Infectious Diseases Watch

October 31, 2022

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General Infectious Diseases

Diagnostic Accuracy of a Bacterial and Viral Biomarker Point-of-Care Test in the Outpatient Setting

JAMA Netw Open published online October 18, 2022

doi:10.1001/jamanetworkopen.2022.34588

This study evaluated the FebriDx bacterial and viral test, a point-of-care immunoassay designed to detect and differentiate bacterial- from viral-associated host immune response by measuring myxovirus resistance protein (MxA) and C-reactive protein (CRP) biomarkers in finger-prick blood samples. Increased MxA levels in blood are associated with viral infection, while elevated CRP levels indicate a clinically significant immune response which on their own does not reliably distinguish between bacterial and viral infections. Bacterial infection stimulates increased CRP levels; however, some viral infections, including influenza, adenovirus, and SARS-CoV-2, can also be associated with increased CRP levels.

To evaluate the immunoassay's performance in differentiating bacterial from viral infections, a team that included emergency medicine specialists and researchers enrolled 520 patients 1 year and older who had symptoms of an acute respiratory infection (ARI) and a control group of 170 patients who were asymptomatic. The primary outcome was bacterial- or viral-associated systemic host response to infection, and the test results were compared with the results of an adjudicated comparator algorithm. Treating clinicians and adjudicators were blinded to the results.

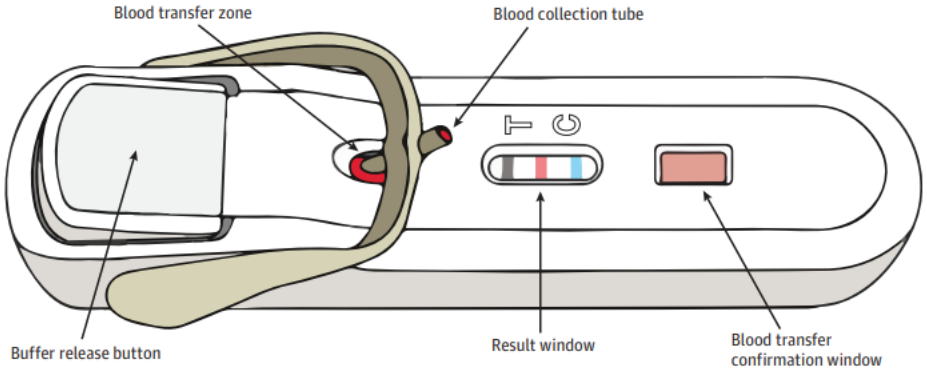
Of the 520 participants with symptomatic ARIs (44.2% male, 55.8% female, mean age 35.3 years), 496 had a clinically adjudicated final diagnosis with an immunoassay test result. Among these participants, the comparator algorithm classified the diagnosis as bacterial in 73 (14.7%), viral in 296 (59.7%), and negative for infection in 127 (25.6%).

FebriDx correctly diagnosed a bacterial infection in 68 of 73 participants, demonstrating a sensitivity of 93.2% (95% confidence interval [CI], 84.9% to 97.0%), a specificity of 374 of 423 participants (88.4%; 95% CI, 85.0% to 91.1%), a positive predictive value (PPV) of 68 of 117 participants (58.1%; 95% CI, 49.1% to 66.7%), and a negative predictive value (NPV) of 374 of 379 participants (98.7%; 95% CI, 96.9% to 99.4%).

In the 296 patients classified as having a virus by the comparator algorithm, FebriDx correctly diagnosed a virus in 208 patients, for a sensitivity of 70.3% (95% CI, 64.8% to 75.2%), a specificity of 176 of 200 participants (88%; 95% CI, 82.8% to 91.8%), a PPV of 208 of 232 participants (89.7%; 95% CI, 85.1% to 92.9%), and an NPV of 176 of 264 participants (66.7%; 95% CI, 60.8% to 72.1%).

Among the 158 control-group participants with confirmed negative test results in the comparator algorithm, the FebriDx test results were negative in 156 (98.7%; 95% CI, 95.5% to 99.7%).

Figure 1. Bacterial and Viral Test



Comment: In summary, this diagnostic study of 520 participants with suspected ARI, the bacterial and viral test had a sensitivity of 93.2%, negative predictive value of 98.7%, specificity of 88.4%, and positive predictive value of 58.1% to detect a bacterial-associated host immune response. This study suggests that this immunoassay may differentiate bacterial from viral infection in patients with ARI. However, only a minority of patients in this study were older than 65 years. The enrolled cohort represents (new-onset ARI) a low-risk population presenting to an outpatient setting. The study did not include patients who were immunocompromised, and perhaps most importantly, there is a lack of a criterion standard to differentiate viral and bacterial respiratory infections. This assay is currently under review by the US FDA but has been approved for use in Canada, Europe, and Australia. The current biomarker in use in the US would be procalcitonin which does have a high negative predictive value for bacterial infections.

Effectiveness of Ultraviolet-C Disinfection on Hospital-Onset Gram-Negative Rod Bloodstream Infection: A Nationwide Stepped-Wedge Time-Series Analysis Clin Infect Dis published online September 17, 2022

doi.org/10.1093/cid/ciac776

Ultraviolet-C (UV-C) disinfection of patients' rooms has a variable effect on incidence of hospital-onset *C. difficile* and vancomycin-resistant enterococcal infections, but the effect on hospital-onset gram-negative rod bloodstream infection (HO-GNR BSI) is unknown. Investigators evaluated the incidence of HO-GNR BSI at 120 Veterans Administration (VA) hospitals (40 with UV-C disinfection and 80 without) between 2010 and 2018.

Among 13,383 HO-GNR BSI episodes throughout the study period, incidence declined at a rate of −0.43% per month. Implementation of UV-C disinfection was associated with a significant decrease of 19% in HO-GNR BSI, but the effect varied by hospital (range, −30.7% to +8.3%). The decline was significant in hospitals with high baseline HO-GNR BSI incidence but not in those with low incidence. UV-C implementation was associated with a 33.5% decline in incidence of non–lactose fermenting HO-GNR BSI episodes, but not HO *Klebsiella spp*. and *Escherichia coli* BSI.

Comment: The effect of UV-C disinfection was limited to HO-GNR BSI by non-lactose fermenting organisms and this effect varied by hospital. This study was nonrandomized, and the use of UV-C strategies were highly variable by the participating hospitals. In all, the roles of specific disinfection strategy as well as hospital characteristics in the use of UV-C effect on HO-GNR BSI still remain unclear but based on this paper additional studies are warranted given the promising overall results.

Clinical Impact of Ceftriaxone Resistance in Escherichia Coli Bloodstream Infections: 2 A Multicenter Prospective Cohort Study OFID published online October 27, 2022

doi.org/10.1093/ofid/ofac572

This is a multicenter prospective cohort study coordinated by the Antibacterial Resistance Leadership Group (ARLG). They analyzed data on adult and pediatric patients with *E coli* BSIs at 14 US hospitals from November 12, 2020, to April 18, 2021. For each patient with a ceftriaxone-resistant (CRO-R) *E coli* BSI who was enrolled, the next consecutive patient with ceftriaxone-susceptible *E coli* BSI was included. The primary outcome was the desirability of outcome ranking (DOOR) at day 30 after collection of index culture, which the study authors say they chose because it captures a more wide-ranging experience of patients infected with drug-resistant pathogens.(see table 1)

A total of 300 patients (median age, 68 years) were included in the analysis, with 150 in the CRO-R group and 150 in the CRO-S group. In CRO-R E. coli, the median ceftriaxone MIC was ≥32 mcg/mL (IQR ≥32- ≥32) versus 0.06 mcg/mL (IQR 11 0.03-0.06) in CRO-S E. coli. Patients with CRO-R infections had more overall comorbidities than those with CRO-S infections. In the unadjusted DOOR analysis, there was a 58% probability of a worse clinical outcome in patients with CRO-R *E coli* BSI versus a CRO-S *E coli* BSI. However, in the IPW-adjusted cohort to reduce confounders, no difference was observed (54% [95% CI 47%-61%]). Although the difference in mortality between the two groups was not statistically significant, patients with CRO-R *E coli* BSI were almost more likely to have longer hospital stays (8 vs 6 days), to remain in the hospital at day 30 (10% vs 4%), and to be transferred to long-term care facilities (22% vs 12%) than those with CRO-S infections.

Table 1. Ordinal outcomes for desirability of outcome rankings in a cohort of 300 patients infected with ceftriaxone-resistant *versus* ceftriaxone-susceptible *Escherichia coli* bloodstream infections

Category	Criteria[1,2]
1 (Most desirable)	Alive and no events
2	Alive and one events
3	Alive and at least two events
4 (Least desirable)	Death
Events Definition	
• Failure to achieve a favorable clinical response within 30 days	
• New *E. coli* bloodstream infection within 30 days	
• Remaining in the hospital at day 30 AND/OR readmission to the same hospital within 30 days	
• Discharge to a nursing home or skilled nursing facility (if originally admitted to the hospital from home)	

[1]All criteria evaluated compared to day 1, with day 1 being the first day a positive blood culture was collected.

[2]If the reason for hospital readmission was a new *E. coli* bloodstream infection, it is counted as a single event.

Comment: The incidence of CRO-R E. coli BSI continues to rise in the US, with the CDC estimating a 53% increase in CRO-R E. coli in clinical cultures from 2012 through 2017 [N Engl J Med 2020; 382:1309-1319]. ESBL production is the most common mechanism of ceftriaxone resistance in E. coli, and ceftriaxone resistance is frequently used as a proxy for the production of ESBLs. Earlier studies suggested poorer outcomes in patients infected with CRO-R E coli. However, it is unclear if poorer outcomes persist after adjustment for confounding factors such as delays in time to an active antibiotic, immunocompromise, and challenges with achieving source control - all generally more prevalent in patients infected with drug-resistant phenotypes. Furthermore, errors in determination the MICs have been documented with automated susceptibility testing platforms used to define ceftriaxone susceptibility. Although physicians often equate CRO-R E. coli with ESBL production, E. coli can exhibit ceftriaxone resistance due to a number of mechanisms including ESBL genes (e.g., blaCTX-M-15[the most common], blaSHV-12), plasmid-mediated bla $_{ampC}$ genes, chromosomally derepressed bla $_{ampC}$ genes, and hyper-expressed narrow-spectrum β-lactamase genes with associated mutations in permeability. In addition, susceptibility of CRO-R E. coli isolates to fluoroquinolones and trimethoprim-sulfamethoxazole, was significantly lower than for CRO-S E. coli isolates. They did attempt to adjust the impact of cofounders on clinical outcomes through IPW-propensity score adjusted analysis. Nonetheless, residual confounding may persist. The associated differential impact of specific antibiotics on clinical outcomes could not be investigated given the heterogeneity of antibiotic therapy prescribed to study participants. Nonetheless, this paper shows that patients infected with CRO-R E. coli generally have worse clinical outcomes as compared to patients infected with CRO-S E. coli. This observation is primarily driven by host

factors such as increased comorbidities. The investigators conclude: "These findings underscore the importance of judicious antibiotic use to reduce the development of antibiotic resistance and its subsequent negative impacts on patient outcomes." It is hoped that precision medicine can provide clinicians real time risk estimates of MDROs.

Changes in Burnout and Satisfaction With Work-Life Integration in Physicians During the First 2 Years of the COVID-19 Pandemic Mayo Cl Proc published online September 13, 2022

doi.org/10.1016/j.mayocp.2022.09.002

Associations of physician burnout with career engagement and quality of patient care: systematic review and meta-analysis BMJ 2022;378: e070442

doi.org/10.1136/ bmj-2022-070442

In the fourth triennial burnout survey of U.S. physicians, conducted between November 2020 and March 2021, 38% of physicians reported at least one burnout symptom (e.g., emotional exhaustion, detachment and depersonalization, perceived ineffectiveness), and 54% were dissatisfied with their work-life balance. These results were similar to those in previous surveys. To determine the effect of the mature COVID-19 pandemic on burnout, investigators conducted a mid-cycle survey in December 2021 and January 2022, after all areas in the U.S. had experienced multiple COVID-19 surges.

The mid-cycle survey showed that the prevalence of burnout symptoms and dissatisfaction with work-life balance had risen significantly to 63% and 70% of physicians, respectively. Female physicians were twice as likely as male physicians to have symptoms of burnout, a significant increase since 2020. Physicians practicing emergency medicine, family medicine, and general pediatrics were at excess risk for burnout, compared with physicians in other specialties.

The second article provides additional perspective. This is a meta-analysis of 170 observational studies (involving >240,000 physicians) that reported associations between physician burnout and outcomes related to career engagement and quality of care. Compared with physicians who didn't report burnout, those who did report burnout were three to four times more likely to have decreased job satisfaction, career dissatisfaction, intent to leave their current jobs, and negative career development, and were almost twice as likely to report reduced productivity. Burnout also was associated with twice as many patient safety incidents, low professionalism, and patient dissatisfaction. Burnout appeared to be most common in hospital settings, particularly in emergency departments and intensive care units.

Comment: Physician burnout has been recognized for at least the last decade accelerated by the pandemic. Attributable causes include short staffing, attitudes of anti-science, incivility, and work conditions. This not only impacts physicians, but all healthcare professionals. Contributing to this crisis include physician, nursing, pharmacy etc. shortages, high turnover rates, and quality and safety of patient care. Solutions include improving the work environment and organizational culture. I fear it will take years to correct this urgent problem. In the meantime, we need to invest in processes to improve quality and the work environment while we rebuild our workforce.

Ebola: Uganda as outbreak grows to 100 confirmed cases October 24, 2022

Uganda's health ministry reported 14 more lab-confirmed Ebola cases, raising the outbreak total to 95. Infections in the greater Kampala area have risen to 15 over the past 48 hours. Earlier this week, the country's health minister detailed 9 recently confirmed cases from the Kampala, all of them contacts of a patient from outside the city who recently died from his infection in a Kampala hospital.

No new deaths in lab-confirmed patients were reported, keeping the total at 28. Currently, 33 people are receiving medical care, and 1,830 contacts have been identified for follow-up. Earlier in the outbreak before the first lab-confirmed cases were identified, officials reported 20 suspected cases, all of them fatal.

Comment: The outbreak involves the less common Sudan Ebola strain. There are no approved vaccines or treatments for the strain, but health officials are planning vaccine trials in the outbreak area for as many as three vaccines targeting Sudan Ebola that are in the development stages.

Fungal Special Report

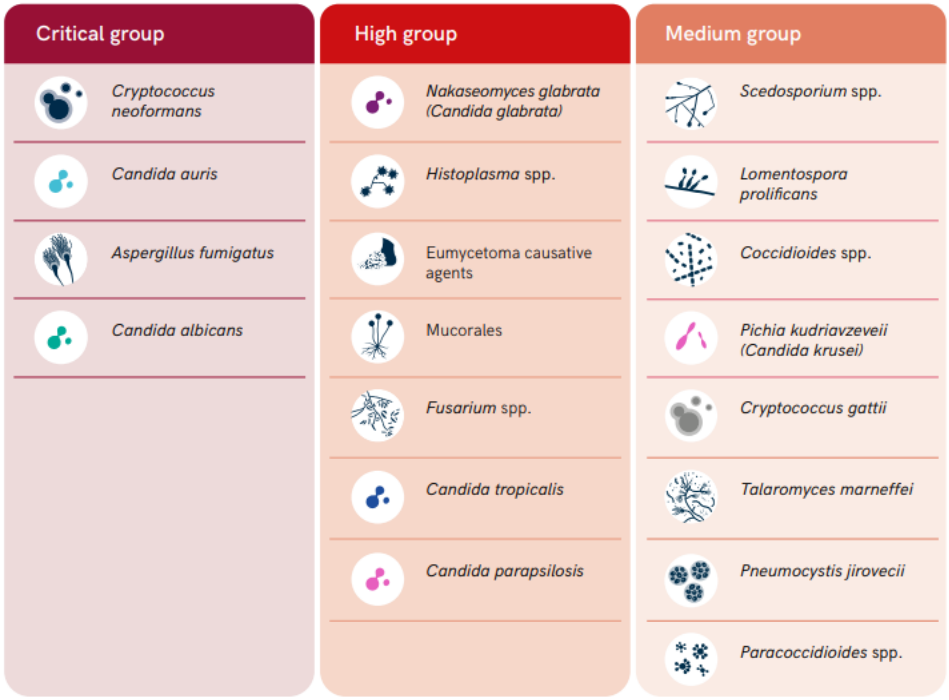
WHO fungal priority pathogens list to guide research, development, and public health action October 25, 2022

The WHO released its first-ever list of fungal "priority pathogens," identifying 19 fungi that have emerged as significant public health threats because of their ability to cause severe invasive infections and their growing resistance to antifungal drugs.

