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Infectious Diseases Watch

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General Infectious Diseases

Foodborne Illness Outbreaks at Retail Food Establishments — National Environmental Assessment Reporting System, 25 State and Local Health Departments, 2017–2019 MMWR 2023; 72:1–11

Investigators from CDC performed this study, which involved collecting environmental health data during the investigation of 800 foodborne illness outbreaks at 875 retail food establishments reported to the National Outbreak Reporting System (NORS) by 25 state and local health departments from 2017 to 2019.

Among the 800 outbreaks, 27.0% occurred in 2017, 38.3% in 2018, and 34.8% in 2019. Of these outbreaks, 90.6% involved a single establishment, and 9.4% involved multiple establishments. A total of 3.5% were multistate outbreaks. The most common pathogens, which were involved in 69.4% of the outbreaks with a confirmed or suspected agent, were norovirus and *Salmonella*, making up 47.0% and 18.6% of outbreaks, respectively. Most identified agents were viral (48.1%) and bacterial (46.8%), followed by parasitic (2.3%) and toxic or chemical (2.5%) causes. A total of 819 contributing factors were identified.

Of the 500 outbreaks with an identified contributing factor (e.g., bare-handed contact with ready-to-eat food), 85.2% had at least one contamination factor, 25.8% had at least one proliferation factor (conditions allowed pathogens in food to grow), and 14.2% had at least one survival factor (pathogens survived processes designed to kill or reduce their numbers).

Of the contributing factors identified in 62.5% of outbreaks, about 40% had at least one reported factor related to food adulteration by an ill or infectious worker. When investigators interviewed an establishment manager in 679 outbreaks (84.9%), they found that 91.7% said they had a policy requiring food workers to notify them when they were ill, with 66.0% reporting that their policies were written. A total of 23.0% of managers said their policy listed all five symptoms in the FDA Food Code requiring manager notification (vomiting, diarrhea, jaundice, sore throat with fever, and lesion with pus). The vast majority of managers (85.5%) said they had a policy limiting tasks or excluding ill employees from working, and 62.4% said the policy was written. These components include a policy requiring workers to notify a manager when they are ill, a list of all five symptoms mandating workers to notify a manager, a policy that limits or excludes employees from working, and a policy listing all five symptoms requiring limiting or excluding employees from work. Less than half (43.6%) of managers said their establishments offered paid sick leave to at least one food worker.

Comment: Restaurants can prevent viral foodborne illness outbreaks by mandating proper hand hygiene and excluding ill or infectious employees from working. Norovirus was the most identified cause of outbreaks, and contamination of food by ill or infectious food workers contributed to approximately 40% of outbreaks with identified contributing factors. Although most managers reported their establishment had an ill worker policy, often these policies were missing elements intended to reduce foodborne illness risk. The enforcement of existing policies needs to be re-examined. See next review

Preliminary Incidence and Trends of Infections Caused by Pathogens Transmitted Commonly Through Food — Foodborne Diseases Active Surveillance Network, 10 U.S. Sites, 2022 MMWR 2023; 72:701-706

To evaluate progress toward prevention of enteric infections in the United States, the Foodborne Diseases Active Surveillance Network (FoodNet) conducts surveillance for laboratory diagnosed infections caused by eight pathogens transmitted commonly through food at 10 U.S. sites. During 2020–2021, FoodNet detected decreases in many infections that were due to behavioral modifications, public health interventions, and changes in health care–seeking and testing practices during the COVID-19 pandemic. This report presents preliminary estimates of pathogen-specific annual incidences during 2022, compared with average annual incidences during 2016–2018.

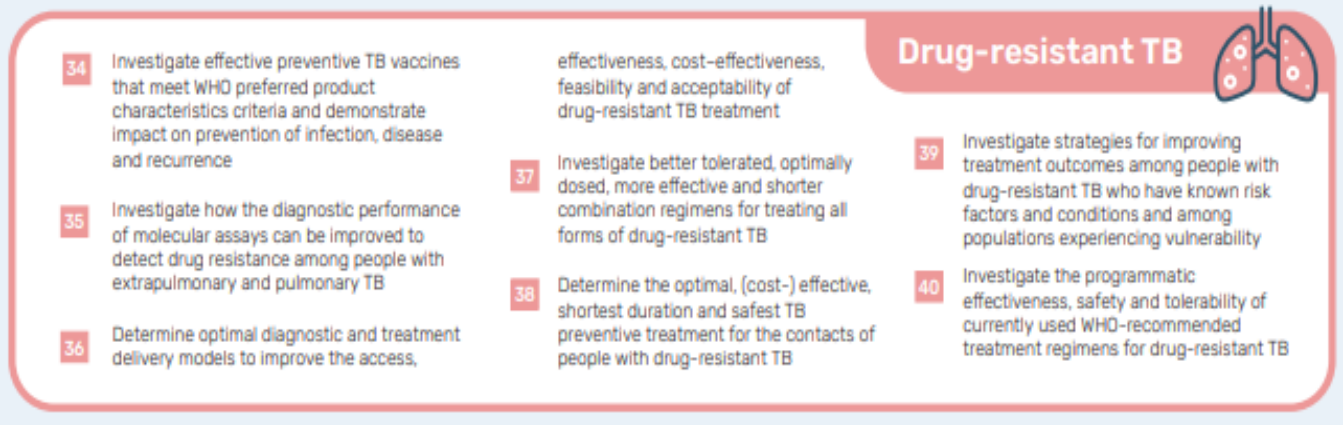
During 2022, annual incidences of illnesses caused by the pathogens Campylobacter, Salmonella, Shigella, and Listeria were similar to average annual incidences during 2016–2018; however, incidences of Shiga toxin-producing Escherichia coli (STEC), Yersinia, Vibrio, and Cyclospora illnesses were higher. Increasing culture-independent diagnostic test (CIDT)[GI Syndromic panels] usage likely contributed to increased detection by identifying infections that would have remained undetected before widespread CIDT usage.

Comment: This report highlights the lack of progress in reducing enteric infection incidence. Many pandemic interventions ended by 2022, resulting in a resumption of outbreaks, international travel, and other factors leading to enteric infections. Collaboration among food growers, processors, retail stores, restaurants, and regulators are needed to reduce pathogen contamination during poultry slaughter and to prevent contamination of leafy greens.

WHO Global research agenda for antimicrobial resistance in human health June 2023

Antimicrobial resistance poses a significant threat to human health, with an estimated 4.95 million deaths associated with bacterial antimicrobial resistance in 2019. Globally, there were an estimated 450,000 new cases of rifampicin- and multidrug-resistant tuberculosis in 2021. In addition, invasive fungal infections are increasing worldwide, and their management is challenged by antifungal resistance and difficulties in diagnosis. C auris has become more widespread. [see ID Watch April 2023 and reviews below] The goal of this research agenda is to identify and give priority to the research topics with the greatest impact on mitigating antimicrobial resistance in the human health sector. Below is a summary of research priorities.


Prevention
1 Investigate the impact and contribution of community WASH and waste management interventions on the burden and drivers of antimicrobial resistance
2 Investigate implementation strategies and the impact of WASH-related interventions in health-care settings on the burden of health care–associated infections and antimicrobial medicine prescribing
3 Identify (cost-) effective, acceptable and feasible multimodal infection prevention and control strategies and the relative effect of their components on reducing health care–associated infections
4 Assess the impact of vaccines on colonization and infection by resistant pathogens, and on reducing the use of antimicrobial medicines, health-care encounters and health system costs
Diagnosis
5 Investigate and evaluate rapid point-of-care tests to discriminate bacterial versus non-bacterial infections
6 Investigate and evaluate rapid antimicrobial susceptibility testing methods from blood cultures
7 Investigate and evaluate diagnostic tests for detecting pathogens and antimicrobial susceptibility testing
8 Investigate and evaluate diagnostic tests for detecting fungal pathogens
9 Investigate the clinical and diagnostic value of phenotypic antifungal susceptibility testing
10 Investigate, assess and evaluate the implementation of novel rapid point-of-care assays and optimal testing approaches for (resistant) Neisseria gonorrhoeae
Treatment and Care
11 Investigate antimicrobial stewardship interventions that are context specific, feasible, sustainable, effective and cost-effective in outpatient and inpatient settings
12 Identify feasible, effective and scalable pharmacist antimicrobial medicines dispensing practices and related regulatory frameworks to improve antimicrobial stewardship in the community, especially in low- and middle-income countries
13 Investigate criteria and strategies to optimize empirical antimicrobial therapy for main infectious syndromes, especially in settings with limited medicine availability, diagnostic capacity and access to health care services
14 Determine optimal methods, metrics and targets to monitor antimicrobial use and consumption
15 Determine the patterns and drivers of appropriate and inappropriate prescribing, use and consumption of antibiotics
16 Investigate approaches to effectively use antimicrobial consumption and antimicrobial resistance surveillance data to inform stewardship and guidelines
17 Investigate antibiotic treatment regimens for infections, especially for extended-spectrum beta-lactamase–producing and carbapenem-resistant Enterobacterales
18 Investigate antibiotic treatment regimens for infections by drug-resistant typhoid and non-typhoidal salmonellae
19 Investigate empirical antibiotic treatments for gram-negative bacteria causing bloodstream infections among neonates and young children in settings with high antimicrobial resistance prevalence
20 Investigate antifungal regimens for infections caused by WHO fungal priority pathogens with critical importance for antimicrobial resistance
21 Investigate regimens for urogenital and extragenital sexually transmitted infections in the context of increasing antimicrobial resistance levels
Cross-cutting
22 Investigate the epidemiology, mortality, morbidity and impact of infections by resistant WHO bacterial priority pathogens
23 Investigate the epidemiology, morbidity, mortality and impact of infections by resistant WHO fungal priority pathogens with critical importance for antimicrobial resistance
24 Investigate factors driving colonization and infection by resistant WHO bacterial priority and fungal pathogens
25 Identify optimal surveillance methods to generate accurate and reliable data on the epidemiology and burden of antimicrobial resistance
26 Assess the impact of mass administration of antimicrobial medicines on antimicrobial resistance
27 Evaluate how currently recommended syndromic sexually transmitted infection management and treatment of people with asymptomatic sexually transmitted infections affect antibiotic prescribing and antimicrobial resistance
28 Determine the most (cost-) effective behavioural change interventions to mitigate antimicrobial resistance emergence and spread
29 Evaluate the implementation of antimicrobial resistance–related policies and regulations and their effectiveness in mitigating antimicrobial resistance and improving health outcomes
30 Investigate implementation strategies for national policies, legislation and regulations to improve infection prevention, patient care and the use of antimicrobial medicines
31 Identify the most (cost-) effective interventions and an investment case to mitigate antimicrobial resistance globally and across countries
32 Investigate strategies to integrate antimicrobial resistance interventions into broader health, health financing, development and welfare structures and evaluate their impact
33 Investigate how regulatory frameworks, marketing incentives and financing models affect the sustainable development, availability, equitable access and use of new antimicrobial medicines
Antimicrobial-resistant bacterial and fungal infections



Comment: The research agenda was developed through an adapted Child Health and Nutrition Research Initiative method in close collaboration with a multidisciplinary expert group on antimicrobial resistance. Research Initiative knowledge matrix comprising four research domains (descriptive, delivery, development, or discovery) and three themes in accordance with the people-centered framework for addressing antimicrobial resistance (antimicrobial resistance prevention, diagnosis, treatment, and care), to ensure that different types of research and topics were captured. Each of the 40 topics should not be surprising. This document unfortunately does not provide a roadmap on how to accomplish and ultimately execute the evidence-based solutions to address this important growing problem. It is up to us to roll up our sleeves and work together to address this public health ticking time bomb.

Locally Acquired Malaria Cases Identified in the United States June 27, 2023

The CDC issued a Health Alert Network (HAN) Alert due to Identification of locally acquired malaria cases (*P. vivax*) in two US states (Florida-4 and Texas-1) within the last 2 months. The CDC is concerned for a potential rise in imported malaria cases associated with increased international travel in summer 2023, and the need to plan for rapid access to IV artesunate, which is the first-line treatment for severe malaria in the US.

Comment: Locally acquired mosquito-borne malaria has not occurred in the US since 2003 when eight cases of locally acquired *P. vivax* malaria were identified in Palm Beach County, FL [MMWR. 2003 Sep 26; 52(38):908-911]. Despite these cases, the risk of locally acquired malaria remains extremely low in the US. However, *Anopheles* mosquito vectors, found throughout many regions of the country, are capable of transmitting malaria if they feed on a malaria-infected person.[Curr Trop Med Rep. 2021; 8(1):43-51] The risk is higher in areas where local climatic conditions allow the *Anopheles* mosquito to survive during most of or the entire year and where travelers from malaria-endemic areas are found. Malaria is caused by any of five species of protozoan parasite of the genus *Plasmodium*: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale,* and *P. knowlesi*. Worldwide, more than 240 million cases of malaria occur each year (95% in Africa). Almost all cases of malaria in the US are imported and occur in people traveling from countries with malaria transmission, many from sub-Saharan Africa and South Asia. Most imported cases of malaria in the US are diagnosed during summer and early fall. Clinical manifestations of malaria are non-specific and include fever, chills, headache, myalgias, and fatigue. Nausea, vomiting, and diarrhea may also occur. For most people,

symptoms begin 10 days to 4 weeks after infection, although a person may feel ill as early as 7 days or as late as 1 year after infection. *P. falciparum* and *P. knowlesi* infections can cause rapidly progressive severe illness or death, while the other species, including *P. vivax*, are less likely to cause severe disease. Laboratory abnormalities can include anemia, thrombocytopenia, hyperbilirubinemia, and elevated transaminases, varying from normal or mildly altered in uncomplicated disease to very abnormal in severe disease. *P. vivax* and *P. ovale* can remain dormant in the liver and such infections require additional treatment for the extraerythrocytic phase. Relapses may occur after months or even years without symptoms.

Patients suspected of having malaria should be urgently evaluated in a facility that is able to provide rapid diagnosis and treatment, within 24 hours of presentation. Order microscopic examination of thin and thick blood smears, and a rapid diagnostic test (RDT) if available, to diagnose malaria as soon as possible. “BinaxNOW™,” a malaria RDT, is approved for use in the US. RDTs are less sensitive than microscopy and cannot confirm each specific species of the malaria parasite or the parasite density. [Clin Infect Dis 2012; 545:1637] Binax NOW has >90% sensitivity for *P falciparum* and 50% sensitivity for low non-falciparum parasitemia.

Artemether-lumefantrine is the preferred option, if readily available, for the initial treatment of uncomplicated *P. falciparum* or unknown species of malaria acquired in areas of chloroquine resistance. Atovaquone-proguanil is another recommended option. *P. vivax* infections acquired from regions other than Papua New Guinea or Indonesia should initially be treated with chloroquine (or hydroxychloroquine). IV artesunate is the only drug available for treating severe malaria in the US. Artesunate for Injection is approved by FDA and is commercially available. Hospitals should have a plan for rapidly diagnosing and treating malaria within 24 hours of presentation. Primaquine or tafenoquine is added to *P vivax* treatment to eradicate latent parasites in the liver.

The public should take steps to prevent mosquito bites and control mosquitos at home to protect yourself from any mosquito-borne illness since malaria is not the only mosquito borne illness. West Nile virus, Dengue, and Zika are other mosquito borne diseases to name a few others. See comment below.

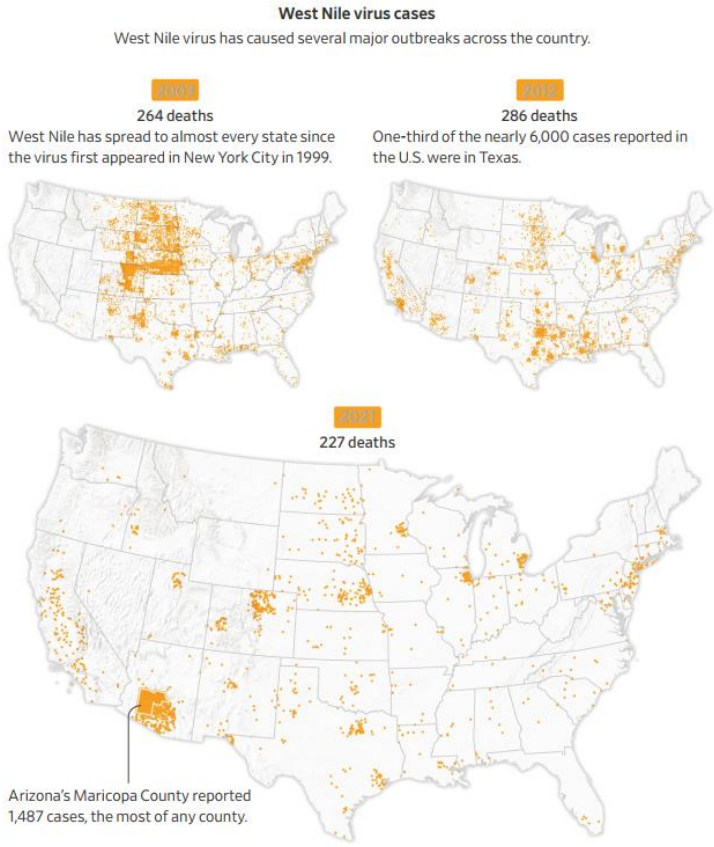
ID Watch Alert: Ticks and Mosquitoes Are Carrying Diseases to More of the US

With the summer upon us we are entering the tick and mosquito season. Changing land use and climate change have allowed ticks to expand their habitat. Warming temperatures can encourage mosquito-borne outbreaks, and more global travel risks moving the bugs and their diseases to new areas. That can challenge doctors and communities unaccustomed to dealing with these diseases. Lyme disease and West Nile virus are among the infections that ticks and mosquitoes are spreading in more of the US. Reported infections after tick, flea and mosquito bites have surged over the past two decades, according to data from the CDC.

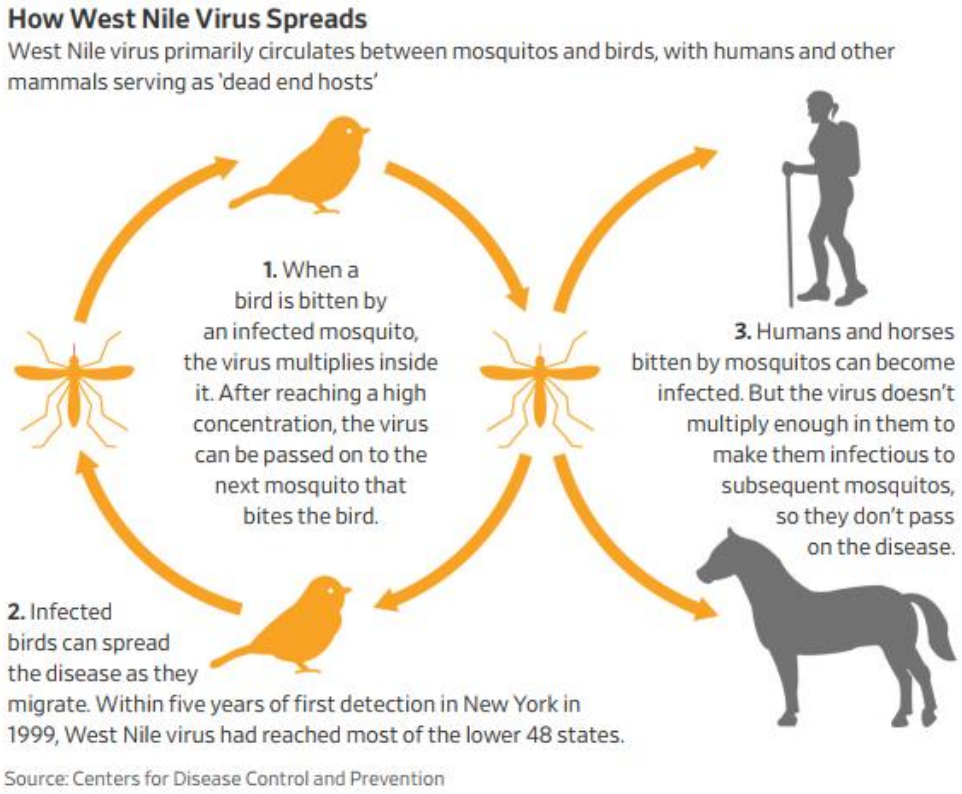
West Nile

According to the CDC, there have been over 15 human cases of West Nile virus so far in 2023. In 2022, there were 1,126 cases, including 90 deaths. Among this year’s 15 cases reported to the CDC so far, eight people have severe neuroinvasive disease. Such severe symptoms typically occur in 1 in every 150 cases of West Nile virus and can include encephalitis

or meningitis. Three of the neuroinvasive cases occurred earlier this year amid an outbreak in Maricopa County, AZ, where the disease is considered endemic, according to an April 28 report from the CDC.

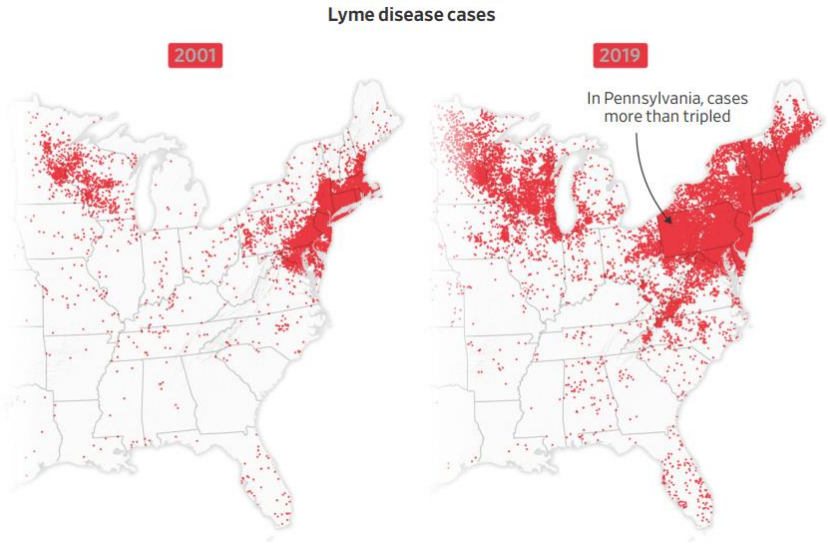


The spread of West Nile virus often relies on infected migrating birds. There also tend to be more outbreaks when it's warmer, partly because the virus can replicate faster within the mosquitoes and make them infectious earlier.

