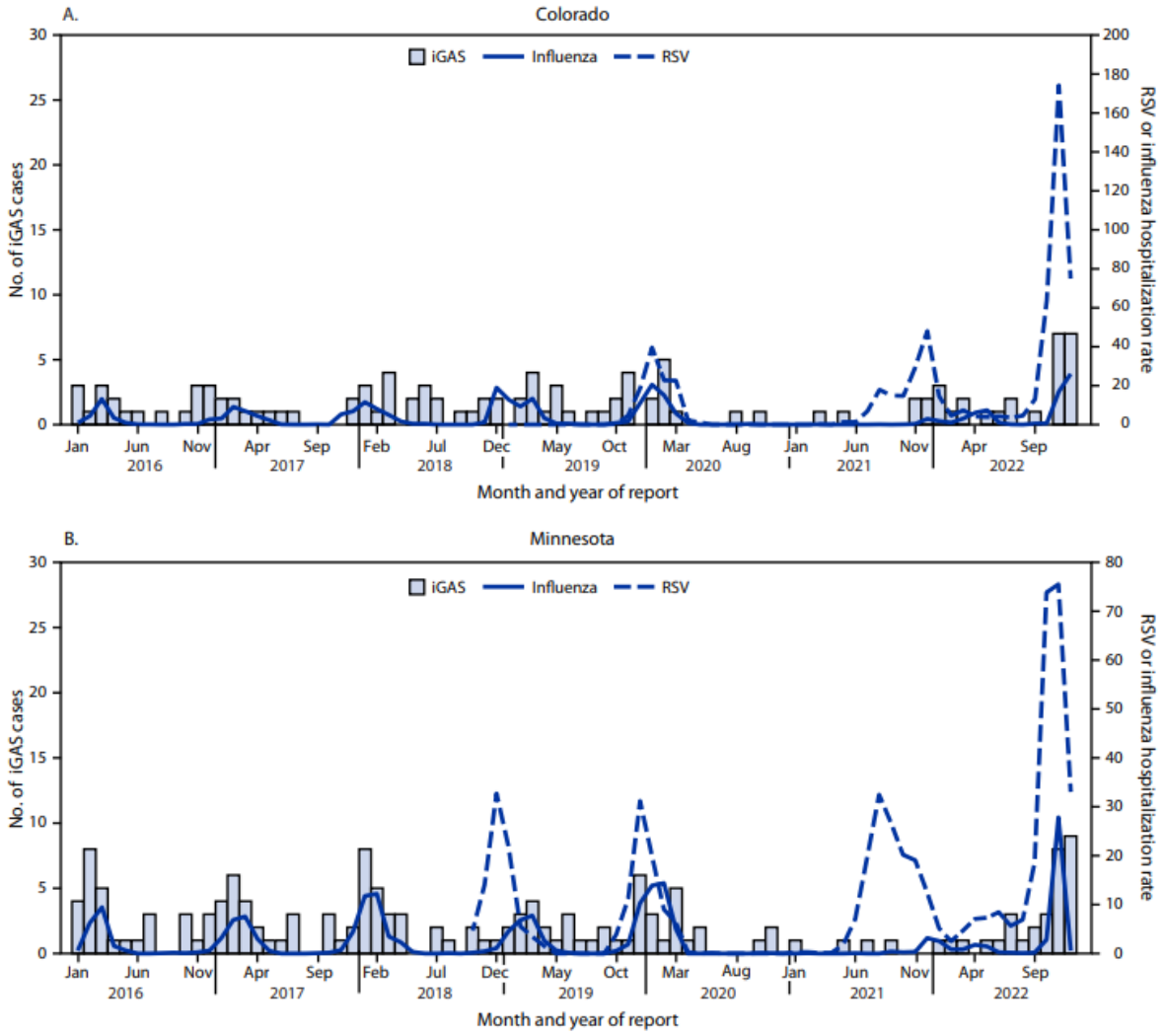
confidence intervals are wide. The authors state: "Dependence of RSV vaccines on the activity of neutralizing antibodies against a specific epitope of one protein conformation may be risky, as such reliance may provide selective pressure for the development of mutant viruses capable of neutralizing antibody escape."

Final Comment: These last 3 articles provide hope we will have an RSV vaccine(s) soon.

Increase in Pediatric Invasive Group A Streptococcus Infections(iGAS) — Colorado and Minnesota, October–December 2022 MMWR 2023; 72:265-267.

Surveillance for iGAS was conducted by 10 US sites as part of EIP's Active Bacterial Core surveillance (ABCs). An analysis of cases among Colorado and Minnesota EIP site residents aged <18 years who met criteria for iGAS was conducted using ABCs data from the Colorado and Minnesota surveillance sites. Case counts, age distribution, and clinical characteristics of patients with iGAS infection were compared over three periods: baseline (January 1, 2016–December 31, 2019), pandemic (January 1, 2020–December 31, 2021), and recent increase (October 1–December 31, 2022).

During October 1–December 31, 2022, a combined total of 34 cases was reported in the Colorado and Minnesota ABCs sites. In comparison, a 3-month average of 11 cases and four cases were observed during the same period in 2016–2019 and 2020–2021, respectively. Colorado patients identified during the recent increase were younger (median age = 3.1 years) than were those during the baseline period (5.6 years) and the pandemic period (6.2 years); this was not observed in Minnesota (median age = 4.0, 6.0, and 6.5 years in the baseline, pandemic, and recent increase periods, respectively). Two deaths (one each in Colorado and Minnesota) were noted during the recent increase period; overall, during 2016–2021, five deaths occurred (one in Colorado and four in Minnesota). Frequency of intensive care unit admission and length of hospital stay were similar during the recent increase (35.3% [12 of 34 patients]; 4.5 days) and baseline periods (34.4% [62 of 180], 5.0 days). Most cases (73.5% [25 of 34]) that occurred during the recent increase were in children and adolescents without underlying medical conditions. Among the 34 cases that occurred during the recent increase, 21 (61.8%) patients had an upper respiratory tract infection noted within the 2 weeks preceding their iGAS infection, six (17.6%) reported sore throat, and seven (20.6%) reported no preceding illness. Fifteen (44.1%) patients received positive test results for one or more respiratory viral pathogen during the 2 weeks before, or concurrent with, their iGAS infection. Viral respiratory pathogens identified included RSV (six, 17.6%), influenza A or B (six, 17.6%), and SARS-CoV-2 (three, 8.8%). Comparison of pediatric iGAS case counts, and influenza and RSV hospitalization rates during 2016–2022 showed an increase in iGAS infections coinciding with seasonal peaks in RSV and influenza hospitalization rates during most years except in 2021, when influenza and RSV hospitalizations were lower than those in previous or subsequent years. Among the 26 (76%) iGAS cases from the recent increase period with M protein gene (emm) typing results available, 22 (85.0%) were type 1 (nine, 34.6%) or type 12 (13, 50.0%); these were also the two most common types detected during the baseline period (55.1% type 1; 17.9% type 12). Whole genome sequencing results did not indicate changes in predicted antibiotic susceptibility compared with earlier years or expansion of a single clone.



Comment: Increased activity of respiratory viruses, in combination with reduced exposure to GAS and associated development of protective immunity to common emm types during the Covid-19 pandemic [Clin Infect Dis 2020;71:e244–54], might have predisposed children to iGAS infection when pandemic restrictions were lifted. The proportion of patients with preceding or concurrent influenza infections suggests that influenza vaccination might reduce the risk for iGAS, as has been demonstrated for varicella vaccination. [J Pediatric Infect Dis Soc 2020;9:236–9.]

Worldwide Prevalence of Antibiotic-Associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis A Systematic Review and Meta-analysis JAMA Dermatol. 2023; 159:384-392.

doi:10.1001/jamadermatol.2022.6378

The purpose of this study was to evaluate the prevalence of antibiotics associated with Stevens-Johnson and Toxic Epidermal Necrolysis (SJS/TEN) worldwide. The MEDLINE and Embase databases were searched for experimental and observational studies that described SJS/TEN risks since database inception to February 22, 2022. They included studies adequately describing SJS/TEN origins and specified the antibiotics associated with SJS/TEN.

Among the 64 studies included in this systematic review, there were 38 studies that described patient-level associations; the meta-analysis included these 38 studies with 2917 patients to determine the prevalence of single antibiotics associated with SJS/TEN. For this meta-analysis, researchers searched for published case series with at least 30 patients with SJS/TEN and focused on antibiotic culprit drugs. Thirty-eight studies — comprising 3000 patients from 5 continents — were identified. In 86% of cases, a drug was the presumed cause of SJS/TEN. An antibiotic was the offending drug in one third of these cases. In descending order, the most commonly implicated antibiotic classes were sulfonamides (32%), penicillins (22%), cephalosporins (11%), fluoroquinolones (4%), and macrolides (2%).

Table 1. Relative Proportions of Antibiotic Classes Associated With Antibiotic-Associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis Among Patients (n = 985)

Antibiotic class	Studies, No.	Proportion (95% CI), %	I^2, %	τ^2	*P* value[a]
Sulfonamides	38	32 (22-44)	91	0.112	<.001
Penicillins	38	22 (17-28)	63	0.019	<.001
Cephalosporins	38	11 (6-17)	77	0.038	<.001
Fluoroquinolones	38	4 (1-7)	69	0.025	<.001
Macrolides	38	2 (1-5)	43	0.009	<.001

[a] Test of heterogeneity.