Although the data on the prevalence of invasive fungal infections and patterns of antifungal resistance are limited, and little is known about some of these pathogens, WHO officials say emerging evidence suggests the incidence and geographic range of fungal diseases are expanding due to climate change and increased global travel. The COVID-19 pandemic has also put the spotlight on the issue, with the reported incidence of invasive fungal infections growing in hospitalized COVID patients. In addition, the population most at risk from invasive infections caused by these pathogens—including cancer patients, people with HIV/AIDS, organ transplant recipients, and other immunocompromised patients—is growing.

The pathogens included were ranked, then categorized into three priority groups (critical, high, and medium). The critical group includes Cryptococcus neoformans, Candida auris, Aspergillus fumigatus and Candida albicans. The high group includes Nakaseomyces glabrata (Candida glabrata), Histoplasma spp., eumycetoma causative agents, Mucorales, Fusarium spp., Candida tropicalis and Candida parapsilosis. Finally, pathogens in the medium group are Scedosporium spp., Lomentospora prolificans, Coccidioides spp., Pichia kudriavzeveii (Candida krusei), Cryptococcus gattii, Talaromyces marneffei, Pneumocystis jirovecii and Paracoccidioides spp.

Three primary areas for action are proposed, focusing on: (1) strengthening laboratory capacity and surveillance; (2) sustainable investments in research, development, and innovation; and (3) public health interventions.



Comment: WHO officials are concerned that the limited number of antifungal medications, lack of rapid and sensitive diagnostics, and limited financial resources devoted to fungal infections will hamper the ability to detect and respond to this growing problem. Among fungi in the critical priority group is *Candida auris,* the multidrug-resistant yeast that was first-discovered in Japan in 2009 and since then has spread worldwide and increased during the pandemic. Invasive infections caused by *C auris,* which spreads easily in healthcare settings and in some cases is resistant to all classes of antifungal medication, are fatal in as many as 53% of patients. In addition, WHO officials also highlighted the fact that the emergence of resistant fungal pathogens as a global public health threat is a One Health issue, driven in part by inappropriate use of antifungals in agriculture. The report notes that widespread use of azoles as fungicides to protect plants against fungal infections has contributed to rising rates of azole-resistant *A fumigatus* infections in humans. Azoles are the first-line treatment for invasive aspergillosis.

The WHO is hoping that the fungal priority pathogens list could have a similar impact as the document on which it was modeled—the 2017 WHO list of bacterial priority pathogens. Currently, fungal infections receive less 1.5% of all infectious disease research funding.

Evolution of the human pathogenic lifestyle in fungi Nat Microbiol 2022; 7: 607–619

doi.org/10.1038/s41564-022-01112-0

Approximately 150,000 species the kingdom of fungi is the lesser known of the ‘big’ three eukaryotic kingdoms after animals and plants. The kingdom Fungi is extraordinarily diverse and contains more than two hundred orders and a dozen phyla, with new ones being described continuously. However, most infections and deaths caused by fungi result from a few hundred fungal species that belong to a few lineages One reason for the lack of attention to fungal

pathogens lies in their opportunistic nature. In contrast to bacteria and viruses, fungi only emerged as important human pathogens in the past few decades, primarily owing to changes in the landscape of human disease (see figure below); these changes include the dramatic increase in the number of immunocompromised patients and the advent of new diseases that seriously compromise immune-system function (for example, AIDS). Unfortunately, but not surprisingly, fungal pathogens cause secondary infections in individuals with severe COVID-19. Of the 150,000 fungal species described, only about 200 of them are infectious to people. Invasive forms of fungal infections often impact severely ill patients and those with underlying conditions. Populations at greatest risk of infection include those with cancer, HIV/AIDS, organ transplants, chronic respiratory disease, and post-primary tuberculosis infection.

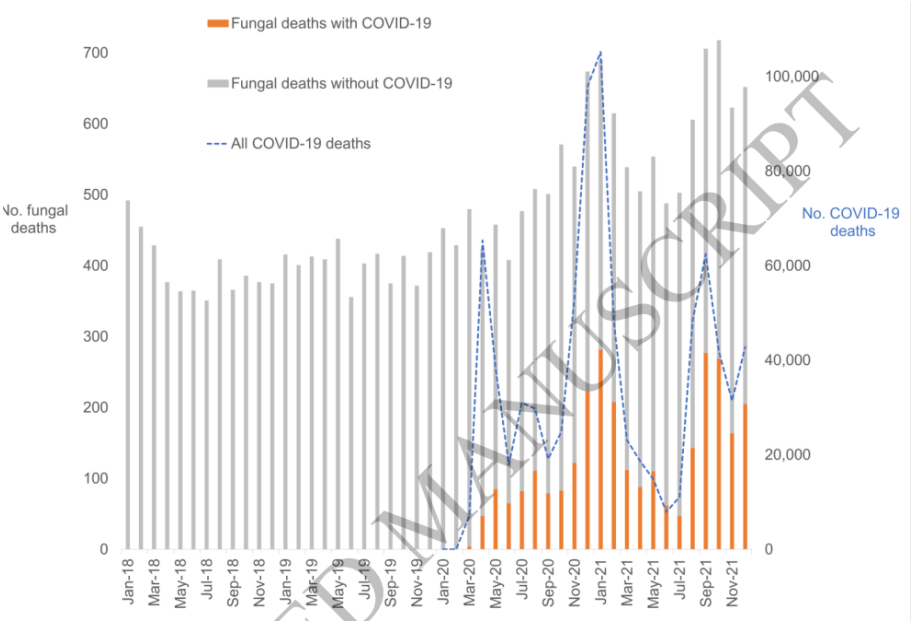
Comment: Recent data suggest that the global annual burden of fungal disease is enormous; superficial (for example, skin, hair, nail and eye) infections are estimated to affect a billion people, mucosal (for example, oral and vaginal) infections affect approximately 135 million, allergic infections affect about 23.3 million, and chronic severe and acute invasive infections affect several additional millions of people and have extremely high mortality rates. The mortality rates in certain groups of severely immunocompromised patients with invasive aspergillosis can be as high as 50%. Fungal diseases are responsible for more than 1.6 million deaths annually, a rate on par with that of tuberculosis and more than three times higher than that of malaria. See next article on impact of Covid-19 and secondary fungal infections

Increased deaths from fungal infections during the COVID-19 pandemic — National Vital Statistics System, United States, January 2020–December 2021 Clin Infect Dis published online June 19, 2022

doi/10.1093/cid/ciac489/6611491

Using the US NVSS's (National Vital Statistics System) January 2018–December 2021 Multiple Cause of Death Database, the investigators examined numbers and age-adjusted rates (per 100,000 population) of fungal deaths by fungal pathogen, COVID-19 association, demographic characteristics, and year.

Numbers and age-adjusted rates of fungal deaths increased from 2019 (n = 4,833, rate 1.2, 95% confidence interval [CI] = 1.2–1.3) to 2021 (n = 7,199, rate: 1.8, 95% CI = 1.8–1.8); of 13,121 fungal deaths during 2020–2021, 2,868 (21.9%) were COVID-19–associated. Compared with non-COVID-19–associated fungal deaths (n = 10,253), COVID-19–associated fungal deaths more frequently involved *Candida* (n = 776 [27.1%] versus n = 2,432 [23.7%]) and *Aspergillus* (n = 668 [23.3%] versus n = 1,486 [14.5%]) and less frequently involved other specific fungal pathogens. Fungal death rates were generally highest in non-White and non-Asian populations. Death rates from *Aspergillus* infections were approximately two times higher in the Pacific US census division compared with most other divisions.



Comment: There are a few limitations to this study. First provisional mortality data from 2021 are incomplete and subject to change, particularly during recent months, as delayed reports might later increase death counts. Their use of broad single race categories limited the level of detail with which could assess racial/ethnic disparities, particularly among multiracial persons. Another limitation was that they could not assess all underlying medical conditions among patients with COVID-19–associated fungal deaths; this is because the CDC-WONDER platform does not allow for the tabulation of more than two sets of conditions in combination. Despite these limitations fungal infections have increased across the globe during this pandemic.

It has been demonstrated that viral respiratory infections can predispose patients to secondary opportunistic infections or co-infections by fungi and bacteria. It is well established that patients

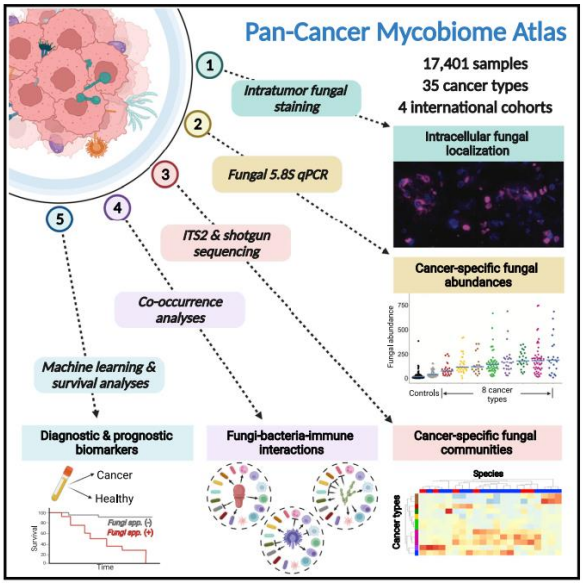
with severe influenza infections can sometimes acquire secondary *Aspergillus* infections [OFID, 2016; 3, ofw171]. Secondary fungal infections have also been associated with SARS-CoV-2. A considerable percentage of patients with COVID-19 can harbor secondary *Aspergillus* infections [Lancet Respir. Med. 2020; 8, e48–e49] and it is now widely recognized that COVID-19-associated pulmonary aspergillosis is an important complication in the context of COVID-19 infection, especially in patients with severe lung damage, structural lung defects or who received broad-spectrum antibiotics or corticosteroids [J. Fungi 2020; https://doi.org/10.3390/ jof6020091]. More recently, an increase in secondary infections with the zygomycetes group has been noted in patients with COVID-19, which also seems to be the result of opportunism, namely severe COVID-19 infections in patients with poorly controlled diabetes mellitus. [J. Fungi 2021; 7: 298] The genomic and phenotypic characteristics of fungal isolates from patients with COVID-19-associated pulmonary aspergillosis do not seem to differ from those typically isolated from patients with aspergillosis. Bottom line we are seeing more invasive fungal infections and more attention needs to be directed at prevention, early diagnosis, and treatment.

A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors Cell 2022; 185, 3789–3806

doi.org/10.1016/j.cell.2022.09.015

The investigators characterized the mycobiomes of 17,401 tissue and blood samples in four independent cohorts across 35 cancer types with complementary strategies.

The investigators report fungal DNA and cells at low abundances across many major human cancers, with differences in community compositions that differ among cancer types, even when accounting for technical background, however, although fungi were detected in all examined cancer types, not all individual tumors were found positive for fungal signal. The study did reveal cancer-type specific fungal ecologies with lower diversities and abundances than matched bacteriomes. Fungal histological staining of tissue microarrays supported intratumoral presence and frequent spatial association with cancer cells and macrophages. Comparing intratumoral fungal communities with matched bacteriomes and immunomes revealed co-occurring bi-domain ecologies, often with permissive, rather than competitive, microenvironments and distinct immune responses. Clinically focused assessments suggested prognostic and diagnostic capacities of the tissue and plasma mycobiomes, even in stage I cancers, and synergistic predictive performance with bacteriomes. They found significant correlations between specific fungi and age, tumor subtypes, smoking status, response to immunotherapy, and survival measures.

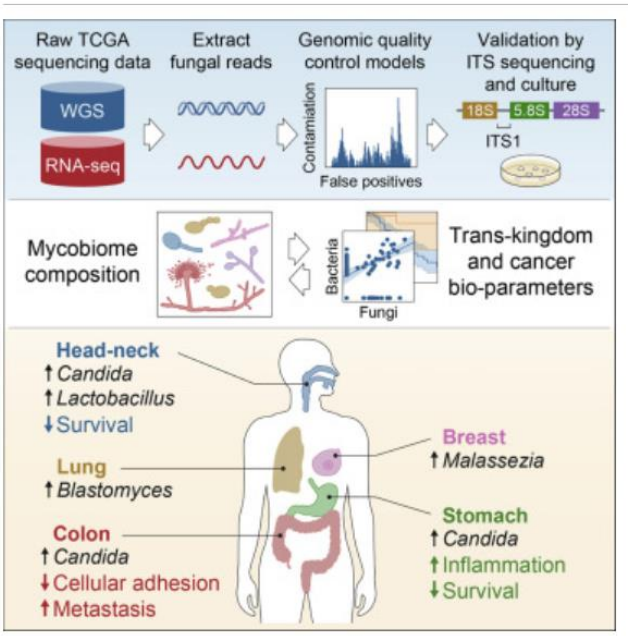


Comment: In this article fungi were detected in 35 cancer types and were often intracellular. Multiple fungal-bacterial-immune ecologies were detected across tumors. Intratumoral fungi stratified clinical outcomes, including immunotherapy response. Cell-free fungal DNA diagnosed healthy and cancer patients in early-stage disease. This article highlights a pan-cancer analysis demonstrating human samples harboring tumor associated microbiota. Fungal genome coverage analysis removes contamination and false-positive alignments. Alive, transcriptionally active Candida is associated with gastrointestinal cancers. Candida DNA is enriched in tumors and predictive of reduced survival in GI cancers. Whether these fungi are correlated or causally associated is yet to be determined.

A pan-cancer mycobiome analysis reveals fungal involvement in gastrointestinal and lung tumors Cell 2022; 185, 3807–3822

Fungal microorganisms (mycobiota) comprise a small but immunoreactive component of the human microbiome, yet little is known about their role in human cancers. Pan-cancer analysis of multiple body sites revealed tumor-associated mycobiomes at up to 1 fungal cell per 104 tumor cells. In lung cancer, Blastomyces was associated with tumor tissues. In stomach cancers, high rates of Candida were linked to the expression of pro-inflammatory immune pathways, while in colon cancers Candida was predictive of metastatic disease and attenuated cellular adhesions. Across multiple GI sites, several Candida species were enriched in tumor samples and tumor-associated Candida DNA was predictive of decreased survival. The presence of Candida in human GI tumors was confirmed by external ITS sequencing of tumor samples and by culture-dependent analysis in an independent cohort. These data implicate the mycobiota in the pathogenesis of GI cancers and suggest that tumor-associated fungal DNA may serve as diagnostic or prognostic biomarkers. Fungal microorganisms (mycobiota) comprise a small but immunoreactive component of the human microbiome, yet little is known about their role in human cancers. Pan-cancer analysis of multiple body sites revealed tumor-associated mycobiomes at up to 1 fungal cell per 104 tumor cells. In lung cancer, Blastomyces

was associated with tumor tissues. In stomach cancers, high rates of Candida were linked to the expression of pro-inflammatory immune pathways, while in colon cancers Candida was predictive of metastatic disease and attenuated cellular adhesions. Across multiple GI sites, several Candida species were enriched in tumor samples and tumor-associated Candida DNA was predictive of decreased survival. The presence of Candida in human GI tumors was confirmed by external ITS sequencing of tumor samples and by culture-dependent analysis in an independent cohort. These data implicate the mycobiota in the pathogenesis of GI cancers and suggest that tumor-associated fungal DNA may serve as diagnostic or prognostic biomarkers.



Comment: A pan-cancer analysis reveals human samples harbor tumor associated mycobiota. Fungal genome coverage analysis removes contamination and false-positive alignments. Alive, transcriptionally active Candida is associated with gastrointestinal cancers. Candida DNA is enriched in tumors and predictive of reduced survival in GI cancers.