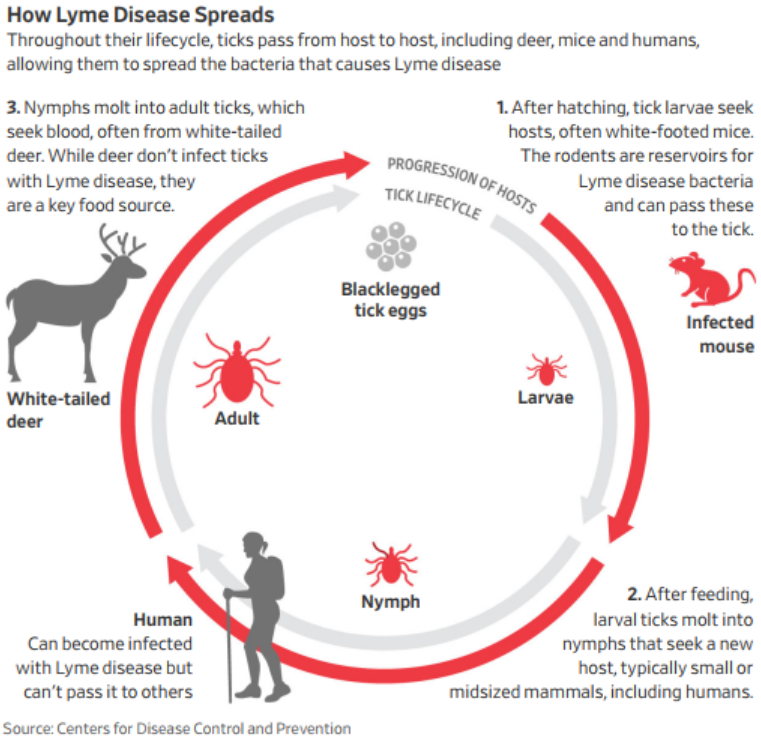


Lyme Disease

Lyme disease is the most common tick or mosquito–borne disease in the US. It is most prevalent in the Northeast and Midwest, where the blacklegged tick (Iodes) that carries Lyme causing bacteria (Borrelia burgdorferi) has expanded its range, leading to more infections. To infect you with Lyme disease, a tick must bite and attach to your skin, typically for at least 36 hours.



The razing and regrowth of forest in the Northeast has facilitated a boom in the deer population, which has brought blacklegged ticks back with them. White-footed mice can also be a host of Lyme-causing bacteria.



Comment: Tips on prevention: When outside wear long sleeves and tuck pant cuffs into socks or shoes and use insect repellents that contain ingredients such as DEET or picaridin which will decrease ticks and mosquito bites. People should also dump standing water and put air conditioners or screens in windows during the summer. When in areas with Lyme do a thorough full-body tick check using a mirror when back inside. When removing a tick, try not to twist it, as this may cause its mouth parts to break off and remain in the skin. In instead use clean, fine-tipped tweezers to grasp the tick as close to the skin's surface as possible. Pull upward with steady, even pressure. After removing the tick, thoroughly clean the bite area and your hands with alcohol or soap and water. Don't crush the tick with your fingers. Flush it down the toilet, put it in alcohol, or put it in a sealed bag or container. Showering within two hours of coming inside reduces the risk of getting Lyme disease. Babesiosis coinfection can occur in up to 15% of Lyme cases.

Lyme disease treatment:

1. Antibiotic prophylaxis can be considered if all criteria below are present (doxycycline)
    a. Tick is estimated to have been attached for ≥36 hours
    b. Prophylaxis begins within 72 hours of tick removal.
    c. Attached tick is identified as an adult or nymphal *I. scapularis* tick (deer tick)

2. Erythema migrans (early disease)
    a. 10-day course of doxycycline or a 14-day course of amoxicillin or cefuroxime.
3. Acute neurological disease (meningitis, VII nerve palsy)
    a. Doxycycline 14-21 days
    b. Ceftriaxone 14-28 days
4. Severe neurological (encephalitis)
    a. Ceftriaxone 14-28 days
5. Carditis
    a. Mild (1st degree heart block)
        i. Doxycycline, amoxicillin, or cefuroxime 14-21 days
    b. More severe (i.e., second- and third-degree block)
        i. Ceftriaxone 14-21 days
6. Arthritis
    a. Initial treatment amoxicillin or doxycycline 28 days
    b. Persistent-ceftriaxone 14-28 days

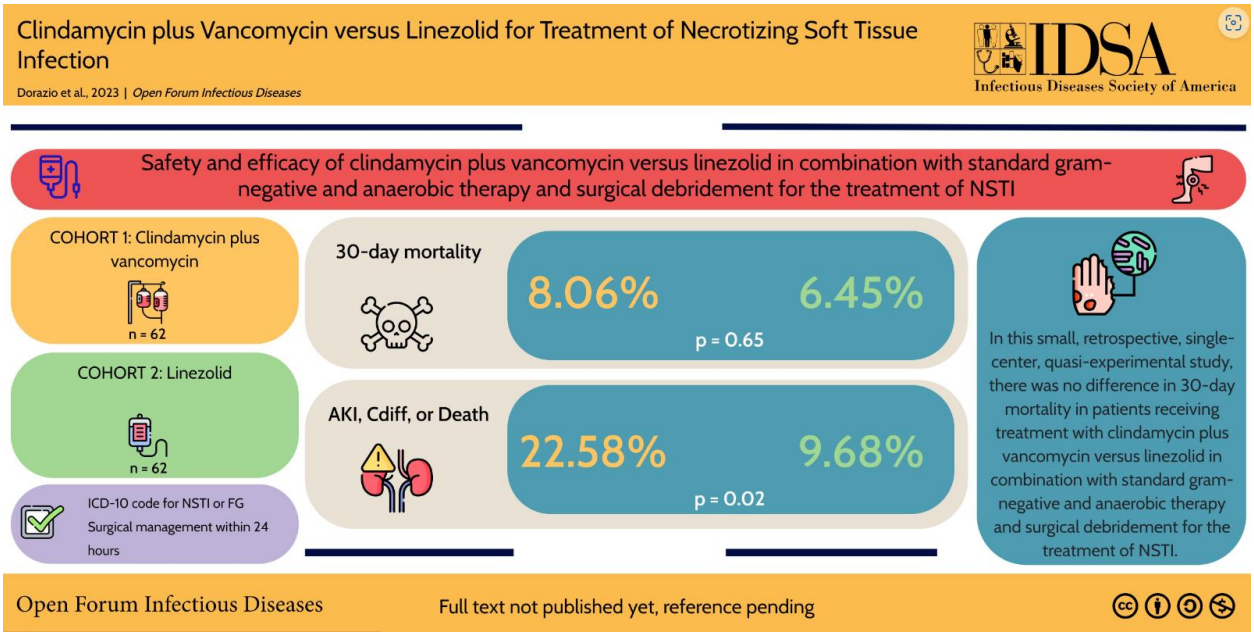
Clindamycin plus Vancomycin versus Linezolid for Treatment of Necrotizing Soft Tissue Infection OFID published online May 6, 2023

DOI: 10.1093/ofid/ofad258

This is a retrospective, single-center, quasi-experimental study of patients admitted from June 1, 2018 to June 30, 2019 (pre-intervention) and May 1, 2020 to October 15, 2021 (post-intervention). Patients who received surgical management within 24 hours of necrotizing soft tissue infection (NSTI) and at least one dose of linezolid or clindamycin were included. The primary endpoint was death at 30 days. The secondary outcomes included rates of acute kidney injury (AKI) and Clostridioides difficile infection (CDI).

274 patients were identified by admission diagnosis code for NSTI or Fournier's Gangrene; 164 patients met the inclusion criteria. Sixty-two matched pairs were evaluated. There was no

difference in rates of 30-day mortality (8.06% vs. 6.45%, HR 1.67 95%CI (0.32, 10.73), p = 0.65). There was no difference in CDI (6.45% vs. 1.61%, HR Inf 95%CI (0.66, Inf), p = 0.07) but more AKI in the pre-intervention group (9.68% vs. 1.61%, HR 6 95% CI (0.73, 276), p = 0.05). However, a composite outcome of death, AKI, or CDI within 30 days was more common in the clindamycin plus vancomycin group. There were no differences in secondary outcomes in the matched cohort, including total duration of antibiotic exposure, time to leukocytosis resolution and discontinuation of vasopressors, and ICU or hospital lengths of stay. Numerically more patients in the pre-intervention group experienced inpatient mortality within 60 days of surgery (7 (11.29%) vs 3 (4.84%), HR 5.00 95% CI (0.56,236), p = 0.22). Only five patients in the pre-intervention group and three patients in the post-intervention group had a culture positive for Group A Streptococcus (GAS).



Comment: Empiric treatment is targeted toward the most common causative pathogens, including Staphylococcus spp., Streptococcus spp., Clostridium spp., gram-negative and anaerobic bacteria. Treatment with antibiotics that inhibit protein synthesis and suppress toxins produced by GAS has been shown to lowers patient mortality. Rates of clindamycin resistance in Streptococcus spp. have steadily increased across the United States. [Sentry Antimicrobial Surveillance] Additionally, treatment with clindamycin is associated with an increased risk of Clostridioides difficile infection (CDI) compared to other antibiotic alternatives, and treatment with vancomycin is associated with acute kidney injury (AKI). Linezolid is a protein synthesis inhibitor that decreases toxin production through inhibition of exotoxin expression. [Lancet Infect Dis. 2009; 9:281- 290] It also demonstrates higher in vitro susceptibility rates against common gram-positive pathogens when compared to clindamycin. This study builds upon previous work demonstrating that linezolid was a safe and effective alternative to clindamycin plus vancomycin for a surgical population and for patients with documented GAS infections. However, this study was a small retrospective, single center observational study and was not adequately powered to conduct a multivariable regression to determine factors associated with 30-day mortality. In addition, the post-intervention group occurred during the Covid-19 pandemic where hospital care paradigms shifted, due to limited ICU resources, which could explain the initial disparity of less ICU patients in the post-intervention group (prior to matching).

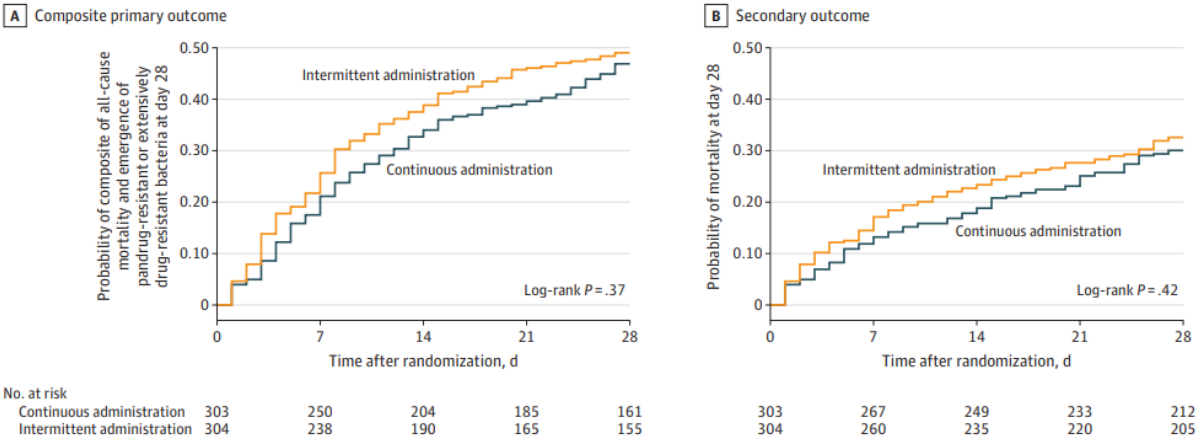
Continuous vs Intermittent Meropenem Administration in Critically Ill Patients With Sepsis JAMA published online June 16, 2023

doi:10.1001/jama.2023.10598

The investigators set out to determine whether continuous administration of meropenem reduces a composite of mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria compared with intermittent administration in critically ill patients with sepsis who are not immunosuppressed. The primary outcome was a composite of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria on day 28. The prespecified secondary outcomes included days alive and free from antibiotics at day 28, days alive and free from the ICU at day 28, and all-cause mortality at day 90. Cumulative SOFA score at day 28 also was a prespecified secondary outcome, but there was poor data collection for this outcome after day 7. The design was a double-blind, randomized clinical trial enrolling critically ill patients with sepsis or septic shock who had been prescribed meropenem by their treating clinicians at 31 intensive care units of 26 hospitals in 4 countries. Patients were enrolled between June 5, 2018, and August 9, 2022, and the final 90-day follow-up was completed in November 2022. Patients were randomized to receive an equal dose of the antibiotic meropenem by either continuous administration (n = 303) or intermittent administration (n = 304) after al loading dose.

The majority (369 patients, 61%) had septic shock. The median time from hospital admission to randomization was 9 days (IQR, 3-17 days) and the median duration of meropenem therapy was 11 days (IQR, 6-17 days). The most common site of infection was the respiratory tract. *Klebsiella* species, *Pseudomonas* species*, Escherichia coli*, and *Acinetobacter* species were the most common gram-negative organisms. A sizeable proportion of patients had organisms with high minimum inhibitory concentrations to carbapenem antibiotics or intrinsically resistant pathogens like *Pseudomonas* and *Acinetobacter.* The primary outcome occurred in 142 patients (47%) in the continuous administration group and in 149 patients (49%) in the intermittent administration group (relative risk, 0.96 [95% CI, 0.81-1.13], P = .60). Of the 4 secondary outcomes, none was statistically significant including 90-day mortality (42% in both groups), all-cause mortality at 28 days (30% in the continuous administration group vs 33% in the intermittent administration group; *P* = .50), or emergence of pan drug resistant or extensively drug-resistant bacteria at day 28 (24% vs 25%, respectively; *P* = .70). No adverse events of seizures or allergic reactions related to the study drug were reported. At 90 days, mortality was 42% both in the continuous administration group (127 of 303 patients) and in the intermittent administration group (127 of 304 patients).

Figure 2. Kaplan-Meier Analysis for the Composite Primary Outcome and the Secondary Outcome of Probability of Mortality at Day 28



Comment: β-Lactam antibiotics demonstrate time dependent killing, meaning that they are most effective with time above the MIC. Systemic reviews suggest that prolonged infusions improve mortality, clinical cure rates, or both, with the greatest benefit seen in severely ill patients. [PLoSOne 2021; 16:e0244966] Many hospitals[including my own] have already implemented prolonged infusion of β-lactam antibiotics as a default hospital wide dosing strategy. This study was a well done study using a double-blind design, in a multinational setting, and with a large sample size compared with prior trials. Furthermore, the trial enrolled severely ill patients (61% with septic shock, median Sequential Organ Failure Assessment score of 9). In this study overall, there was no difference in the continuous administration group vs the intermittent administration group for the primary composite outcome of all-cause mortality and emergence of pandrug-resistant or extensively drug-resistant bacteria at day 28 (47% vs 49%, respectively; *P* = .60). Furthermore, there were no significant differences in any of the secondary outcomes examined, including 90-day mortality (42% in both groups), all-cause mortality at 28 days (30% in the continuous administration group vs 33% in the intermittent administration group; *P* = .50), or emergence of pan drug resistant or extensively drug-resistant bacteria at day 28 (24% vs 25%, respectively; *P* = .70). The results of this trial cannot be extrapolated to prolonged infusion for all β-lactam antibiotics since at least 1 meta-analysis suggests that this may be an agent specific benefit for prolonged infusion. [Int J Antimicrob Agents 2014; 43:403-411] In addition, only 10% had confirmed bloodstream infections. This trial did not address high-dose therapy (6 gram/day) in which continuous infusion may be helpful in patients with augmented renal clearance. In addition, the exclusion of immunocompromised patients omits an important subgroup for whom optimization may help compensate for reduced immunity. Despite the negative results of this trial, guidelines and clinical practice may continue to favor prolonged dosing of β-lactam antibiotics given the possible benefit and lack of harm of prolonged infusion.

Patient-Level Meta-Analysis of Low-Dose Hydrocortisone in Adults with Septic Shock NEJM Evidence 2(6) published online May 22, 2023

DOI: 10.1056/EVIDoa2300034

Investigators conducted a patient-level meta-analysis of 17 trials that involved more than 7800 patients with sepsis or septic shock who were treated with as much as 400 mg of hydrocortisone daily for at least 72 hours. Patients treated with hydrocortisone or placebo had similar 90-day mortality. Patients treated with hydrocortisone plus fludrocortisone had a significant, but small, lowering of 90-day mortality; however, this finding was based on the results of only two studies. Patients who received hydrocortisone averaged 1.24 more days alive and off vasopressors; no difference was noted in days free of mechanical ventilation or organ failure. Hospital and intensive care unit days were similar among groups. Subgroup analyses, including pattern of administration of hydrocortisone, site of infection, pathogen or type of admission (i.e., medical vs. surgical) revealed no differences among treatments.

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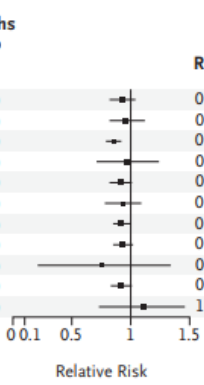
Treatment	Subgroup	Total No. of Patients (treatment+ control) (%)	No. Treated (%)	No. of Deaths in Treated (%)	No. Placebo (%)	No. of Deaths in Placebo (%)	Relative Risk (CI)
Overall		5929 (100)*	2966 (100)	1026 (36)	2963 (100)	1069 (37)	0.93 (0.82–1.04)
Hydrocortisone	Without fludrocortisone	4389 (74)	2202 (74)	665 (31)	2187 (74)	656 (31)	0.96 (0.82–1.12)
	With fludrocortisone	1540 (26)	764 (26)	361 (47)	776 (26)	413 (53)	0.86 (0.79–0.92)
Taper	Taper	657 (11)	329 (11)	135 (51)	328 (11)	127 (49)	0.97 (0.71–1.24)
	No taper	5272 (89)	2637 (89)	891 (34)	2635 (89)	942 (36)	0.92 (0.82–1.01)
Continuous	Continous	3844 (65)	1922 (65)	538 (29)	1922 (65)	552 (30)	0.93 (0.78–1.09)
	Bolus	2085 (35)	1044 (35)	488 (48)	1041 (35)	517 (51)	0.92 (0.85–1.00)
Steroid duration	Fixed	5771 (97)	2888 (97)	999 (35)	2883 (97)	1043 (37)	0.93 (0.85–1.02)
	Shock reversal	158 (3)	78 (3)	27 (60)	80 (3)	26 (63)	0.75 (0.21–1.34)
Steroid initiation	<24 h	5723 (97)	2865 (97)	982 (35)	2858 (97)	10,255 (37)	0.92 (0.83–1.01)
	>24 h	176 (3)	85 (3)	40 (56)	91 (3)	39 (50)	1.11 (0.73–1.46)



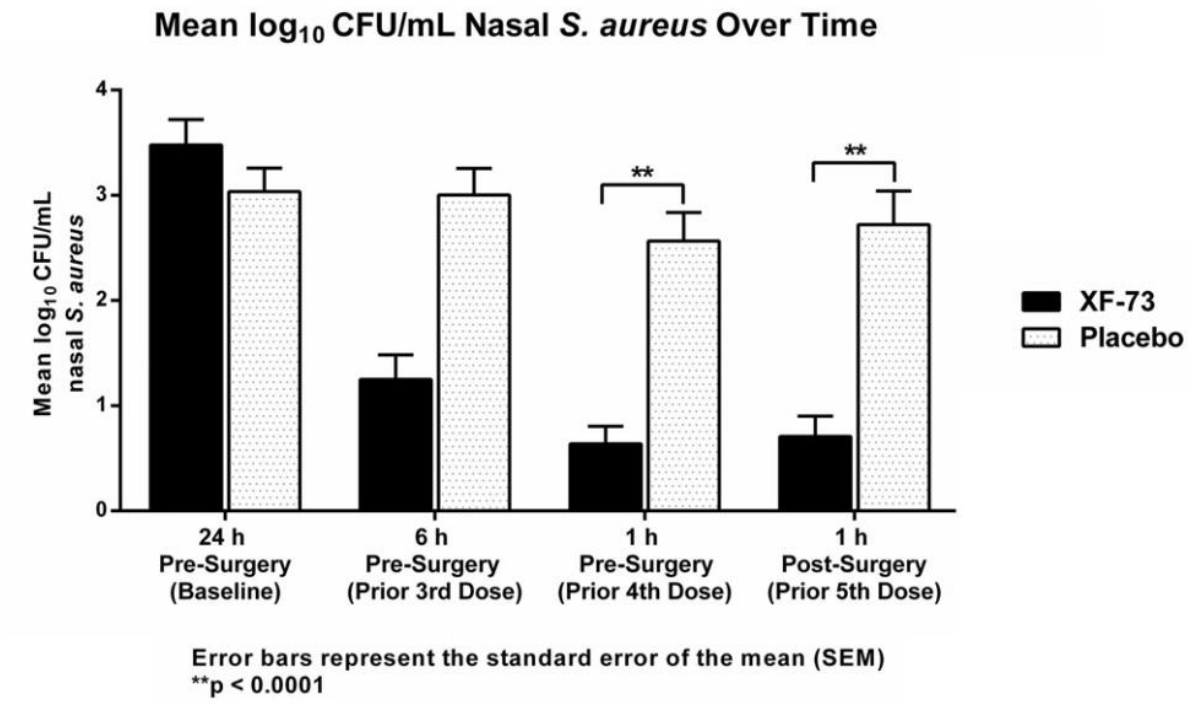
Comment: Debate continues because three recent, large, randomized trials have yielded conflicting results [N Engl J Med 2018; 378:809(Patients treated with hydrocortisone plus fludrocortisone were significantly less likely to have died at 90 days (43% vs. 49%). They also were liberated significantly more quickly from mechanical ventilation and vasopressors)]**;** [N Engl J Med 2018; 378:797 (An international group of investigators randomized 3658 patients with septic shock and respiratory failure who required mechanical ventilation to continuous infusion of hydrocortisone (200 mg for 24 hours) or placebo. Mortality at both 28 days and 90 days was similar in the steroid and placebo groups and in six prespecified subgroups, including those based on vasopressor dose, duration of shock, or severity of illness)]; and [JAMA Intern Med published online March 27, 2023 (primary composite outcome of death in hospital or discharge to hospice occurred among 1076 (47.2%) patients treated with hydrocortisone-fludrocortisone vs 43 669 (50.8%) treated with hydrocortisone alone (adjusted absolute risk difference, -3.7%; 95% CI, -4.2% to -3.1%; *P* < .001 plus more vasopressor free days with hydrocortisone-fludrocortisone vs hydrocortisone alone-reviewed in ID Watch earlier this year]. Most studies have shown a more rapid reversal of shock with glucocorticoid administration, but questions remain about whether treatment lowers short-term mortality in specific populations. In addition, based on the recent JAMA Intern Med paper should we be routinely adding fludrocortisone?