Comment: Antibiotics, allopurinol, anticonvulsants (Dilantin), and nonsteroidal anti-inflammatory drugs are considered the most frequent precipitant of SJS/TEN. Sulfonamides ranked #1 among implicated antibiotics. Drug-associated SJS/TEN is considered the most severe type of drug hypersensitivity reaction and carries a mortality rate of up to 50%. [JAMA Dermatol. 2017; 153:587-592; Expert Rev Clin Immunol. 2011; 7:803-813] These findings highlight the importance of antimicrobial stewardship, clinician education and awareness, and weighing the risk-benefit assessment of antibiotic choice and duration.

COVID-19

European Centre for Disease Prevention and Control (ECDC) released on COVID vaccination April 5, 2023

- According to ECDC surveillance data, with every new wave of Covid-19 infection, individuals in older age groups are more likely to be hospitalized.
- Although no clear seasonal pattern of virus circulation has emerged so far, data show that the disease's impact has been much higher during the autumn-winter period, corresponding with the traditional influenza season.
- Mathematical models detailed in the report indicate that an autumn 2023 vaccination program with very high vaccine uptake targeting individuals 60 years of age and older is expected to prevent up to 32 percent of COVID-19-related hospitalizations across the EU.

Comment: The US FDA is now recommending high-risk individuals receive an additional booster based on internal data. See next review.

FDA and CDC Authorizes Changes to Simplify Use of Bivalent mRNA COVID-19 Vaccines April 18, 2023 and April 19, 2023

The FDA amended the EUAs of the Moderna and Pfizer Covid-19 bivalent mRNA vaccines to simplify the vaccination schedule for most individuals. This action includes authorizing the current bivalent vaccines (original and omicron BA.4/BA.5 strains) to be used for all doses administered to individuals 6 months of age and older, including for an additional dose or doses for certain populations. The monovalent Moderna and Pfizer-BioNTech Covid-19 vaccines are no longer authorized for use in the US. Below are updated recommendations.

- Most individuals, depending on age, previously vaccinated with a monovalent COVID-19 vaccine who have not yet received a dose of a bivalent vaccine may receive a single dose of a bivalent vaccine.
- Most individuals who have already received a single dose of the bivalent vaccine are not currently eligible for another dose. The FDA intends to make decisions about future vaccination after receiving recommendations on the fall strain composition at an FDA advisory committee in June.
- Individuals 65 years of age and older who have received a single dose of a bivalent vaccine may receive one additional dose at least four months following their initial bivalent dose.
- Most individuals with certain kinds of immunocompromise who have received a bivalent COVID-19 vaccine may receive a single additional dose of a bivalent COVID-19 vaccine at least 2 months following a dose of a bivalent Covid-19 vaccine, and additional doses may be administered at the discretion of, and at intervals determined by, their healthcare provider.

- Most unvaccinated individuals may receive a single dose of a bivalent vaccine, rather than multiple doses of the original monovalent mRNA vaccines.
- Children 6 months through 5 years of age who are unvaccinated may receive a two-dose series of the Moderna bivalent vaccine (6 months through 5 years of age) OR a three-dose series of the Pfizer bivalent vaccine (6 months through 4 years of age). Children who are 5 years of age may receive two doses of the Moderna bivalent vaccine or a single dose of the Pfizer bivalent vaccine.
- Children 6 months through 5 years of age who have received one, two or three doses of a monovalent Covid-19 vaccine may receive a bivalent vaccine, but the number of doses that they receive will depend on the vaccine and their vaccination history.

Comment: It makes sense to harmonize vaccine to bivalent to simplify recommendations. Once again, the FDA and CDC refuse to consider natural disease. The recommendation of a single dose of bivalent vaccine for children caught my eye. In reading the justification for single dose for some children, the immune response after one dose of vaccine among participants with evidence of prior infection was comparable to the immune response after two doses among participants without evidence of prior infection. This change will have little practical impact for most people in the US. About 23 million elderly Americans are now eligible for the second booster with the new bivalent vaccine, though only 42.6% of this age group have gotten the first bivalent booster. Relatively few people are getting vaccinated against Covid-19 for the first time, while some of those at high risk have already been getting a second updated booster. Vaccines made by Novavax and Johnson & Johnson are now only recommended for people who cannot or will not take an mRNA vaccine. The FDA's Vaccines and Related Biologics Products Advisory Committee (VRBPAC) will meet in June to discuss the composition of updated bivalent vaccines for fall 2023, adopting the method used for seasonal influenza vaccines that identifies the viruses that are most likely to circulate in the upcoming year. See next review

SARS-CoV-2 neutralising antibodies after bivalent versus monovalent booster.

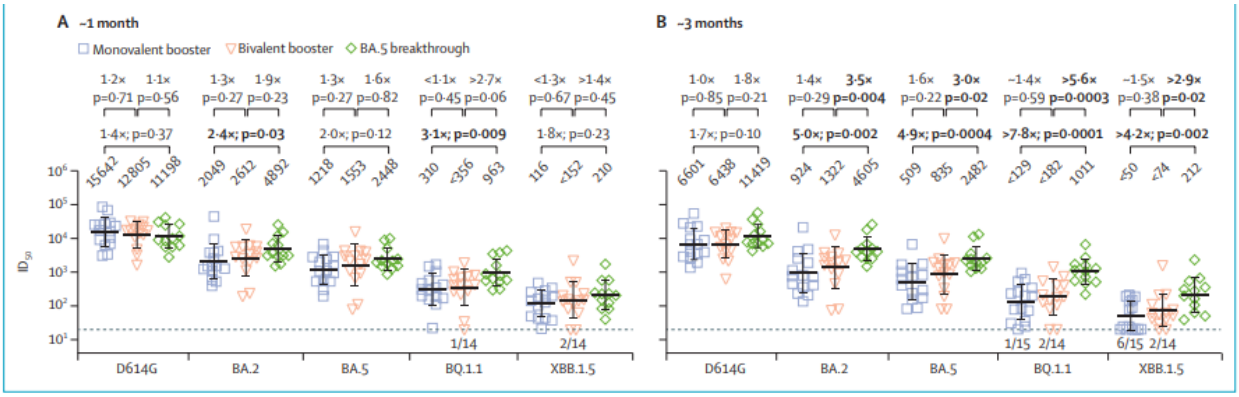
Lancet Infect Dis published online March 29, 2023

doi.org/10.1016/ S1473-3099(23)00181-0

The investigators assessed serum virus-neutralizing titers in 41 participants who received three monovalent mRNA vaccines followed by a bivalent booster, a monovalent booster, or a BA.5 breakthrough infection. They collected serum samples at nearly 1 month and approximately 3 months following the last vaccine dose or breakthrough infection and determined their NAb titers using a pseudovirus neutralization assay against the ancestral D614G strain and a panel of omicron subvariants (BA.2, BA.5, BQ.1·1, and XBB.1·5).

Participants who received a monovalent booster were older (mean 55·3 years) than those who received a bivalent booster (mean 37·8 years) or those who had a breakthrough infection (mean 44·0 years). Each cohort exhibited the highest serum NAb titers (i.e., the serum dilution at which 50% viral neutralization occurs [ID_{50}]) against D614G and substantially lower titers against the latest omicron subvariants. There was no significant difference at nearly 1 month after the last booster for the two vaccine cohorts. At approximately 3 months after the last booster there were, again, no statistical differences between the two groups, although there was a trend toward higher titers in the bivalent group against omicron lineages (1·4–1·6 times higher,

e.g., 509 VS 835 against BA.5). The BA.5 breakthrough cohort exhibited significantly higher NAb titers at 3 months against all tested omicron subvariants when compared with both monovalent and bivalent booster cohorts.



Comment: These new results support other studies suggesting that boosting with the bivalent mRNA vaccines is not evidently better than boosting with the original monovalent vaccine, as judged by serum SARS-CoV-2-neutralising potency and breadth. Perhaps the inclusion of the ancestral spike in the bivalent vaccine demonstrates the challenge posed by immunological imprinting. Hope remains that a second bivalent vaccine booster could induce a superior NAb response against current and future viral variants. The FDA and CDC are now supporting a second bivalent booster for high-risk individuals. See next review.

Durability of Bivalent Boosters against Omicron Subvariants. N Engl J Med published online April 12, 2023

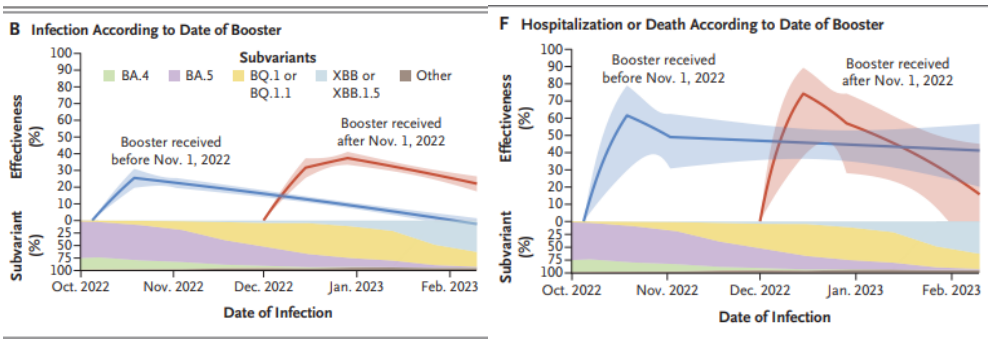
DOI: 10.1056/NEJMc2302462

Investigators used data on booster doses and clinical outcomes from September 1, 2022, to February 10, 2023, for all North Carolina residents who were aged ≥12 years. During this period, 1,279,802 individuals received a bivalent booster.