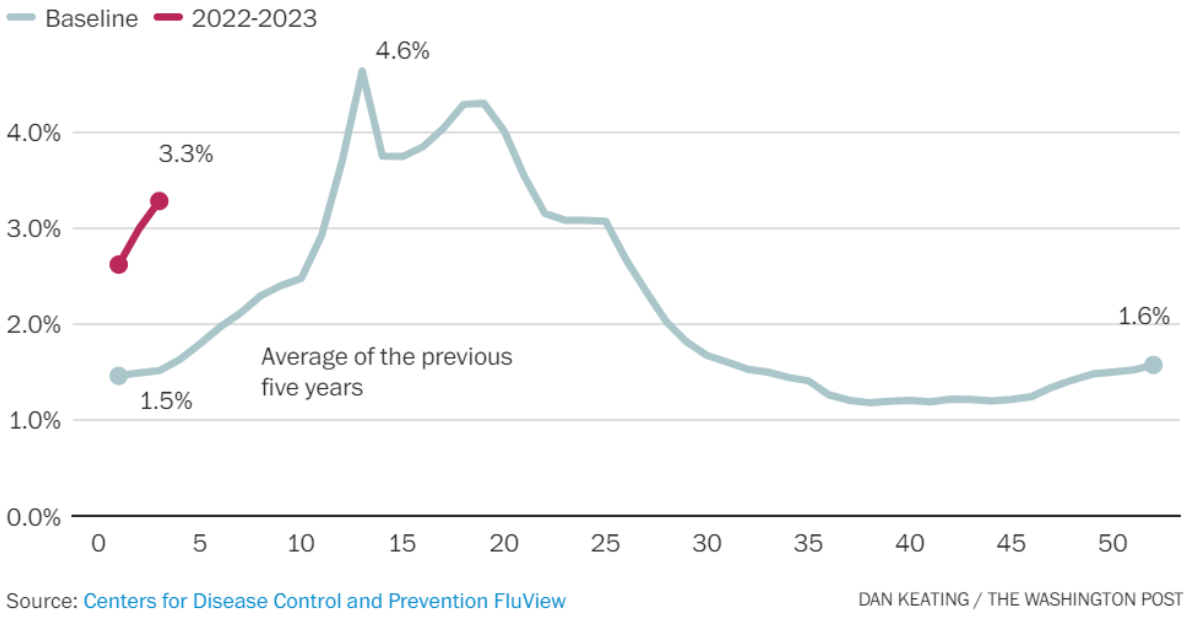
Final Comments: In the past several research teams showed that tumors can harbor various combinations of bacteria. The two studies reviewed above from the journal Cell found that tumors can harbor many species of fungi. This so-called “tumor microbiome” is proving so distinctive in each type of cancer that some investigators hope to find early signs of hidden tumors by measuring the microbial DNA they shed into the blood. In addition, some research hints that microbes may make tumors more aggressive or resistant to treatments. If that proves to be the case, it may be possible to treat certain cancers by attacking a tumor’s microbiome along with the tumor itself.

Respiratory Viruses

Tripledemic?

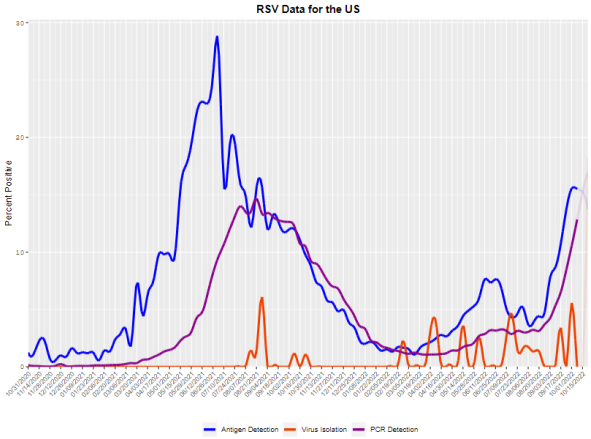
A surge in respiratory syncytial virus is already putting severe strain on children's hospitals nationwide. Hospitals first began seeing the unseasonable RSV rise in August. Now, many are reporting a case increase of over 300 percent compared to last month. On September 8th the CDC data shows the nation's RSV positivity rate (based on antigen and PCR tests) was around 8 percent. By October 15th, the positivity rate jumped to more than 15 percent.

While influenza season is usually between October and May, peaking in December and January, it's arrived about six weeks earlier this year with uncharacteristically high illness. There have already been at least 880,000 cases of influenza illness, 6,900 hospitalizations and 360 flu-related deaths nationally, including one child, according to estimates released Friday by the CDC. Activity is high in the US south and southeast and is starting to move up the Atlantic coast. About 3.3% of samples tested for influenza came back positive during the first week of October according to the CDC, most of which are H3N2. In the southeast, the positivity rate was about 10%, At the Houston Methodist, laboratory-confirmed influenza cases have risen to 975 as of October 20th, up from 561 the week before. Not only is influenza early, but it also looks like it may be more severe. Adding to my concern, is that influenza vaccine uptake has been disappointing lagging behind prior seasons. [see influenza below] An early uptick in flu activity has been reported in some parts of the U.S., particularly in the southeast and south-central states such as Texas and Georgia, according to the CDC's flu report released last Friday.

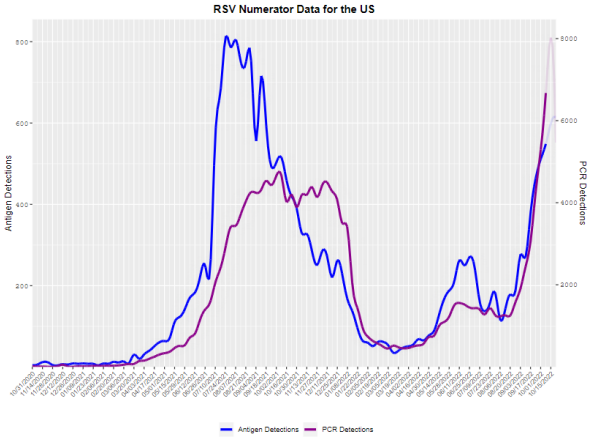


Respiratory Syncytial Virus (RSV)

Percent Positive



Detections



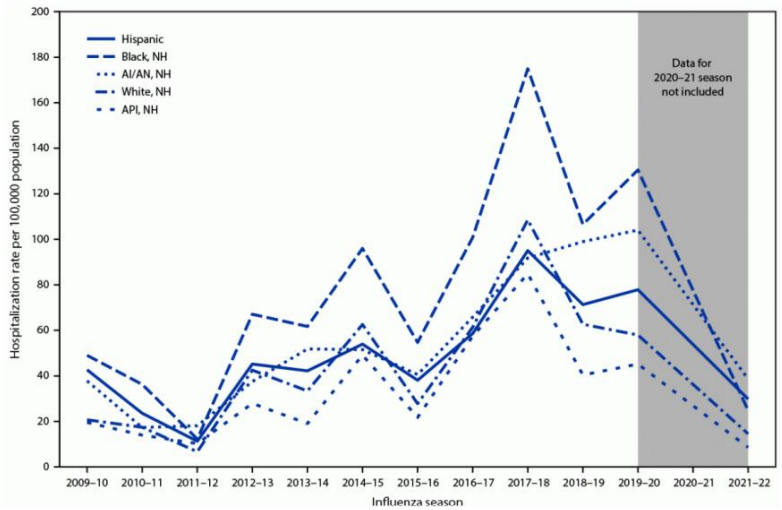
Although COVID-19 cases are trending down we always have our eyes on emerging variants. [see Covid-19 below] Hospitalizations, however, have been nearly flat during that same period, and in much of the Northeast they are up by ~ 10 percent. For COVID-19, some models are predicting a surge before Christmas and others see a new wave in 2023.

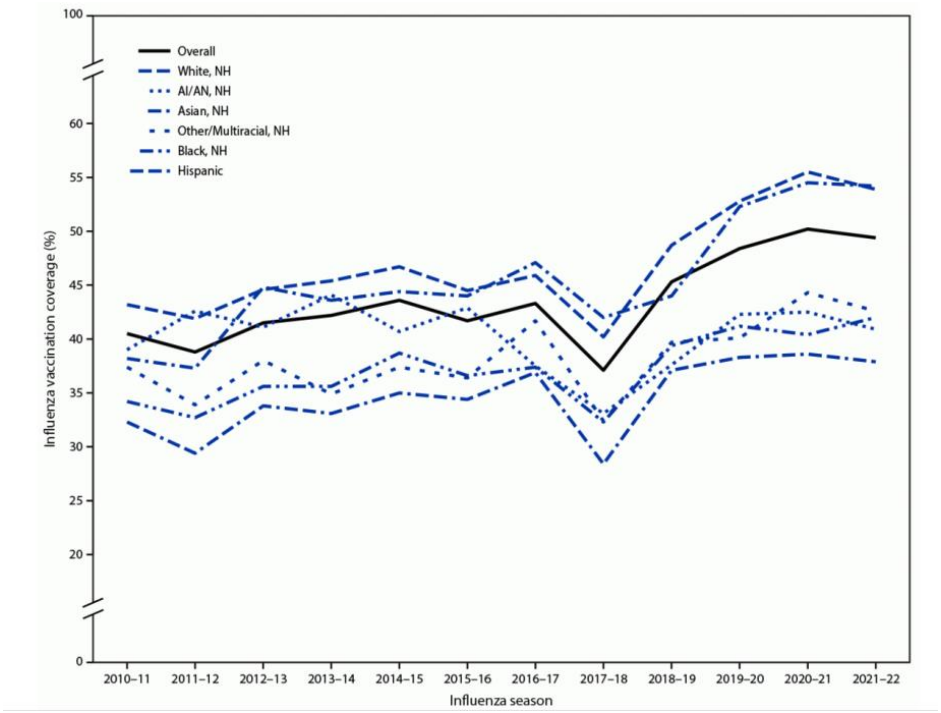
Comment: These trends come as the US faces poor uptake of the bivalent vaccine booster. Since its introduction last month, less than 10 percent of eligible Americans have gotten the booster and we are behind on influenza vaccinations compared to previous seasons.

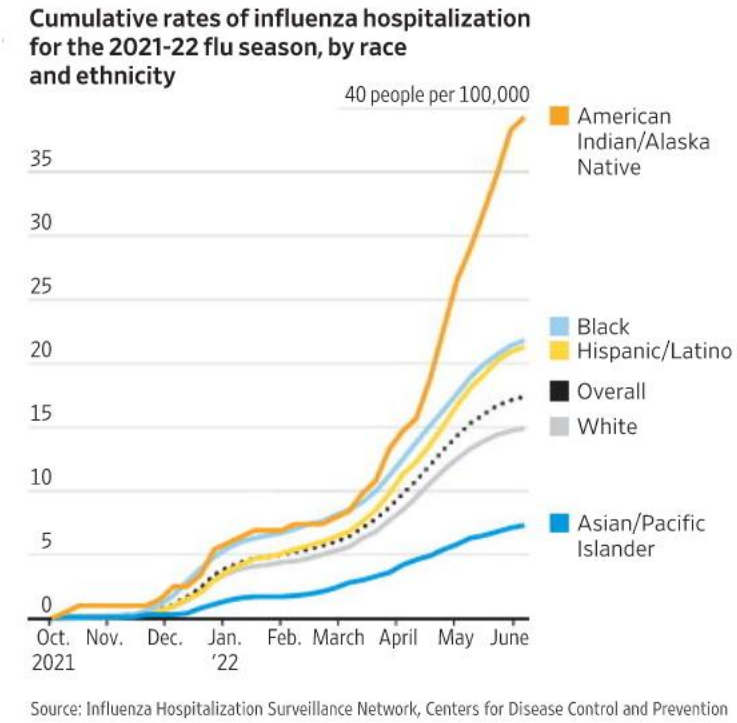
Vital Signs: **Influenza Hospitalizations and Vaccination Coverage by Race and Ethnicity—United States, 2009–10 Through 2021–22 Influenza Seasons** MMWR early release October 18, 2022

Between 140,000 and 710,000 people were hospitalized with flu each year during 2010–2020. People from some racial and ethnic minority groups are more likely to be hospitalized with flu. Compared to White adults, flu hospitalization rates* are:

- **Nearly 80% higher** among Black adults
- **30% higher** among American Indian/Alaska Native (AI/AN) adults
- **20% higher** among Hispanic adults


Hispanic
Black, NH
AI/AN, NH
White, NH
API, NH
Data for 2020–21 season not included
Hospitalization rate per 100,000 population
0
20
40
60
80
100
120
140
160
180
200
2009–10
2010–11
2011–12
2012–13
2013–14
2014–15
2015–16
2016–17
2017–18
2018–19
2019–20
2020–21
2021–22
Influenza season


Overall
White, NH
AI/AN, NH
Asian, NH
Other/Multiracial, NH
Black, NH
Hispanic
Influenza vaccination coverage (%)
0
20
25
30
35
40
45
50
55
60
100
2010–11
2011–12
2012–13
2013–14
2014–15
2015–16
2016–17
2017–18
2018–19
2019–20
2020–21
2021–22
Influenza season



During the 2021-2022 flu season, vaccination coverage was 54% among white and Asian adults in the US, compared with 42% among Black adults, 38% among Hispanic adults and 41% among American Indian adults. Lower vaccine uptake isn't the only factor for the disparities in hospitalizations, CDC officials said, but targeted outreach and increasing influenza vaccinations could help lower the differences in severe outcomes. See graph above

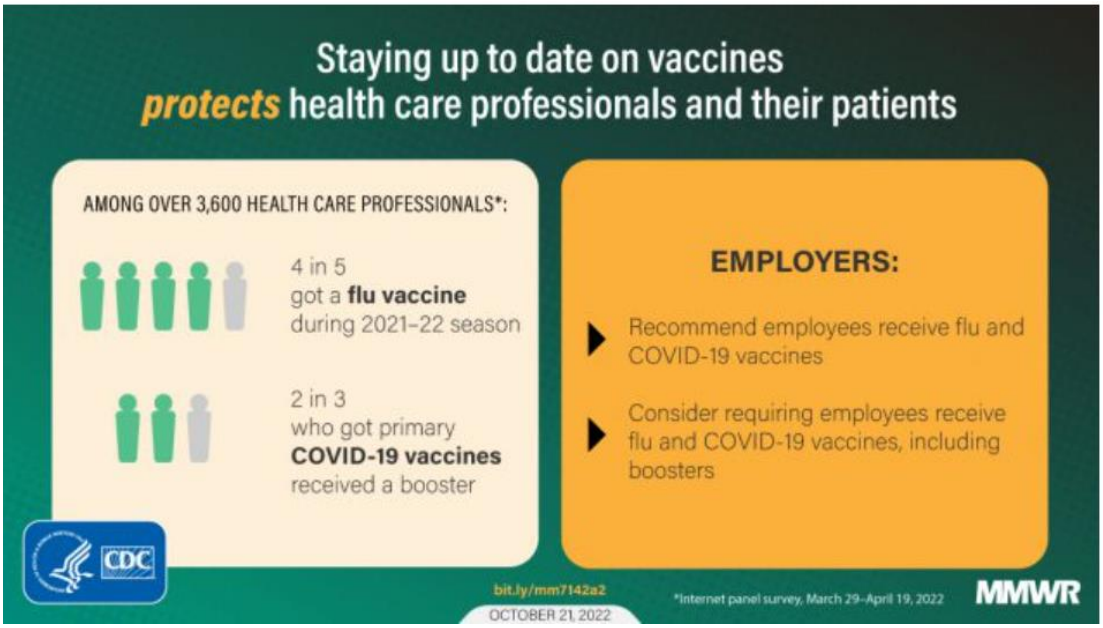
A separate CDC report from February 2022 also found gaps in influenza vaccination among pregnant women, with vaccination rates at 52% for white women and 50% for Hispanic women compared with 36% among Black women. Pregnant people are at higher risk of severe illness from influenza.

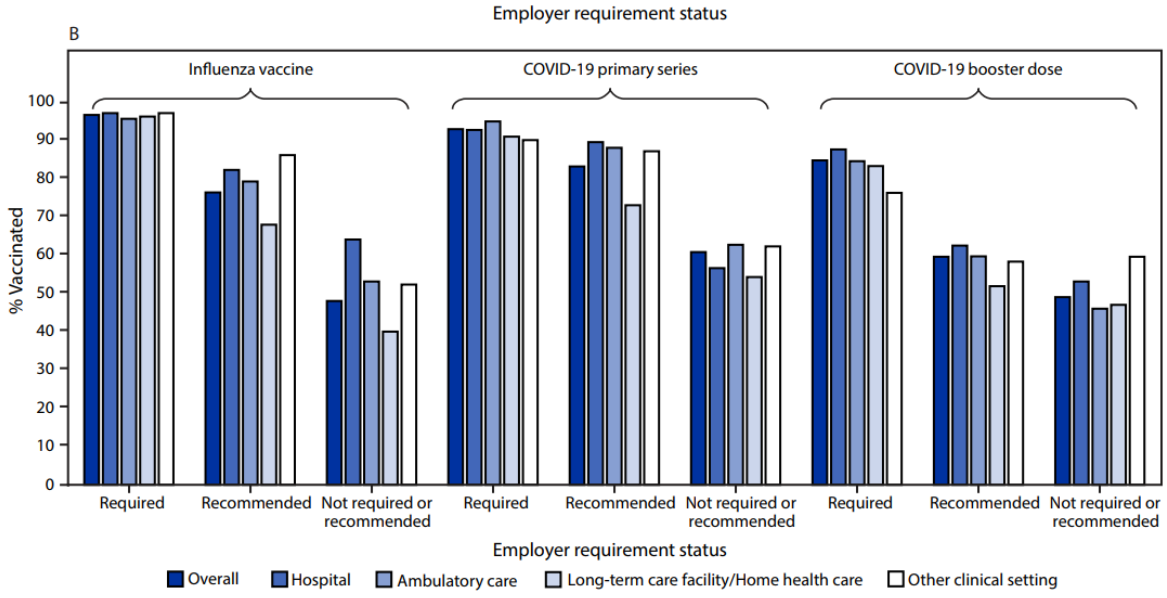
Comment: As we saw with Covid-19, racial and ethnic minorities disparities remain a significant barrier in improving community health. More needs to be done to bridge this gap.