Exeporfinium chloride (XF-73) nasal gel dosed over 24 hours prior to surgery significantly reduced Staphylococcus aureus nasal carriage in cardiac surgery patients: Safety and efficacy results from a randomized placebo-controlled phase 2 study Infect Control Hospital Epidemiol published online March 23, 2023

doi:10.1017/ice.2023.17

Exeporfinium chloride (XF-73) is a dicationic porphyrin derivative with rapid potent bactericidal properties and a low propensity for engendering bacterial resistance. This was a multicenter, randomized, placebo-controlled, phase 2 study, in which investigators assessed the effect of nasal XF-73 versus placebo on S. aureus nasal burden in patients undergoing cardiac surgery. Patients were initially screened using a PCR to identify nasal S. aureus carriage to be eligible to participate. Patients were randomized (1:1) to receive 0.2% (w/w) XF-73 or color-matched placebo as 3 doses, 1 dose immediately before cardiac surgery, and a fifth dose after surgery (i.e., 5 doses in total). Nasal swab cultures were obtained just prior to the next application of XF-73 or placebo by research staff. All nasal swabs were analyzed in a central laboratory within each country and the same techniques were followed in all laboratories. Nasal swabs were plated onto BBL ChromAgar plates. Perioperative antibiotic use and preoperative antiseptic skin decolonization were left up to each center's standard of care and were recorded. The primary end point of interest in this study was change in S. aureus log10 CFU/mL from baseline to 1 hour before surgery (after 3 doses).

Most of these patients were male (75.9%). The most common surgeries were coronary artery bypass graft (63.8%). MSSA colonization occurred in 96.8% of patients, and 3.2% had MRSA. The baseline nasal S. aureus log10 CFU/mL were similar in both groups (Fig. 1). After 3 applications of XF-73 nasal gel over <24 hours (1 hour prior to surgery, the primary end point), they detected a greater decrease in nasal S. aureus observed in the XF-73 arm (-2.842 log10 CFU/mL) versus placebo (-0.469 log10 CFU/mL). The adjusted least-squares mean difference between the 2 groups was -2.1 log10 CFU/mL and was statistically significant (95% CI, -2.7 to -1.5; P < .0001). Within 1 hour of incision closure, the decrease in S. aureus was also significantly greater in the XF-73 cohort compared to the placebo group, with a least-squares mean difference of -2.2 log10 CFU/mL (95% CI, -2.7 to -1.6; P < .0001). When assessing the percentage of patients exhibiting zero nasal S. aureus carriage, (decolonization), or a ≥2 log10 CFU/ml reduction, 83.7% of patients treated with XF-73 met this metric within 1 hour prior to surgery. No SSIs were identified during the study or follow-up periods of 1 month or 3 months (for those with a foreign implant). Overall, 95.2% of patients received prophylactic skin decolonization preoperatively. No safety or tolerability issues were identified.



Comment: This is a small study and most patients enrolled were from the country of Georgia. The numbers are too small to conclude that XF-73 reduced HAIs. A much larger study would need to be done. There is concern about increased mupirocin resistance, so investigators have been looking for a suitable alternative. XF-73 has some potential advantages which include a shorter presurgical dosing period, rapidity of S. aureus decolonization, and previously demonstrated remote likelihood of generating staphylococcal strains that are resistant to XF-73. [Antimicrob Agents Chemother 2011; 55:1177–1181] Phase 3 trials are needed to determine if XF-73 can decrease SSIs. See next review.

Effectiveness and acceptability of intranasal povidone-iodine decolonization among fracture fixation surgery patients to reduce Staphylococcus aureus nasal colonization Infect Control Hosp Epidemiol 2023; 44:982-984.

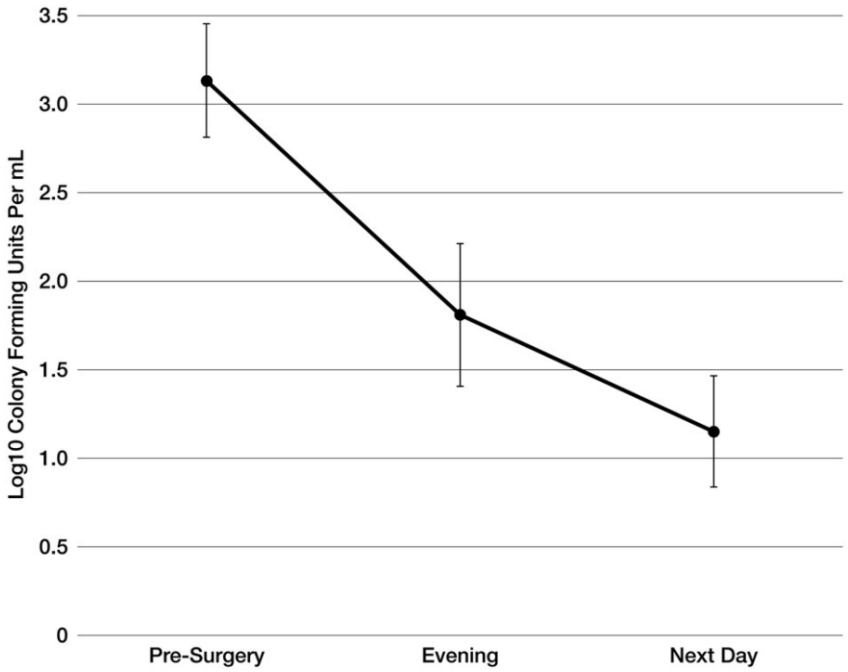
doi.org/10.1017/ice.2022.134

Preoperative decolonization with mupirocin may be impractical for fracture-fixation surgery given the urgent nature of trauma care. Intranasal povidone-iodine (PVI) may be a pragmatic option for nasal decolonization before fracture fixation because it can be used on the day of surgery. Patients received a 15-second application of a swab with PVI to the circumference of each naris and 6 revolutions inside each anterior naris. This process was performed twice to each naris (4 swabs per application). PVI was administered by the patient's nurse or self-applied by the patient with supervision. The primary outcome was reduction in S. aureus nasal colonization after surgery. Patients were tested for S. aureus nasal colonization before surgery, the evening after surgery, and the day after surgery. Initial samples were obtained before the application of

PVI. At each time point, a rayon swab was used to sample the anterior apex of both nostrils. The swabs performed the evening and day after surgery were inoculated into 1 mL Dey-Engley neutralizer and spun in a vortexer for 15 seconds. For all swabs, a series of dilutions were performed and plated on mannitol salt agar (MSA) plates. The cultures were quantitatively assessed to determine the reduction in S. aureus after use of PVI.

Overall, 51 patients received 2 doses of PVI and were tested for S. aureus colonization. Nasal samples from 12 participants (23.5%) grew S. aureus. Of these, samples from 9 participants were cultured quantitatively. Samples from the other 3 participants had such small quantities of S. aureus that they were only detected via overnight growth. Among the 9 samples that were cultured quantitatively, there was a statistically significant reduction in the concentration of S. aureus across the 3 time points (P = .032). No patient experienced SSI within 30 days of surgery.

In total, 51 patients were surveyed on the day after surgery. Among them, 16 (31%) reported at least 1 side effect while using PVI. Reported side effects included dripping (14%), itching (12%), dryness (8%), stinging (8%), staining (6%), unpleasant taste (6%), runny nose (4%), burning (2%), sneezing (2%), sore throat (2%), tickling (2%), and cough (2%). No serious adverse events were reported.



Comment: In a randomized, nonblinded, placebo-controlled trial, a single application of a 10% PVI preparation significantly reduced nasal MRSA at 1 and 6 hours after application, but suppression was not sustained at 12 or 24 hours. [Am J Infect Control 2020; 48:456–459] A single center randomized controlled trial found no difference in SSI rates when comparing a single preoperative application of nasal PVI with a 5-day application of nasal mupirocin among patients undergoing arthroplasty or spine fusion surgery. The proportion of post-operative nasal culture with no growth was 78 of 85 (92%) mupirocin subjects and 45 of 84 (54%) povidone-iodine subjects, (p=0.03). [Infect Control Hosp Epidemiol 2014; 35:826–832]

In this study the sample size was very small, and they lacked a control group, which limits conclusions about the effectiveness of intranasal PVI for preventing SSIs. Although they found that intranasal PVI significantly reduced concentrations of nasal S. aureus colonization, the amount of S. aureus suppression necessary to decrease the risk of SSI is unknown. Larger clinical trials would need to be done to determine if PVI is a suitable alternative to mupirocin.

In-Class Cross-Reactivity among Hospitalized Patients with Hypersensitivity Reactions to Fluoroquinolones Antimicrob Agents Chemother published online May 6, 2023

doi.org/10.1128/aac.00374-23

Health system evaluation of fluoroquinolone hypersensitivity: an assessment of cross-reactivity J Antimicrob Chemother published online May 10, 2023

doi.org/10.1093/jac/dkad136

Among antibiotic classes on patients' allergy lists, fluoroquinolones (FQ) are second only to β-lactams. Drug challenge is the only way to confirm tolerance to FQ. The first study performed a retrospective chart review across 19 hospitals within the University of Pittsburgh Medical Center; participants comprised inpatients with confirmed true hypersensitivity reactions to levofloxacin (LVX), moxifloxacin (MOX), or ciprofloxacin (CIP) and a documented receipt of a different FQ. Among 230 eligible patients (80% female; 95% white; median age, 59), 161 received a different FQ after the index allergy and 69 had received a FQ before the index allergy. Reactions included rash and hives (81%), respiratory distress (6%), angioedema (6%), and anaphylaxis (4%). Of the 161 patients who were challenged with a different FQ after a hypersensitivity reaction, 6% (all female) experienced a hypersensitivity reaction, one of which involved angioedema. Thirty of the 161 patients received a subsequent course of FQ. The two who developed respiratory distress had an index reaction of rash and hives to LVX and MOX, tolerated a course of CIP, but developed respiratory distress with the second CIP course. Risk for reaction was highest with MOX (9%), followed by CIP (6%), and LVX (2%); differences were not statistically significant.

In a second article (JAC), investigators evaluated 94 hospital patients from 2013 to 2021 at the Yale New Haven Health System who had received at least one dose of FQ after a medical history of a hypersensitivity reaction to a different FQ. Only 21 of these patients were deemed to have true hypersensitivity reactions (3 of which were physician reported). Cross-reactivity was observed in 14% of patients, with a median time of 6 years between incident hypersensitivity to one FQ and challenge with a different FQ.

Comment: These two studies demonstrated that cross-sensitivity among FQ is relatively uncommon. Therefore, avoidance of the FQ class for patients allergic to one agent in a class may not always be necessary. See next review.

Development and Validation of a Sulfa Antibiotic Allergy Clinical Decision Rule.
JAMA Netw Open 2023;6:e2316776.

doi:10.1001/jamanetworkopen.2023.16776

Trimethoprim-sulfamethoxazole is a first-line treatment for many infections; however, use may be limited by history of sulfa allergy. Use of trimethoprim-sulfamethoxazole (TMP-SMX) is frequently recommended by antimicrobial stewardship programs to prevent use of more restricted antibiotics. Studies with non-standardized challenge criteria suggest that those with low-risk allergy phenotypes can safely undergo direct oral challenges (OCs); however, no current risk-stratification tool exists to guide challenges. The investigators sought to adapt PEN-FAST, a penicillin allergy clinical decision tool [JAMA Intern Med 2020; 180:745], for TMP-SMX allergy.

Patients aged 18 years or older with a TMP-SMX allergy referred to drug allergy services in Melbourne, Australia (Austin Health, Peter MacCallum Cancer Centre; November 1, 2015, to July 31, 2022), or Nashville, Tennessee (Vanderbilt University Medical Center; October 1, 2015, to February 28, 2019), were prospectively assessed. Patients with a non-severe sulfa or TMP-SMX allergy (i.e., excluding anaphylaxis within 5 years and severe cutaneous adverse drug reaction), provided written consent to undergo OC at clinician discretion. A positive test result was defined as a positive patch test (PT) result or a clinician-observed or patient-reported presumed immune-mediated reaction after the challenge. A PEN-FAST score and its diagnostic performance were calculated for each cohort and allergy phenotype subgroup.

PEN-FAST (SULF-FAST) criteria are as follows:

- Allergy event occurred ≤5 years ago (2 points)
- Allergy event was anaphylaxis/angioedema or severe cutaneous adverse reaction (SCAR; 2 points)
- Treatment was required for allergy event (1 point)

Most patients had oral challenges, but a small number of patients with histories of severe reactions had patch tests. A SULF-FAST score of <3 had lower than 5% risk for a hypersensitivity reaction, whereas a score of ≥3 was associated with >20% risk for a reaction.

Challenge Type	Criteria	Dose(s)	Obsesrvation Protocol*
Single-dose challenge	Nonsevere delayed reactions without multiple features consistent with IgE-mediated reaction Nonsevere immediate (eg, isolated urticaria, maculopapular rash, or gastrointestinal symptoms) reaction (<1 hr) more than 5 years ago Unknow, remote history	TMP-SMX (Co-T) 80-400mg	1-2 hr observation in clinic after full dose
2-dose challenge	Nonsevere immediate reaction (<1 h) within past 5 years Nonsevere accelerated reaction (>1 but <36 h) within the past 5 y Anaphylaxis at any time point in the past Multiple (2 or more) features potentially compatible with IgE-mediated reaction at any time point in the past • Urticaria • Angioedema • Shortness of breath • Hypotension • Significant patient anxiety surrounding single-dose challenge	TMP-SMX (Co-T) 8-40 mg TMP- SMX (Co-T) 80-400 mg	30 min to 1 hr observation in clinic after first dose 1 hr to 2 hr observation in clinic after second, full dose
Prolonged challenge	Nonsevere delayed reaction (>36 h) at any time point in past	TMP-SMX (Co-T) 80-400mg TMP-SMX (Co-T) 160-800 mg daily for 3 days	1 hr observation for single dose challenge in clinic, follow up call 24-48 hours after completion of 3 day outpatient course

Comment: Application of PEN-FAST criteria provides a good initial framework for identifying appropriate challenge candidates among patients with low-risk TMP-SMX allergy. Although sensitivities of 66.7% and 38.5% for the challenge reaction were lower than with PEN-FAST (70.7% [95% CI, 57.3%-81.9%]), the tool's safety is reinforced by high specificity and NPV within both cohorts. Although I believe the tool still requires further validation it provides some guidance for choosing patients in whom TMP-SMX oral challenge is safe [mainly patients with history of mild cutaneous reactions or remote more severe reactions]. I would be reluctant to prescribe TMP-SMX in patients with a history of SJS/TEN, hemolytic anemia, or aseptic meningitis.

Candida auris–Associated Hospitalizations, United States, 2017–2022 Emerging Infect Dis published online June 8, 2023

DOI: 10.3201/eid2907.230540

US data on *C. auris* come primarily from case series and outbreak investigations and are geographically limited, and national surveillance data lack detail on patients' underlying conditions, healthcare use, and outcomes. Therefore, the investigators used a large healthcare services database to describe features of hospitalized patients with *C. auris* infection or colonization. This database contains hospital-based all-payer database that contains healthcare use, financial, and pharmacy data from >1,000 US hospitals. Laboratory data was available from ≈25% of those hospitals. They identified all hospitalizations with a culture positive

for *C. auris* from any specimen type during 2017–2022. They used diagnosis codes from the ICD 10th Revision to identify underling conditions and complications and billing data to identify medical devices. They then compiled features of *C. auris* hospitalizations and compared those with versus those without bloodstream infection (BSI) by using χ^2, Fisher exact, and Wilcoxon tests ($\alpha = 0.05$).

A total of 192 *C. auris* hospitalizations (38 [20%] with BSI) occurred in 42 hospitals. *C. auris* hospitalizations primarily occurred among older adults (median age 68 years [range 21–89 years]), male patients (54%), and non-Hispanic White patients (60%). Non-Hispanic Black patients more frequently had BSI than did other races/ethnicities (39% vs. 29%; p = 0.022). The first positive *C. auris* specimen was collected within 2 days of admission for 63% of bloodstream and 48% of nonbloodstream *C. auris* hospitalizations. Among hospitalizations with bloodstream *C. auris*, 58% also had another positive specimen type. Among hospitalizations without bloodstream *C. auris*, the most common positive specimen types were axilla (38%) and urine (34%).

Underlying conditions and complications were similar for patients with bloodstream and nonbloodstream *C. auris* and most commonly were sepsis (64%), diabetes (55%), chronic kidney disease (44%), and pneumonia (43%). Compared with nonbloodstream *C. auris*, bloodstream *C. auris* hospitalizations more frequently involved central venous catheters (CVC) (76% vs. 53%; p = 0.010) and tracheostomies (29% vs. 12%; p = 0.008). Echinocandin use was more frequent for bloodstream (76%) vs. nonbloodstream (25%) hospitalizations; median time from first positive culture to echinocandin use was 2 days (interquartile range 1–3 days).Most (75.5%) hospitalizations involved an intensive care unit stay; mechanical ventilation was used in 43% of intensive care unit cases. Median hospitalization length was 13 days (range, 1–209 days). In-hospital mortality rate was 21%; discharge locations included hospice (13%), skilled nursing facility (28%), and long-term acute care (15%). Estimated crude mortality rates were 47% for bloodstream *C. auris* vs. 31% for nonbloodstream.

Comment: Their results support smaller previous reports showing that infection and colonization with *C. auris* occurs most commonly in patients with complex medical conditions. [Clin Infect Dis. 2023;76: e1436–43]The proportion of *C. auris* cases involving BSI (20%) was comparable to the 9%–28% BSI rate among clinical and screening cases found in previous state-specific studies [Clin Infect Dis. 2020;71:e718–25]. Including in-hospital deaths and discharges to hospice, the overall estimated crude mortality rate of 34% (47% for BSI) was similar to the 30-day mortality rate from a previous study in New York (27% overall and 39% for BSI) [Emerg Infect Dis. 2018;24:1816–24].

Hospitalizations involving *C. auris* BSI were associated with non-Hispanic Black race, similar to those for non–*C. auris* candidemia. The association between CVC use and *C. auris* BSI is not surprising, given that CVC use is a well-documented risk factor for candidemia and is common among patients with *C. auris*, because extensive healthcare exposure, intensive care unit stays, and use of medical devices are key factors in *C. auris* acquisition. Many BSI patients were probably admitted with *C. auris,* based on first positive blood specimens occurring soon after admission. They could not assess previous healthcare exposures and prehospitalization laboratory data, which can be major considerations because patients with *C. auris* usually acquire it in healthcare settings and can remain colonized for months [Open Forum Infect Dis. 2039;5(Suppl 1): S594–5]. The study lacked antifungal susceptibility testing data. There is a need for strengthened national surveillance and further studies to identify risk factors for *C.*

auris infection and colonization. ID Watch reported in April [Ann Intern Med March 21, 2023] on the growing spread of C auris in US. See next review.

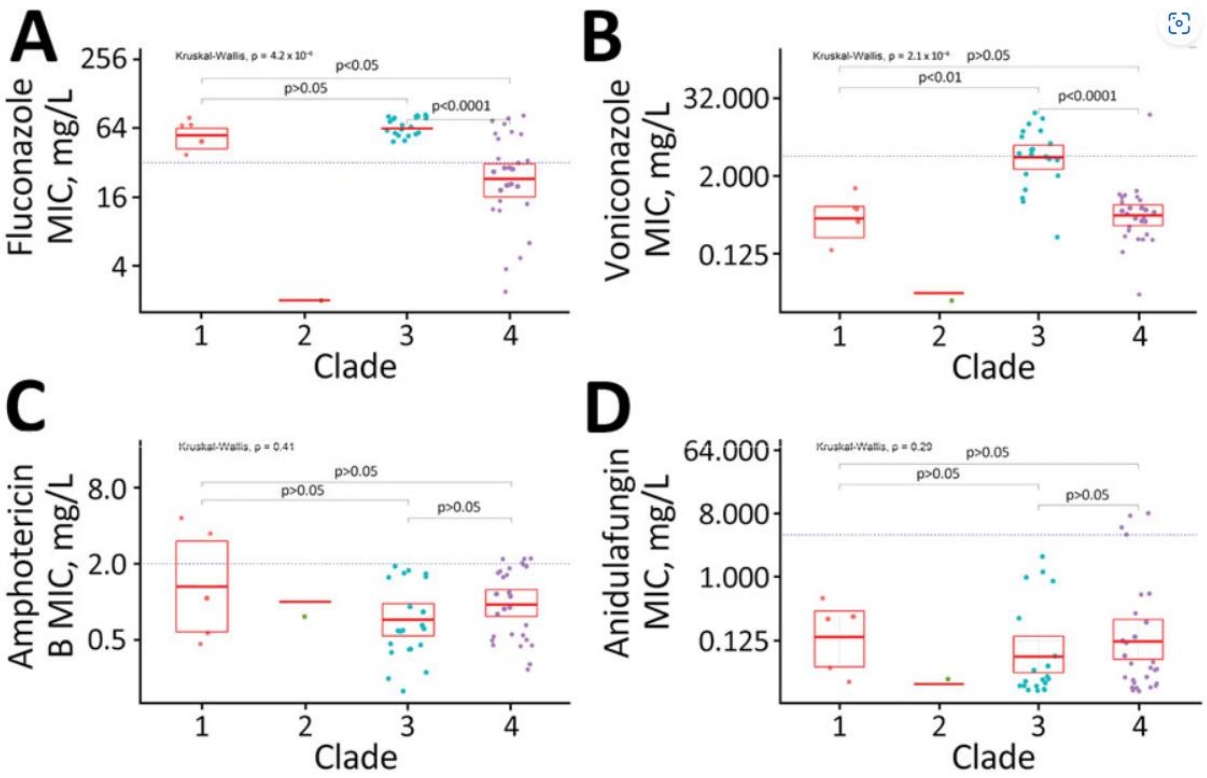
Nationwide Outbreak of *Candida auris* Infections Driven by COVID-19 Hospitalizations, Israel, 2021–2022 Emerg Infect Dis published online June 9, 2023

doi.org/10.3201/eid2907.221888

In a nationwide survey, investigators identified 209 patients with *C auris* infection or colonization from May 2014 to May 2022. Twenty-four of those cases were reported in seven hospitals from May 2014 to December 2020. The *C auris* incidence rate increased 30-fold in 2021, with an annual incidence of 120 cases reported from 10 hospitals and 3 long-term care facilities. During 2021 and 2022, *C auris* incidence corresponded with Covid-19 surges in Israel, peaking during the Alpha (January to March 2021), Delta (June to November 2021), and Omicron (January to May 2022) variant waves.