A total of 19,462 of the 154,581 severe SARS-CoV-2 infections, 253 of the 2,208 Covid-19-related hospitalizations, and 79 of the 867 Covid-19-related deaths occurred after receipt of the bivalent booster. Effectiveness of the bivalent booster against severe infection resulting in hospitalization or death reached a level of 67.4% (95% confidence interval [CI], 46.2-80.2) after 2 weeks and decreased to 47.5% (95% CI, 32.6-59.2) after 4 weeks, to 44.3% (95% CI, 35.7-51.7) after 10 weeks, and to 38.4% (95% CI, 13.4-56.1) after 20 weeks.

Effectiveness against severe infection resulting in hospitalization was slightly lower and effectiveness against infection was much lower. The effectiveness against severe infection resulting in death was the highest despite uncertainty because of the small number of events. A separate analysis of data from participants who received bivalent boosters before November 1, 2022 (when the BA.4/BA.5 subvariants were predominant) and after November 1, 2022 (when the BQ.1/BQ.1.1 subvariants were more prevalent and then were gradually replaced by the XBB/XBB.1.5 subvariants) showed that effectiveness was similar between the 2 booster cohorts. They also performed subgroup analyses according to the participant's age

and previous infection status and according to the manufacturers of the bivalent vaccine and the previous vaccine. Effectiveness against infection(VE) was higher for the Moderna bivalent vaccine than for the Pfizer bivalent vaccine and higher among previously infected participants than among those with no previous infection.



Comment: The VE reported in this article pertains to the benefit of the first booster compared with primary vaccination only, second booster compared with first booster, or third booster compared with second booster. As expected, the VE of bivalent boosters compared with being unvaccinated would be much higher. In addition, VE was higher among previously infected participants than among those with no previous infection. The findings in this study are encouraging, but the effect is short lived.

Association of SARS-CoV-2 Vaccination or Infection With Bell Palsy A Systematic Review and Meta-analysis JAMA Otolaryngol Head Neck Surg. Published online April 27, 2023

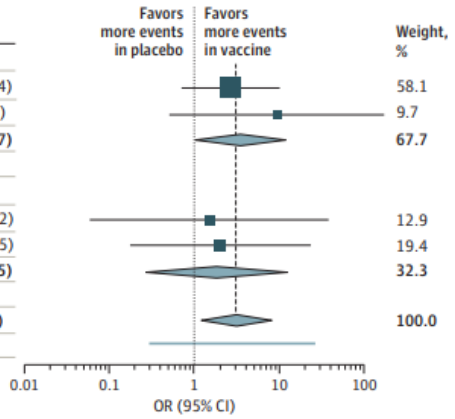
doi:10.1001/jamaoto.2023.0160

Bell palsy (BP) has been reported as an adverse event following the SARS-CoV-2 vaccination. The purpose of this review was to compare the incidence of BP in SARS-CoV-2 vaccine recipients vs unvaccinated individuals or placebo recipients. A systematic search of MEDLINE (via PubMed), Web of Science, Scopus, Cochrane Library, and Google Scholar from the inception of the Covid-19 report (December 2019) to August 15, 2022, was conducted. This study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline and was conducted with the random- and fixed-effect models using the Mantel-Haenszel method. The quality of the studies was evaluated by the Newcastle-Ottawa Scale. The outcomes of interest were to compare BP incidence among (1) SARS-CoV-2 vaccine recipients, (2) nonrecipients in the placebo or unvaccinated cohorts, (3) different types of SARS-CoV-2 vaccines, and (4) SARS-CoV-2–infected vs SARS-CoV-2–vaccinated individuals.

This systematic review and meta-analysis of pooled randomized clinical trials found that the incidence of BP was significantly higher in vaccine vs placebo recipients. The occurrence of BP

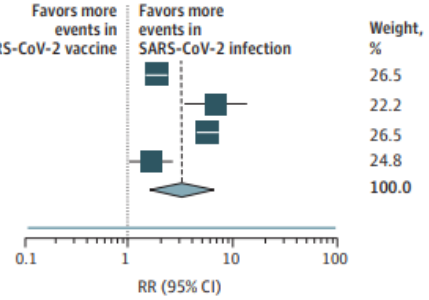
did not differ between recipients of the Pfizer and AstraZeneca vaccines, and there was a greater risk of BP with SARS-CoV-2 infection compared with SARS-CoV-2 vaccination.

Source	Vaccine group Events, No.	Vaccine group Participants, No.	Placebo group Events, No.	Placebo group Participants, No.	OR (95% CI)
mRNA vaccine platform					
El Sahly et al,[35] 2021 (Moderna)	8	15184	3	15162	2.66 (0.71-10.04)
Thomas et al,[36] 2021 (Pfizer/BioNTech)	4	18860	0	18846	9.00 (0.48-167.09)
Total		**34044**		**34008**	**3.57 (1.09-11.67)**
Heterogeneity: $\chi^2_1 = 0.55$ ($P = .46$), $I^2 = 0\%$					
Viral vector vaccine platform					
Falsey et al,[38] 2021 (Oxford/AstraZeneca)	1	21587	0	10792	1.50 (0.06-36.82)
Sadoff et al,[37] 2022 (Janssen)	2	21894	1	21882	2.00 (0.18-22.05)
Total		**43481**		**32674**	**1.80 (0.26-12.35)**
Heterogeneity: $\chi^2_1 = 0.02$ ($P = .89$), $I^2 = 0\%$					
Total		**77525**		**66682**	**3.00 (1.10-8.18)**
Prediction interval					**(0.29-26.13)**
Heterogeneity: $\chi^2_3 = 0.84$ ($P = .84$), $I^2 = 0\%$					
Test for subgroup differences: $\chi^2_1 = 0.35$ ($P = .55$)					



Dashed line indicates the point estimate of the overall effect; dotted line, no effect; diamonds, overall effects. OR indicates odds ratio.

Source	Total No. of infected patients	Total No. of vaccine recipients/doses	RR (95% CI)
Patone et al,[56] 2021	2005280	32552534	1.84 (1.45-2.33)
Tamaki et al,[55] 2021	348088	63551	6.80 (3.50-13.21)
Li et al,[57] 2022 (SIDIAP database)	288030	4372633	5.71 (4.50-7.25)
Barda et al,[41] 2021	180674	923692	1.64 (1.06-2.55)
Total	**2822072**	**37912410**	**3.23 (1.57-6.62)**
Prediction interval			**(0.11-96.91)**
Heterogeneity: $\chi^2_2 = 57.14$ ($P < .001$), $I^2 = 95\%$			