Influenza and COVID-19 Vaccination Coverage Among Health Care Personnel — United States, 2021–22 MMWR 2022; 71:1319-1326

An Internet panel survey of HCP was conducted during March 29–April 19, 2022, to provide estimates of influenza and COVID-19 vaccination coverage among HCP during the 2021–22 influenza season. Similar surveys have been conducted annually since the 2010–11 influenza season, and previously published results. Respondents were recruited from two preexisting national opt-in Internet sources: Medscape, and general population Internet panels operated by Dynata. Responses were weighted to the distribution of the U.S. population of HCP by occupation, age, sex, race and ethnicity, work setting, and US Census Bureau region. A poststratification weight for each survey respondent was calculated by fitting a generalized exponential model and estimating the model parameters using calibration equations. Among 3,830 eligible participants, a total of 3,679 completed the survey (completion rate = 96.1%)

HCP influenza vaccination coverage was 79.9% during the 2021–22 season; 87.3% completed primary COVID-19 vaccination, 67.1% of whom received a COVID-19 booster dose. Influenza, primary COVID-19, and COVID-19 booster coverage was higher among HCP who reported employer vaccination requirements for those vaccines; coverage was lowest among HCP working in long-term care settings





Comment: Influenza, primary COVID-19, and COVID-19 booster coverage was higher among HCP who reported employer vaccination requirements for those vaccines; coverage was lowest among HCP working in long-term care settings. Vaccination status was self-reported and might be subject to recall or social desirability bias. In addition, insufficient sample size resulted in the coverage estimates in some subgroups not meeting the National Center for Health Statistics reliability criteria for reporting proportions. Enhanced efforts are still needed to improve HCP

vaccination coverage, especially with COVID-19 booster doses and annually for influenza vaccines. Staying up to date with COVID-19 and influenza vaccines can protect HCP and their patients.

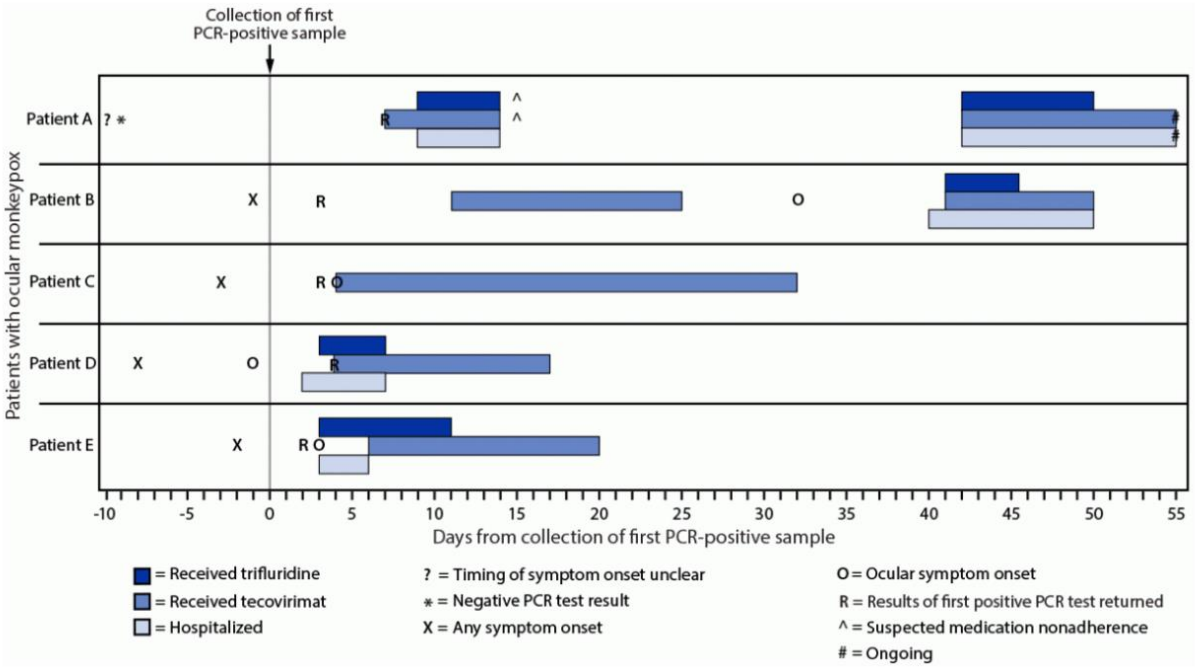
Monkeypox

Ocular Monkeypox — United States, July–September 2022 MMWR early release October 14, 2022

Ocular monkeypox can occur when Monkeypox virus (MPXV) is introduced into the eye (e.g., from autoinoculation), potentially causing conjunctivitis, blepharitis, keratitis, and loss of vision. This report describes 5 patients who acquired ocular monkeypox during July–September 2022.

In addition to body and genital rashes commonly seen in monkeypox patients, the case-patients with ocular monkeypox also developed eye redness, pain, discharge, itching, and photosensitivity.

Four of the five patients with ocular monkeypox required hospitalization, and two were also HIV-positive, according to a study from CDC and state researchers. Four of the five patients were men. One patient experienced significant vision impairment, and the authors caution that ocular monkeypox infection could result in permanent vision loss. The patient with significant vision impairment has been hospitalized since August, and the prognosis for vision recovery is unknown. Two patients had HIV-associated immunocompromise and experienced delays between clinical presentation with monkeypox and initiation of monkeypox-directed treatment.All patients received treatment with tecovirimat (Tpoxx); four also received topical trifluridine (Viroptic) treatment.



Comment: The authors say these cases should serve as a warning against autoinoculation. To decrease the risk for autoinoculation, persons with MPXV should be advised to practice hand

hygiene and to avoid touching their eyes, which includes refraining from using contact lenses. Patients with signs and symptoms compatible with ocular monkeypox should be considered for urgent ophthalmologic evaluation and initiation of monkeypox-directed treatment.

Monkeypox Virus Infection Resulting from an Occupational Needlestick — Florida, 2022 MMWR early release October 17, 2022

A handful of healthcare occupational exposure cases of monkeypox have been reported during the ongoing global monkeypox outbreak, and a Florida nurse's infection is the first such reported case in the United States.

The nurse worked in an emergency department, and a needlestick occurred when capping a needle used to swab the rash of a monkeypox patient. The nurse used a needle to create an opening in the vesicular lesion to facilitate direct contact of the swab with fluid in the lesion Within 15 hours of the event, the nurse received the first dose of Jynneos vaccine, but 10 days after the stick she developed a single lesion at the site of the accident.

During the next 19 days, the lesion at the needlestick site increased in size (remaining <1 cm in diameter) and became pruritic, deep-seated, and umbilicated, then scabbed over and a new layer of skin formed under the scab. Apart from this single lesion at the puncture site, no additional lesions or other clinical signs or symptoms were reported, and tecovirimat was not indicated. Last month, it was reported that a Brazilian nurse also contracted monkeypox via needlestick.

Comment: During the current outbreak, MPXV PCR testing cycle threshold values from swabbed skin and mucosal lesion specimens have been very low, indicating that surface swabbing collects enough viral material without a need to unroof lesions. Infection Prevention and Occupational Health should ensure that HCP are trained in proper specimen collection methods, follow recommended infection prevention and control precautions for the care of patients with monkeypox, and implement safety practices for managing sharps including not recapping needles.

Severe Monkeypox in Hospitalized Patients — United States, August 10–October 10, 2022 MMWR early release October 26, 2022

This article summarized findings from 57 patients hospitalized with severe monkeypox between August and October, 47 of whom (82%) had HIV infection. Most patients were male, more than two-thirds were non-Hispanic Black and nearly one-quarter of patients (23%) were experiencing homelessness. Overall, 17 patients (30%) received ICU-level care and 12 (21%) died. Among those who died, monkeypox was determined to be the cause of death or a contributing factor in five patients. Among the 47 patients with monkeypox who also HIV had, four (9%) were receiving ART before they were diagnosed with monkeypox. There were also two patients with HIV who were undergoing chemotherapy for a hematologic malignancy, three were solid organ transplant recipients, and three were pregnant.

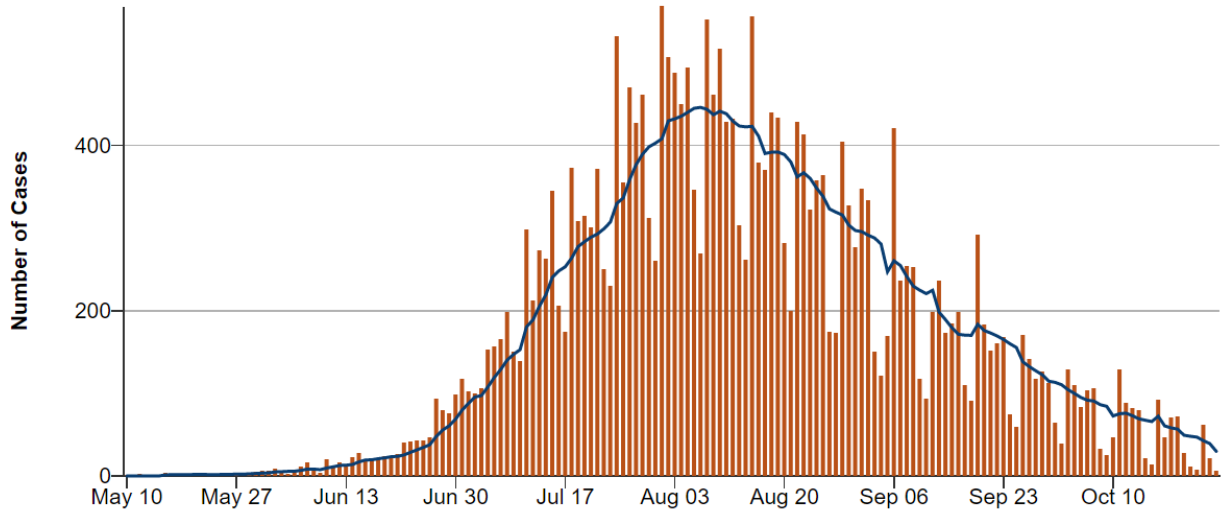
Comment: Authors recommend that health care providers should be testing all sexually active patients with suspected monkeypox for HIV at the time they test for monkeypox — unless their HIV status is known — and to start monkeypox therapy early, possibly before test results are

known, to limit risk for severe disease. This report also supports the importance for intense outreach to communities at most risk for monkeypox.

Monkeypox by the Numbers

U.S. Cases	U.S. Deaths	Global Cases
Total Cases	Total Deaths	Total Cases
28,302	6	76,806

Daily Monkeypox Cases Reported* and 7 Day Daily Average



Comment: The curve speaks for itself as cases continue to decrease. I think this trend is probably the result of changes in behavior and vaccination. The US still leads the world in number of cases.

COVID-19

Covid-19 News

FDA Authorizes Novavax Covid-19 Shot as Booster for Adults October 19, 2022

The Novavax booster was authorized on Wednesday for adults who received a primary series of vaccines at least six months prior and who don't want or can't access or might have medical reasons to avoid the dual-target booster shots from Pfizer or Moderna. CDC the signed off approving the booster.

Comment: The FDA's decision was based on clinical trial data showing that Novavax's booster increased antibodies both in patients who earlier received Novavax primary shots or who received messenger RNA shots. The shot was already authorized as a booster in the European Union, Japan, Australia, New Zealand, Switzerland, and Israel. According to CDC data, only 50% of adults who received their primary series have yet to receive their first booster dose. It is hoped that offering another vaccine choice may help increase Covid-19 booster vaccination rates for these adults, but I am skeptical.

ACIP Support Adding Covid-19 Vaccines to Regular Immunizations October 20, 2022

ACIP, voted unanimously on October 20th in support of including Covid-19 shots on the lists of measles, tetanus and other inoculations that adults and children 6 months and older should get in the US. The CDC has sign off. The CDC will publish the updated immunization lists in February.

Comment: To be clear, the addition of the Covid-19 vaccine to the lists would not mean the CDC would require them. Rather, the CDC is recommending people get the vaccine as a regular part of their vaccinations against long-running infectious diseases vaccinations. All states require schoolchildren to be vaccinated, with some specific exemptions, against communicable diseases such as polio, diphtheria, varicella, and MMR. ACIP said they went ahead with endorsing the vaccines for children, though the vaccines are not fully approved yet for children of all ages, because the benefits from use outweighed the risks. This recommendation will raise concerns about the safety of Covid-19 vaccines in children. We know that Covid-19 mRNA vaccination increased the incidence of diagnosed myocarditis in males 16 to 24. Studies also showed the risk of cardiac events are higher with natural infection, but based on the current high level of global immunity to Covid-19, does this change the equation? In the last edition of ID Watch I shared that in a pediatric serology study that over 85% of children now have some form of immunity to Covid-19 which may reduce the risk benefit of vaccination. In the end one of the major advances in public health has been the reduction and/or elimination of vaccine preventable diseases. An example, at ID Week investigators demonstrated since introducing varicella vaccination cases declined overall by more than 97% and fell in all age groups — including infants, who are not recommended to receive the vaccine, and adults, who are not routinely vaccinated and who can experience a more severe disease. Additionally, varicella hospitalizations and deaths declined 94% and 97% in people aged younger than 50 years. This achievement is highlighted in a supplement in J Infect Dis this month. [J Infect Dis 2022;226(S4):S375–9]

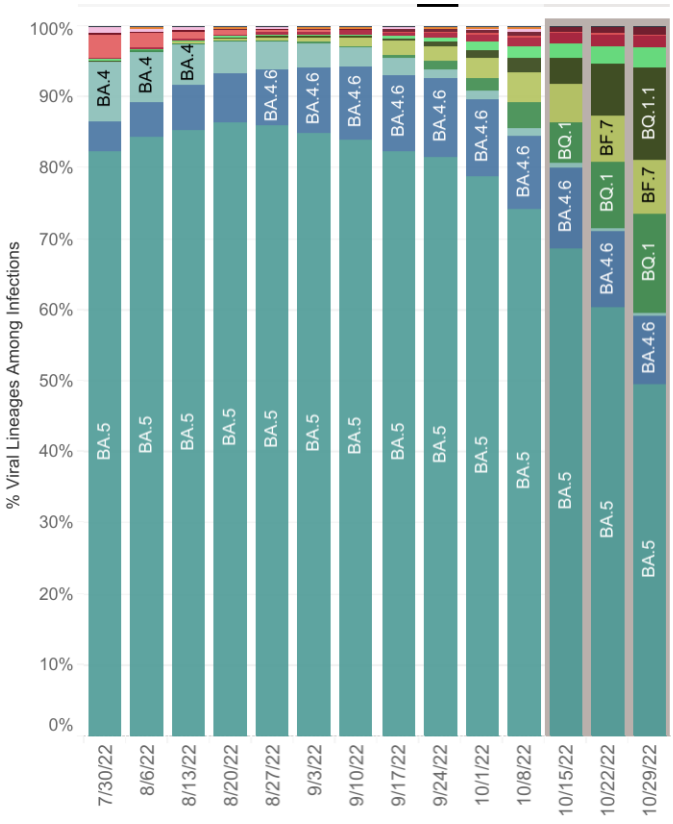
ACIP is a well-respected group of US scientists who have examined the evidence and unanimously recommended Covid-19 vaccines be added to regular vaccinations.