Almost one quarter (23%) of patients with *C auris* infection or colonization were infected with SARS-CoV-2, and 78% received mechanical ventilation. Analysis of outbreaks at the three hospitals with the most cases indicated *C auris* spread first among mechanically ventilated Covid-19 patients, then infected ventilated non-Covid-19 patients in intermediate care units and from there spread to non-ventilated patients. Patients were predominantly men (68.3%); median age was 70 years (IQR 55–80 years). Patients had multiple comorbidities; 50% had significant functional impairment and 30% had dementia. Most patients (78%) required mechanical ventilation during the same hospitalization, and 67% had a central venous catheter. Carriage or infection with other drug-resistant organisms was detected in 55% of patients. Of 177 patients, 82 (46.3%) had positive clinical specimens, and 95 (53.6%) were colonized with *C. auris* with no evidence of invasive candidiasis. The proportion of colonized versus infected patients was significantly greater for patients with Covid-19 (70.7% vs. 48%; p = 0.013) and in hospital H1, where screening was implemented (77.7% vs. 14.9% in other hospitals; p<0.0001). Clinical specimens consisted of urine (59.8%, n = 49), blood (36.6%, n = 30), and wounds (17.1%, n = 14). In-hospital death occurred in 70 (39.5%) patients. The in-hospital mortality rate did not differ significantly between patients with clinical infections, including those with *C. auris* bloodstream infections, and patients who were only colonized with *C. auris*. Increasing age and comorbidity (Charlson score) were predictors of in-hospital death. Of the surviving patients, 27 (29.0%) were discharged to home, 27 (29.0%) to ventilator-capable skilled nursing facilities, 19 (20.4%) to rehabilitation facilities, and 17 (18.2%) to long-term care facilities.

Multilocus sequence typing revealed that a clade 3 clone, responsible for three cases prior to December 2020, accounted for 55.8% of isolates collected after January 2021. Resistance to fluconazole (MIC $\geq$32 mg/L) was detected in 100% (27/27) of clade III isolates versus 63.1% (24/38) of non–clade III isolates (p = 0.00017). Voriconazole MIC values above the calculated ECOFF (MIC $\geq$4 mg/L) were detected in 74.0% (20/27) of clade III isolates versus 5.2% (2/38) of non–clade III isolates (p<0.0001). Patients were predominantly men (68.3%); median age was 70 years (IQR 55–80 years).



Comment: The expansion of clade III in Israel and its spread beyond H1 to other medical facilities is troublesome and may limit the already limited treatment options for *C. auris*. They identified 2 main drivers of *C. auris* healthcare-associated dissemination in this outbreak. The first was Covid-19. The second driver appeared to be mechanical ventilation. 46% had clinical *C. auris* infection, including 30 patients with candidemia. The in-hospital mortality rate was 40% and was similar for patients colonized and infected with *C. auris*, likely reflecting the multiple acute and chronic comorbidities in this patient population. This study lacked systematic active surveillance and environmental sampling in most medical centers. The trend of increased *C auris* has been seen in other countries and needs heighten surveillance, antimicrobial stewardship, and infection prevention.

Harald zur Hausen, 87, Dies

You may ask, why did I decide to mention Dr. Harlad zur Hausen death? Dr. zur Hausen, was a German virologist who won the Nobel Prize in Medicine in 2008 for his discovery that HPV, known for genital warts, also caused cervical cancer. He died on May 29th at his home in Heidelberg, Germany. He was 87. Dr. zur Hausen's discovery paved the way for vaccines against HPV, a sexually transmitted disease but can also cause other cancers, including of the vagina, vulva, penis, anus and oropharyngeal. Below is a brief summary of a recent review in N Eng J Med.

Human Papillomavirus Vaccination N Engl J Med 2023; 388:1790-1798.

DOI: 10.1056/NEJMcp2108502

Summary:

1. Human papillomavirus (HPV) is a common sexually transmitted virus. Most HPV infections clear or become undetectable within 1 to 2 years, but persistent infection can lead to cervical, vaginal, vulvar, penile, anal, or oropharyngeal cancer. Most HPV infections are asymptomatic.
2. Among the oncogenic HPV types, HPV16 is the most likely type to progress to cancer and causes most of the HPV-attributable cancers in women and men.

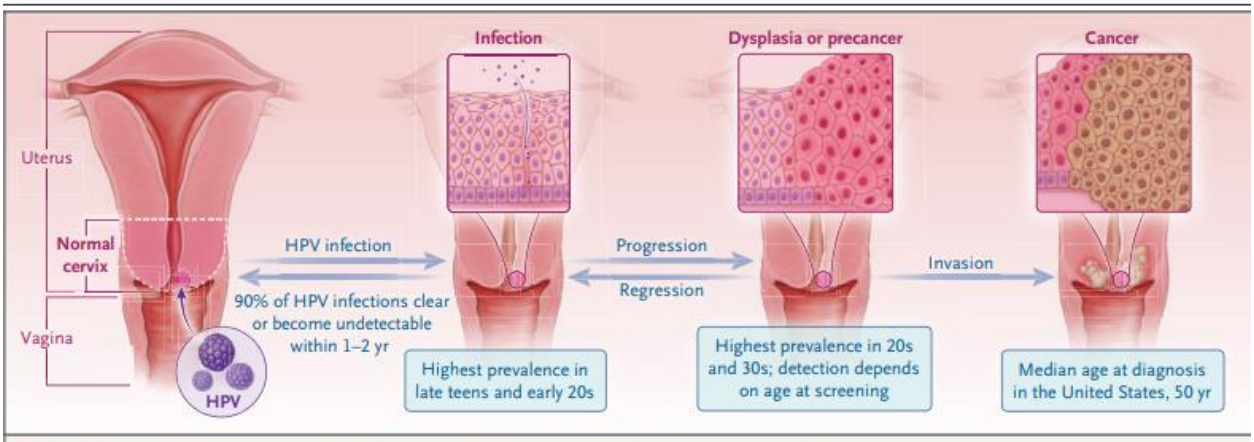
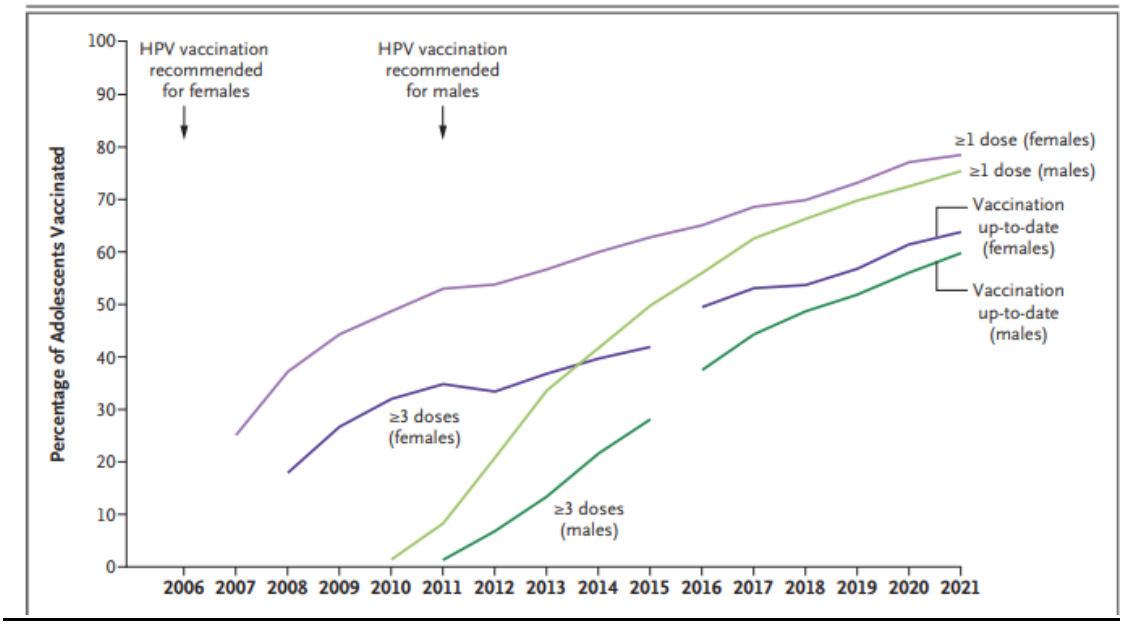


Figure 1. Natural History of Human Papillomavirus (HPV) Infection and Progression to Cervical Cancer.

Table 1. Cancers Associated with and Attributed to Human Papillomavirus (HPV) Infection in the United States, 2015–2019.*

Cancer Site	No. of HPV-Associated Cancers	Percentage of Cancers Probably Caused by Any HPV Type	Estimated No. of Cancers Probably Caused by Any HPV Type†		
			Among Females	Among Males	Among Both Sexes
Cervix	12,293	91	11,100	0	11,100
Vagina	879	75	700	0	700
Vulva	4,282	69	2,900	0	2,900
Penis	1,375	63	0	900	900
Anus‡	7,531	91	4,700	2,200	6,900
Oropharynx	20,839	70	2,300	12,500	14,800
Total	47,199	79	21,700	15,600	37,300

3. HPV vaccines target HPV types that cause most HPV-attributable cancers. In clinical trials, vaccines had high efficacy for the prevention of HPV vaccine–type attributable precancers. Protection after vaccination is long-lasting.
4. In the US, routine HPV vaccination is recommended at 11 or 12 years of age; vaccination can be started at 9 years of age. Vaccination is recommended through 26 years of age for previously unvaccinated persons. Shared clinical decision-making regarding vaccination is recommended for some persons 27 to 45 years of age.
5. Screening for cervical cancer, according to established guidelines, is recommended regardless of HPV vaccination history.
6. HPV vaccination coverage has increased gradually but remains lower than the approximately 90% coverage that has been achieved for other vaccines recommended for adolescents. See below.



Comment: Sexually transmitted HPV is now increasing in the US. In addition, HPV is the leading cause (70%) of this oropharyngeal cancer. Only 54.5% of young people ages 13-15 have taken the recommended two to three doses! (see above) The first two vaccines that were licensed were a quadrivalent vaccine (Gardasil [Merck], licensed in 2006), which is composed of HPV16, HPV18, HPV6, and HPV11 viruslike particles, and a bivalent vaccine (Cervarix [GlaxoSmith-Kline Biologicals], licensed in 2009), which is composed of HPV16 and HPV18 viruslike particles. Later Merck developed a 9-valent vaccine (Gardasil 9, licensed in 2014), which contains viruslike particles of five additional oncogenic types: HPV31, HPV33, HPV45, HPV52, and HPV58. The HPV types that are prevented by 9-valent vaccination account for approximately 90% of HPV-attributable cancers worldwide. Controlled trials involving female adolescents and women 15 to 26 years of age have shown vaccine efficacy of at least 96% for the prevention of cervical precancers (cervical intraepithelial neoplasia grade ≥2 or adenocarcinoma in situ). In 2018 the FDA approved the 9-valent vaccine for persons up through 45 years of age based on a trial of the efficacy of quadrivalent vaccine in women 24 to 45 years of age that showed efficacies of 84.7% and 41.6% in the intention-to-treat population for the prevention of a combined end point of persistent infection, cervical intraepithelial neoplasia, or external genital lesions. [Br J Cancer 2011; 105:28-37]. The lower efficacy in the intention-to-treat population, a result that has been observed in all HPV vaccine trials involving

persons with sexual experience, was attributed to previous exposure to one or more HPV vaccine types. There is no evidence from clinical trials that vaccination can prevent the progression of preexisting infection to disease or can promote the clearance of infection or disease already present at the time of vaccination. [Vaccine 2012;30: Suppl 5: F123-F138] HPV vaccines were initially licensed as a three-dose series; however, the long-lasting high efficacy of HPV vaccine stimulated interest in the use of fewer doses. Subsequent data supported the use of a two-dose series in children and adolescents 9 to 14 years of age. Single dose is now being studied. We need to increase HPV vaccination especially in adolescence.

Table 2. Recommendations for HPV Vaccination in the United States.*

Variable	Recommendation
Age group	
11 or 12 yr; can be initiated starting at 9 yr	Routine-vaccination age group
13–26 yr	Catch-up vaccination for previously unvaccinated persons
27–45 yr	Shared clinical decision making for previously unvaccinated persons
No. of doses	
Among persons 9–14 yr of age at vaccine initiation	2 doses, with the second dose administered 6–12 mo after the first dose†
Among persons ≥15 yr of age at vaccine initiation or those with an immunocompromising condition	3 doses, with the second dose administered 1–2 mo after the first dose and with the third dose administered 6 mo after the first dose‡

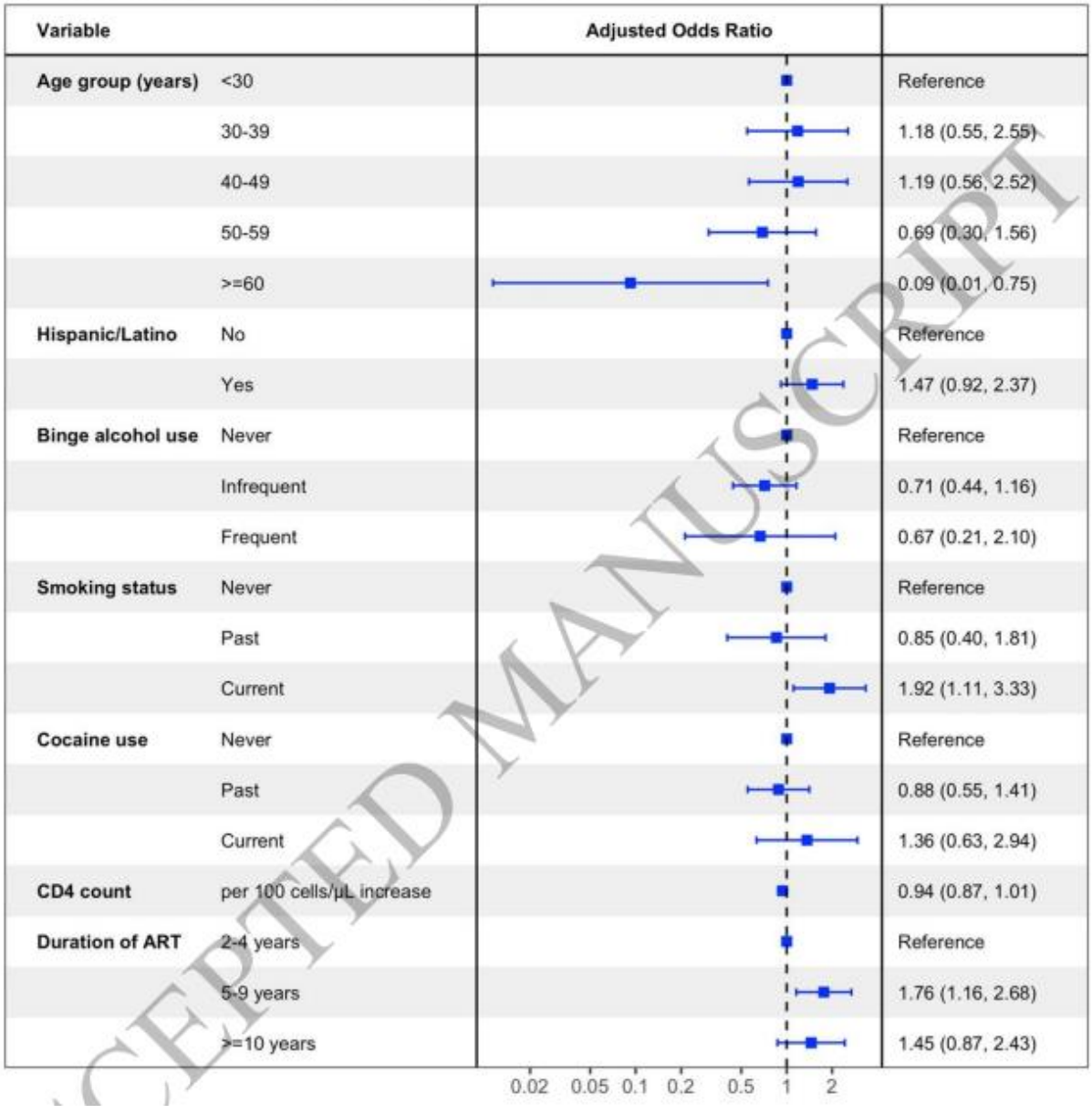
Risk of HIV Viral Rebound in the Era of Universal Treatment in a Multi-Center Sample of Persons with HIV in Primary Care OFID published online May 10, 2023

doi.org/10.1093/ofid/ofad257

The investigators conducted a multi-site, retrospective study of people with HIV (PWH) with a two-year period of sustained viral suppression in the US using the Centers for AIDS Research Network of Integrated Clinical Systems (CNICS) cohort. This study included data from eight sites (Baltimore, Maryland; Birmingham, Alabama; Boston, Massachusetts; Chapel Hill, North Carolina; Cleveland, Ohio; San Diego, California; San Francisco, California; Seattle, Washington) that participated in CNICS since 2010. The CNICS database includes information on participant demographics, risk factors, clinical encounters, diagnoses, HIV treatments, laboratory test results, and self-reported health measures and outcomes (e.g., ART adherence, sexual behaviors, substance use, mental health symptoms, health-related quality of life). They used multivariable logistic regression to identify characteristics independently associated with any viral rebound [viral load (VL) ≥200 copies/mL] and sustained viral rebound (VL ≥200 copies/mL followed by a VL that was also ≥200 copies/mL within six months), within two years of follow-up.

Among 3,496 eligible patients with a two-year period of sustained viral suppression, most (90%) continued to have viral suppression over two additional years; 10% experienced viral rebound, and 4% experienced sustained viral rebound. In multivariable analyses, Black race, current smoking, integrase strand transfer inhibitor use, and five-to-nine-year duration of ART were positively associated, and being age ≥50 years was negatively associated, with any viral rebound. Only current smoking and five-to-nine-year (vs. two-to-four-year) duration of ART were positively associated, and being age ≥60 years was negatively associated, with sustained viral rebound**.**

Figure 5. Characteristics independently associated with sustained viral rebound[†].



Comment: ART is recommended for people with HIV (PWH), irrespective of CD4 cell count, to improve their health and reduce the risk of transmission to sexual partners through long-term viral suppression. This study suggests that a relatively small percentage of people in stable

HIV care on ART experience viral rebound once they have achieved sustained viral suppression, highlighting that once viral suppression is achieved, it is maintained by most patients who are retained in care, which bodes well for their long-term health. The CNICS data set did not include information about social determinants of health, e.g., housing stability, that if more common among smokers and Black patients, might suggest that concomitant structural adversities are playing a role. Studies have demonstrated that single pill regimens in comparison to multiple pill regimens lead to improved retention in care and viral suppression. Other risk factors noted in prior studies but not independently associated with viral rebound in this study include lower education level, being non-MSM, history of incarceration, history of injection drug use, higher CD4 count, and year of ART initiation. [BMC Infect Dis 2016; 16:590; Open Forum Infect Dis 2020; 7: ofaa529] Their analysis in this paper was limited to PWH engaged in care at clinics that participated in CNICS; the results may not be generalizable to other patient populations and care centers.

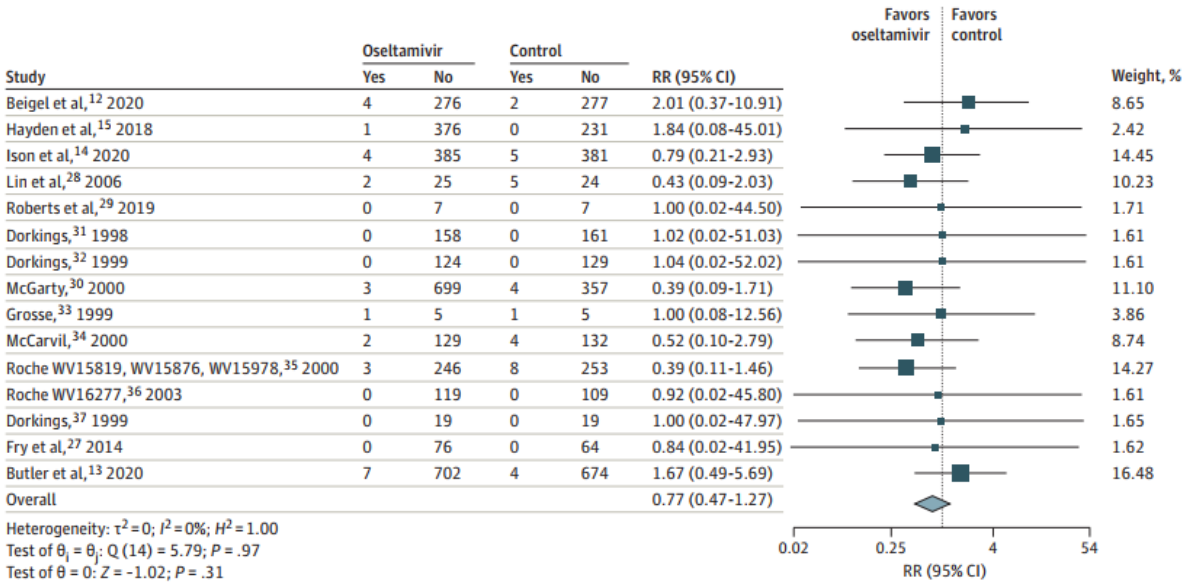
Evaluation of Oseltamivir Used to Prevent Hospitalization in Outpatients With Influenza A Systematic Review and Meta-analysis JAMA Intern Med published online June 12, 2023 suggested by Josh Septimus

doi:10.1001/jamainternmed.2023.0699

The authors asked the question, is the administration of oseltamivir to adult and adolescent outpatients with confirmed influenza associated with a reduced risk of first hospitalization? They state it is unclear whether oseltamivir reduces severe complications requiring hospitalization. They reference three prior reviews which arrived at different conclusions. [BMJ. 2014;348: g25459, Ann Intern Med. 2003;163:1667-1672; Lancet. 2015; 385:1729-1737]

In this paper the authors used PubMed, Ovid MEDLINE, Embase, Europe PubMed Central, Web of Science, Cochrane Central, ClinicalTrials.gov, and WHO International Clinical Trials Registry searched from inception to January 4, 2022. They included studies of RCTs comparing oseltamivir vs placebo or nonactive controls in outpatients with confirmed influenza infection.