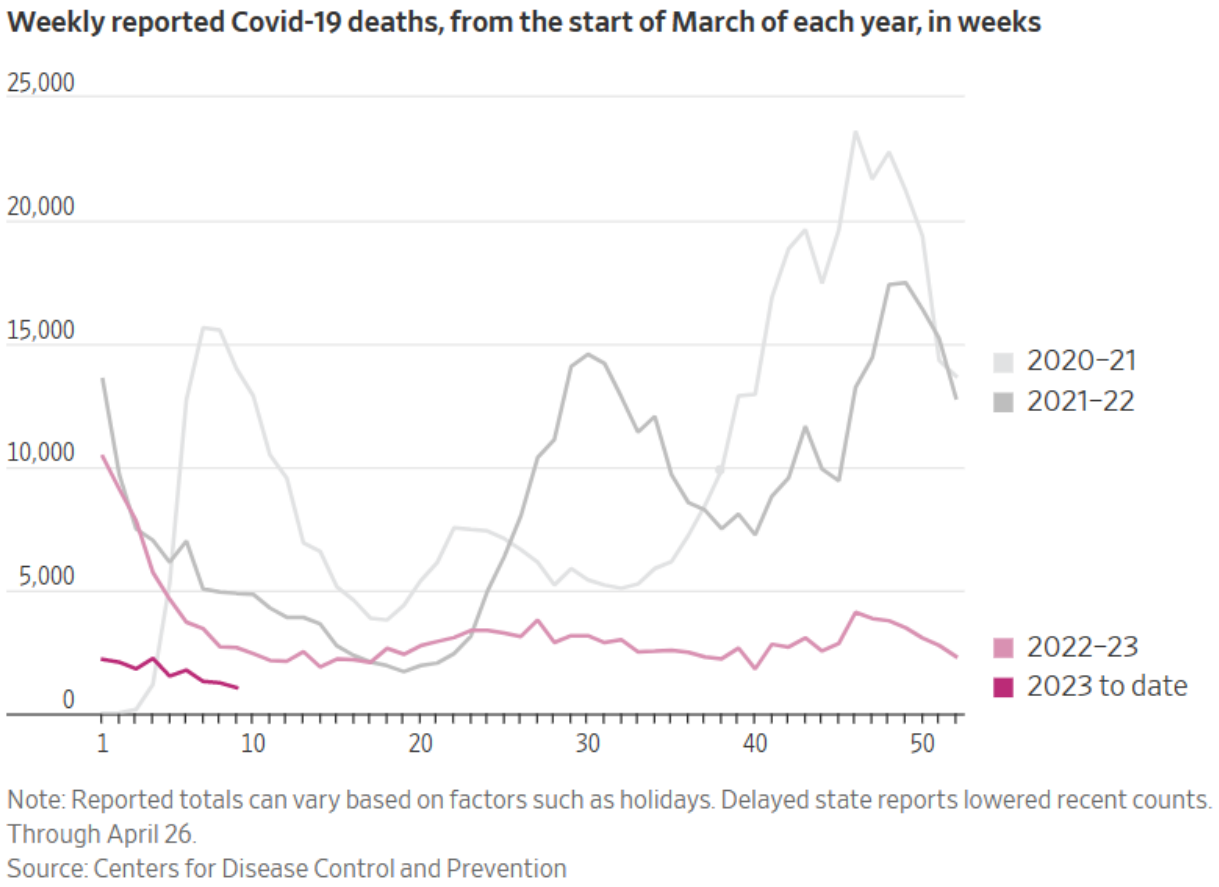


Dotted line indicates no effect; diamond, overall effect. RR indicates risk ratio; SIDIAP, Spanish database of Information System for Research in Primary Care.

Comment: This review suggests a higher incidence of BP among SARS-CoV-2–vaccinated vs placebo groups. The occurrence of BP did not differ significantly between recipients of the Pfizer vs AstraZeneca vaccines. However, SARS-CoV-2 infection posed a significantly greater risk for BP than SARS-CoV-2 vaccination. [Lancet Infect Dis. 2022; 22:64-72] It is speculated that the vaccine antigens that can reactivate T cells by mimicking human cell surface molecules may elicit an autoimmune response. BP has been associated with intranasal influenza vaccine, seasonal influenza vaccine, H1N1 influenza vaccines, and meningococcal conjugate vaccine. They used previously published data since no individual patient-level data were available in this study. This limitation hampered their ability to perform subgroup analyses based on parameters such as age, sex, vaccine dose, or vaccination-to-event time span. It was also not possible to control some of the known BP risk factors, such as diabetes, obesity, hypertension, upper respiratory tract disease, or pregnancy, because most studies have not provided sufficient data on these risk factors. There was also some heterogeneity among the studies that compared BP incidence in mRNA vaccinated vs unvaccinated individuals and among the studies that compared vaccination with SARS-CoV-2 infection. This heterogeneity could be attributable to different inclusion criteria or sampling methods. This review does not equate to causality, and further research is required to verify this association and investigate possible mechanisms.

COVID-19 by the Numbers

US Covid-19 hospitalizations and deaths are close to new lows. Increased immunity from vaccines and prior infections are helping most of the population avoid severe illness. The latest weekly data shows around the US reported 1,052 deaths for the week ended April 26th, according to the CDC. This caps several weeks where reports have come in below a prior low of about 1,700 reached during a summer week nearly two years ago. Hospitalizations seven-day average for confirmed Covid-19 cases was about 9,950 on Friday. This marks a new low for the average since the CDC began tracking widespread hospital metrics closely, falling slightly below a prior low reached a year ago. The average topped 42,000 this past winter and reached a record peak above 150,000 a year earlier, during the initial Omicron surge.

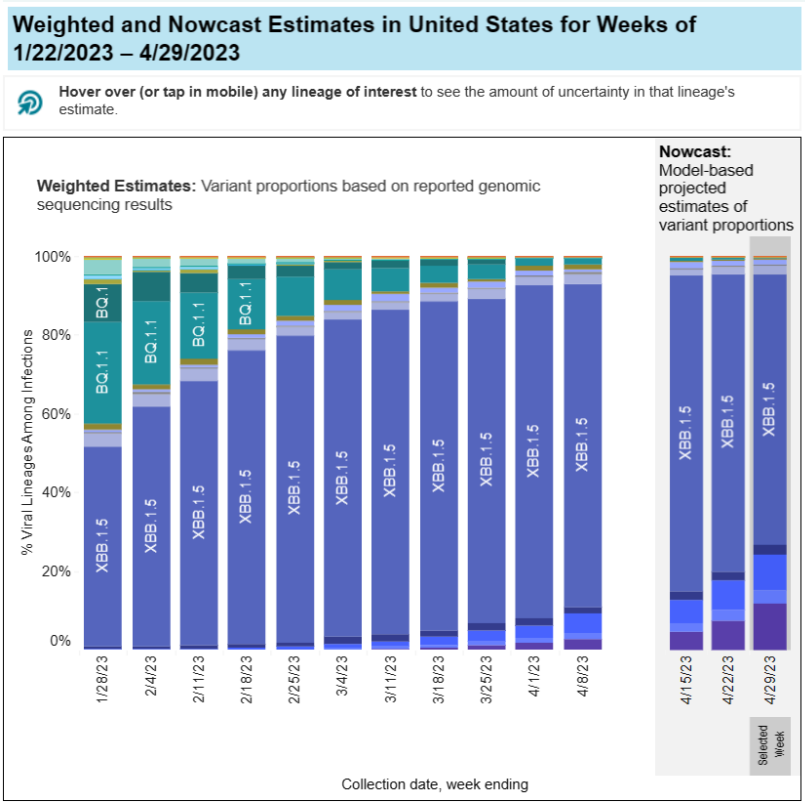


Note: Reported totals can vary based on factors such as holidays. Delayed state reports lowered recent counts. Through April 26.
Source: Centers for Disease Control and Prevention

Comment: Covid-19 remains a risk for some patients, particularly the elderly and immunocompromised. Some new Omicron subvariants have emerged including XBB.1.16. which needs to be watched. The US plans to lift its Covid-19 public-health emergency on May 11th. See next review.

Arcturus (formally, Omicron subvariant XBB.1.16) Now a VOI and XBB.1.9.1

Data show that XBB.1.16 now makes up 11.7% of US samples, up from 7.4% the previous week, the CDC said in its latest variant report. XBB.1.16 already makes up 21.3% of viruses in the south-central region of the country, which includes Arkansas, Louisiana, New Mexico, Oklahoma, and Texas. Meanwhile, the XBB.1.9.1 proportion increased from 7.4% to 9% over the past week, with levels highest in the region that includes Iowa, Kansas, Missouri, and Nebraska, where it makes up an estimated 23.9% of samples. A prominent pediatrician in India is seeing children with "itchy" or "sticky" eyes, as if they have conjunctivitis or pinkeye with XBB.1.16. The new itchy eye symptoms are in addition to a high fever and cough.



Nowcast Estimates in United States for 4/23/2023 – 4/29/2023

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	XBB.1.5	VOC	68.8%	65.3-72.2%
	XBB.1.16	VOC	11.7%	9.2-14.6%
	XBB.1.9.1	VOC	9.0%	7.3-10.9%
	XBB.1.9.2	VOC	3.7%	2.8-4.9%
	XBB	VOC	2.4%	1.4-4.0%
	XBB.1.5.1	VOC	2.2%	1.7-2.8%
	FD.2	VOC	1.3%	0.7-2.4%
	BQ.1.1	VOC	0.4%	0.3-0.7%
	CH.1.1	VOC	0.3%	0.2-0.4%
	BQ.1	VOC	0.1%	0.0-0.1%
	BN.1	VOC	0.0%	0.0-0.0%
	BA.5	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.1%
	BA.2	VOC	0.0%	0.0-0.0%
	BA.2.75	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.2.75.2	VOC	0.0%	0.0-0.0%
	BF.7	VOC	0.0%	0.0-0.0%
	BA.5.2.6	VOC	0.0%	0.0-0.0%
	BF.11	VOC	0.0%	0.0-0.0%
	BA.4.6	VOC	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

Comment: WHO last week boosted the XBB.1.16 Omicron subvariant to a variant of interest (VOI) from a variant under monitoring (VUM), based on the latest assessments from its technical advisory group on virus evolution. XBB.1.16 is now the second most common VOI, alongside XBB.1.5. According to the WHO current available information does not suggest that XBB.1.16 poses an additional public health risk relative to XBB.1.5 and the other currently circulating Omicron descendent lineages at this time. The European Centre for Disease Control and Prevention (ECDC) in its latest weekly update last week said cases overall were declining or stable for the week ending April 16. In the US, COVID trends continue to decline slowly. See review above on Covid-19 by the Numbers.