Variants' BQ.1 and BQ.1.1

The European Centre for Disease Prevention and Control (ECDC) late last week projected that the Omicron BQ.1 sublineage and its offshoots will likely fuel rises in COVID-19 activity in the weeks and months ahead. In its latest projections last week, the CDC said the BA.5 proportion is dropping steadily and is now at 62.2%. It also reported notable rises in other Omicron subvariants, with BQ.1 rising to 9.4%, followed by BQ.1.1 at 7.2% and BF.7 at 6.7%. see below

Early lab studies conducted in Asia suggest BQ.1 can evade immunity from vaccines or past infection but may not cause more severe illness, according to an October. 21 update from the ECDC. The WHO SARS-CoV-2 virus evolution advisory group held off on designating XBB (a recombinant of the BA.2.10.1 and BA.2.75 subvariants) and BQ.1 sublineages as variants of concern this past week even though BQ.1 proportions are rapidly rising in Europe and the United States. The WHO rationale is that XBB and BQ.1 don't currently diverge sufficiently from each other or from other Omicron lineages that have extra immune escape mutations to warrant a variant of concern designation or a new label. "The two sublineages remain part of Omicron, which continues to be a variant of concern," the group said.

In its updated variant proportion Friday October 28th, the CDC reported another steady rise in BQ.1 and BQ.1.1, which together make up 27.1% of subtyped lineages. The proportion of BA.5 viruses continues to drop steadily and is now at 49.6%, down from 60.3% the week before



USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	49.6%	45.3-53.9%
	BQ.1	VOC	14.0%	11.2-17.5%
	BQ.1.1	VOC	13.1%	9.8-17.3%
	BA.4.6	VOC	9.6%	8.6-10.7%
	BF.7	VOC	7.5%	6.6-8.5%
	BA.5.2.6	VOC	2.8%	2.3-3.5%
	BA.2.75	VOC	1.8%	1.5-2.2%
	BA.2.75.2	VOC	1.2%	0.9-1.6%
	BA.4	VOC	0.2%	0.2-0.3%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2 and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are

Comment: Now that we have 85-90% of our population with some form of immunity from natural disease and/or vaccination there is a lot more pressure for SARS-CoV-2 to diversify, which explains the number of subvariant circulating right now. With this diversity it is possible we may have several lineages circulating this fall/winter. Almost no one is masking. and we

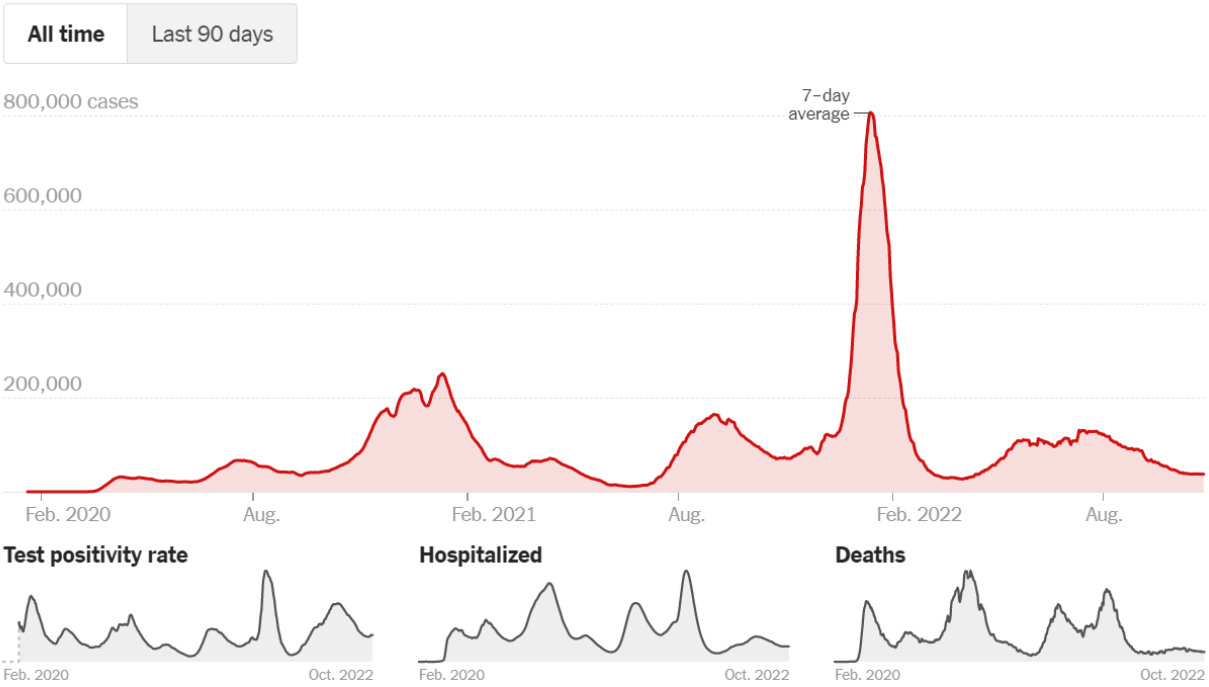
have low vaccination rates for the updated boosters, on top of as well as waning neutralizing immunity. The concern of a winter COVID-19 surge comes amid warnings of a severe influenza season at a time when much of the public has abandoned public health precautions. Daily global COVID-19 infections are projected to rise slowly to about 18.7 million by February from the current 16.7 million average daily cases, driven by the northern hemisphere's winter months, according to the University of Washington's Institute for Health Metrics and Evaluation. The report projects far fewer infections than last winter's estimated peak daily average of about 80 million cases in January of 2022 that was driven by the rapid spread of the Omicron variant. The increase in cases this winter, however, is not expected to cause a surge in deaths. Obviously, this could change if a new virulent variant emerges. See next report

The NIH COVID-19 Treatment Guidelines Panel's Statement on Omicron Subvariants and Anti-SARS-CoV-2 Monoclonal Antibodies October 19, 2022

The subvariants BQ.1 and BQ.1.1 are likely to be resistant to bebtelovimab, and the subvariants BA.4.6, BA.2.75.2, BF.7, BQ.1, and BQ.1.1 are likely to be resistant to tixagevimab plus cilgavimab (Evusheld). The anticipated loss of susceptibility is based on knowledge about amino acid mutations that confer antibody resistance and on available data from in vitro neutralization studies. [bioRxiv. 2022 at: biorxiv.org/content/10.1101/2022.09.15.507787v3.]

Comment: Although the proportions of these potentially resistant SARS-CoV-2 subvariants are increasing, their prevalence is currently low or moderate. The NIH COVID-19 Treatment Guidelines Panel continues to recommend bebtelovimab for the treatment of COVID-19 only when ritonavir/nirmatrelvir or remdesivir cannot be used in nonhospitalized adults who are at high risk of progressing to severe COVID-19. The good news: ritonavir/nirmatrelvir, remdesivir, and molnupiravir are expected to be active against these subvariants. The NIH Panel continues to recommend the anti-SARS-CoV-2 mAbs tixagevimab plus cilgavimab as pre-exposure prophylaxis (PrEP) for eligible individuals. The recommendations for the use of bebtelovimab for the treatment of COVID-19 and for the use of tixagevimab plus cilgavimab for PrEP will be updated if the prevalence of these subvariants increases which appears to be happening.

Covid-19 by the Numbers



Comment: The rate of improvement for cases and hospitalizations has begun to level off in recent weeks, and test positivity rate suggest we may see an uptick in the next month. The number of deaths announced each day has fallen steadily but slowly since September and remains above 350. [was 400 per day]

GAO Report: Maternal Health

Hundreds of women in the U.S. die each year from complications related to pregnancy and childbirth. Pregnant women with COVID-19 are more likely to experience complications.

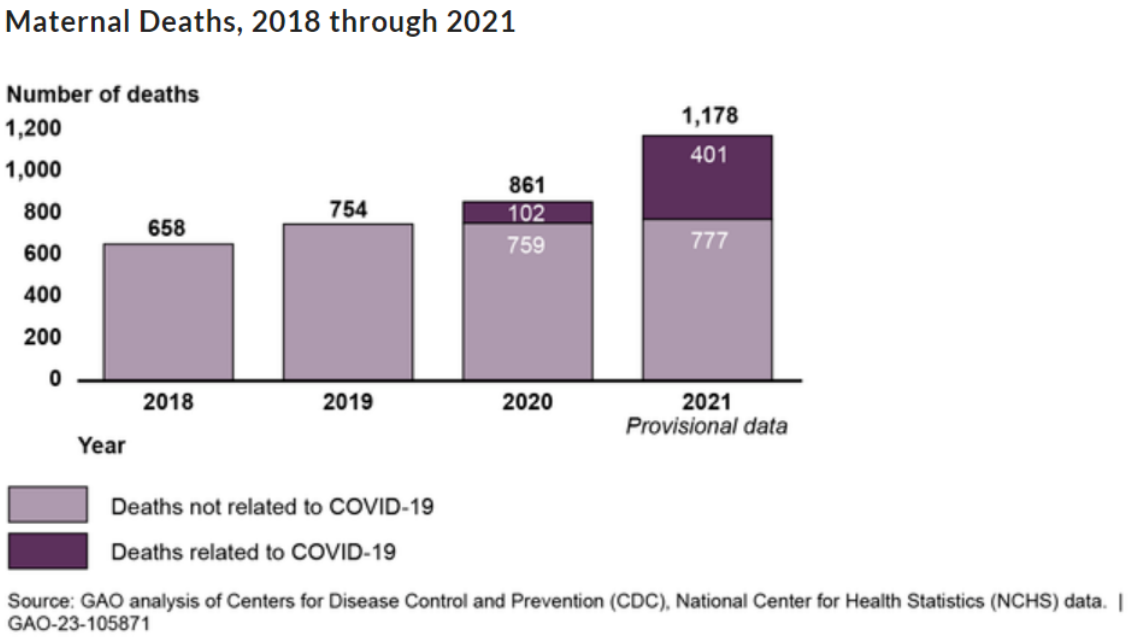
We analyzed CDC data and found:

- Maternal deaths increased during the pandemic compared to 2018 and 2019
- COVID-19 contributed to 25% of maternal deaths in 2020 and 2021
- The maternal death rate for Black or African American women was disproportionally higher compared to White and Hispanic or Latina women

CDC data also show racial and ethnic disparities in the rate of maternal deaths per 100,000 live births per year. For example:

- The maternal death rate for Black or African American (not Hispanic or Latina) women was 44.0 per 100,000 live births in 2019, then increased to 55.3 in 2020, and 68.9 in 2021. In contrast, White (not Hispanic or Latina) women had death rates of 17.9, 19.1, and 26.1, respectively.
- The maternal death rate for Hispanic or Latina women was lower (12.6) compared with White (not Hispanic or Latina) women (17.9) in 2019, but increased significantly during the pandemic in 2020 (18.2) and 2021 (27.5).

Disparities in other adverse outcomes, such as preterm and low birthweight births, persisted for Black or African American (not Hispanic or Latina) women, according to GAO analysis of CDC data.



Source: GAO analysis of Centers for Disease Control and Prevention (CDC), National Center for Health Statistics (NCHS) data. | GAO-23-105871

Comment: The pandemic exacerbated the effects of social determinants of health—factors such as access to care, transportation, or technology; living environment; and employment—on maternal health disparities. The issue of social disparities is not new. The challenge is how do we address this need in a meaningful and sustainable way.

COVID-19 Journal Review

A multicenter comparison of prevalence and predictors of antimicrobial resistance in hospitalized patients before and during the SARS-CoV-2 pandemic

OFID published online October 17, 2022

doi/10.1093/ofid/ofac537/6761815

To evaluate changes in AMR rates among hospital patients before and during the pandemic, researchers from 271 US facilities in the BD Insights Research 7 Database with Merck and Becton, Dickinson and Company analyzed record on adults hospitalized for at least 1 day at 271 US hospitals from July 2019 through October 2021. The goal of our study was to evaluate changes in AMR rates in bacteria in the United States before and 26 during the COVID-19 pandemic among inpatients admitted to facilities included in the BD Insights Research Database.

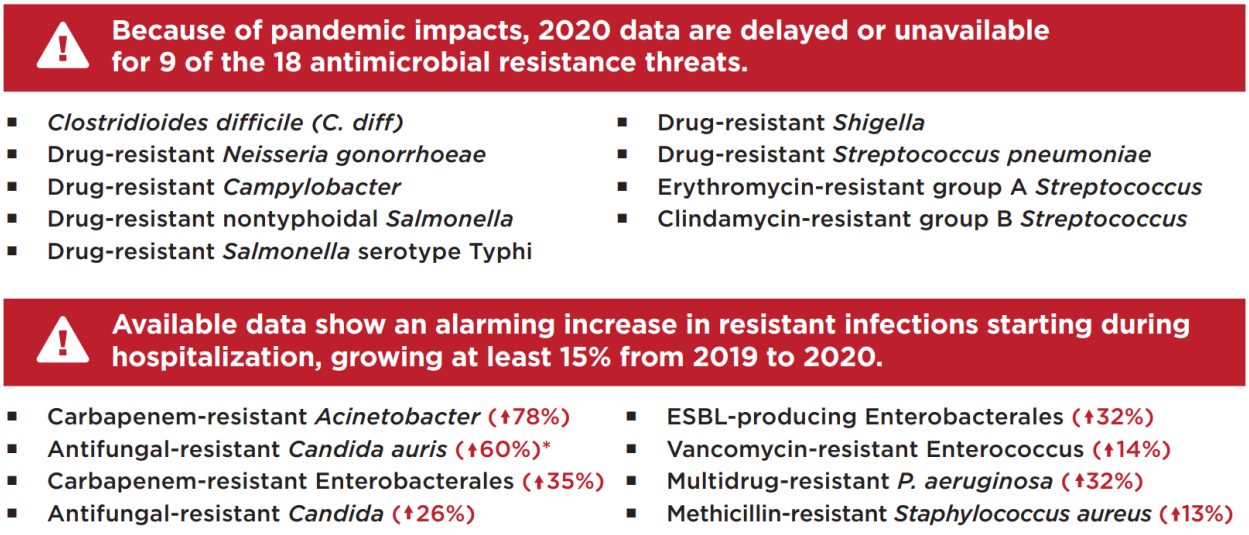
All admissions with an AMR event [defined in Table 1 in article], defined as a non-contaminated first positive culture for gram-negative or gram-positive pathogens of interest with reported non-susceptibility, were included in the analysis. as a non-contaminated first positive culture for Gram-negative (GN) and Gram-positive (GP) pathogens of interest 17 from respiratory, blood,

urine, skin/wound, intraabdominal or other source. The investigators evaluated overall AMR rates, comparing the pre-pandemic period (July 2019 through February 2020) with the pandemic period (March 2020 through October 2021).

Of the more than 5.5 million admissions evaluated, AMR events were detected in 35.4 per 1,000 admissions during the pre-pandemic period and 34.7/1,000 admissions during the pandemic period. Patients tested for SARS-CoV-2 had a significantly higher AMR rate than that observed in the pre-pandemic period (49.2/1,000 admissions for patients who tested positive, 41.1/1,000 admissions for negative patients, and 25.7/1,000 admissions for untested patients).

AMR rates among community-onset (CO) infections during the pandemic were lower compared with pre-pandemic levels (26.1/1,000 admissions vs 27.6/1,000), while AMR rates for hospital-onset (HO) infections were higher (8.6/1,000 admissions vs 7.7/1,000), driven largely by SARS-CoV-2–positive admissions (21.8/1,000 admissions). Multivariable analysis found that rates of AMR were associated with overall antibiotic use, rates of positive cultures, longer hospital stays, and higher use of inadequate empiric antibiotic therapy.

Comment: Although overall AMR rates did not substantially increase from pre-pandemic levels, patients tested for SARS-CoV-2 infection did have a significantly higher rate of AMR and HO infections. Antimicrobial and diagnostic stewardship is key to identifying this high-risk AMR population infections. This report is consistent with a recent CDC report that highlights increased AMR during the pandemic reported in ID Watch.



Most studies have focused on AMR patterns in the ICU, additional information on AMR in the overall inpatient population is needed. Moreover, because most AMR analyses were conducted relatively early in the pandemic, so the influence of COVID-19 therapeutics, vaccinations, and variants on AMR has yet to be thoroughly evaluated.

Estimated Protection of Prior SARS-CoV-2 Infection Against Reinfection With the Omicron Variant Among Messenger RNA–Vaccinated and Nonvaccinated Individuals in Quebec, Canada

JAMA Netw Open 2022;5(10): e2236670.

doi:10.1001/jamanetworkopen.2022.36670

Investigators conducted a test-negative case-control study of 224,007 infected participants and 472,432 uninfected controls aged 12 years and older tested for COVID-19 in Quebec from Dec 26, 2021, to Mar 12, 2022, before the emergence of the more highly contagious Omicron BA.4 and BA.5 subvariants.