Of 2352 studies identified, 15 were included. The intention-to-treat infected (ITTi) population was comprised of 6295 individuals with 54.7% prescribed oseltamivir. Across study populations, 53.6% (5610 of 10 471) were female and the mean age was 45.3 (14.5) years. Overall, oseltamivir was not associated with reduced risk of hospitalization within the ITTi population (RR, 0.77; 95% CI, 0.47-1.27; RD, -0.14%; 95% CI, -0.32% to 0.16%). Oseltamivir was also not associated with reduced hospitalization in older populations (mean age ≥65 years: RR, 0.99; 95% CI, 0.19-5.13) or in patients considered at greater risk of hospitalization (RR, 0.90; 95% CI, 0.37-2.17). Within the safety domain, oseltamivir was associated with increased nausea (RR, 1.43; 95% CI, 1.13-1.82) and vomiting (RR, 1.83; 95% CI, 1.28-2.63) but not serious adverse events (RR, 0.71; 95% CI, 0.46-1.08).



Comment: Based on these analyses, it appeared unlikely that administration of oseltamivir to a general outpatient population had a meaningful effect on serious influenza-related outcomes culminating in hospitalization. However, it should be noted that the rate of hospitalization was very low, with a control event rate of 0.6% (95% CI, 0.14%- 1.07%). The authors analyzed CSRs together with published and nonindustry trials which differed in the time frame over which they took place, the mechanism for diagnosing infection, and the granularity of the data included. The mean age of the patients was young (mid-40s) and the rate of hospitalization was low. This might have limited the power to detect an effect. However, oseltamivir was not associated with reduced hospitalization even in the older population [still may have been underpowered]. They did not study symptomatic improvement, which, along with the associated outcome of return to work, could be an important factor. They claim this is the first systematic review and meta-analysis focusing on oseltamivir specifically for the reduction of all-cause hospitalization. The BMJ article [BMJ. 2014;348: g25459] was a systemic review on the use of oseltamivir for prophylaxis which concluded oseltamivir reduces the proportion of symptomatic influenza. In treatment studies it also modestly reduces the time to first alleviation of symptoms, but it causes nausea and vomiting and increases the risk of headaches and renal and psychiatric syndromes. The evidence of clinically significant effects on complications, hospitalizations, and viral transmission was limited because of rarity of such events and problems with study design. The Annals article [Ann Intern Med. 2003; 163:1667-1672] on the other hand analyzed prospectively collected data on LRTCs(lower respiratory tract complications) and antibiotic use from 3564 subjects with influenza like illness enrolled in 10 placebo-controlled, double-blind trials of oseltamivir treatment. They concluded oseltamivir treatment of influenza illness reduces LRTCs, antibiotic use, and hospitalization in both healthy and "at-risk" adults. Lastly, the Lancet article [Lancet. 2015; 385:1729-1737] was in fact a meta-analysis of prior RCTs which concluded oseltamivir in adults with influenza accelerates time to clinical symptom alleviation, reduces risk of LRTCs, and admittance to hospital, but had increased GI side effects.

In preparing this review I also asked my colleague and influenza expert Dr. Robert Atmar, Professor of Medicine at Baylor College of Medicine to weigh in. With his permission I have

added some of his comments as well. "– that the hospitalization rate was very low, limiting the ability of even a meta-analysis to show benefit for a low-frequency event. So, although the point estimate was 0.77 (23% reduction), the confidence interval encompassed no protection. I think it is highly unlikely that an RCT will be done to answer this question – the only kind of trial that was included in the meta-analysis. Most of the studies agree it decreases influenza illness duration and most agree it is at a cost of GI symptoms (especially after first dose) although most patients don't stop it for these symptoms (which many blame on the flu rather than their illness)."

So where do we go from here. It still seems reasonable to offer oseltamivir to the elderly and high-risk population based on current studies. Future studies should focus on identifying the groups of higher-risk participants, with laboratory confirmed influenza, who may derive benefit. Conducting an adequately powered trial, however, would require a large sample size and like Dr Atmar I doubt this will be done.

Influenza Southern Hemisphere

The US is already thinking about flu season. We look to the Southern Hemisphere to predict this fall and winter in the Northern Hemisphere. Australia is off to an early start with some parts of the country seeing a spike in illness, and the highest number of cases are among children. This flu pattern could be an indicator of what's to come in the US. In the Southern Hemisphere, where it is now winter, cases began increasing "sharply" in early May. It's an earlier start of the season than some years. The WHO just updated influenza surveillance. Flu activity remains mixed in the Southern Hemisphere, with increasing activity in a region that includes Australia and some declines in South America. At national influenza labs over this reporting period, 62.9% of positive respiratory samples were influenza A, and, of subtyped influenza A samples, 73.6% were the 2009 H1N1 virus. All influenza B viruses that were subtyped belonged to the Victoria lineage.

Comment: The Covid-19 pandemic made flu season even more unpredictable. Looking at this fall, we will face new challenges. In addition to urging everyone to get their annual influenza vaccine, we're going to have a new updated Covid vaccine that will be available. And in addition, there are two new RSV vaccines [see below] just approved by the FDA. So, some people will be recommended to get not just one, not just two, but three vaccines. Whether adults will go for all three shots remains to be seen. The fall/winter viral respiratory season will be difficult to predict because predicting what any infectious disease will do is also dependent on predicting human behavior.

FDA Approves Pfizer's RSV Vaccine for Older Adults May 31, 2023

The FDA approved Pfizer's vaccine against RSV on May 31st , for adults age 60 and older, the second approval granted for vaccines offering protection from the virus this month.

GSK was the first drugmaker to get the FDA's approval to market an RSV vaccine on May 3rd. The vaccines are expected to be available in the fall before the winter RSV season.

Pfizer's vaccine proved nearly 67 percent effective against cases of the virus with two symptoms and 86 percent effective against cases with three or more symptoms, according to data submitted to the FDA. The GSK vaccine was nearly 83 percent effective against severe R.S.V. However, the advisory panel also raised concerns about a few cases in which vaccine recipients developed autoimmune syndromes shortly after receiving the shots. In the Pfizer study of about 34,000 patients who received the RSV vaccine, a week after the shot, one patient developed a case of Guillain-Barré syndrome. A second patient developed a subtype of that condition called Miller Fisher syndrome eight days after receiving the shot. These cases put the incidence rate of the condition at about one in 9,000 — though they are typically seen at a rate of about one in 100,000 in the general population. Some advisers, also noting the low incidence of severe RSV in the patient pool, found those numbers troubling. The final vote of the FDA's advisory panel in favor of the Pfizer vaccine's safety and efficacy was 7 to 4. The panel voted 10 to 2 in favor of the GSK vaccine, which was also linked to one Guillain-Barré case and two others of a possibly related disorder.

Comment: see next review and comment

RSV Adult Vaccine Update

As expected, the CDC vaccine advisory group on June 21 recommended newly approved RSV vaccines for use in two older age-groups, people ages 60 to 64 and those ages 65 and older. In the first vote, which passed 9 to 5, advisers said adults ages 65 and older may receive a single dose of the vaccine, using shared clinical decision making. In the second vote, which passed with 13 yes votes and 1 abstention, they said *individual* adults ages 60 to 64 may receive a single dose of RSV vaccine using shared clinical decision making.

Comment: The language of the recommendation — that older patients "may receive" an RSV vaccine — is not as strong as saying they "should" receive one. The CDC estimates that 60,000 to 160,000 older adults are hospitalized for RSV infections each year, with the virus leading to the deaths of 6,000 to 10,000 people each year. Those at highest risk for severe disease include those ages 65 and older, people with chronic heart and lung problems, and patients who are immunosuppressed. The CDC estimated that in one year, more than 21,000 people in that age group would need to take the GSK vaccine to prevent one RSV death; the number was nearly 25,000 for the Pfizer vaccine. While it's possible they could be offered in the fall, along with the updated Covid-19 vaccine and the annual flu shot, it's not clear how timing would work for the new RSV vaccines.

Unfortunately, vaccine hesitancy may reduce uptake. According to a new study by the Vaccine Confidence Project only 79% of Americans surveyed reported confidence in vaccines, compared with about 93% before the pandemic. This level of support is the lowest since at least 2015. Other examples show a minority of those eligible in the US got the latest Covid-19 booster. In addition, rates of vaccinations for HPV and influenza have declined and more children have received exemptions from getting vaccines.

RSV Antibody Treatment Nirsevimab Approval

FDA antimicrobial drugs advisory committee unanimously recommended approval of AstraZeneca and Sanofi's antibody treatment for preventing RSV in infants during their first RSV season. The committee also voted 19 to 2 to recommend the drug, called nirsevimab—given as a single-dose intramuscular injection—for children as old as 24 months who are at risk for RSV during the second season. If the FDA accepts the committee's recommendation, the drug will be available ahead of the United States' 2023-2024 RSV season.

Comment: Nirsevimab is a single dose long-acting antibody, developed and commercialized in partnership by AstraZeneca and Sanofi using AstraZeneca's YTE technology. It is designed to protect infants born during or entering their first RSV season and for children up to 24 months of age who remain vulnerable to severe RSV disease through their second RSV season. Nirsevimab, provided directly to newborns and infants as a single dose, offers RSV protection via an antibody to help prevent LRTI (lower respiratory track infection) caused by RSV.

Aztreonam-avibactam (ATM-AVI)

The results from the two trials indicate that ATM-AVI, which combines an old beta-lactam antibiotic (aztreonam) with a newer beta-lactamase inhibitor (avibactam), is safe and effective in treating serious infections caused by multidrug-resistant, gram-negative pathogens. The combination of aztreonam with avibactam can restore aztreonam's activity against some gram-negative bacteria. ATM-AVI can combat beta-lactam antibiotics—beta-lactamase enzymes and metallo-beta-lactamase (MBL) enzymes. While aztreonam is not degraded by MBLs, it is susceptible to other beta-lactamase enzymes, which has limited its clinical effectiveness. The addition of avibactam protects aztreonam from those beta-lactamases.

In the phase 3 REVISIT trial, the safety and efficacy of ATM-AVI with or without metronidazole was compared against meropenem with or without colistin in 422 patients in 20 countries who were hospitalized with complicated intra-abdominal infections (cIAI) or hospital-acquired and ventilator-associated pneumonia (HAP/VAP). The patients were in regions where carbapenem resistance was emerging or endemic and where MBL-producing pathogens were suspected. For patients with cIAI, the cure rate in the intention-to-treat (ITT) analysis was 76.4% for patients in the ATM-AVI treatment arm and 74.0% for patients in the meropenem arm, with a treatment difference of 2.4%. In the clinically evaluable (CE) analysis, the cure rate was 85.1% vs 79.5%. For HAP/VAP patients, the ITT cure rate was 45.9% for ATM-AVI and 41.7% meropenem (treatment difference, 4.3%) and the CE cure rate 46.7% vs 54.5%. All-cause 28-day mortality rates for cIAI patients were 1.9% in the ATM-AVI group and 2.9% for meropenem, and 10.8% for ATM-AVI versus 19.4% for meropenem in HAP/VAP patients. ATM-AVI was well-tolerated, with a similar incidence of serious adverse events (19.3%) as in the meropenem treatment arm (18.2%).

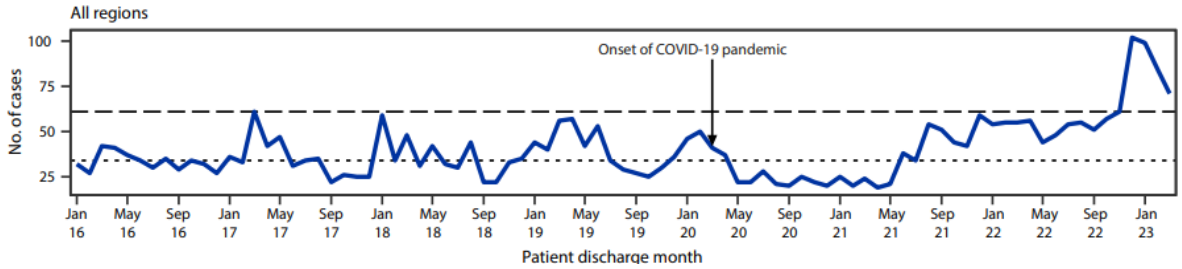
In the ASSEMBLE trial, ATM-AVI was compared with the best available therapy (BAT) in 15 patients in nine countries who had infections due to confirmed MBL-producing gram-negative bacteria. The results showed that 41.7% of patients in the ATM-AVI arm were cured at test-of-cure, compared with none of the patients in the BAT arm. None of the patients treated with ATM-AVI experienced a treatment-related serious adverse event.

Comment: These trials are promising in patients infected with NDM producing organisms. Data from US reported in ID Watch in April [OFID] on carbapenemases in the US found a decrease in KPCs and an increase in NDMs. The addition of ATM-AVI would be a welcomed addition for the treatment of patients infected with NDM gram negatives. The IDSA guidelines recommend the combination of ceftazidime-avibactam and aztreonam which can be used to overcome the activity of both the L1 and L2 β-lactamases. The L1 metallo-β-lactamase hydrolyzes ceftazidime but not aztreonam. The L2 serine β-lactamase hydrolyzes ceftazidime and aztreonam but is inactivated by avibactam.

Update on Pediatric Intracranial Infections — 19 States and the District of Columbia, January 2016–March 2023 MMWR 2023; 72(22);608–610

In May 2022, CDC began an investigation of a possible increase in pediatric intracranial infections, particularly those caused by *Streptococcus* bacteria, during the preceding year. January 2016–May 2022 data from a large, geographically diverse network of children's hospitals showed altered patterns in pediatric intracranial infections after the onset of the Covid-19 pandemic. In this update, they extended hospitalization data through March 2023 from 37 hospitals in 19 states and the District of Columbia. CDC analyzed pediatric hospitalizations for brain abscesses, epidural empyemas, and subdural empyemas reported to the Children's Hospital Association's Pediatric Health Information System (PHIS) by 37 tertiary referral children's hospitals in 19 states and the District of Columbia. All inpatient encounters with persons aged ≤18 years that had a primary or secondary ICD-10 discharge diagnosis code G06.0 (intracranial abscess and granuloma) or G06.2 (extradural and subdural abscess, unspecified) during the study period were included. Data were analyzed in aggregate and by U.S. Census Bureau region (Northeast, Midwest, South, and West) using R software (version 4.0.3; R Foundation) with RStudio (version 1.3.1093; Posit, PBC).

Using pediatric intracranial infection hospitalization data collected during 2016–2019, the monthly median (34; IQR = 29.75–42.00) and maximum (61) number of cases were calculated as a prepandemic baseline. After the onset of the Covid-19 pandemic in March 2020, monthly intracranial infection case counts remained below the baseline median during May 2020–May 2021. Monthly case counts exceeded the median during August 2021–March 2023 but did not exceed the baseline maximum until a large peak (102 cases) in December 2022. During January–March 2023, case counts began to decline but remained above the baseline maximum. Although some variability between US Census Bureau regions was observed, overall patterns were generally similar: consistently low case counts after the onset of the pandemic, then a period of increase beginning in mid- to late 2021 followed by a large peak during winter 2022–2023. Demographic characteristics of patients (age, race and ethnicity, and sex), measures of severity (length of hospitalization, intensive care unit admission, and in-hospital mortality), and the percentage of patients with a complex chronic condition remained approximately stable over the study period and were similar to values reported previously.



Comment: They demonstrated a higher-than-expected number of pediatric intracranial infections beginning in August 2021, with a large peak during winter 2022–2023. Pediatric intracranial infections are recognized as a severe complication of viral respiratory infection and sinusitis (Arch Otolaryngol Head Neck Surg 2006; 132:969–762), and the winter 2022–2023 peak coincided with spikes in respiratory virus circulation. Even during this peak, intracranial infections remained rare. CDC continues to track trends in pediatric intracranial infections and recommends that all persons aged ≤18 years remain current with recommended vaccinations, including influenza and Covid-19.

Utility of Urine Cultures During Febrile Neutropenia Workup in Hematopoietic Stem Cell Transplantation Recipients Without Urinary Symptoms OFID published online May 3, 2023

doi.org/10.1093/ofid/ofad236

The incidence of febrile neutropenia (FN) after HCT is estimated to be as high as 80%, only 20–25% of FN episodes result from microbiologically documented infections. Identification of UTIs during FN may be complicated by the potential absence of pyuria, and transplant centers take a variety of different approaches in evaluating HCT patients with FN for UTIs based on conflicting society guidelines. Retrospective studies in adult patients with hematologic malignancies, have reported that urine culture results rarely impacted antibiotic choice or clinical outcomes in patients without urinary symptoms, suggesting that urine cultures should be limited to symptomatic patients [Infect Dis 2016; 48:872–4]. This study set out to investigate the utility of obtaining urine cultures in HCT recipients with FN in a large, single-center cohort.

They included patients ≥18 years of age undergoing HCT with documented FN during the first admission and a urine culture collected during the initial FN episode. Urine cultures were considered positive (i.e., bacteriuria) at a threshold of 1×10^4 CFU/mL. UTIs were defined by the presence of both urinary symptoms (dysuria, frequency, hematuria, acute incontinence, flank pain, or suprapubic pain) and bacteriuria of $\geq 10^4$ CFU/mL. Asymptomatic bacteriuria (ABU) was defined by the absence of urinary symptoms noted in the chart (dysuria, frequency, hematuria, acute incontinence, flank pain, or suprapubic pain) at the time the urine culture was obtained. Data were obtained via EHRs. The primary outcome was a composite of either antibiotic changes based on urine culture results or the development of severe urinary infectious complications including pyelonephritis, UTI-related bacteremia, or escalation to a higher level of care (e.g., ICU) due to UTI. Secondary outcomes included 30-day infectious-related mortality and 30-day all-cause mortality.

A total of 1136 HCT admissions for 1062 patients between 2014 and 2021 were screened, and 667 patients were identified who met inclusion criteria. Of the 667 patients, 40 (6%) were found to have bacteriuria at the time of FN without urinary symptoms (ABU). The median age of patients was 58 (19–78) years and most were male (63%), undergoing autologous HCT (68%), primarily for multiple myeloma (41%). There were no significant differences between those with asymptomatic bacteriuria versus nonbacteriuria except for a higher percentage of female patients in the former (68% vs 35%, $P = .0001$). None of the patients had urinary catheters at the time of urine culture. All patients received prophylactic antibiotics at the time of transplant with levofloxacin being the most common antibacterial agent (92%). All patients with FN received empiric IV antibiotics after transplant with the majority receiving cefepime (78%). Patients with bacteriuria did not significantly differ from the nonbacteriuria group in timing of antibiotics relative to urine culture, total duration of antibiotics during hospitalization, or urinalysis results. No patients developed symptomatic UTI, pyelonephritis, or UTI-related bacteremia or required escalation of care due to infection from a urinary source. Of those with asymptomatic bacteriuria, there was no difference in time to resolution of fever, escalation of care, or duration of hospitalization.

Comment: Antimicrobial resistance is an increasing threat to the effective management of severely immunocompromised patients, particularly those undergoing HCT. Although antimicrobial stewardship has grown in priority among transplant centers, the integration of effective diagnostic stewardship has lagged. To the best of my knowledge, this is the only analysis to date assessing the utility of routine urine cultures in HCT patients with FN. These results provide preliminary evidence against the use of routine urine cultures in FN patients undergoing HCT without urinary symptoms. As rates of antimicrobial resistance rise, implementing antimicrobial stewardship together with diagnostic stewardship is likely to offer a more comprehensive and effective approach.

Comparison of Medical and Mental Health Sequelae Following Hospitalization for COVID-19, Influenza, and Sepsis JAMA Intern Med published online June 20, 2023

doi:10.1001/jamainternmed.2023.2228

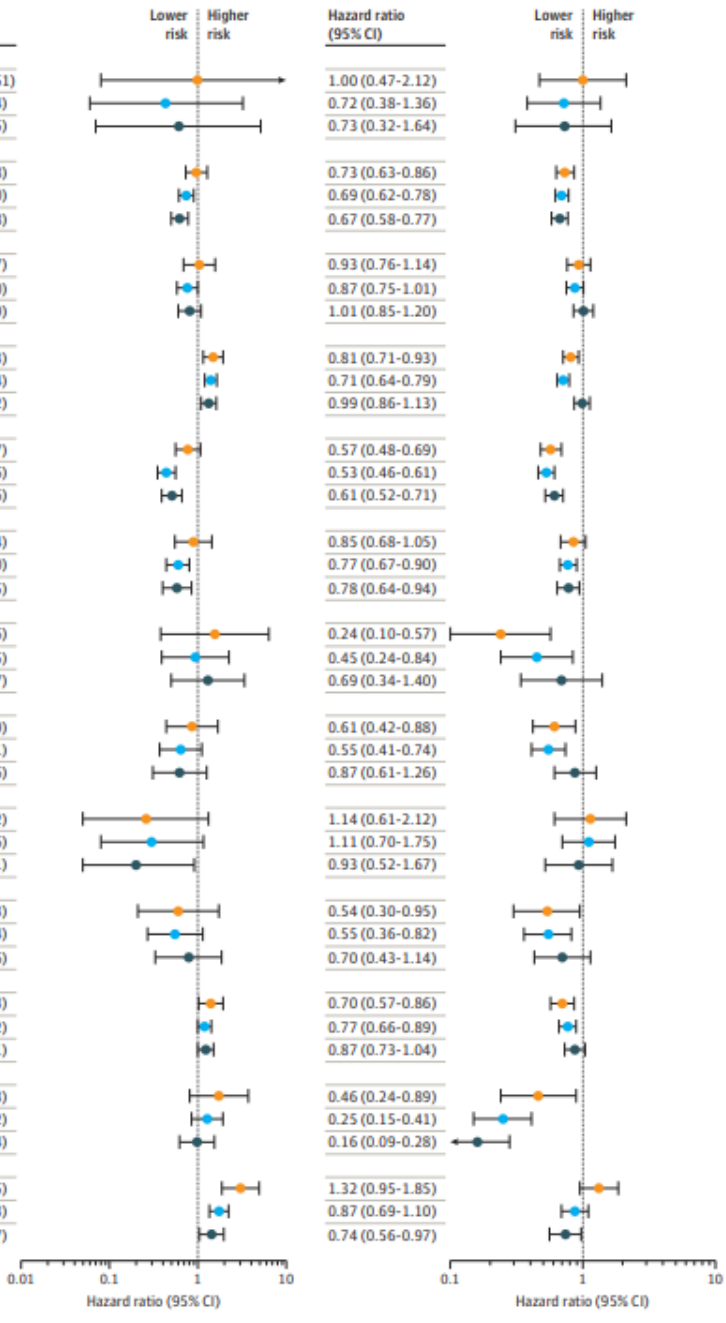
The question this study asks-People who survive hospitalization for Covid-19 are at risk for developing new cardiovascular, neurological, mental health, and inflammatory autoimmune conditions. It is unclear how posthospitalization risks for Covid-19 compare with those for other serious infectious illnesses including another viral illness influenza and sepsis. The investigators examined the risks of the incidence of cardiovascular, neurological, and mental health conditions and rheumatoid arthritis in 1 year following Covid-19 hospitalization against 3 comparator groups: prepandemic hospitalization for influenza and hospitalization for sepsis before and during the Covid-19 pandemic.