Virological characteristics of the SARS-CoV-2 Omicron XBB.1.16 variant bioRxiv posted online April 9, 2023

doi.org/10.1101/2023.04.06.535883

The current analyses showed that as compared to its predecessor mutant strains, XBB.1.16 had two S substitutions, including E180V and T478R in the N-terminal domain (NTD) and receptor-binding domain (RBD), respectively. Furthermore, the dissociation constant (K_D) of the XBB.1.16 RBD for the host receptor angiotensin-converting enzyme 2 (ACE2) was 2.4-fold higher than XBB.1.5; however, its K_D values were markedly poorer than that of XBB.1, thus reflecting the binding affinities of this novel subvariant. Pseudovirus assays showed that the infectivity of XBB.1.16 was comparable to that of XBB.1 but unlike XBB.1.5, the latter of which had higher infectivity than the parental XBB.1 mutant. Note that the S: T478R and S: E180V substitution mutations have a significant influence on the infectivity of this viral variant. Whereas the S: T478R mutation increases the infectivity of XBB.1.16, the S: E180V substitution significantly reduced its viral infectivity. Regarding sensitivity to sera, neutralization assays showed that XBB.1.16 was highly resistant to sera from individuals reinfected with Omicron BA.2/BA.5, 18- and 37-fold more resistant than Omicron B.1.1/B.1.1. However, the sensitivity of this variant to convalescent sera of hamsters infected with XBB.1 was similar to XBB.1/XBB.1.5 mutants. XBB.1.16 was highly resistant to all six clinically available monoclonal antibodies for SARS-CoV-2. Only sotrovimab exhibited antiviral activity against XBB.1.16; however, this effect was weak. Lastly, antigenic cartography showed that XBB.1.16 had antigenicity close to XBB.1; however, this characteristic differed considerably from that associated with XBB.1.5.

Comment: XBB.1.16 likely acquired these two S protein mutations simultaneously as a strategy to evolve. This behavior has been previously observed in other Omicron subvariants, including BA.5 and XBB.1. Indeed, XBB.1.16 follows the evolutionary path of Omicron subvariants that emerged earlier. XBB.1.16 exhibits a higher immune-evasion potential that is similar to that of XBB.1 and XBB.1.5. The SARS-CoV-2 XBB.1.16 variant is associated with a 1.27- and 1.17-fold higher effective reproductive number (R_e) as compared to the XBB.1 and XBB.1.5 subvariants. The increased fitness of XBB.1.16 may be due to (1) different antigenicity from XBB.1.5; and/or (2) the mutations in the non-S viral protein(s) that may contribute to increased viral growth efficiency.

IDSA Guideline on the Treatment and Management of COVID-19 Update April 11, 2023 Convalescent Plasma

In hospitalized patients, convalescent plasma appears to have trivial little or no effect on mortality based on the body of evidence from RCTs (RR: 0.98; 95% CI: 0.93, 1.03; moderate certainty of evidence. Recipients of COVID-19 convalescent plasma may have a greater need for mechanical ventilation (RR: 1.10; 95% CI: 0.94, 1.29; low CoE); however, the evidence is uncertain because of concerns with risk of bias and imprecision. In hospitalized immunocompromised patients, convalescent plasma failed to show or to exclude a beneficial effect on mortality based on the body of evidence from two RCTs (RR: 0.65; 95% CI: 0.37, 1.13; very low evidence).

The guideline panel does suggest FDA-qualified high-titer Covid-19 convalescent plasma in the ambulatory setting for persons with mild-to-moderate Covid-19 at high risk for progression to severe disease, who have no other treatment options. In ambulatory patients, convalescent plasma may be more effective if the product used contains high titers of neutralizing antibodies and is used early in clinical presentation or in subpopulations of patients who do not have an adequate humoral immune response even at later stages of disease.

Comment: This review discouraged use of convalescent plasma in hospitalized patients. Convalescent plasma may have a limited role in ambulatory setting if given early when other options are not appropriate. Paxlovid and remdesivir are still preferred for high-risk patients with early symptoms.

The US FDA gives an EUA for a new monoclonal antibody treatment (vilobelimab)

April 4, 2023

Vilobelimab is a recombinant chimeric monoclonal IgG4 antibody that specifically binds to the soluble human complement split product C5a after cleavage from C5 to block its interaction with the C5a receptor, both of which are components of the complement system thought to contribute to inflammation and worsening of Covid-19.

Based on the totality of scientific evidence available to FDA, including data from the Phase 3 portion of the clinical trial, PANAMO (NCT04333420): a randomized, double-blind, placebo controlled study to evaluate the safety and efficacy of vilobelimab in adult (>18 years) patients with Covid-19 pneumonia who required invasive mechanical ventilation (IMV) or extracorporeal membrane oxygenation (ECMO), it is reasonable to believe that vilobelimab may be effective for the treatment of Covid-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO.

Comment: To my knowledge there is no adequate, approved, and available alternative to the emergency use of vilobelimab for the treatment of Covid-19 in hospitalized adults when initiated within 48 hours of receiving IMV, or ECMO. Fortunately, we are not seeing as many patients who require IMV or ECMO, but vilobelimab may offer an additional therapeutic tool in patients with severe Covid-19 pneumonia.

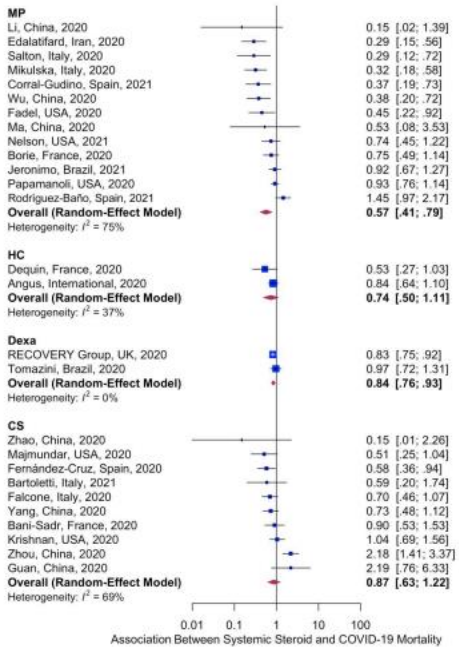
Optimal Duration of Systemic Corticosteroids in Coronavirus Disease 2019 Treatment: A Systematic Review and Meta-analysis OFID published online February 24, 2023

doi.org/10.1093/ofid/ofad105

They identified 27 eligible studies consisting of 13,404 hospitalized Covid-19 patients. Seven randomized controlled trials and 20 observational studies were included in the meta-analysis of mortality, which suggested a protective association with corticosteroid therapy (risk ratio [RR], 0.71 [95% confidence interval {CI}, .58–.87]). Pooled analysis of 18 studies showed the greatest survival benefit for a treatment duration up to 6 days (RR, 0.54 [95% CI, .39–.74]). Survival benefit was 0.65 (95% CI, .51–.83) up to 7 days, and no additional survival benefit was observed beyond 7 days of treatment (RR, 0.64 [95% CI, .44–.93]). The survival benefit was not

confounded by severity of disease, age, duration of symptoms, or proportion of control group given steroids.

Subgroup analyses and meta-analyses were conducted to assess the optimal duration of corticosteroid treatment while adjusting for the severity of disease, age, duration of symptoms, and proportion of control group given steroids. The analyses demonstrated the greatest reduction in mortality in patients who received methylprednisolone (RR, 0.57 [95% CI, .41–.79].



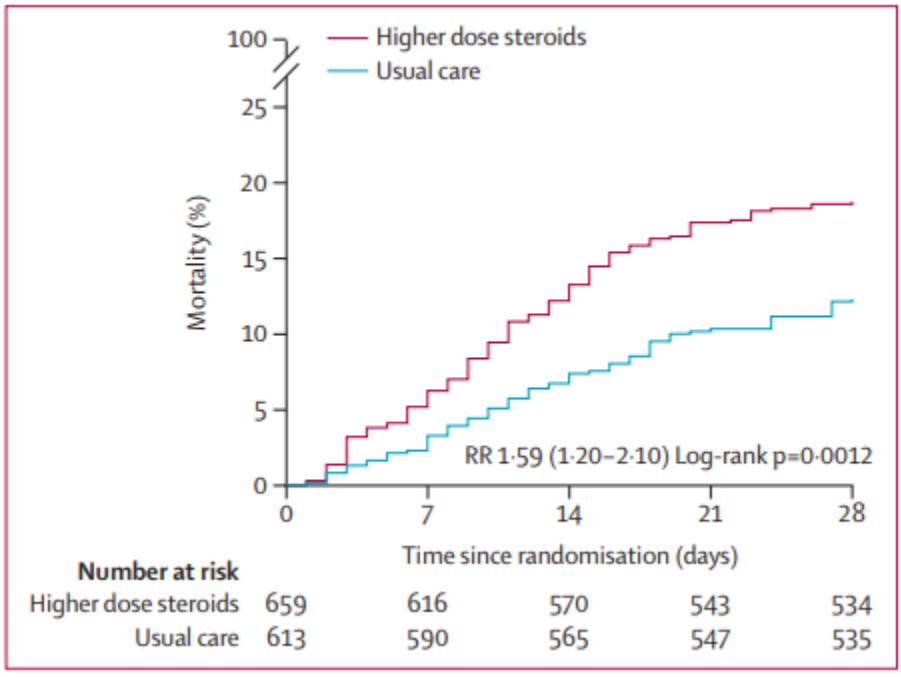
Comment: Review and meta-analysis limitations include the design nature of a review; publication bias; the inclusion of a small number of studies in the meta-analysis, most of which were observational some of which were low quality; high heterogeneity between studies; and incomplete capture of the benefit of longer corticosteroid courses in the most critically ill. However, the findings of the present study support the positive impact of administration of corticosteroids on mortality in hospitalized patients who require oxygen supplement. Interestingly, administration of corticosteroids for up to a median of fewer than 7 days demonstrated a greater mortality reduction than systemic steroids for equal or more than 7 days. These findings were not impacted by severity of disease, age, duration of symptoms, or proportion of control group given steroids. Current guidelines for the use of systemic steroids in Covid-19 suggest up to 10 days of steroid treatment without clear guidance on criteria to discontinue use. [IDSA and NIH]. Systemic steroids are known to cause hyperglycemia, opportunistic infection, delayed viral clearance, gastrointestinal bleeding, suppression of the hypothalamic-pituitary-adrenal axis, and neuromuscular weakness. Lastly, should we be switching to methylprednisolone?