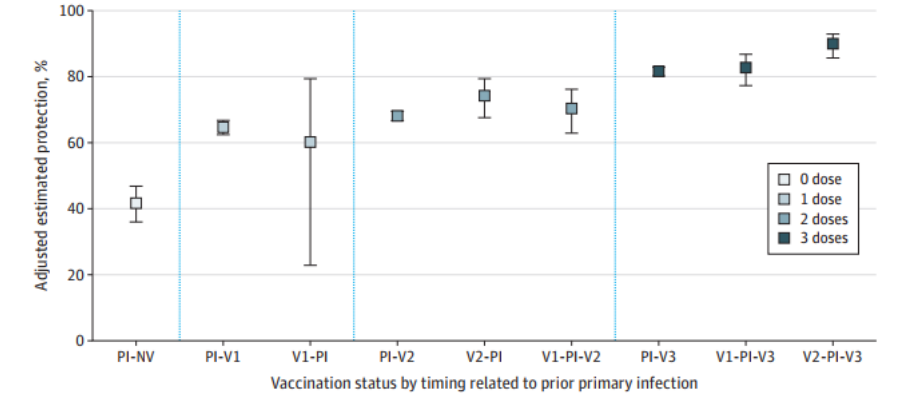
In the respective cohorts, 62.2% and 63.9% of participants were female, 87.4% and 75.5% were aged 18 to 69 years, and 4.2% of infected participants and 6.3% of controls had been previously infected with a non-Omicron strain. In unvaccinated participants, previous non-Omicron infection was linked to a 44% lower risk of Omicron infection; protection was 66% 3 to 5 months post-infection, falling to 35% at 9 to 11 months and to under 30% thereafter. Severe previous infection conferred the greatest protection.

Among previously infected participants, mRNA COVID-19 vaccination was associated with risk reductions in Omicron infection of 65% after one dose (vs 20% among the unvaccinated), 68% after two doses (vs 42%), and 83% after three doses (vs 73%).

Estimated protection against Omicron-related hospitalization among previously infected participants was 81%, rising to 86% after one vaccine dose, 94% after two doses, and 97% after three doses, with no evidence of waning.

The study authors noted that Omicron is the most highly transmissible and immune-evasive SARS-CoV-2 variant to date, and protection against Omicron infection and hospitalization from a previous infection was comparable to the protection provided by two mRNA vaccine doses.

Figure. Prior SARS-CoV-2 Infection and Messenger RNA Vaccine Effectiveness Against Omicron Reinfection in Quebec, Canada, by Number of Doses and Timing



PI=prior infection

Comment: The findings of this study suggest that vaccination with 2 or 3 mRNA vaccine doses among individuals with prior heterologous SARS-CoV-2 infection provided the greatest protection against Omicron-associated hospitalization. In the context of program goals to prevent severe outcomes and preserve health care system capacity, a third mRNA vaccine dose may add limited protection in twice-vaccinated individuals with prior SARS-CoV-2 infection. Unrecognized or undocumented PIs may have led to underestimation of infection-induced protection.

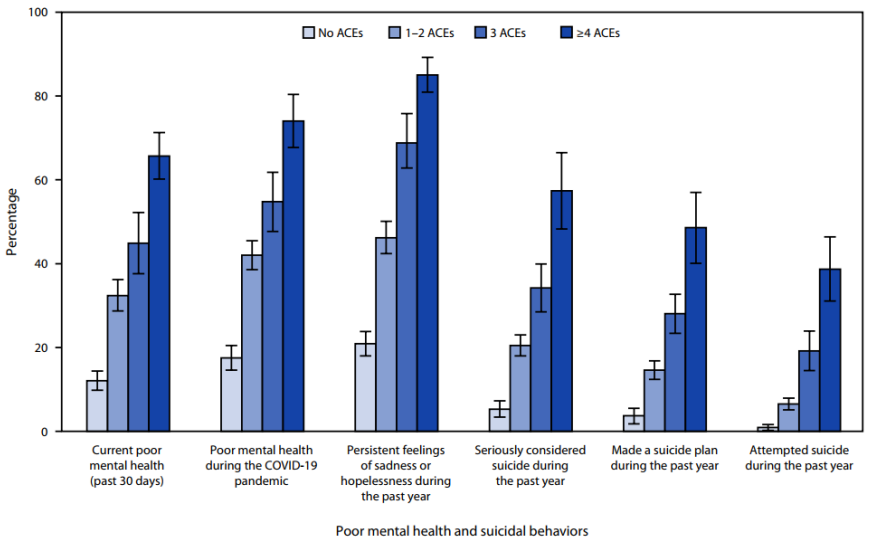
Adverse Childhood Experiences During the COVID-19 Pandemic and Associations with Poor Mental Health and Suicidal Behaviors Among High School Students — Adolescent Behaviors and Experiences Survey, United States, January–June 2021 MMWR 2022; 71:1301-1305

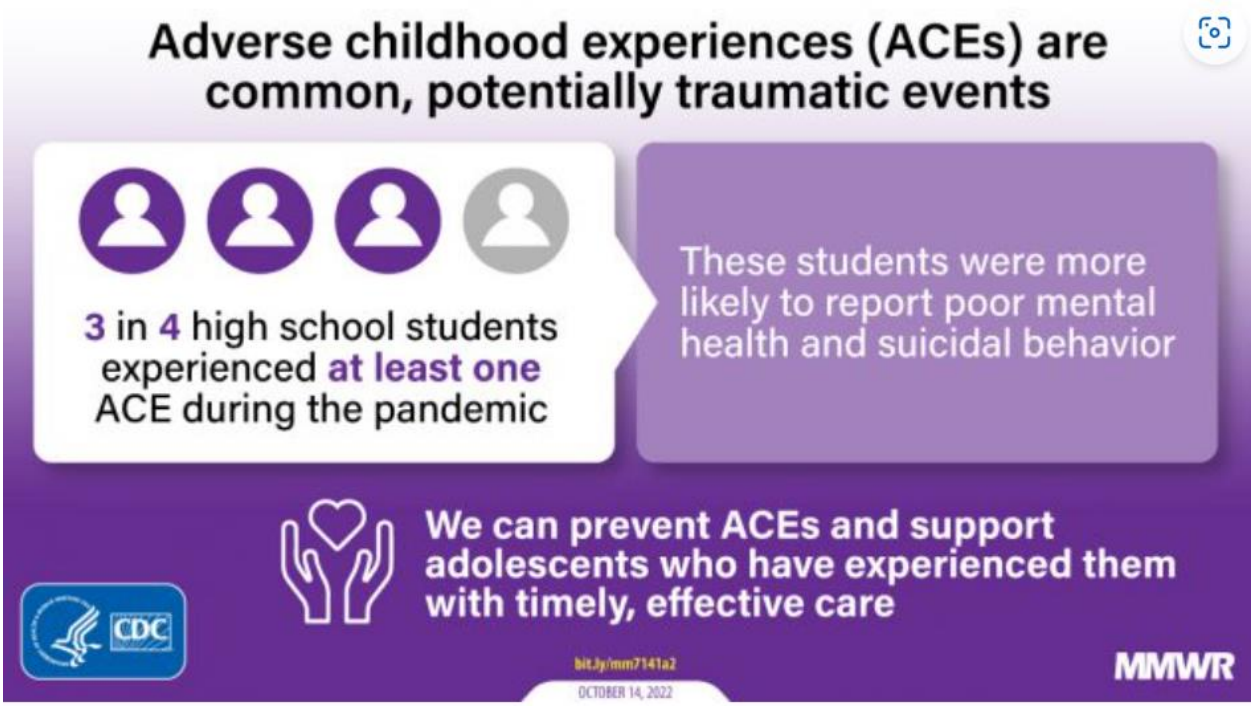
Data from the 2021 Adolescent Behaviors and Experiences Survey (ABES) indicate that 37.1% of U.S. high school students reported poor mental health during the COVID-19 pandemic, with 19.9% considering and 9.0% attempting suicide in the preceding year (MMWR Suppl 2022;71(Suppl 3):16–21). Adverse childhood experiences (ACEs) are associated with poor mental health and suicidal behaviors (Child Abuse Negl 2019;97:104127), and high prevalence of some ACEs have been documented during the pandemic (MMWR Suppl 2022;71(Suppl 3):28–34)

The voluntary, probability-based online ABES used stratified, three-stage cluster sampling to obtain nationally representative data from U.S. public and private high school students in grades 9–12 during January–June 2021. Students self-reported experiences of some adversities during the COVID-19 pandemic (i.e., emotional abuse, physical abuse, parent or caregiver job loss, and food insecurity) or during the past 12 months (i.e., sexual violence by any perpetrator, physical teen dating violence, and electronic bullying), as well as their mental health (i.e., current poor mental health, poor mental health during the pandemic, and persistent feelings of sadness or hopelessness during the past year) and suicidal behaviors (i.e., seriously considering suicide, making a suicide plan, or attempting suicide during the past year). The analysis was restricted to 4,390 high school students aged <18 years with complete data on analytic variables, to align with the ACEs focus. ACEs were examined by type (e.g., emotional abuse), category (e.g., exposure to either of the two abuse-related ACEs), and cumulative number of ACEs (zero, one to two, three, and four or more). Weighted pairwise prevalence estimates and 95% CIs for reported ACE exposure by poor mental health or suicidal behaviors were calculated. Adjusted prevalence ratios (aPRs) and 95% Cis were calculated using Poisson regression with robust SEs to examine associations between reported ACE exposure during the pandemic and mental health or suicidal behaviors, with and without inclusion of other ACEs.

Nearly three quarters (73.1%) of high school students aged <18 years reported at least one ACE during the COVID-19 pandemic (53.2%, 12.0%, and 7.8% reported one to two, three, and four or more ACEs, respectively (mean = 1.47; SE = 0.04). Compared with adolescents without ACEs, adolescents who reported one to two ACEs during the pandemic had higher prevalence of poor mental health and suicidal behaviors (aPR range = 1.97–2.39 and 3.29–5.92, respectively). A dose-response relationship between accumulating exposure to ACEs during the pandemic and poor mental health and suicidal behaviors was observed. Compared with adolescents without ACEs, adolescents with four or more ACEs during the pandemic had a prevalence of poor mental health three to four times as high (aPR range = 3.04–4.06) as well as substantially higher prevalence of past-year suicidal behaviors (seriously considering suicide: 57.4% versus 5.3%, aPR = 7.06, 95% CI = 5.02–9.93; making a suicide plan: 48.6% versus 3.7%, aPR = 8.27, 95% CI = 5.09–13.42; attempted suicide: 38.7% versus 0.9%, aPR = 25.06, 95% CI = 11.35–55.30), after adjusting for demographic characteristics (Table 1). After adjusting for demographic characteristics, experience of each ACE type was associated with a higher prevalence of current poor mental health (aPR range = 1.26–2.22), poor mental health during the COVID-19 pandemic (aPR range = 1.28–1.87), and past-year persistent feelings of sadness or hopelessness (aPR range = 1.21–1.94).

FIGURE. Number of adverse childhood experiences during the COVID-19 pandemic and crude prevalences of poor mental health and suicidal behaviors* among high school students (N = 4,390) — Adolescent Behaviors and Experiences Survey, United States, 2021





Comment: Nearly three of every four US high school students reported at least one ACE, and one in 13 (7.8%) reported four or more ACEs during the COVID-19 pandemic. Comparable prepandemic estimates of cumulative ACE exposure among US adolescents are limited. Concerns about poor adolescent mental health and suicidal behaviors preceded the COVID-19 pandemic but escalated during the pandemic. Exposure to specific ACE types (e.g., emotional abuse) were associated with higher prevalence of poor mental health and suicidal behaviors. Primary prevention and intervention strategies for ACEs and their acute and long-term impacts, including early identification and trauma-informed mental health service and support provision, are critical to address the US child and adolescent mental health and suicide crisis.

Clinical Effectiveness and Safety of Remdesivir in Hemodialysis Patients with COVID-19 Kidney International Rep published online September 9, 2022

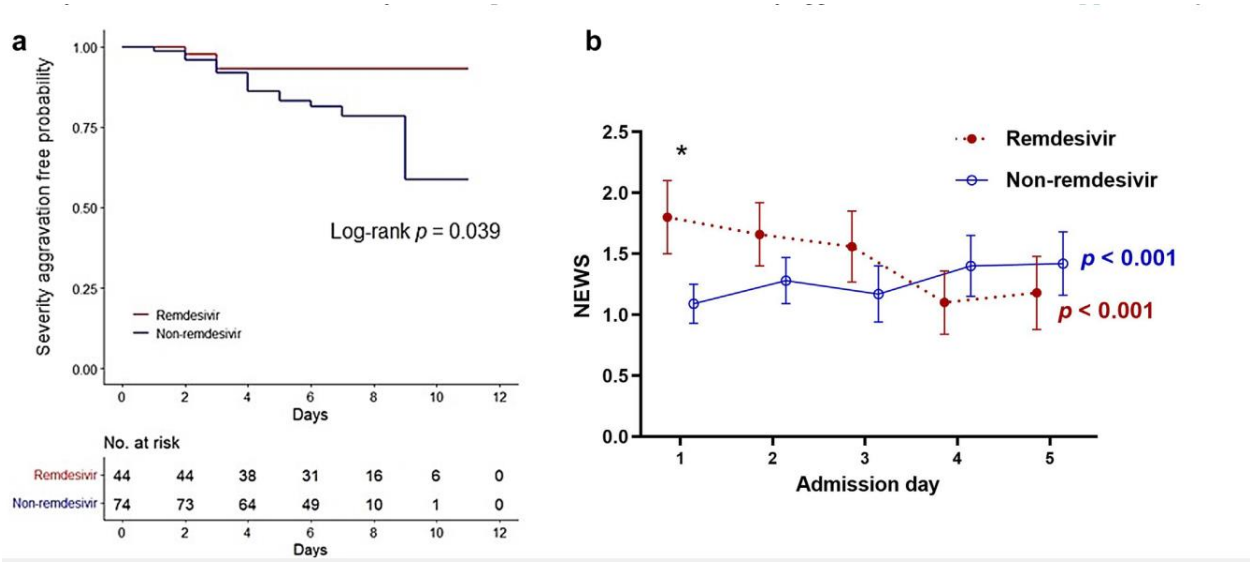
doi.org/10.1016/j.ekir.2022.08.031

Clinical trials that evaluated the effect of remdesivir did not include patients with an estimated glomerular filtration rate < 30 ml/min per 1.73 m^2; therefore, the safety and clinical effectiveness of remdesivir remain to be confirmed in patients with end-stage kidney disease. Therefore, drugs like RDV are restricted in patients on hemodialysis(HD) because of the lack of safety and efficacy data.

All hospitalized patients with COVID-19 who are on HD were analyzed from a retrospective cohort between January 26, 2022, and March 31, 2022, when the Omicron variant was the dominant variant. The primary outcome was a composite of in-hospital mortality, use of a high-flow nasal cannula, or transfer to the ICU. The secondary outcomes were aggravation of disease severity according to the National Institutes of Health COVID-19 severity criteria and changes in the National Early Warning Score (NEWS) during hospitalization.

All hospitalized patients received symptomatic care, including oxygen, antipyretics, and antitussive agents. Specialists in infectious diseases and nephrology prescribed remdesivir, antibiotics, and dexamethasone. RDV was administered to patients with moderate severity within 7 days of symptom onset or to those with severe COVID-19. The loading dose was 100 mg; the maintenance dose was 50 mg for the next 2 to 4 days depending on the patient's status, and it was injected after hemodialysis on the day of dialysis.

The proportion of antibiotics used was similar, and the RDV group required more dexamethasone than the non-RDV group. The proportion of patients who received oxygen therapy, a high-flow nasal cannula, and mechanical ventilation did not differ between the 2 groups. Six deaths occurred during hospitalization (1 [2.3%] in the RDV group and 5 [6.8%] in the non-RDV group), and the mortality was not different between the 2 groups (P = 0.284). Nevertheless, the composite outcome of mortality, use of a high-flow nasal cannula, and transfer to the ICU occurred less frequently in the RDV group (1 [2.3%] vs. 10 [13.5%], P = 0.042). Disease severity aggravation rate was also lower in the RDV group (3 [6.8%] vs. 15 [20.3%], P =0.049). In the multivariate logistic regression analyses, RDV use was independently associated with a lower occurrence of the composite outcome (adjusted odds ratio, 0.01, 95% confidence interval, 0.001–0.31, P¼ 0.009) and severity aggravation (adjusted odds ratio, 0.08, 95% confidence interval, 0.02–0.42, P ¼ 0.003). In the Kaplan–Meier estimate of disease severity aggravation, the RDV group also showed a better prognosis with a lesser incidence of severity aggravation (log rank P = 0.039). In the RDV group, dexamethasone was not associated with the aggravation of disease severity in the multivariate logistic regression model and Kaplan–Meier analysis. NEWS significantly decreased over time in the RDV group (P < 0.001), whereas the non RDV group showed an increase in the NEWS (P < 0.001). The incidence of elevation of liver enzymes during hospitalization did not differ between the RDV and non-RDV groups (22.7% vs. 17.6%, P = 0.494).