To answer the question, the investigators conducted a population-based cohort study included all adults hospitalized for Covid-19 between April 1, 2020, and October 31, 2021, historical comparator groups of people hospitalized for influenza or sepsis, and a contemporary comparator group of people hospitalized for sepsis. They captured new occurrences of 13 prespecified conditions, including cardiovascular, neurological, and mental health conditions and rheumatoid arthritis, within 1 year of hospitalization.

Of 379,366 included adults (median [IQR] age, 75 [63-85] years; 54% female), there were 26, 499 people who survived hospitalization for Covid-19, 299,989 historical controls (17,516 for influenza and 282,473 for sepsis), and 52,878 contemporary controls hospitalized for sepsis. Hospitalization for Covid-19 was associated with an increased 1-year risk of venous thromboembolic disease compared with influenza (adjusted hazard ratio, 1.77; 95% CI, 1.36-2.31) but with no increased risks of developing selected ischemic and nonischemic cerebrovascular and cardiovascular disorders, neurological disorders, rheumatoid arthritis, or mental health conditions compared with influenza or sepsis cohorts.

Figure 3. Secondary Analysis of Outcomes After Hospital Discharge

Outcome	A: Outcomes <30 d from hospital discharge — Hazard ratio (95% CI)	B: Outcomes ≥30 d from hospital discharge — Hazard ratio (95% CI)
Acute myocardial infarction		
COVID-19 vs historical influenza	0.99 (0.08-11.51)	1.00 (0.47-2.12)
COVID-19 vs historical sepsis	0.43 (0.06-3.24)	0.72 (0.38-1.36)
COVID-19 vs contemporary sepsis	0.61 (0.07-5.15)	0.73 (0.32-1.64)
Cardiovascular disease		
COVID-19 vs historical influenza	0.96 (0.73-1.28)	0.73 (0.63-0.86)
COVID-19 vs historical sepsis	0.74 (0.61-0.90)	0.69 (0.62-0.78)
COVID-19 vs contemporary sepsis	0.62 (0.50-0.78)	0.67 (0.58-0.77)
Dementia		
COVID-19 vs historical influenza	1.04 (0.69-1.57)	0.93 (0.76-1.14)
COVID-19 vs historical sepsis	0.76 (0.58-1.00)	0.87 (0.75-1.01)
COVID-19 vs contemporary sepsis	0.81 (0.60-1.09)	1.01 (0.85-1.20)
Depression/anxiety		
COVID-19 vs historical influenza	1.49 (1.15-1.93)	0.81 (0.71-0.93)
COVID-19 vs historical sepsis	1.40 (1.20-1.64)	0.71 (0.64-0.79)
COVID-19 vs contemporary sepsis	1.33 (1.09-1.62)	0.99 (0.86-1.13)
Heart failure		
COVID-19 vs historical influenza	0.77 (0.56-1.07)	0.57 (0.48-0.69)
COVID-19 vs historical sepsis	0.44 (0.35-0.56)	0.53 (0.46-0.61)
COVID-19 vs contemporary sepsis	0.51 (0.39-0.66)	0.61 (0.52-0.71)
Hypertension		
COVID-19 vs historical influenza	0.89 (0.55-1.44)	0.85 (0.68-1.05)
COVID-19 vs historical sepsis	0.60 (0.44-0.80)	0.77 (0.67-0.90)
COVID-19 vs contemporary sepsis	0.58 (0.40-0.85)	0.78 (0.64-0.94)
Parkinson disease		
COVID-19 vs historical influenza	1.56 (0.38-6.36)	0.24 (0.10-0.57)
COVID-19 vs historical sepsis	0.94 (0.39-2.25)	0.45 (0.24-0.84)
COVID-19 vs contemporary sepsis	1.30 (0.50-3.37)	0.69 (0.34-1.40)
PCI/CABG		
COVID-19 vs historical influenza	0.86 (0.44-1.69)	0.61 (0.42-0.88)
COVID-19 vs historical sepsis	0.64 (0.37-1.11)	0.55 (0.41-0.74)
COVID-19 vs contemporary sepsis	0.62 (0.31-1.26)	0.87 (0.61-1.26)
Rheumatoid arthritis		
COVID-19 vs historical influenza	0.26 (0.05-1.32)	1.14 (0.61-2.12)
COVID-19 vs historical sepsis	0.30 (0.08-1.16)	1.11 (0.70-1.75)
COVID-19 vs contemporary sepsis	0.20 (0.05-0.91)	0.93 (0.52-1.67)
Seizure		
COVID-19 vs historical influenza	0.60 (0.21-1.73)	0.54 (0.30-0.95)
COVID-19 vs historical sepsis	0.55 (0.27-1.14)	0.55 (0.36-0.82)
COVID-19 vs contemporary sepsis	0.79 (0.33-1.86)	0.70 (0.43-1.14)
Stroke		
COVID-19 vs historical influenza	1.40 (1.02-1.93)	0.70 (0.57-0.86)
COVID-19 vs historical sepsis	1.19 (1.00-1.42)	0.77 (0.66-0.89)
COVID-19 vs contemporary sepsis	1.23 (1.00-1.51)	0.87 (0.73-1.04)
Substance use disorder		
COVID-19 vs historical influenza	1.73 (0.81-3.73)	0.46 (0.24-0.89)
COVID-19 vs historical sepsis	1.28 (0.85-1.92)	0.25 (0.15-0.41)
COVID-19 vs contemporary sepsis	0.98 (0.62-1.54)	0.16 (0.09-0.28)
Venous thromboembolism		
COVID-19 vs historical influenza	3.04 (1.87-4.95)	1.32 (0.95-1.85)
COVID-19 vs historical sepsis	1.74 (1.35-2.23)	0.87 (0.69-1.10)
COVID-19 vs contemporary sepsis	1.43 (1.04-1.97)	0.74 (0.56-0.97)



Comment: Apart from an elevated risk of venous thromboembolism, the burden of post-acute conditions among those who survive hospitalization for Covid-19 may be comparable with other acute infections. This suggests that many of the post-acute consequences of Covid-19 may be related to the severity of infectious illness necessitating hospitalization rather than being direct consequences of infection with SARS-CoV-2. The study cohort was largely composed of older adults, with expected differences observed in median age between those with Covid-19 and those with sepsis and influenza. These demographic differences may reflect the predisposition of older adults to develop severe sepsis and influenza compared with those with Covid-19, which they tried to account for in their propensity overlap weights. These findings may also not generalize to outpatient settings.

COVID-19

FDA Panel Recommendation of COVID-19 Booster June 15, 2023

The 21-member panel unanimously recommended targeting the XBB variant of the coronavirus in the vaccine to be available in the fall. If the full FDA agrees manufacturers will need time to make tens of millions of doses.

Comment: Agency officials had earlier said they hoped to move toward an annual vaccine against the coronavirus. But the discussion on June 15th did not involve any timetables as to how often adults should receive new vaccine, or which populations should be offered the latest vaccine. Novavax said its XBB.1.5 candidate prompts a functional immune response against XBB.1.5, XBB.1.16, and XBB.2.3 subvariants, suggesting that its adjuvanted protein-based vaccine may be useful against drifted subvariants. In the US, XBB.1.5 is most common, but the proportion is declining as newer XBB subvariant levels rise.

The FDA said in an addendum to its strain selection announcement that although the XBB sublineages continue to evolve, the spike protein sequences of XBB.1.5, XBB.1.16, and XBB.2.3 are similar, with few amino acid differences.

Those who remain vulnerable include the unvaccinated, people who are immunocompromised and those who have diabetes or chronic kidney, lung, cardiovascular or neurologic diseases. People 65 and older are also at risk, and that rises with age. See next update.

COVID-19 By the Numbers

As COVID-19 variant XBB.1.5 declines in prominence, the CDC began tracking new omicron variants June 23, including XBB.1.5 descendant EU.1.1.

In the U.S., 1.7 percent of Covid-19 infections are from EU.1.1, and in the Northwest region including Montana, Wyoming, Utah, Colorado and the Dakotas, the variant already accounts for 8.7 percent of cases. It is unclear which new variant will assume dominance as the CDC now lists 22 variants jockeying for control.

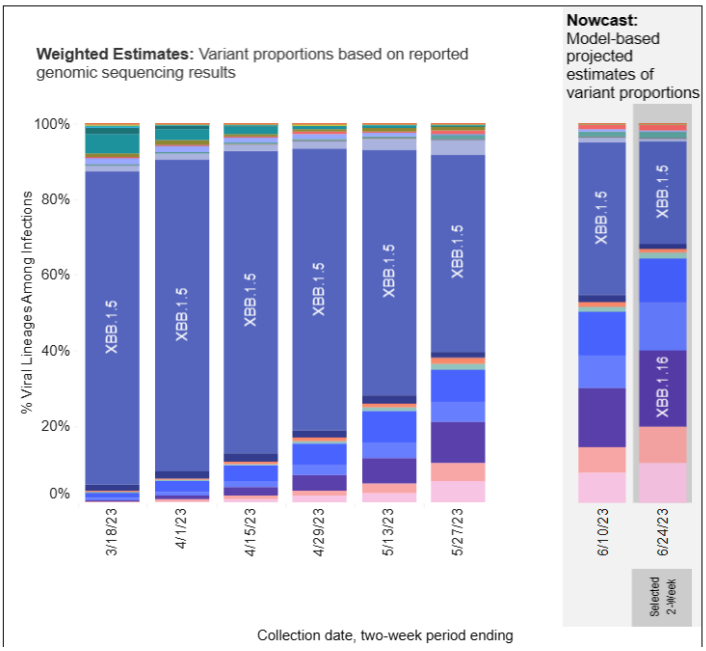
Here are two things to know about Covid-19:

1. More hospitalizations and deaths are from reinfections, according to the CDC. (see next review)

2. The FDA instructed vaccine makers to update their Covid-19 vaccine formulas to solely focus on the XBB variant, and Moderna filed its version for approval. As of June 24, XBB variants make up 96.1 percent of infections.

Weighted and Nowcast Estimates in United States for 2-Week Periods in 3/5/2023 – 6/24/2023

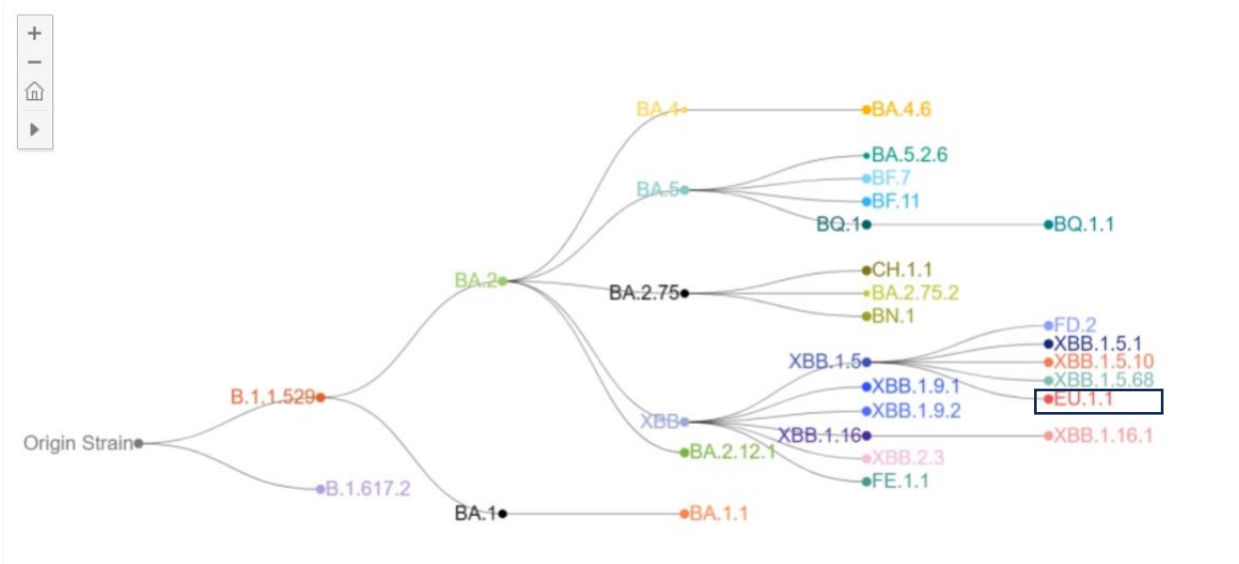
Hover over (or tap in mobile) any lineage of interest to see the amount of uncertainty in that lineage's estimate.



Nowcast Estimates in United States for 6/11/2023 – 6/24/2023

USA

WHO label	Lineage #	%Total	95%PI
Omicron	XBB.1.5	27.0%	23.8-30.5%
	XBB.1.16	19.9%	17.1-23.0%
	XBB.1.9.2	13.0%	7.9-20.4%
	XBB.1.9.1	11.4%	10.0-13.0%
	XBB.2.3	10.6%	7.7-14.4%
	XBB.1.16.1	9.5%	7.7-11.8%
	EU.1.1	1.7%	1.0-2.7%
	FE.1.1	1.6%	0.8-2.8%
	XBB.1.5.68	1.4%	0.8-2.3%
	XBB.1.5.1	1.2%	0.8-1.6%
	XBB.1.5.10	1.2%	0.7-1.9%
	XBB	0.9%	0.6-1.4%
	FD.2	0.4%	0.1-1.0%
	CH.1.1	0.2%	0.1-0.2%
	BA.2.12.1	0.1%	0.0-0.4%
	BQ.1.1	0.0%	0.0-0.1%
	BA.2	0.0%	0.0-0.0%
	BQ.1	0.0%	0.0-0.0%
	BN.1	0.0%	0.0-0.0%
	BA.2.75	0.0%	0.0-0.0%
	BA.5	0.0%	0.0-0.0%
	BF.7	0.0%	0.0-0.0%
Other	Other*	0.0%	0.0-0.1%



Weekly Update for the United States

Hospitalizations

Hospital Admissions (In Past Week)

6,373

Trend in Hospital Admissions

-5.3% in past week

May 19, 2023 Jun 17, 2023

Deaths

% Due to COVID-19 (In Past Week)

1.1%

Trend in % COVID-19 Deaths

No change in past week

May 6, 2023 Jun 24, 2023

Total Hospitalizations

6,189,621

Total Deaths

1,133,620

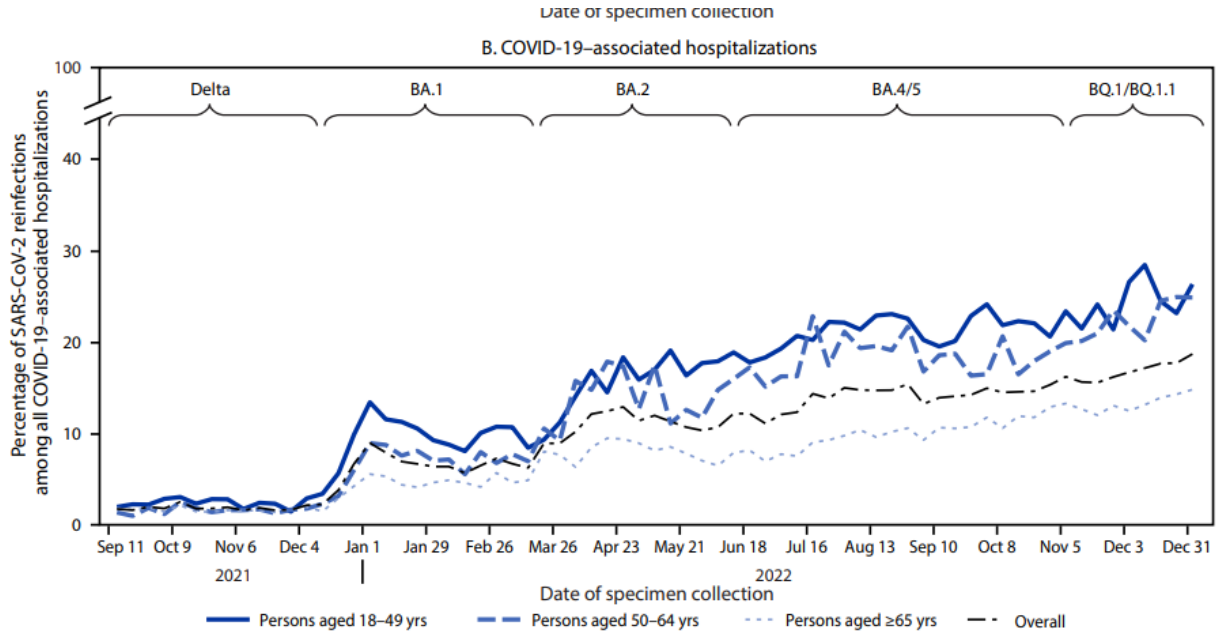
Comment: In its update on variant activity, the WHO said the proportion of the Omicron XBB.1.5 subvariant continues to decline steadily, dropping from 32.1% to 19.8% over the past month. Meanwhile, the XBB.1.16 subvariant for the first time topped the XBB.1.5 proportion, now accounting for 20.5% of sequences globally.

In the US hospitalizations continue to decline and deaths show no change. Tragically over 1.1 million have died of Covid-19 since the start of the pandemic.

Trends in Laboratory-Confirmed SARS-CoV-2 Reinfections and Associated Hospitalizations and Deaths Among Adults Aged ≥18 Years — 18 U.S. Jurisdictions, September 2021–December 2022 MMWR 2023; 72:683-689

Although reinfections with SARS-CoV-2 have occurred in the US with increasing frequency, US epidemiologic trends in reinfections and associated severe outcomes have not been fully characterized. Weekly counts of SARS-CoV-2 reinfections, total infections, and associated hospitalizations and deaths reported by 18 US jurisdictions during September 5, 2021–December 31, 2022, were analyzed overall, by age group, and by five periods of SARS-CoV-2 variant predominance (Delta and Omicron [BA.1, BA.2, BA.4/BA.5, and BQ.1/BQ.1.1]). Among reported reinfections, weekly trends in the median intervals between infections and frequencies of predominant variants during previous infections were calculated.

As a percentage of all infections, reinfections increased substantially from the Delta (2.7%) to the Omicron BQ.1/BQ.1.1 (28.8%) periods; during the same periods, increases in the percentages of reinfections among Covid-19–associated hospitalizations (from 1.9% [Delta] to 17.0% [Omicron BQ.1/BQ.1.1]) and deaths (from 1.2% [Delta] to 12.3% [Omicron BQ.1/BQ.1.1]) were also substantial. Percentages of all Covid-19 cases, hospitalizations, and deaths that were reinfections were consistently higher across variant periods among adults aged 18–49 years compared with those among adults aged ≥50 years. The median interval between infections ranged from 269 to 411 days by week, with a steep decline at the start of the BA.4/BA.5 period, when >50% of reinfections occurred among persons previously infected during the Alpha variant period or later.



Analysis of surveillance data reported by 18 jurisdictions shows that cases of SARS-CoV-2 reinfection and associated hospitalizations and deaths increased in relative frequency as new Omicron lineages emerged with enhanced transmissibility and/or immune escape. Surprisingly higher percentages of reinfections among Covid-19 cases and associated hospitalizations and deaths were observed among younger adults compared with older adults, particularly in late 2022. The higher percentages in younger age groups might be attributable to multiple factors,

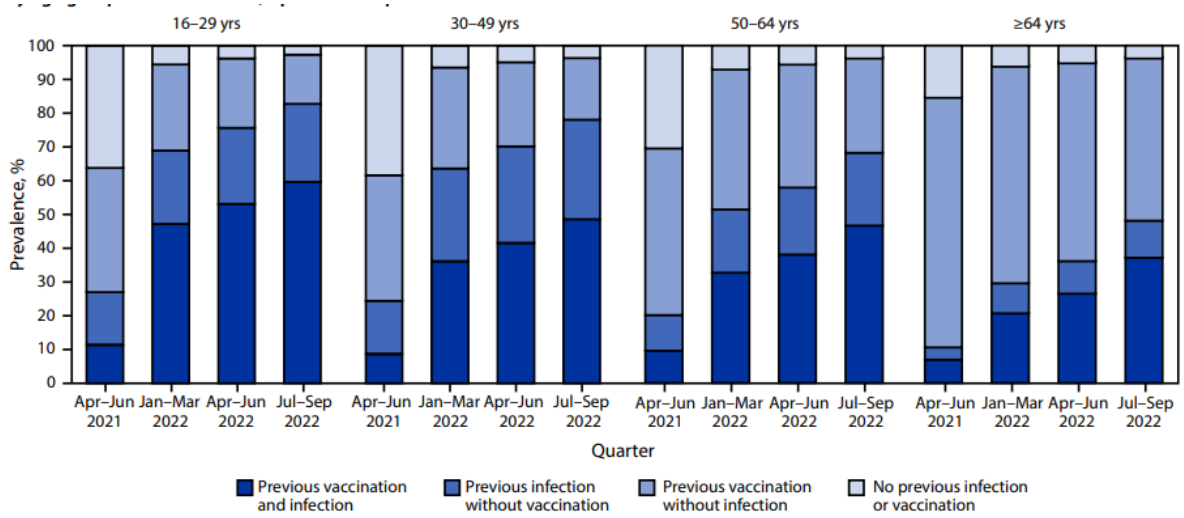
including higher cumulative incidence of first infections, later eligibility for vaccination, lower vaccination coverage, increased exposure risk, and a possible survival bias because of less severe initial infections. Reinfections occurred at lower frequencies among persons who were hospitalized or died compared with cases, consistent with evidence that previous infection induced immunity provides better protection against severe outcomes than against subsequent infections [Lancet Infect Dis 2023;23:556–67]. The risk of severe outcomes from reinfection can be reduced through vaccination, although vaccine effectiveness was not evaluated in this analysis.