Higher dose corticosteroids in patients admitted to hospital with COVID-19 who are hypoxic but not requiring ventilatory support (RECOVERY): a randomised, controlled, open-label, platform trial Lancet published online April 12, 2023

doi.org/10.1016/ S0140-6736(23)00587-1

This is a randomized, controlled, open-label platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]) in assessing multiple possible treatments in patients hospitalized for Covid-19. Eligible and consenting adult patients with clinical evidence of hypoxia (i.e., receiving oxygen or with oxygen saturation <92% on room air) were randomly allocated (1:1) to either usual care with higher dose corticosteroids (dexamethasone 20 mg once daily for 5 days followed by 10 mg dexamethasone once daily for 5 days or until discharge if sooner) or usual standard of care alone (which included dexamethasone 6 mg once daily for 10 days or until discharge if sooner). The primary outcome was 28-day mortality among all randomized participants.

Between May 25, 2021, and May 13, 2022, 1272 patients with Covid-19 and hypoxia receiving no oxygen (eight [1%]) or simple oxygen only (1264 [99%]) were randomly allocated to receive usual care plus higher dose corticosteroids (659 patients) versus usual care alone (613 patients, of whom 87% received low-dose corticosteroids during the follow-up period). Of those randomly assigned, 745 (59%) were in Asia, 512 (40%) in the UK, and 15 (1%) in Africa. 248 (19%) had diabetes and 769 (60%) were male. Overall, 123 (19%) of 659 patients allocated to higher dose corticosteroids versus 75 (12%) of 613 patients allocated to usual care died within 28 days (rate ratio 1·59 [95% CI 1·20–2·10]; p=0·0012). There was also an excess of pneumonia reported to be due to non-Covid infection (64 cases [10%] vs 37 cases [6%]; absolute difference 3·7% [95% CI 0·7–6·6]) and an increase in hyperglycemia requiring increased insulin dose (142 [22%] vs 87 [14%]; absolute difference 7·4% [95% CI 3·2–11·5]). On May 11, 2022, the independent data monitoring committee recommended stopping recruitment of patients receiving no oxygen or simple oxygen only due to safety concerns.



Comment: In patients hospitalized for Covid -19 with clinical hypoxia who required either no oxygen or simple oxygen only, higher dose corticosteroids significantly increased the risk of death compared with usual care, which included low-dose corticosteroids. The RECOVERY trial continues to assess the effects of higher dose corticosteroids in patients hospitalized with Covid-19 who require non-invasive ventilation, invasive mechanical ventilation, or extracorporeal membrane oxygenation. This randomized trial was open label (i.e., participants and local hospital staff were aware of the assigned treatment), which could potentially lead to bias in outcomes that might be affected by knowledge of treatment allocation, such as the diagnosis of hyperglycemia or non-SARS-CoV-2 infections. Information on radiological, virological, or physiological outcomes was not collected. Only about 10% of participants in this evaluation of higher dose corticosteroids received an IL-6 antagonist or baricitinib so they were unable to assess any possible interactions between corticosteroid dose and other immunomodulatory treatments.

SARS-CoV-2 Variants and Multisystem Inflammatory Syndrome in Children N Engl J Med published online March 22, 2023

DOI: 10.1056/NEJMc2215074

Investigators in the US and Canada examined data from the International Kawasaki Disease Registry to identify children hospitalized from April 2020 through June 2022 who met CDC criteria for MIS-C. Records of 2017 children were reviewed to investigate changes in clinical presentation and outcome as significant SARS-CoV-2 variants emerged. Patients with MIS-C diagnosed during Delta and Omicron circulation were younger, had symptoms more consistent with Kawasaki disease (KD), and were less likely to have coronary artery dilatation or require ICU care compared with those diagnosed at the start of the pandemic (ancestral and Alpha variants). After the ancestral period, immunomodulatory management evolved to include greater use of steroids. Concurrently, the risks of serious complications (arrhythmia, cardiac arrest, renal complications, coagulopathy, and thrombosis), admission to an intensive care unit, and death decreased, with the most pronounced decrease occurring during the omicron period. Across all the variant periods, the risk of ventricular dysfunction was highest among the patients hospitalized during the alpha period as compared with those during the ancestral period (35% vs. 28%, relative risk, 1.19; 95% confidence interval, 1.04 to 1.35). Although the clinical phenotype became milder over time, severe disease was still prevalent, with 23% of the patients during the omicron period presenting with shock and with 37% being admitted to an intensive care unit.

Comment: Why the incidence of MIS-C has declined, and its clinical presentation changed is unclear. To better understand this change, it is important to determine if these changes are related to the variant or other factors such as prior immunity from infections and or vaccination.

Risk of Death in Patients Hospitalized for COVID-19 vs Seasonal Influenza in Fall-Winter 2022-2023 JAMA published online April 6, 2023

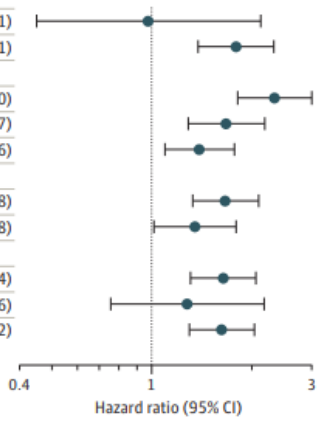
doi:10.1001/jama.2023.5348

The investigators used the electronic health databases of the US Department of Veterans Affairs (VA). Between October 1, 2022, and January 31, 2023, they enrolled all individuals with at least 1 hospital admission record between 2 days before and 10 days after a positive test result for SARS-CoV-2 or influenza and an admission diagnosis for COVID-19 or seasonal influenza. The cohort was followed up until the first occurrence of death, 30 days after hospital admission, or March 2, 2023. They evaluated the risk of death in people hospitalized for Covid-19 vs influenza through inverse probability-weighted Cox survival models. Logistic regression was used to generate a propensity score, which was then applied in inverse probability weighting to balance the 2 groups.

There were 8996 hospitalizations (538 deaths [5.98%] within 30 days) for Covid-19 and 2403 hospitalizations (76 deaths [3.16%]) for seasonal influenza. After propensity score weighting, the 2 groups were well balanced (mean age, 73 years; 95% male). The death rate at 30 days was 5.97% for Covid-19 and 3.75% for influenza, with an excess death rate of 2.23% (95% CI, 1.32%-3.13%). Compared with hospitalization for influenza, hospitalization for Covid-19 was associated with a higher risk of death (hazard ratio, 1.61 [95% CI, 1.29-2.02]). The risk of death decreased with the number of Covid-19 vaccinations (P = .009 for interaction between unvaccinated and vaccinated; P < .001 for interaction between unvaccinated and boosted). No statistically significant interactions were observed across other subgroups.

Figure. Hazard Ratio, Death Rates, and Percentage of Excess Deaths in COVID-19 Compared With Seasonal Influenza

	Death rate at 30 d, % (95% CI)		Excess deaths at 30 d, % (95% CI)	Hazard ratio (95% CI)	*P* value for interaction
	COVID-19	Influenza			
Age, y					
≤65	1.29 (0.77-1.82)	1.33 (0.46-2.20)	-0.04 (-1.06 to 0.98)	0.97 (0.45-2.11)	Reference
>65	6.42 (5.85-6.98)	3.66 (2.77-4.54)	2.76 (1.71 to 3.81)	1.78 (1.37-2.31)	.10
COVID-19 vaccination status					
Unvaccinated	8.75 (7.46-10.01)	3.86 (3.09-4.63)	4.88 (3.39 to 6.37)	2.32 (1.80-3.00)	Reference
1 or 2 doses of vaccine	6.23 (5.22-7.23)	3.79 (3.03-4.56)	2.44 (1.17 to 3.70)	1.66 (1.28-2.17)	.009
Boosted	5.18 (4.55-5.79)	3.77 (3.00-4.53)	1.41 (0.43 to 2.39)	1.38 (1.09-1.76)	<.001
SARS-CoV-2 infection					
Primary infection	6.14 (5.58-6.69)	3.76 (2.99-4.51)	2.38 (1.44 to 3.32)	1.65 (1.32-2.08)	Reference
Reinfection	5.11 (4.11-6.09)	3.85 (3.08-4.62)	1.26 (0.00 to 2.52)	1.34 (1.01-1.78)	.15
Outpatient COVID-19 antiviral treatment					
No	6.03 (5.53-6.53)	3.75 (2.99-4.51)	2.28 (1.37 to 3.19)	1.63 (1.30-2.04)	Reference
Yes	4.81 (2.49-7.07)	3.81 (3.04-4.57)	1.01 (-1.41 to 3.42)	1.27 (0.75-2.16)	.42
Overall	5.97 (5.48-6.46)	3.75 (2.98-4.50)	2.23 (1.32 to 3.13)	1.61 (1.29-2.02)	



Comment: This study found that, in a VA population in fall-winter 2022-2023, being hospitalized for Covid-19 vs seasonal influenza was associated with an increased risk of death. This finding should be interpreted in the context of a 2 to 3 times greater number of people being hospitalized for Covid-19 vs influenza in the US during this period. The increased risk of death due to Covid-19 was greater among unvaccinated individuals compared with those vaccinated or boosted supporting the importance of vaccination in reducing risk of Covid-19 death especially in high-risk individuals. Study limitations include that the older and predominantly

male VA population may limit generalizability to broader populations. The results may not reflect risk in the outpatient setting.