Comment: This study found an association between the clinical effectiveness and RDV use in SARS-CoV-2 infected patients on HD. The RDV group had a lower risk of the composite outcome and aggravation of disease severity, despite the higher disease severity at hospitalization than the non-RDV group. In addition, there were no serious side effects, such as hepatic failure. This is a retrospective study; therefore, there is always a chance of unaccounted bias. Second, the number of patients was too small to make a clear conclusion, and the long-term effect of RDV use could not be identified. The result of this study nonetheless suggests RDV may be used in patients with COVID-19 who are on hemodialysis after considering its benefits and risks.

Association of mRNA Vaccination With Clinical and Virologic Features of COVID-19 Among US Essential and Frontline Workers JAMA. 2022; 328:1523-1533.

doi:10.1001/jama.2022.18550

In this study, HEROES-RECOVER Network investigators analyzed the weekly self-collected nasal swabs and whole-genome sequencing results from 1,199 frontline workers infected with COVID-19 from December 14, 2020, to April 19, 2022, with follow-up until May 9, 2022.

The workers, primarily HCP and first responders, were located in Arizona, Florida, Minnesota, Oregon, Texas, and Utah. Median age was 41 years, 59.5% were women, 72.6% were White, 19.3% were Hispanic, 14% were infected with the wild-type strain, 24.0% had a Delta variant case, and 62.0% had Omicron.

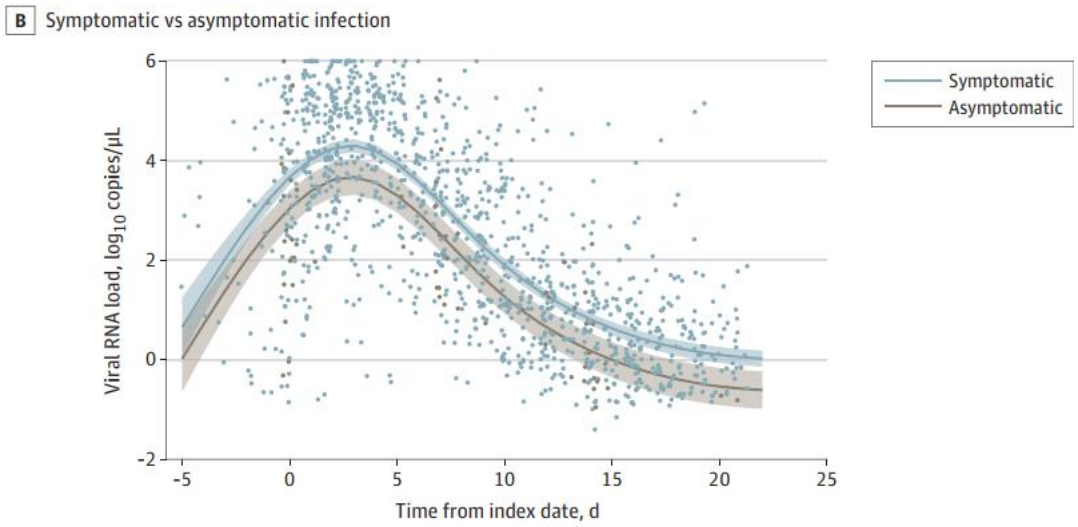
Of the 352 COVID-19 infections among the unvaccinated, 12.5% were asymptomatic, and 6.8% had uncharacteristic symptoms. Asymptomatic cases were more often linked to Omicron than Delta infections (odds ratio [OR], 5.6).

Among participants with symptoms, those with Omicron infections had symptoms for, on average, 12.3 days, compared with 15.6 days with wild-type infections and 16.4 days with Delta. Omicron-infected participants reported an average of 2.6 days sick in bed, 1.2 days fewer than those with wild-type infections and 2.0 days fewer than those with Delta. Vaccinated patients had milder Delta illnesses, but the precision of the estimates varied.

Workers who received their second vaccine dose 14 to 149 days before Delta infection were significantly less likely than their unvaccinated participants to have symptoms (77.8% vs 96.1%; OR, 0.13). When they were symptomatic, third-dose recipients were significantly less likely to have fever or chills (38.5% vs 84.9%; OR, 0.07), had symptoms for fewer days (10.2 vs 16.4; difference, -6.1), and reported fewer hours of work missed (47.1 vs 62.8; difference, -15.2).

Among Omicron-infected workers, the risk of symptoms didn't differ significantly between two-dose compared with unvaccinated participants but was significantly higher for three-dose recipients (88.4% vs 79.4%; OR, 2.0). Workers with symptomatic Omicron infections who received a third vaccine dose 7 to 149 days earlier were significantly less likely to have fever or chills than the unvaccinated (51.5% vs 79.0%; OR, 0.25) and were less likely to seek medical attention (14.6% vs 24.7%; OR, 0.45).

Symptomatic participants had significantly higher average viral loads than those with no symptoms. Delta- and Omicron-infected workers who received a second vaccine dose 14 to 149 days earlier had a significantly lower average viral load than their unvaccinated counterparts. (3 vs 4.1 log10 copies/μL; difference, -1.0 [95% CI, -1.7 to -0.2] for Delta and 2.8 vs 3.5 log10 copies/μL, difference, -1.0 [95% CI, -1.7 to -0.3] for Omicron).

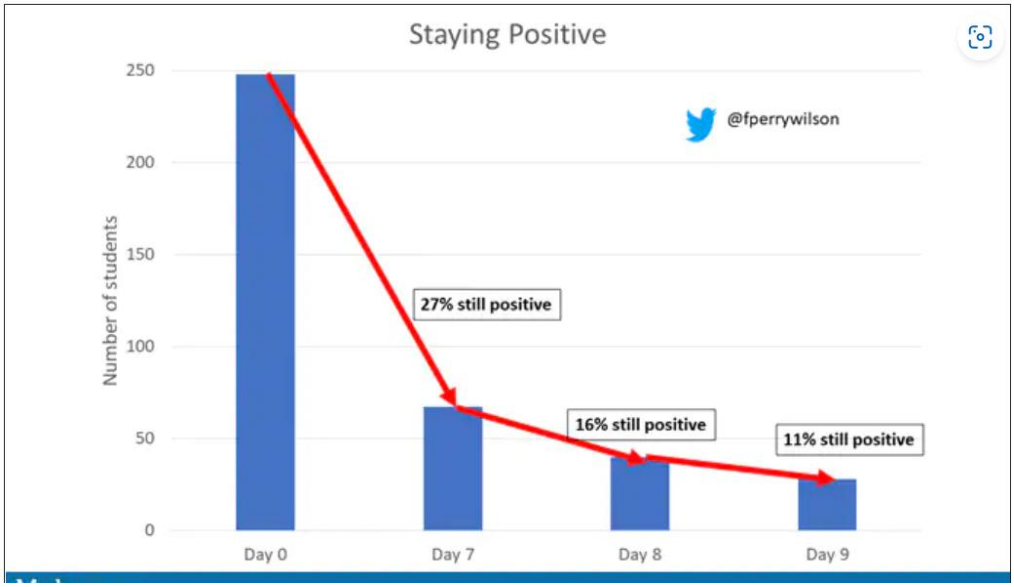


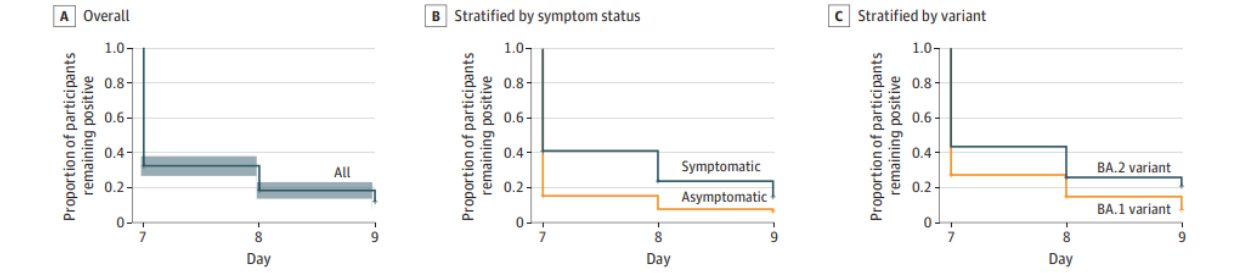
Comment: This study of essential and frontline workers in six US states who tested positive for COVID-19 and received two or three mRNA vaccine doses before Delta infections and three doses before Omicron infections suggests that they had significantly milder infections and lower viral loads than their unvaccinated peers. Although viral RNA shedding cannot be directly attributable to transmission, the relatively high viral load of Omicron infections together with the higher frequency of asymptomatic infection supports previous studies suggesting an association with increased transmission, particularly during the first 3 to 5 days when viral load peaked especially if symptomatic. See below

Prevalence of Positive Rapid Antigen Tests After 7-Day Isolation Following SARS-CoV-2 Infection in College Athletes During Omicron Variant Predominance JAMA Netw Open published online October 18, 2022

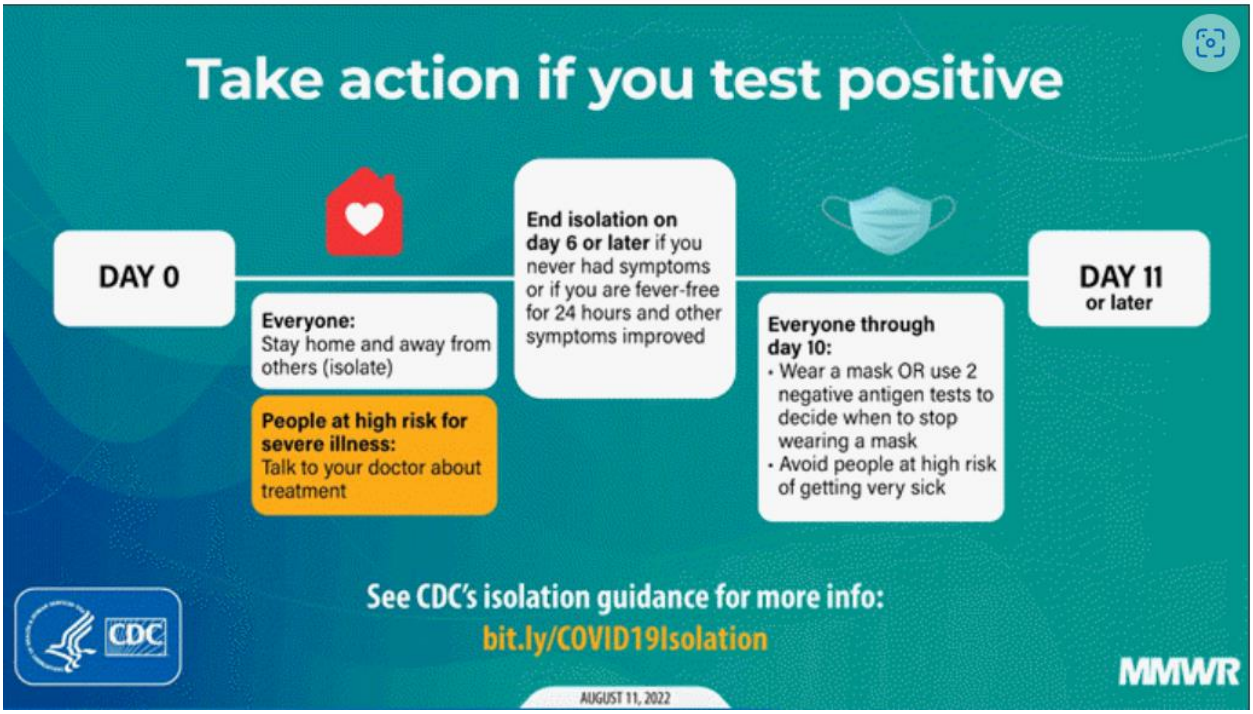
doi:10.1001/jamanetworkopen.2022.37149

In this case series, 268 collegiate student athletes who tested positive for SARS-CoV-2 underwent rapid antigen testing starting 7 days after the initial positive test. At 7 days, the results of testing were still positive in 27% of the individuals tested, with a higher percent positive in symptomatic individuals and those infected with the Omicron BA.2 variant.





Comment: One of the more baffling decisions the CDC made during this pandemic was when they reduced the duration of isolation after a positive COVID test from 10 days to 5 days and did *not* require a negative antigen test to end isolation. Multiple studies had suggested, after all, that positive antigen tests, while not perfect, were a decent proxy for infectivity. [Sc Reports 2021 11:22863]



The CDC–recommended 5-day isolation period may be insufficient in preventing ongoing spread of disease. Further studies are needed to determine whether these findings are present in a more heterogeneous population and in subsequent variants. (See above) Wastewater samples were used to infer the circulating variant rather than clinical samples because a large number of students in the cohort never underwent PCR testing, limiting the availability of samples for sequencing. The university discontinued mandatory surveillance testing partway through the study period; thus, there are fewer asymptomatic infections in the BA.2 variant cohort, which represents the latter half of the testing period. All participants in this study were college-aged, fully vaccinated, and had received booster doses if eligible, limiting the generalizability to unvaccinated or partially vaccinated populations and to the general population.

Neutralization Escape by SARS-CoV-2 Omicron Subvariant BA.4.6 N Engl J Med published online October 19, 2022

DOI: 10.1056/NEJMc2212117

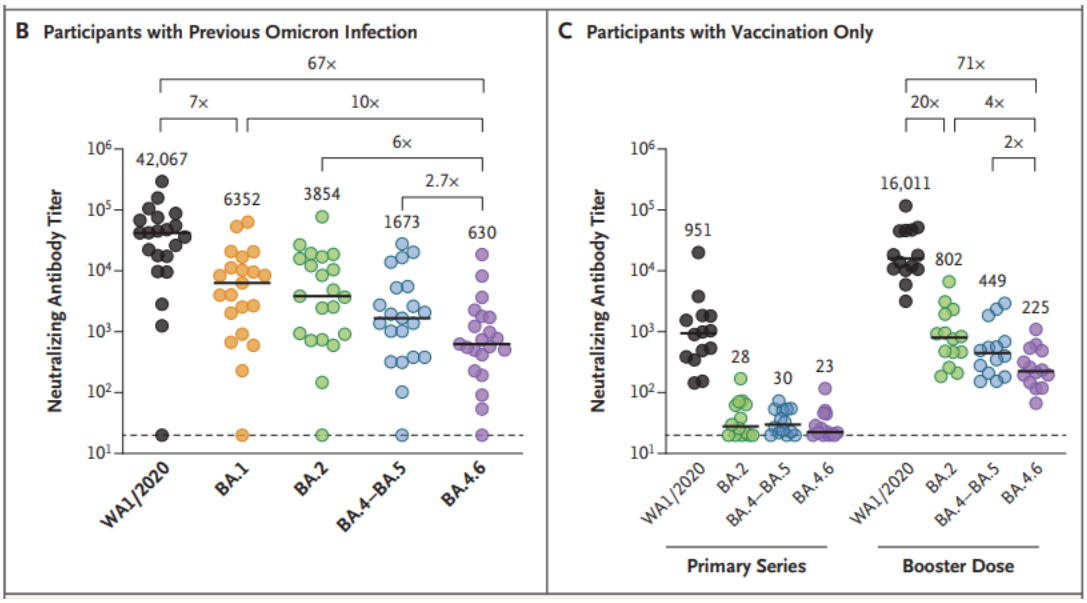
BA.4.6 is a sublineage of BA.4 with two additional mutations in the spike protein (R346T and N658S) and has recently increased in prevalence in certain regions currently dominated by BA.5, including in the US. The ability of BA.4.6 to evade neutralizing antibodies that were induced by infection or vaccination remains unclear.

In the study, investigators evaluated neutralizing antibody titers against five SARS-CoV-2 strains — WA1/2020(ancestral strain) and omicron subvariants BA.1, BA.2, BA.4–BA.5, and BA.4.6 — in 19 participants (median age 33 years) who had been recently infected with the omicron BA.1 or BA.2 subvariant and in 16 participants (median age 36 years) who had been vaccinated and boosted with the original Moderna vaccine.

In the cohort with previous omicron infection, all participants except for one had been vaccinated. Of these vaccinated participants, 15 had received three vaccine doses. Samples were obtained a median of 21 days after diagnosis of omicron infection. In this cohort, the median pseudovirus neutralizing antibody titer was 42,067 against WA1/2020, 6,352 against BA.1, 3,854 against BA.2, 1,673 against BA.4–BA.5, and 630 against BA.4.6. The median neutralizing antibody titers against BA.4.6 were found to be lower than the median titers against WA1/2020 by a factor of 67, against BA.1 by a factor of 10, against BA.2 by a factor of 6, and against BA.4–BA.5 by a factor of 2.7.