Comment: Cases and severe outcomes associated with SARS-CoV-2 reinfection have increased across the United States since September 2021. To prevent severe Covid-19 outcomes, including those following reinfection, CDC recommends staying up to date with Covid-19 vaccination and receiving timely antiviral treatments, if eligible. Trends in reinfections before September 1, 2021, were not determined because of the lack of a nationally standardized surveillance definition for reinfection before that time. The use of the 90-day definition for reinfections based on national guidance excludes reinfections occurring ≤90 days, which would need to be confirmed using genomic sequencing to rule out prolonged viral shedding. Lastly, the analysis of epidemiologic changes in reinfection by period of SARS-CoV-2 variant predominance could not be adjusted for important confounders, including changes in immunity, behavior, and the population at risk over time.

Estimates of SARS-CoV-2 Seroprevalence and Incidence of Primary SARS-CoV-2 Infections Among Blood Donors, by COVID-19 Vaccination Status — United States, April 2021–September 2022 MMWR 2023; 72;601–605

The CDC investigators studied SARS-CoV-2 antibodies from blood samples from 72,748 donors aged 16 and older. From April to June 2021, an estimated 68.4% of blood donors had SARS-CoV-2 antibodies from previous infection or vaccination, including 47.5% from vaccination alone, 12.0% from infection alone, and 8.9% from both. From January to March 2022, 93.5% of donors had antibodies from previous infection or vaccination, including 39.0% from vaccination alone, 20.5% from infection alone, and 34.1% from both. During July to September 2022, 96.4% of participants had antibodies from previous infection or vaccination, including 26.1% from vaccination alone, 22.6% from infection alone, and 47.7% from both. From July to September 2022, the prevalence of infection-induced immunity was 85.7% among unvaccinated participants and 64.3% among their vaccinated peers. The incidence of first Covid-19 infections was higher among younger than older participants.

From July to September 2022, donors aged 65 years and older had the lowest prevalence of hybrid immunity (36.9%), and those aged 16 to 29 years had the highest (59.6%). From January through June 2022, Covid-19 incidence among unvaccinated participants was 21.7%, compared with 13.3% among the vaccinated. And from April to September 2022, the incidence among unvaccinated donors was 28.3%, compared with 22.9% among their vaccinated peers.



Comment: Low prevalence of infection-induced and hybrid immunity among older adults, who are at increased risk for severe disease if infected, reflects the success of public health infection prevention efforts while also highlighting the importance of this group staying up to date with recommended Covid-19 vaccination. Immunity wanes over time, but time since vaccination or infection was not included in the analysis. Second, vaccination status was self-reported, potentially leading to misclassification. Lastly, although Covid-19 booster vaccine doses and reinfections can strengthen immunity, this analysis did not account for these effects because blood donor vaccination history did not include the number of doses received, and data on reinfections were not captured.

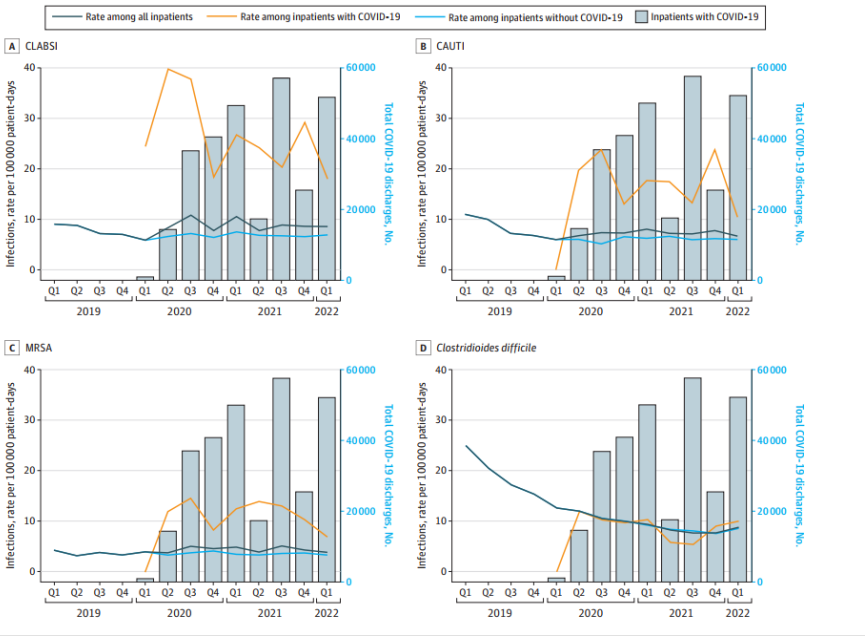
Health Care–Associated Infections Among Hospitalized Patients With COVID-19, March 2020-March 2022 JAMA Netw Open 2023;6(4): e238059.

doi:10.1001/jamanetworkopen.2023.8059

This is a cross-sectional retrospective analysis of inpatients discharged both with and without laboratory-confirmed Covid-19 infection. Data were obtained between January 1, 2019, and March 31, 2022, from community hospitals affiliated with a large health care system in the US[HCA]. The main outcome was the incidence of central line–associated bloodstream infection (CLABSI), catheter-associated urinary tract infection (CAUTI), MRSA bacteremia, and C difficile infections as reported to the National Healthcare Safety Network (NHSN). [HAIs]

Among nearly 5 million hospitalizations in 182 hospitals between 2020 and 2022, the occurrence of HAIs was high among the 313 200 Covid-19 inpatients (median [SD] age, 57 [27.3] years; 56.0% women). Incidence per 100,000 patient-days showed higher HAIs among those with Covid-19 compared with those without. For CLABSI, the incidence for the full 9 quarters of the study was nearly 4-fold higher among the COVID-19 population than the non–Covid-19 population (25.4 vs 6.9). For CAUTI, the incidence in the Covid-19 population was 2.7-fold higher in the Covid-19 population (16.5 vs 6.1), and for MRSA, 3.0-fold higher (11.2 vs 3.7). Quarterly trends were compared with the same quarter in 2019. The greatest increase in the incidence of HAI in comparison with the same quarter in 2019 for the entire population occurred in quarter 3 of 2020 for CLABSI (11.0 vs 7.3), quarter 4 of 2021 for CAUTI (7.8 vs 6.8), and

quarter 3 of 2021 for MRSA (5.2 vs 3.9). When limited to the non–Covid-19 population, the increase in CLABSI incidence vs the 2019 incidence was eliminated, and the quarterly rates of MRSA and CAUTI were lower vs the prepandemic 2019 comparator quarter.



Comment: The analysis in this paper is consistent with previous reports that the incidence of HAIs increased during the Covid-19 pandemic. Their analysis demonstrated that this increase in the overall infection rate appeared to be mostly due to the occurrence of HAIs in the Covid-19 population. Patients without Covid-19 had rates of HAIs that would be expected based on the incidence observed before the pandemic. The differences in HAI rates between the Covid-19 and non–Covid-19 populations for CLABSI, MRSA, and CAUTI were demonstrated every year since the beginning of the pandemic. In a prior study of HAIs during the Covid-19 pandemic in facilities within the HCA system also demonstrated that the relative rates of CLABSI, CAUTI, and MRSA bacteremia were also associated with increasing monthly Covid-19 discharges. Clusters of hospital-onset pathogens also increased during Covid-19 surges, suggesting possible increased transmission. [Clin Infect Dis. 2022; 74:1748-1754] The previous study did not distinguish patients with or without Covid-19. Previous explanations have suggested an association between the increase in HAIs during the Covid-19 pandemic and the enormous stress on hospital personnel during this time, particularly with nursing and infection prevention personnel, and the ability to maintain general infection prevention practices, such as hand hygiene, dressing care, and appropriate use of PPE as well as adequate staffing. The investigators in this study suggest that HAI prevention practices were maintained, at least for the population without Covid-19, but do not provide actual compliance data, staffing, and/or supplies of PPE. Their analysis of patients with Covid-19 showed they had a longer length of stay, which increases the risk of developing and detecting HAI. However, they adjusted for patient-days as the denominator in the analysis which may adjust for this difference in length of stay. Second, HCWs assigned to Covid-19 units may have experienced reduced resources or altered workflows. A previous analysis suggested that the reduction in elective admissions during the Covid-19 pandemic biased the overall population toward patients with conditions of higher acuity. [Emerg Med J. 2021; 38:366-370] In this study, the difference in HAI incidence between those with and without Covid-19, after adjusting for some confounders, suggests that the disease or its treatment preferentially increases the vulnerability of the Covid-19 population

only to HAIs. A propensity matched risk adjustment analysis with more variables would be more robust. They do admit the measure used for comparison is an unadjusted incidence rate and does not address potential factors such as variation in patient acuity, patient conditions, or patient demographic characteristics.

They only report on 4 HAIs and did not report on VAE/VAP which has been shown to significantly increase during Covid-19 in large part due to duration of mechanical ventilation and ICU length of stay. They also did not assess other measures of infection performance, such as the occurrence of clusters or trends in antimicrobial resistance, some of which were part of their previous publication. Nevertheless, their findings suggest that, despite the unprecedented challenges that hospitals experienced during the Covid-19 pandemic, key safety processes appeared to have been maintained, and HAI increases may be associated with the unique risks and increased needs of patients with Covid-19. There are at least 2 prior publications that support the risk is primarily with Covid-19 patients for HO-BSIs.[Intensive Care Med 2021; 47:180–187 ; Am J of Infect Cont 2022; 50: 245-249] With the publication of the "Compendium of Strategies to Prevent Healthcare-Associated Infections in Acute Care Hospitals: 2022 Updates" let us get back to basics, perform a gap analysis, and hard wire best practice interventions to assure the safety of our patients.

Smart Thermometer–Based Participatory Surveillance to Discern the Role of Children in Household Viral Transmission During the COVID-19 Pandemic JAMA Netw Open 2023;6:e2316190.

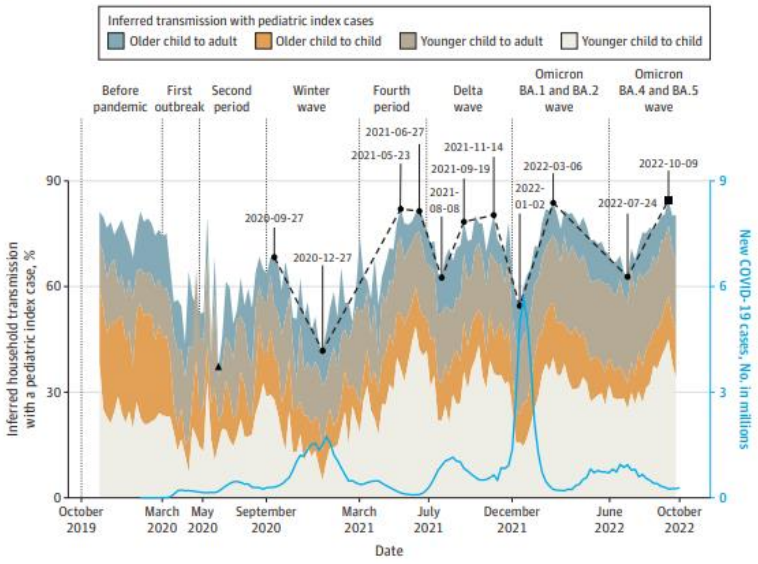
doi:10.1001/jamanetworkopen.2023.16190

This cohort study of a voluntary US cohort tracked data from participatory surveillance using commercially available thermometers with a companion smartphone app from October 2019 to October 2022. Eligible participants were individuals with temperature measurements in households with multiple members between October 2019 and October 2022 who opted into data sharing. Main outcome was the proportion of household transmissions with a pediatric index case and changes in transmissions during school breaks. This was assessed using app and thermometer data. Investigators gave smartphone-connected thermometers to 848,591 households with 1,391,095 members, who took 23,153,925 temperature readings from October 2019 to October 2022. Fevers were a proxy for infection.

A total of 862,577 individuals from 320,073 households with multiple participants (462,000 female [53.6%] and 463,368 adults [53.7%]) were included. The number of febrile episodes forecast new Covid-19 cases. Within-household transmission was inferred in 54,506 (15.4%) febrile episodes and increased from the fourth pandemic period, March to July 2021 (3263 of 32 294 [10.1%]) to the Omicron BA.1/BA.2 wave (16,516 of 94,316 [17.5%]; P < .001). Among 38 787 transmissions in 166,170 households with adults and children, a median (IQR) 70.4% (61.4%-77.6%) had a pediatric index case; proportions fluctuated weekly from 36.9% to 84.6%. A pediatric index case was 0.6 to 0.8 times less frequent during typical school breaks. The winter break decrease was from 68.4% (95% CI, 57.1%-77.8%) to 41.7% (95% CI, 34.3%-49.5%) at the end of 2020 (P < .001). At the beginning of 2022, it dropped from 80.3% (95% CI, 75.1%-84.6%) to 54.5% (95% CI, 51.3%- 57.7%) (P < .001). During summer breaks, rates dropped from 81.4% (95% CI, 74.0%-87.1%) to 62.5% (95% CI, 56.3%-68.3%) by August 2021

(P = .02) and from 83.8% (95% CI, 79.2%-87.5) to 62.8% (95% CI, 57.1%-68.1%) by July 2022 (P < .001). These patterns persisted over 2 school years.

Figure 3. Patterns of Inferred Household Transmissions With a Pediatric Index Case



Lowest and highest percentages during the pandemic are highlighted with black triangle and square points, respectively. Vertical lines define the beginning of each pandemic period. The blue line is the number of new US COVID-19 cases. The points with dates are relatively high and low levels of pediatric transmissions and the dashed line is the trend with these points.

Comment: These findings suggest that children play an important role in within-household viral transmissions. Consistent with demonstrated patterns among other viral illnesses, pediatric-driven transmission was higher when school was in session. During the Covid-19 pandemic, inferred household transmissions increased from the fourth pandemic wave (March 7 to July 14, 2021) to the Omicron BA.1/BA.2 wave. More than 70% of household transmissions in households with adults and children were from a pediatric index case, but this percentage fluctuated weekly. Once US schools reopened in fall 2020 , children contributed more to inferred within household transmission when they were in school, and less during summer and winter breaks, a pattern consistent for 2 consecutive school years.

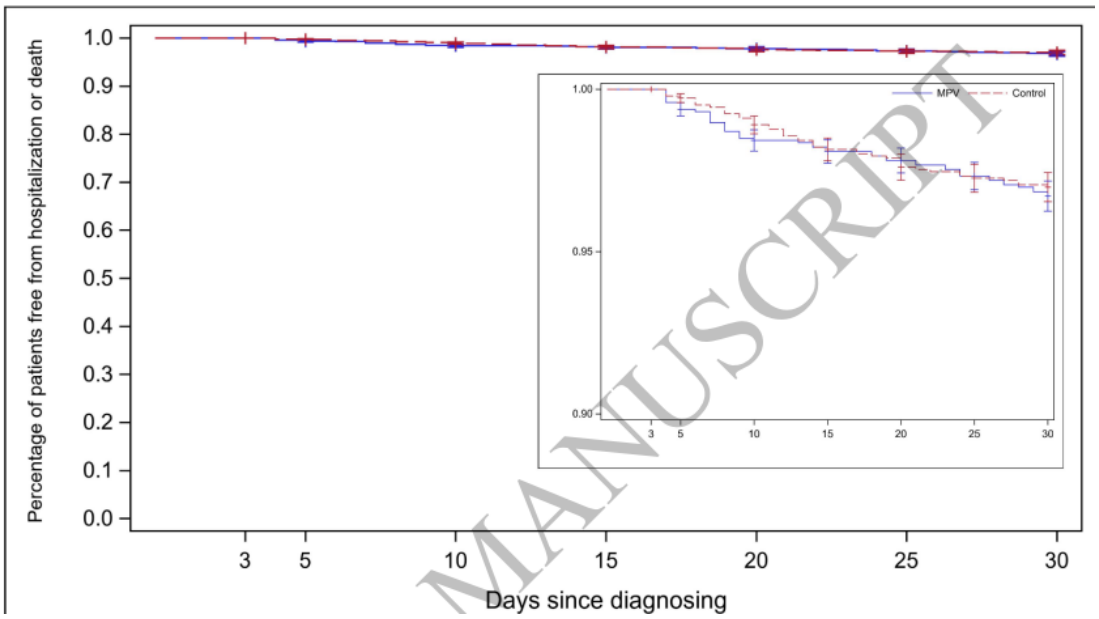
The study design did not permit laboratory or home testing to confirm viral etiologies. Fever as a syndrome can have many etiologies beyond Covid-19. Although confirmatory tests are needed to definitively identify the origin of fever, this study exploited a unique period when the incidence of generally prevalent, non–Covid-19 respiratory viruses declined, including influenza and RSV. Although non–SARS-CoV-2 viruses were circulating, they assumed their prevalence was comparatively low during the study period, with the number of Covid-19 cases during the study period being 10 to over 100 times higher than that of influenza and RSV until August 2022. Parainfluenza and human metapneumovirus were rare. Among patients with symptoms hospitalized or presenting to the ED, the incidence of rhinoviruses and enteroviruses dropped at the beginning of the pandemic until October 2020, but rose between then and February 2021. However, in a community-based study perhaps more reflective of the epidemiology of our home-based cohort, SARS-CoV-2 was more common than rhinovirus from December 2021 to July 2022. [JAMA Netw Open. 2022;5(12): e2245861]. Covid-19 was one of the highest reasons for pediatric ED visits until January 2022, and compared with 2019, visits for non–Covid-19 respiratory illness declined in 2020 and 2021. Vaccinated individuals may experience mild symptoms, [JAMA Netw Open. 2022;5:e2235844] so it is possible that the contribution of adults was underestimated due to higher vaccination coverage.

Molnupiravir Use and 30-Day Hospitalizations or Death in Previously Uninfected Non-hospitalized High-risk Population with COVID-19 J Infect Dis published online June 1, 2023

DOI: 10.1093/infdis/jiad195

The investigators used a matched cohort study design to determine the rate of hospitalization or death within 30 days of COVID-19 diagnosis among MPV treated and untreated controls. Participants were non-hospitalized, previously uninfected Veterans with a first confirmed SARS-CoV-2 infection between January 1 and August 31, 2022, who were prescribed MPV within 3 days of COVID-19 diagnosis, and matched individuals who were not prescribed molnupiravir (MPV).

Among 1,459 matched pairs, the incidence of hospitalization/death was not different among MPV treated vs. untreated controls (48 vs. 44 cases; ARD [95% CI] 0.27 [-0.94,1.49]). No benefit was observed among those >60 or ≤ 60 years old (ARD 0.27 [-1.25,1.79] vs. -0.29 [-1.22,1.80]), those with specific comorbidities, or by vaccination status. A significant benefit was observed in asymptomatic but not in symptomatic persons (ARD -2.80 [-4.74,-0.87] vs. 1.12 [-0.31,2.55]). Kaplan-Meier curves did not show a difference in proportion of persons who were hospitalized or died among MPV treated compared with untreated controls.



Comments: Molnupiravir (MPV) and nirmatrelvir/ritonavir are oral antiviral agents against Covid-19 which have demonstrated efficacy in clinical trials in preventing progression to severe disease or death among those with early and mild disease who are at risk of progression to severe disease. Previous studies of MPV have shown mixed results. In this large, real-world study, the investigators did not observe a clear overall benefit except in a sub-group of individuals who were asymptomatic at presentation. The result of this trial adds to the growing evidence that MPV may be effective only in asymptomatic individuals or mild disease and when given early in the course of illness. Prescribing MPV only to those who may expect a benefit can

prevent untoward adverse events and lower the costs of therapy. The IDSA Guidelines recommend MPV in ambulatory patients (≥18 years) with mild-to-moderate Covid-19 at high risk for progression to severe disease who have no other treatment options *(*nirmatrelvir/ritonavir, or three-day treatment with remdesivir*).* The IDSA guideline panel suggests molnupiravir initiated within five days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence). While Veterans are an optimal population for the study question due to the high risk of disease progression, they may not be representative of the general population. Veterans are older and predominantly male and have a higher burden of comorbidities than the general population. See next review.