SARS-CoV-2 During Omicron Variant Predominance Among Infants Born to People With SARS-CoV-2 Pediatrics published online April 7, 2023

doi/10.1542/peds.2022-061146/1469413/peds.2022-061146.pdf

They used data on infants aged 0 to 6 months born from pregnant people with SARS-CoV-2 infections during 2020 and 2021 reported to the CDC Surveillance for Emerging Threats to Pregnant People and Infants Network (SET-NET) from 6 US jurisdictions. A jurisdiction's data were included if it reported all PCR SARS-CoV-2 laboratory results (Massachusetts, Missouri, Puerto Rico, Tennessee, and the city of Philadelphia) for infants meeting inclusion criteria or reported a random sample of the same (Minnesota). They calculated incidence rates of infants' first laboratory confirmed SARS-CoV-2 infection in the period before (March 22, 2020–December 18, 2021) and during (December 19, 2021–September 9, 2022) Omicron variant predominance. Incidence rate ratios (IRR) comparing the 2 periods were also calculated.

During the period before Omicron variant predominance (n 527,403), the incidence rate of positive SARS-CoV-2 tests among infants aged 0 to 6 months born to people with SARS-CoV-2 infection during pregnancy was 3.1 per 100 person years. During the period of Omicron variant predominance (n 514,115), the rate was 15.3 per 100 person years (IRR, 5.00; 95% confidence interval [CI], 4.83–5.21). Restricted to infants born to pregnant people who had SARS-CoV-2 pre-Omicron, the IRR increased to 5.83 (95% CI, 5.66–6.05). The proportion of infants infected ≤14 days after delivery with maternal infections ≤14 days before delivery declined from 31.4% (95% CI, 27.1–35.8) pre-Omicron to 0.8% (95% CI, 0.5–1.0) during Omicron predominance, suggesting the increased rate of infection was not due to increased perinatal transmission.

Comment: The incidence rate of positive SARS CoV-2 testing among infants born to people with SARS-CoV-2 infection during pregnancy during the period of Omicron predominance was 5 times higher than the preceding period. The increased incidence of SARS-CoV-2 infections mirrors that observed in the general population and the increase in infant hospitalization during the same period. This finding aligns with other evidence of reduced protection against Omicron from previous infection with other variants. This analysis is limited to pregnant people and infants with PCR-confirmed infection and may underreport asymptomatic and nonmedically attended infections. A large portion of infants had no PCR testing (82.3%), limiting the interpretation of incidence. No genomic sequencing was performed to confirm the variant infecting individuals. Increased transmissibility of the Omicron variant to infants who are ineligible to receive Covid-19 vaccination, raises the importance of preventing SARS-CoV-2 transmission through vaccination of pregnant and postpartum people.

Original Investigation | Pediatrics Assessment of Neurodevelopment in Infants With and Without Exposure to Asymptomatic or Mild Maternal SARS-CoV-2 Infection During Pregnancy JAMA Netw Open 2023;6(4):e237396.

doi:10.1001/jamanetworkopen.2023.7396

The investigators studied if asymptomatic or mild maternal SARS-CoV-2 infection compared with no infection during pregnancy is associated with observable infant neurodevelopmental differences at ages 5 to 11 months. Participants were enrolled beginning on May 26, 2020; participants in the ESPI study were enrolled from May 7 to November 3, 2021; and participants in the ESPI COMBO substudy were enrolled from August 2020 to March 2021. For the current analysis, infant neurodevelopment was assessed between March 2021 and June 2022.

In this cohort study involving a geographically diverse cohort of 407 infants born to 403 mothers, no association was found between mild or asymptomatic maternal SARS-CoV-2 infection during pregnancy and infant cognition, language, or motor development as assessed by a novel telehealth-adapted version of the Developmental Assessment of Young Children.

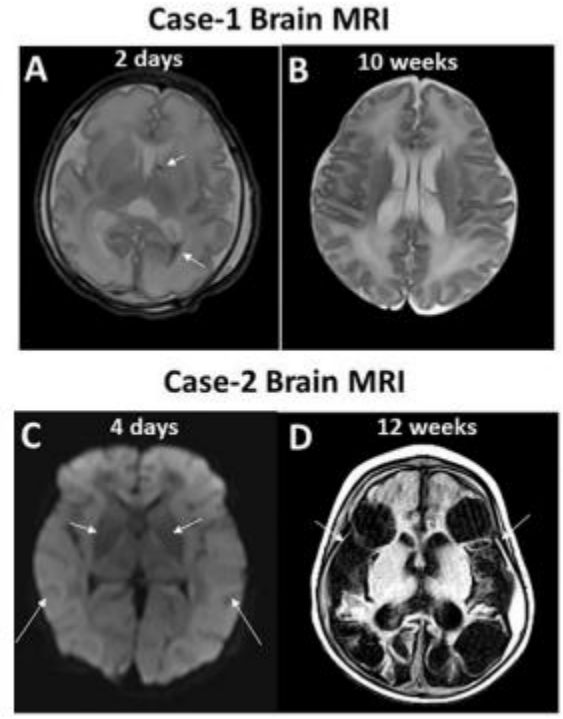
Comment: Understanding the full spectrum of neurodevelopment in children after antenatal SARS-CoV-2 exposure will require longitudinal studies to assess later stages of child development. This study adapted DAYC-2 to a telehealth method. Unlike parent-recorded video-based assessments, the DAYC-2 evaluation occurred in real time, with a research coordinator observing infants' movements using a live telehealth connection. Other studies have found differences in early motor development in infants with SARS-CoV-2 exposure, so it will be important to continue longitudinal follow-up of established cohorts to assess whether any new developmental concerns arise or to conduct follow-up of infants with early motor delays to examine whether they show improvement. [Early Hum Dev. 2022; 175:105694; PLoS One. 2022;17: e0267575] see next review

Maternal SARS-CoV-2, Placental Changes and Brain Injury in 2 Neonates Pediatrics published online February 24, 2023

doi.org/10.1542/peds.2022-058271

Investigators have found for the first time that Covid-19 infection can cross the placenta and cause brain damage in two newborns. One of the infants died at 13 months and the other remained in hospice care. The two infants were admitted in the early days of the pandemic in the Delta wave to the NICU at birth. Both infants tested negative for the virus at birth but had significantly elevated SARS-CoV-2 antibodies in their blood, indicating that either antibodies crossed the placenta, or the virus crossed, and the immune response was the baby's. Both infants were born to mothers who became Covid-19 positive in the second trimester and delivered a few weeks later. One mother delivered at 32 weeks and had a very severe Covid-19 and spent a month in the ICU. The team decided to deliver the child to save the mother. The other mother had asymptomatic Covid-19 infection in the second trimester and delivered at full term. The babies began to seize from the first day of life and had profound hypotonia. As their bodies grew, they had a very small head circumference. Unlike some babies born with the Zika virus, these babies were not microcephalic at birth. Brain imaging over time showed significant

brain atrophy, and neurodevelopment exams showed significant delay. Examination of the placentas found some characteristic Covid-19 changes and presence of the SARS-CoV-2 virus. Inflammation of the feto-placental unit leads to development of the fetal inflammatory response syndrome, which causes fetal hypoxia, blood vessel damage, and blood-brain barrier compromise, and leads to white matter injury of the fetal brain. [Front Neurosci. 2017;11:200]