In the Moderna vaccinated and boosted cohort, participants were excluded if they had a known history of SARS-CoV-2 infection or positive results on nucleocapsid serologic analysis or if they had received immunosuppressive medications or other vaccines against SARS-CoV-2.

Six months after the initial Moderna immunizations, the median neutralizing antibody titer was 951 against WA1/2020, 28 against BA.2, 30 against BA.4–BA.5, and 23 against BA.4.6. At a median of 17 days after the first booster dose, the median neutralizing antibody titer was 16,011 against WA1/2020, 802 against BA.2, 449 against BA.4–BA.5, and 225 against BA.4.6. The median neutralizing antibody titer against BA.4.6 was lower than that against WA1/2020 by a factor of 71, against BA.2 by a factor of 4, and against BA.4–BA.5 by a factor of 2.



Comment: Their data show that the BA.4.6 omicron subvariant markedly escaped neutralizing antibodies induced by infection or vaccination, with values that were lower than BA.5 titers by a factor of 2 to 2.7, which suggests continued evolution of SARS-CoV-2. This may explain the immunologic context for the increasing prevalence of BA.4.6 in populations in which BA.5 is currently dominant although now decreasing.

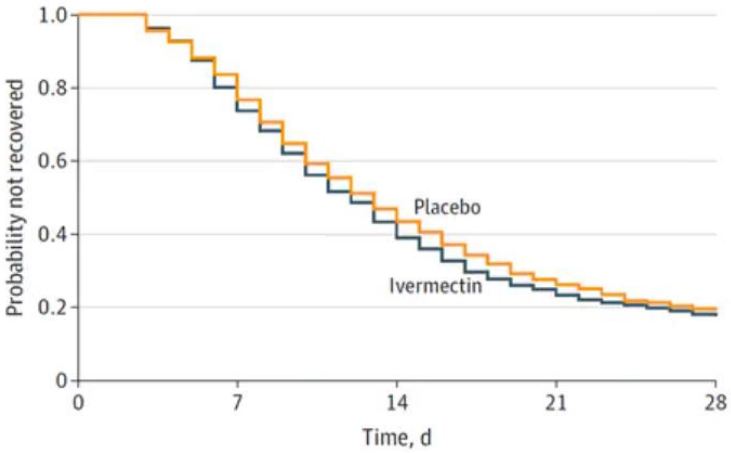
Effect of Ivermectin vs Placebo on Time to Sustained Recovery in Outpatients With Mild to Moderate COVID-19 A Randomized Clinical Trial JAMA published online October 21, 2022

doi:10.1001/jama.2022.18590

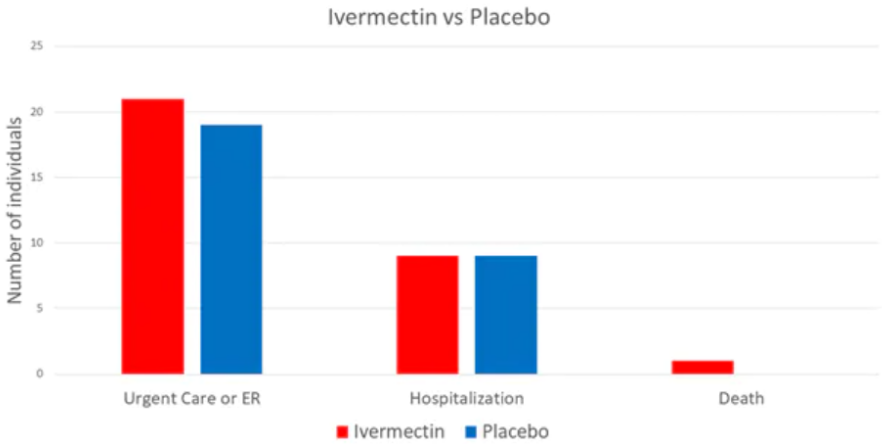
ACTIV-6 is a double-blinded, randomized, placebo-controlled platform trial in outpatients with COVID-19 from 93 sites around the United States to ivermectin or placebo conducted in the US during a period of Delta and Omicron variant predominance, and that included 1591 adult outpatients with COVID-19,

A total of 1591 individuals — median age 47, 60% female — with confirmed symptomatic COVID-19 were randomized from June 2021 to February 2022. About half had been vaccinated.

The primary outcome was time to clinical recovery. The time to recovery, defined as having three symptom-free days, was 12 days in the ivermectin group and 13 days in the placebo group.



Serious outcomes, like death, hospitalization, urgent care, or ER visits, occurred in 32 people in the ivermectin group and 28 in the placebo group. Death itself was rare — just one occurred in the trial, in someone receiving ivermectin.



Comment: These findings do not support the use of ivermectin in outpatients with mild to moderate COVID-19. This study supports the results of the TOGETHER Trial [N Engl J Med March 30, 2022, reported in ID Watch] In the TOGETHER trial treatment with ivermectin did not result in a lower incidence of medical admission to a hospital due to progression of Covid-19 or

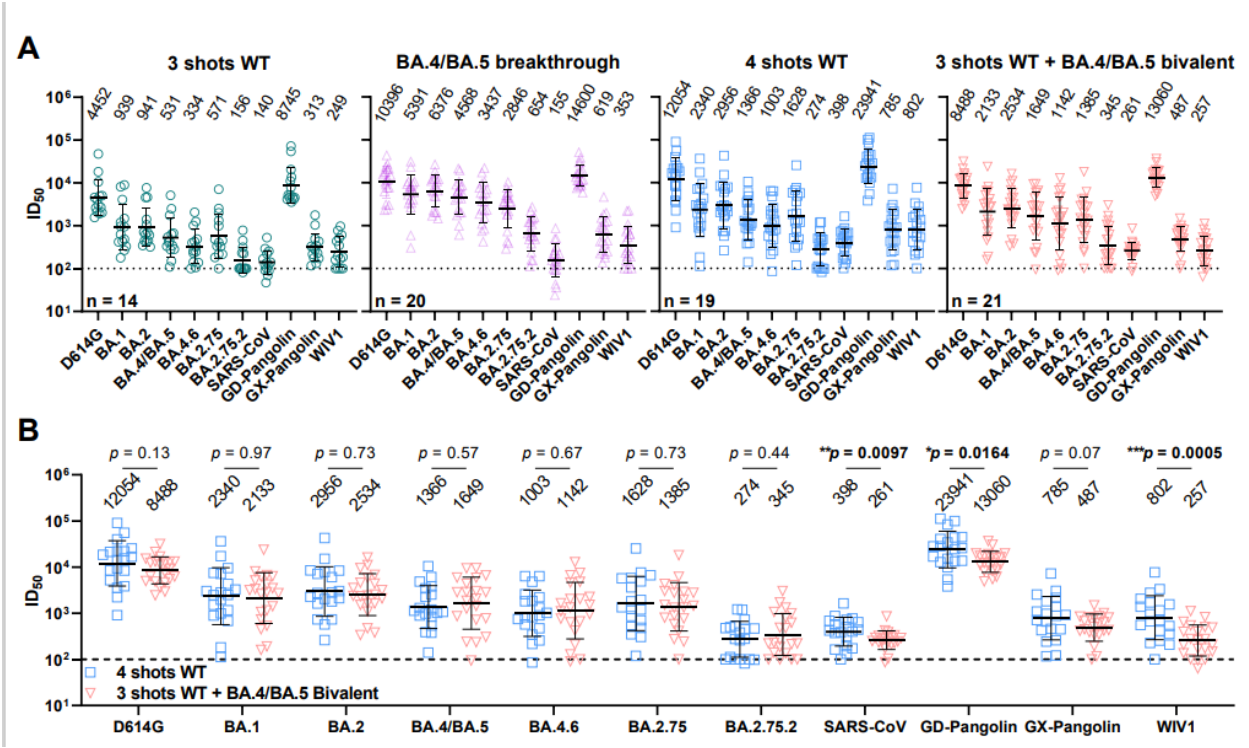
of prolonged emergency department observation among outpatients with an early diagnosis of Covid-19. I think these trials should put an end to the use of ivermectin in patients with mild to moderate Covid-19.

Antibody responses to Omicron BA.4/BA.5 bivalent mRNA vaccine booster shot

bioRxiv posted online October 24, 2022 article provided by Josh Septimus

doi.org/10.1101/2022.10.22.513349

The investigators collected sera from several clinical cohorts: individuals after three or four doses of the original monovalent mRNA vaccines, individuals receiving the new bivalent vaccines as a fourth dose, and individuals with BA.4/BA.5 breakthrough infection following mRNA vaccination. Using pseudovirus neutralization assays assays, all sera were tested against an ancestral SARS-CoV-2 strain (D614G) and Omicron sub-lineages BA.1, BA.2, BA.4/BA.5, 58 BA.4.6, BA.2.75, and BA.2.75.2. To further assess the breadth of antibody responses, they also tested sera for neutralization against several related sarbecoviruses: SARS-CoV, GD-pangolin, 60 GX-pangolin, and WIV1. At ~3-5 weeks post booster shot, individuals who received a fourth vaccine dose with a bivalent mRNA vaccine targeting BA.4/BA.5 had similar neutralizing antibody titers as those receiving a fourth monovalent mRNA vaccine against all SARS-CoV-2 variants tested, including BA.4/BA.5. Those who received a fourth monovalent vaccine dose had a slightly higher neutralizing antibody titers than those who received the bivalent vaccine against three related sarbecoviruses: SARS-CoV, GD-Pangolin, and WIV1. When given as a fourth dose, a bivalent mRNA vaccine targeting Omicron BA.4/BA.5 and an ancestral SARS-CoV-2 strain did not induce superior neutralizing antibody responses in humans, at the time period tested, compared to the original monovalent vaccine formulation.



Comment: These findings may be indicative of immunological imprinting [This means that the immune system most strongly remembers the first version of a virus it encounters. As the virus mutates, the response to a vaccine -- even one targeting newer strains -- may still tilt towards fighting the original pathogen], although follow-up studies are needed to determine if the antibody responses will deviate in time, including the impact of a second bivalent booster. If this study is verified this points to the urgency of developing new vaccine technologies. This was a small study looking at only 21 patients. See next article

Immunogenicity of the BA.5 Bivalent mRNA Vaccine Boosters bioRxiv posted online October 25, 2022

doi.org/10.1101/2022.10.24.513619

The investigators evaluated humoral and cellular immune responses in 15 individuals who received the original monovalent mRNA boosters and in 18 individuals who received the bivalent mRNA boosters. Participants had a median of 3 (range 2-4) prior COVID-19 vaccine doses, and 33% had documented SARS-CoV-2 infection during the Omicron surge, although it is likely that most participants had hybrid immunity prior to boosting given the high prevalence and limited severity of Omicron infection. Both the monovalent and bivalent mRNA boosters led to preferential expansion of WA1/2020 NAb titers and lower BA.1, BA.2, and BA.5 NAb titers (Fig. 1A, B). Median BA.5 NAb titers increased from 184 to 2,829 following monovalent mRNA boosting and from 211 to 3,693 following bivalent mRNA boosting. The Pfizer and Moderna bivalent mRNA boosters induced similar NAb profiles. Binding antibody responses by ELISA and electrochemiluminescence assays were comparable following monovalent and bivalent mRNA boosting.

Comment: This study demonstrated that both monovalent and bivalent mRNA boosters markedly increased antibody responses but did not substantially augment T cell responses. BA.5 NAb titers were comparable following monovalent and bivalent mRNA boosters, with a modest and nonsignificant trend favoring the bivalent booster by a factor of 1.3. These findings suggest that immune imprinting by prior antigenic exposure may pose a greater challenge than currently appreciated for inducing robust immunity to SARS-CoV-2 variants.

Final Comments: Both studies were well done and come from two of the best virology labs in the country. We should also be investigations into how the boosters perform against emerging omicron subvariants such as XBB and BQ.1. Both are limited by their size. Dr. Paul Offit, a member of the FDA's independent vaccine advisory committee, said public health officials should be cautious about overselling the shots as a major upgrade. To be clear, boosters work, but may not be any better than the monovalent vaccines. I will restate my recommendations: people who are in high-risk groups should benefit from booster doses as we enter this late fall and early winter. I define high risk as those who are immunocompromised, who have several high risk medical conditions, and who are elderly (>75).

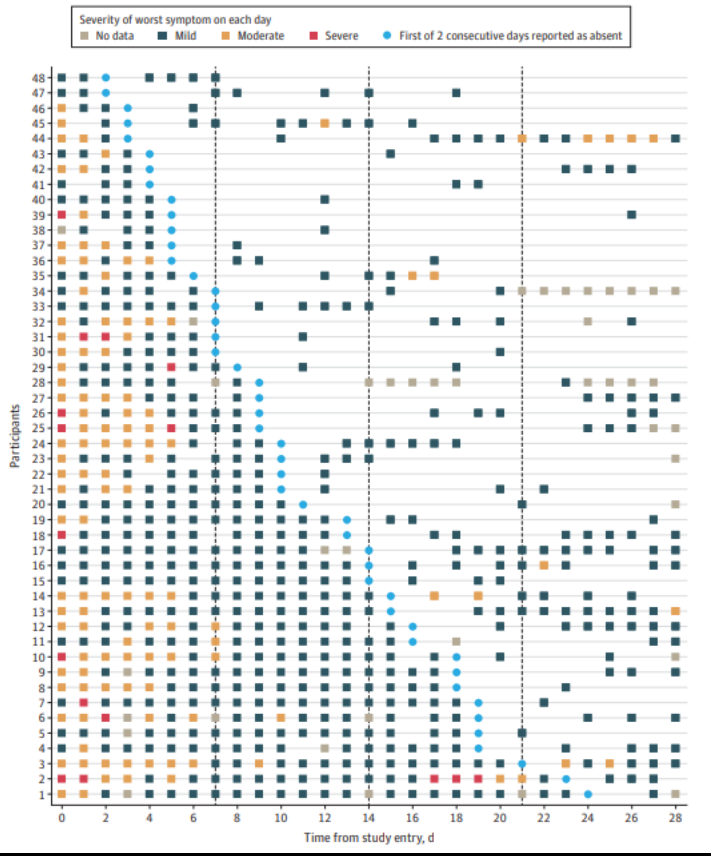
Recurrence of Symptoms Following a 2-Day Symptom Free Period in Patients With COVID-19 JAMA Netw Open published online October 27, 2022 5:e2238867

doi:10.1001/jamanetworkopen.2022.38867

The investigators monitored COVID-19 symptoms for 29 days in untreated participants who received a placebo in the ACTIV-2/A5401 trial between August and November 2020. Participants had documented SARS-CoV-2 infection and 10 or fewer days experiencing COVID-

19 symptoms at study entry. Participants completed a daily symptom diary from enrollment (day 0) to day 28, which included 13 COVID-19 symptoms, scored by the participant as absent, mild, moderate, or severe. The investigators assessed the frequency of targeted symptom recurrence after symptom resolution, defined as all 13 symptoms reported absent for 2 consecutive days.

Among the 158 evaluable participants, 79 (50%) were women, median (IQR) age was 47 years (34-55 years). During 28 days of follow-up, 108 participants (68%) achieved symptom resolution, of which 48 (44%; 30% of the 158 participants) subsequently reported recurrence by the end of the 28 days of follow-up of at least 1 of the 13 targeted symptoms. Among those reporting recurrence of symptoms after reporting resolution of symptoms for 2 consecutive days, 41 participants (85%) reported their symptoms as mild, 7 (15%) reported at least 1 moderate symptom and none reported severe symptoms during recurrence. The most common symptoms reported at time of relapse were cough (21 participants [44%]), fatigue (17 participants [35%]), and headache (17 participants [35%]); these results were similar to symptoms at enrollment, with the exception that body pain and aches were reported more often at enrollment than on recurrence.



Comment: Over one-third of participants who experienced symptom resolution for at least 2 consecutive days within the first 4 to 5 weeks of COVID-19 symptoms reported recurrent symptoms. This observed variation may explain some of the rebound of symptoms after treatment for COVID-19, like in cases of what has been described as nirmatrelvir-ritonavir rebound. This study lacked virologic characterization, including the presence of simultaneous viral rebound. Also, participants were enrolled before COVID-19 vaccinations were available

and when the original and Alpha variant SARS-CoV-2 strains circulated, so these results may not be generalizable to the current pandemic, where Omicron variants predominate.