Effectiveness of COVID-19 Treatment With Nirmatrelvir–Ritonavir or Molnupiravir Among U.S. Veterans: Target Trial Emulation Studies With One-Month and Six-Month Outcome

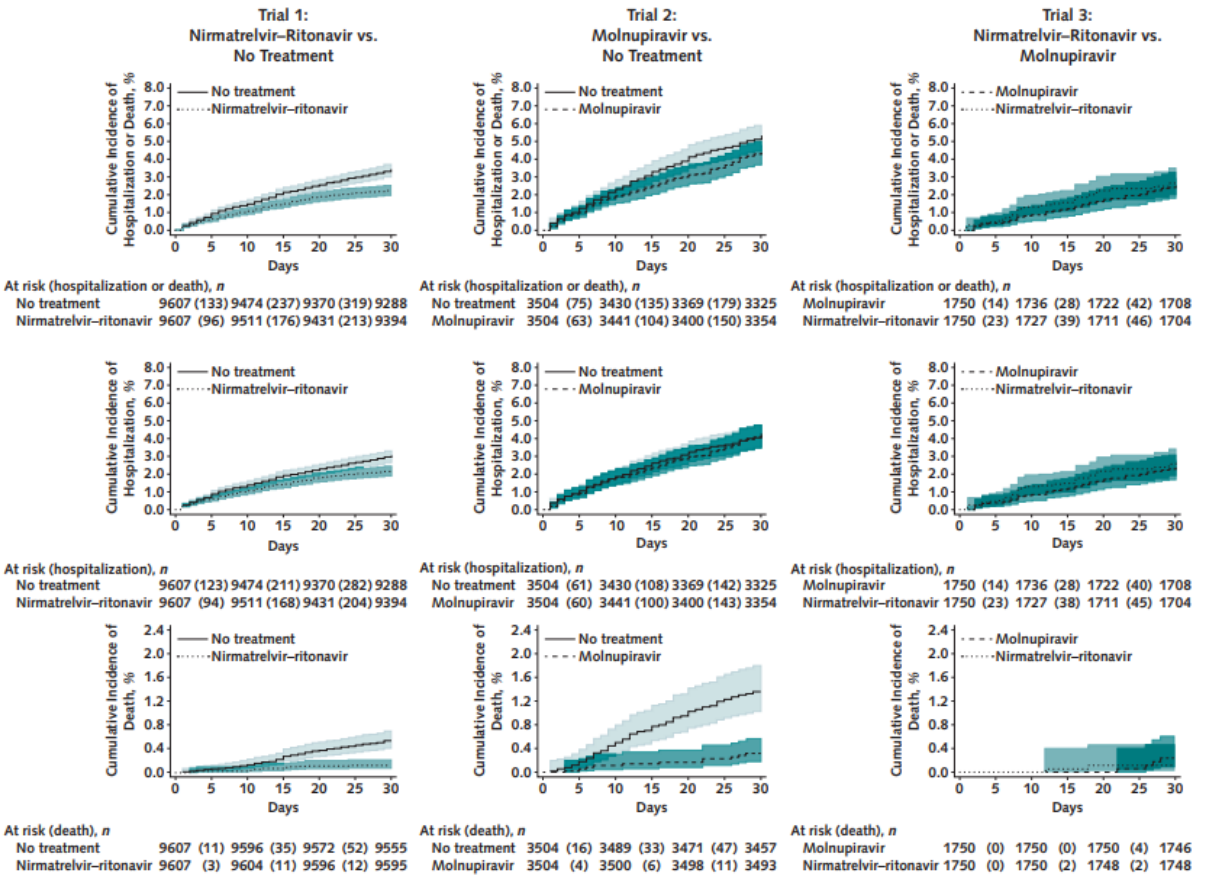
Ann Intern Med published online June 6, 2023

doi:10.7326/M22-3565

The investigators designed this retrospective cohort study to emulate 3 target randomized controlled trials of Covid-19 antivirals among symptomatic, nonhospitalized adult veterans enrolled in the VHA who had a first positive SARS-CoV-2 test result from January 1 through July 31, 2022 and were at high risk for progression to severe Covid-19. The target trials involved nirmatrelvir–ritonavir versus no SARS-CoV-2 antiviral or monoclonal antibody treatment (trial 1), molnupiravir versus no treatment (trial 2), and nirmatrelvir–ritonavir versus molnupiravir (trial 3). Follow-up extended through January 31, 2023, to allow ascertainment of 30-day and 6-month posttreatment outcome. The primary outcome was the incidence of any hospitalization or all-cause mortality at 30 days and from 31 to 180 days. They also examined ICU admissions and mechanical ventilation.

As expected, eighty-seven percent of participants were male; the median age was 66 years, and 18% were unvaccinated. Compared with matched untreated control participants, those treated with nirmatrelvir–ritonavir (n= 9607) had lower 30-day risk for hospitalization (22.07 vs. 30.32 per 1000 participants; risk difference [RD], -8.25 [95% CI, -12.27 to -4.23] per 1000 participants) and death (1.25 vs. 5.47 per 1000 participants; RD, -4.22 [CI, -5.45 to -3.00] per 1000 participants). Among persons alive at day 31, reductions were seen in 31- to 180-day incidence of death (hazard ratio, 0.66 [CI, 0.49 to 0.89]) but not hospitalization (subhazard ratio, 0.90 [CI, 0.79 to 1.02]). Molnupiravir-treated participants (n= 3504) had lower 30-day and 31- to 180-day risks for death (3.14 vs. 13.56 per 1000 participants at 30 days; RD, -10.42 [CI, -13.49 to -7.35] per 1000 participants; hazard ratio at 31 to 180 days, 0.67 [CI, 0.48 to 0.95]) but not hospitalization. A difference in 30-day or 31- to 180-day risk for hospitalization or death was not observed between matched nirmatrelvir- or molnupiravir-treated participants. Reduction associated with molnupiravir was limited to all-cause mortality.

Figure 2. Cumulative 30-day incidence of hospitalization or death among outpatient veterans testing positive for SARS-CoV-2, by study group.



Comment: In 3 target trial emulation studies performed among outpatient U.S. veterans testing positive for SARS-CoV-2 during January through July 2022, nirmatrelvir–ritonavir was effective at preventing 30-day all-cause mortality, hospitalization, ICU admission, and mechanical ventilation, whereas risk reduction associated with molnupiravir was limited to all-cause mortality. Nirmatrelvir–ritonavir and molnupiravir were each associated with a 77% lower risk for death, and nirmatrelvir–ritonavir was also associated with a 27% lower risk for hospitalization. With both antivirals, additional mortality benefit was observed from days 31 to 180, although absolute reductions were small relative to the first 30 days. The date of Covid-19 symptom onset for most veterans was unknown. In addition, this study was not designed to capture prior infections, which confer background immunity and may affect measured real-world effectiveness of antiviral treatments. Lastly, capture of outpatient Covid-19 treatments and outcomes, particularly hospitalizations, was incomplete.

Mother-to-child transmission of SARS-CoV-2 infection in high-income countries: a systematic review and meta-analysis of prospective observational studies Sc Reports 2023; 13:8813

doi.org/10.1038/s41598-023-36097-1

Overall, 26 studies were included, reporting data from 2,653 mothers with SARS-CoV-2 and 2,677 neonates. Among the infected mothers, 126 (4.7%) needed oxygen or ventilatory support. Among the 2,677 neonates, 100 were SARS-CoV-2-positive. Only 5 (5%) of the neonates who tested positive for SARS-CoV-2 needed oxygen supplementation and/or ventilatory support. All studies included infants born through vaginal and caesarean sections.

The proportion meta-analysis pointed out an overall estimate of SARS-CoV-2 infection among infants born to infected mothers of 2.3% (95% confidence interval [CI], 1.4% to 3.2%). The I^2-test was 62.4%, demonstrating a moderate heterogeneity. The sensitivity analysis performed excluding 3 studies with extreme results (pooled prevalence >10%) showed a slight reduction of the overall pooled prevalence (1.4%; 95% CI, 0.9% to 1.8%; I^2-test 0%), without a significant statistical difference compared with the main meta-analysis, considering the overlap of 95% confidence interval values among the 2 analyses.

Meanwhile, the sub-analysis investigating the relationship between rooming-in practice and the proportion of infected neonates showed similar data pooling from studies with (1.4%; 95% CI, 0.8% to 2.0%; I^2-test 10.5%) and without (1.3%; 95% CI, 0.0% to 2.7%, I^2-test 0%) rooming-in. Further, the proportion meta-analysis pooling data from studies applying at least 2 preventive measures showed an infection estimate of 1.0% (95% CI, 0.4% to 1.7%; I^2-test 0%), whereas data from studies with either 1 or no preventive measure provided an estimate of 3.2% (95% CI, 1.2% to 5.2%; I^2-test 82%). Moreover, when analyzing only data from studies with rooming-in, if at least 2 preventive measures were adopted, the infection rate was 1.0% (95% CI, 0.3% to 1.7%; I^2-test 0%), while in the group with rooming-in and only 1 or no preventive measures the infection rate was 1.9% (95% CI, 0.8% to 3.0%; I^2-test 31%).

Comment: The results of this study show a low rate of perinatal infection and support the rooming-in and confirm the effectiveness of preventive measures in reducing the risk of mother-to-child viral transmission. [many scientific societies and hospitals have recommended that SARS-CoV-2 positive mothers adopt practices of distancing themselves from their babies and use personal protective equipment, such as masks and gloves during rooming-in or breastfeeding] WHO, have issued guidelines that did not recommend the precautionary separation of the infected mother from her child. These international policies had significant relevance in protecting the bonding of the dyad and the beneficial effects of breastfeeding even at a time when the lack of knowledge had led some government institutions in some individual countries to promote mother-baby separation. The results cannot be extended to low- and middle-income countries. Finally, it was not possible to accurately assess the risk of infection associated with newer SARS-CoV-2 variants.

Safety of COVID-19 mRNA Vaccination Among Young Children in the Vaccine Safety Datalink Pediatrics e2023061894.

doi.org/10.1542/peds.2023-061894

The authors previously assessed safety of monovalent messenger RNA (mRNA) Covid-19 vaccines using weekly surveillance monitoring known as rapid cycle analysis (RCA) among individuals aged 5 years and older, identifying an increased risk for myocarditis and pericarditis in younger males, particularly following dose 2 of the primary series.[Ann Intern Med 2022; 175:1169 – 1771] Information regarding Covid-19 vaccine safety among children under age 5 is limited. Here they report RCA safety surveillance of mRNA Covid-19 vaccines administered in this youngest age group within the Vaccine Safety Datalink (VSD).

VSD is a collaboration between the CDC and 8 data-contributing health systems (Kaiser Permanente: Colorado, Northern California, Northwest, Southern California, and Washington; Marshfield Clinic; Health Partners; and Denver Health), with approximately 550 000 children under age 5 years. VSD sites maintain comprehensive electronic medical records for their members, including Covid-19 vaccination data from retail pharmacies and state immunization registries. They compared outcomes after any mRNA vaccine dose among primary series vaccinees in a risk interval (1–21 days postvaccination) with outcomes among primary series vaccinated comparators who were concurrently (on the same calendar day), in the comparison interval (22–42 days postvaccination). They estimated adjusted rate ratios (RRs) and corresponding 95% confidence intervals (CIs) using Poisson regression, adjusting for age, race, sex, site, and calendar day. They reviewed medical records of all cases of myocarditis and pericarditis, anaphylaxis, and other selected outcomes.

From June 18, 2022, to March 18, 2023, 135,005 doses of Pfizer-BioNTech Covid-19 vaccine were given to children aged 6 months to 4 years, and 112,006 doses of Moderna Covid-19 vaccine were given to children aged 6 months to 5 years in the VSD population. In this interim analysis of children aged 5 years and younger, safety surveillance of more than 245,000 Covid-19 mRNA vaccine doses over 9 months did not detect a safety signal for any outcome during the 21 days after vaccination. Importantly, no cases of myocarditis or pericarditis occurred after vaccination.

Comment: Limitations include reduced statistical power of early analyses, particularly for rare outcomes. Also, vaccine uptake in the evaluated age group was low and continues to be low; only 24.7% of the eligible VSD population received at least 1 vaccine dose (ranging from 6.6% to 30.2% across VSD sites), although uptake was higher than that reported for this age group in other US populations (~5.9% to 8.8%). Additionally, RCA surveillance focused on prespecified medically attended, serious safety outcomes and did not include all potential safety concerns. Nonetheless, this is the first analysis that looked for serious side effects from the mRNA vaccines in children aged 4 years and younger, and they identified no safety concerns. There are still a large proportion of children in this age group who remain unvaccinated. I hope the results of this analysis provides additional support that mRNA vaccines are generally safe in children ≤4 years of age.

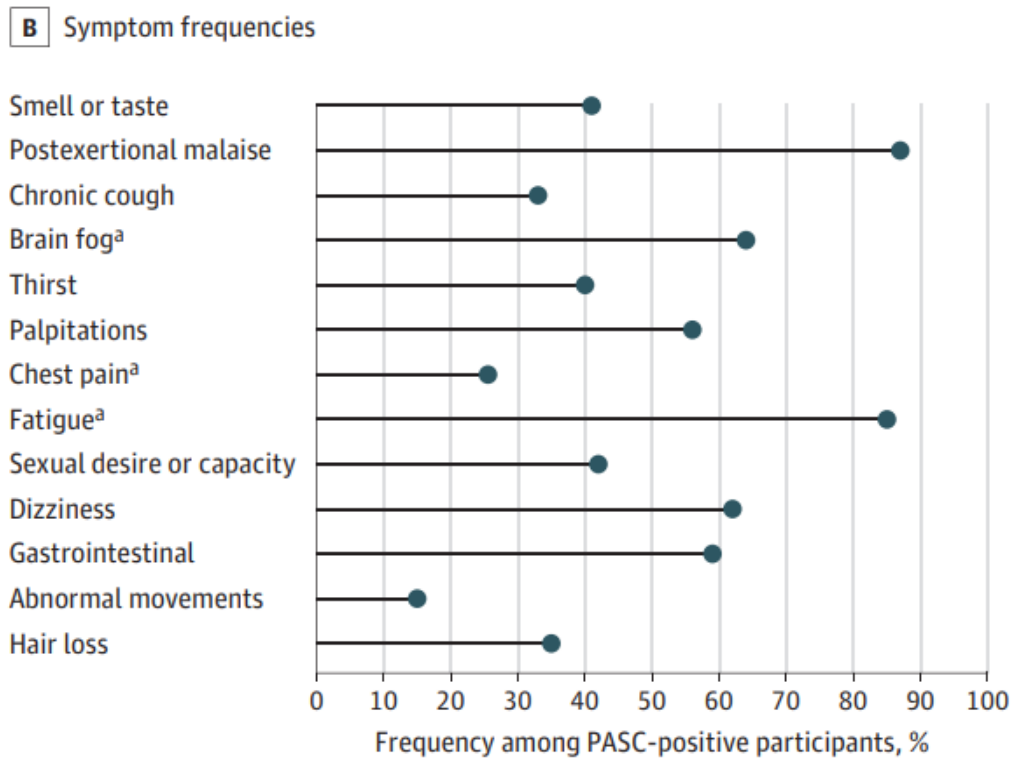
Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection
JAMA published online May 25, 2023

doi:10.1001/jama.2023.8823

In 2021, NIH launched the Researching Covid to Enhance Recovery (RECOVER) initiative. RECOVER aims to understand why some people develop long-term symptoms following Covid-19. The investigators are also testing ways to detect, treat, and prevent the condition. This study captured post-acute sequelae of SARS-CoV-2 infection (PASC)-specific self-reported symptoms based on standardized questionnaires developed with input from patient representatives. This report is an adequately powered, prospective study of PASC based on participant-reported symptoms that included both infected and uninfected individuals over the course of the pandemic. Notably, unlike prior reports, the paradigm presented here does not rely on predefined clinical symptoms; instead, a definition of PASC as a new condition specific to SARS-CoV-2 infection is proposed.

In this new study, RECOVER researchers collected reports of symptoms from about 8,600 people who had been infected with Covid-19 and about 1,100 uninfected people. The researchers focused on symptoms that were reported by at least 2.5% of the study volunteers. The adult cohort was a prospective longitudinal cohort study, looking at 37 symptoms across multiple pathophysiological domains were identified as present more often in SARS-CoV-2–infected participants at 6 months or more after infection compared with uninfected participants. A preliminary rule for identifying PASC was derived based on a composite symptom score.

The team found that 37 symptoms were substantially more likely to occur in people who had recovered from Covid-19. Of these, 12 distinguished those with and without long Covid. The most common of these were fatigue, post-exertional malaise (the worsening of symptoms after physical or mental activity), and brain fog. Others were dizziness, gut symptoms, heart palpitations, sexual problems, and loss of or change in smell or taste. The final common symptoms were thirst, a chronic cough, chest pain, and abnormal movements such as muscle twitching or jerking. By assigning weights to each of these 12 symptoms, the researchers developed a score that could best separate people with long Covid from those without it. Using this score, they found that people who were unvaccinated or who had Covid-19 before the Omicron strain emerged in 2021 were more likely to have long Covid and more severe cases of long Covid. Overall, 23% of participants who had been infected with the virus were scored as having symptoms of long Covid, compared to less than 4% of uninfected participants. Out of around 2,200 people infected when the Omicron variants predominated, about 10% experienced long-term symptoms six months after infection. Reinfections were also linked to higher long Covid frequency and severity compared to people who only had Covid-19 once.



Comment: Given the heterogeneity of PASC symptoms, determining whether PASC represents one unified condition or reflects a group of unique phenotypes is important. Biological samples from these patients may enable the development of biomarkers of PASC and reveal insights into the mechanistic underpinnings of PASC that may provide choices of therapeutic interventions. The PASC score does provide a working definition of PASC further refinement and validation. Uninfected participants may have had prior asymptomatic SARS-CoV-2 infections not detected due to variations in antibody production and persistence, which may impact the discriminant characteristics of this PASC score threshold. Future analyses must consider the relationships among age, sex, race and ethnicity, social determinants of health, vaccination status after index date, comorbidities, and pregnancy status during infection on the risk of PASC and the distribution of PASC subgroups. PASC symptoms for Covid-19 should be applied for other respiratory viruses.

Increased Hospitalizations Involving Fungal Infections during COVID-19 Pandemic, United States, January 2020–December 2021 Emerg Infect Dis. Published online June 6, 2023

DOI: 10.3201/eid2907.221771

The investigators used the Premier Healthcare Database, Special Covid-19 Release (PHD-SR), a US, hospital-based, all-payer database. The database contains deidentified records from >1,000 nongovernment, community, and teaching hospitals that contributed inpatient data during the analytic period. They used diagnosis codes from the ICD-10-CM, listed for each

hospitalization and identified hospitalizations involving fungal infections (fungal hospitalizations) and Covid-19 (Covid-19 hospitalizations) during January 1, 2019–December 31, 2021. They defined Covid-19–associated fungal hospitalizations as those in which both a Covid-19 and fungal infection diagnosis were listed during the same hospitalization. They estimated annual hospitalization rates (per 10,000 population) by fungal infection type and calculated average annual percentage change during 2019–2021. For Covid-19–associated fungal hospitalizations (2020–2021 only), they calculated hospitalization rates per 10,000 COVID-19 hospitalizations. They stratified 2020–2021 fungal hospitalizations by Covid-19 association and fungal infection type and compared patient demographics, lengths of hospital stays, ICU admissions, invasive mechanical ventilation receipt, and in-hospital deaths. They assessed annual trends in fungal hospitalizations by using Cochran-Armitage tests and compared fungal hospitalizations according to Covid-19 status by using χ^2 tests.

During 2019–2021, a total of 59,212 fungal hospitalizations were identified. Rates of fungal hospitalizations (per 10,000 hospitalizations) increased from 22.3 in 2019 to 25.0 in 2020 and 26.8 in 2021 ($p<0.01$), representing an average annual percentage change of 8.5%. Average annual rates of hospitalization significantly increased for each fungal infection, except for those caused by *Pneumocystis* spp., *Cryptococcus* spp., and other specified fungi. Annual rates increased significantly for Covid-19–associated fungal hospitalizations involving blastomycosis (0.2 to 0.5 [65.6% change]; $p<0.01$), aspergillosis (7.9 to 18.9 [58.2% change]; $p<0.01$), mucormycosis (0.7 to 1.1 [39.8% change]; $p = 0.02$), histoplasmosis (1.1 to 1.6 [32.1% change]; $p = 0.03$), pneumocystosis (1.9 to 2.6 [25.4% change]; $p = 0.03$), and other specified mycoses (1.7 to 2.5 [32.9% change]; $p<0.01$). Compared with non–Covid-19–associated fungal hospitalizations, Covid-19–associated fungal hospitalizations more frequently involved aspergillosis (27.8% vs. 16.9%; $p<0.01$), mucormycosis (1.8% vs. 1.4%; $p = 0.03$), and unspecified mycoses (24.3% vs. 18.5%; $p<0.01$) and, in general, less frequently involved other fungal infection types. Longer hospital stays, higher ICU admission rates, more mechanical ventilation, and more deaths were generally observed for hospitalizations caused by Covid-19–associated fungal infections more frequently than for non–Covid-19–associated fungal infections, regardless of the specific fungal pathogens involved.

Fungal pathogen	Any fungal infection	COVID-19–associated	Non–COVID-19–associated	p value
Total no.	39,423	5,288	34,135	NA
Candida	8,289 (21.0)	1,135 (21.5)	7,154 (21.0)	0.40
Aspergillus	7,248 (18.4)	1,471 (27.8)	5,777 (16.9)	<0.01
Coccidioides	6,278 (15.9)	723 (13.7)	5,555 (16.3)	<0.01
Pneumocystis	3,718 (9.4)	235 (4.4)	3,483 (10.2)	<0.01
Histoplasma	2,386 (6.1)	139 (2.6)	2,247 (6.6)	<0.01
Cryptococcus	2,022 (5.1)	138 (2.6)	1,884 (5.5)	<0.01
Blastomyces	543 (1.4)	41 (0.8)	502 (1.5)	<0.01
Mucorales species	569 (1.4)	94 (1.8)	475 (1.4)	0.03
Other specified fungi	2,300 (5.8)	221 (4.2)	2,079 (6.1)	<0.01
Unspecified fungi	7,599 (19.3)	1,286 (24.3)	6,313 (18.5)	<0.01

Comment: Their analysis underscores the substantial burden of patient hospitalizations with fungal infections in the US and indicates that increased hospitalizations involving fungal infections occurred during the Covid-19 pandemic. This analysis is consistent with national mortality data, hospitalization rates for Covid-19–associated aspergillosis and mucormycosis from 2020 to 2021[Clin Infect Dis. 2023;76:e255–62], likely reflecting a greater burden of Covid-19 during 2021 than increased clinician awareness and testing for Covid-19–associated mold infections , and increased use of corticosteroids for Covid-19 treatment, a major risk factor for aspergillosis and mucormycosis[Clin Infect Dis. 2012;54(Suppl 1):S16–22]. Their findings emphasize the importance of maintaining a high index of clinical suspicion for fungal infections in patients at high risk, including those with Covid-19, and the need for increased fungal disease surveillance to detect and evaluate emerging trends. Although ICD-10-CM codes for Covid-19 correlate well with SARS-CoV-2 test results in this dataset, fungal ICD-10-CM codes might be associated with underreporting, misclassification, and nonspecific coding of pathogenic fungi, particularly those causing candidemia and invasive mold disease.