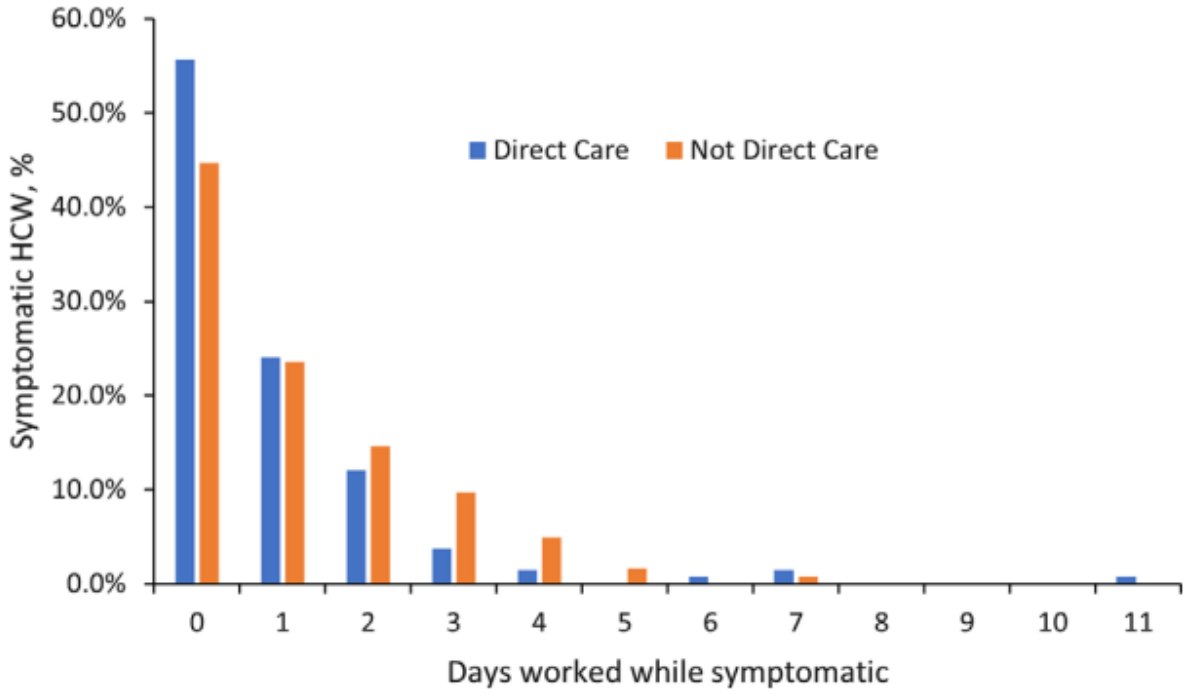


Comment: Previous studies have indicated a relatively benign status in infants who test negative for the Covid-19 virus after birth. These cases demonstrate that midtrimester maternal SARS-CoV-2 infection can infect the placenta and fetal or infant brain and trigger a cascade of inflammatory events in both placenta and fetus. This may be associated with major brain injury and progressive neurologic sequelae in infants beyond the neonatal period. Both these cases occurred early the pandemic when no vaccines were available. Covid-19 vaccination has been found safe in pregnancy and both vaccination and breastfeeding can help passage of antibodies to the infant and help protect the baby.

Sickness presenteeism in healthcare workers during the coronavirus disease 2019 (COVID-19) pandemic: An observational cohort study Infect Control Hosp Epidemiol published online April 12, 2023

This is a new observational cohort study included all HCWs at the Veterans Affairs Boston Healthcare System who tested positive for SARS-CoV-2 infection from December 1, 2020, to September 30, 2021. All HCWs were required to perform a daily self-review of Covid-19 symptoms and to stay home or leave work if symptomatic. During the study period, 327 HCWs tested positive for Covid-19, and 127 (49.8%) of 255 HCWs who had symptomatic infections reported presenteeism at the time of diagnosis.

Of the 127 HCWs with presenteeism, 66 (26% of 255 symptomatic HCW) worked at least part of a day and then returned to work for second and/or additional days with Covid-19 symptoms. HCWs with presenteeism did not differ significantly from those without presenteeism with respect to age, sex, race, vaccination status, or direct patient care. HCWs cited a high workload burden for coworkers and personal responsibility as the main reasons for continuing to work while sick, compared to limits on paid leave or perceived expectations to work while sick. The HCW perception that "they knew how to take precautions at work to avoid getting others sick" may have led to decreased perceived risk.

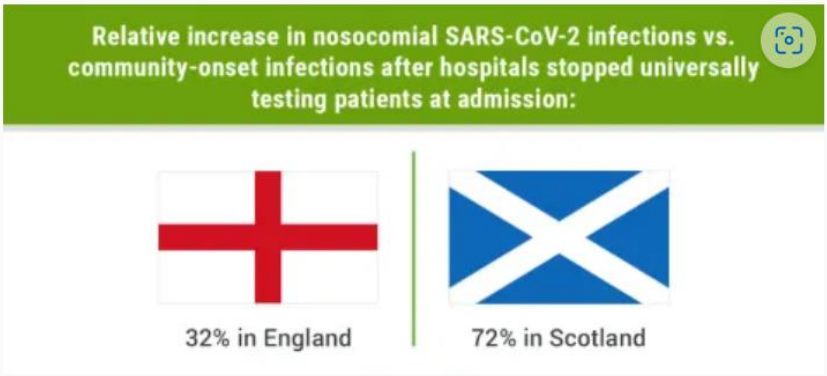


Comment: Covid-19 presenteeism poses risk to both HCW and patients. The prevalence of Covid-19 presenteeism in this study was 49.8% which surprised me. To my knowledge, this is the only systematic estimate of the prevalence of presenteeism due to Covid-19. Many studies have demonstrated the consequences of presenteeism, including Covid-19 clusters among HCWs and HCW transmission to patients. [Int J Environ Res Public Health 2021;18; JAMA Network Open 2022;5: e2216176] Somewhat surprisingly, rates of presenteeism did not differ between HCWs with and without direct patient care, suggesting that the perception of risk of transmission from HCW to patient alone did not modify choices about working while sick. This survey is very disappointing to me. I have preached in all venues to stay home while ill. To remind our readers, influenza causes 140,000 to 800,000 hospitalizations and 12,000 to 60,000 deaths—100- 200 of those deaths occurs in children. RSV causes 150,000 hospitalizations in children and 100 to 300 deaths. In the elderly, RSV causes between 60,000 to 120,000 hospitalizations and 6,000 to 10,000 deaths. Parainfluenza virus causes about 50,000 hospitalizations in children and can cause severe disease in immunosuppressed adults. The survey response rate was relatively low, but respondents were demographically and symptomatically representative of the entire cohort.

Association between stopping universal SARS-CoV-2 admission testing and hospital-onset SARS-CoV-2 in England and Scotland. Presented at: Society for Healthcare Epidemiology of America Spring Meeting; April 11-14, 2023; Seattle.

The question motivating the study is: Should we stop universal screening of all patients admitted for COVID-19? For their study, the researchers used data from the National Health Service England and Public Health Scotland to assess the impact of the end of universal admission testing for SARS-CoV-2 in those two countries on Aug. 31, 2022. They defined hospital-onset SARS-CoV-2 infection as cases diagnosed more than 7 days after admission between July 1, 2021, and Dec. 16, 2022. They calculated the weekly ratio between hospital-onset vs. community-onset SARS-CoV-2 admissions to uncover any changes associated with stopping universal admission testing.

They divided the results into three periods — delta dominance with admission testing, omicron dominance with admission testing, and omicron dominance without admission testing. Throughout the study period, there were a total of 518,379 Covid-19 admissions in England — including 398,264 community-onset and 120,115 hospital-onset infections — and 46,517 Covid-19 admissions in Scotland — including 34,183 community-onset and 12,334 hospital-onset infections. The mean weekly ratio of new hospital-onset infections vs. community-onset admissions in England increased from 0.12 during the delta-dominant period to 0.33 during omicron, and then increased again to 0.48 after universal admission testing was stopped. Similar results were seen in Scotland, where the mean weekly ratio rose from 0.11 to 0.43 and then again to 0.89.



Comment: A recent position paper published online by SHEA in November 2022[review in ID Watch] addressed challenges and considerations regarding universal SARS-CoV-2 screening, a practice that has been in place in many hospitals in the US since early in the pandemic. In the paper, the authors recommended that facilities no longer perform procedure, pre-procedure and pre-admission SARS-CoV-2 testing for asymptomatic patients. [ICHE https://doi.org/10.1017/ice.2022.295] They do add that “facility risk assessments in conjunction with metrics that suggest ongoing transmission of SARS-CoV-2 (despite strengthening existing layers of control and assessment of compliance with infection prevention measures) or particularly at-risk populations (e.g., congregate or behavioral health settings, transplant units) should drive whether asymptomatic screening should be added to institutional practice.”

Universal Masking in Health Care Settings: A Pandemic Strategy Whose Time Has Come and Gone, For Now Ann Intern Med published online April 18, 2023

doi:10.7326/M23-0793

Figure. Key milestones and contextual factors during the pandemic to endemic phases.

Comment: The authors correctly point out that health care remains one of the last settings where widespread masking requirements continue despite the evolution of the pandemic. We are in a more stable phase with extensive population immunity providing protection against severe disease, a less virulent variant, and widespread availability of medical therapeutics. During this time, they recommend away from universal masking as well as other inventions. They conclude: “the time has come to deimplement policies that are not appropriate for an endemic pathogen when the expected bene*fi*ts of such policies are low. Universal masking in health care is a policy whose time has come and gone ... for now.”

I have mixed feelings. I do think it is reasonable to pull back on universal masking based on local rates of transmission, but I would have liked to have a statement when more aggressive measures should be reimplemented such as about the need and value of masking for direct patient care when community transmission rates are up but not just for SARS-CoV-2 but for all other respiratory viruses as well. I continue to believe that the burden of common respiratory viruses, especially for high-risk patients, is underestimated and can be serious.