Infectious Diseases Watch

October 17, 2022

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General Infectious Diseases

FDA Approval- Pertussis Vaccine Approval

The FDA) has approved a pertussis vaccine that protects newborns under 2 months of age. The federal agency on October 7th approved Boostrix for use during the last 3 months of pregnancy to prevent pertussis in infants under 2 months old. The vaccine was previously approved among pregnant people for their own protection. Infants younger than 2 months of age are too young to be protected by the current childhood pertussis vaccine series.

Comment: This is the first vaccine approved specifically for use during pregnancy to prevent a disease in young infants whose mothers are vaccinated during pregnancy. Most cases that result in hospitalizations and death are among infants within 2 months of birth.
The FDA said its decision was based on data from observational studies, which included 108 cases of pertussis in infants younger than 2 months old. According to data evaluated by the FDA, the vaccine was 78% effective in preventing pertussis in infants <2 months old.

Outbreak of Ebola virus disease in Central Uganda

The CDC is issuing this Health Alert Network (HAN) Health Advisory about a recently confirmed outbreak of Ebola virus disease (EVD) in Uganda caused by Sudan virus (species *Sudan ebolavirus)* **No suspected, probable, or confirmed EVD cases related to this outbreak have yet been reported in the US**. However, as a precaution CDC wants to remind clinicians about best practices, CDC is communicating with public health departments, public health laboratories, and HCWs in the US to raise awareness of this outbreak.

Comment: This is the fifth outbreak of EVD caused by Sudan virus in Uganda since 2000. The current outbreak is in the same area as Uganda's most recent EVD outbreak caused by Sudan virus, which occurred in 2012. During the 2012 outbreak, limited secondary transmission was reported, and the outbreak was effectively contained. The outbreak has now spread from rural Uganda into the capital, Kampala. Nineteen people are confirmed dead since Ugandan health authorities announced that a 24-year-old man was killed last month. Nineteen others, including six members of the man's family, are also believed to have died as far back as early August, but were never tested.
Last week, federal officials ordered US-bound passengers who have been in Uganda in the past 21 days to arrive at select airports for enhanced Ebola screening. It is important for clinicians to

obtain a detailed travel history from patients with suspected EVD, especially those that have been in affected areas of Uganda. Early consideration of EVD in the differential diagnosis is important for providing appropriate and prompt patient care, diagnostics, and to prevent the spread of infection. As a reminder a person infected with EVD is not contagious until symptoms appear (including fever, headache, muscle and joint pain, fatigue, loss of appetite, gastrointestinal symptoms, and unexplained bleeding). Specifically, the Sudan virus is spread through direct contact (through broken skin or mucous membranes) with the body fluids (blood, urine, feces, saliva, droplet, or other secretions) of a person who is sick with or has died from EVD, infected animals, or with objects like needles that are contaminated with the virus. EVD is **not** spread through airborne transmission. HCWs should be alert for and evaluate any patients suspected of having VHF or EVD, particularly among people who have recently traveled to affected areas in Uganda, and place in a private room while performing clinical evaluation. If performing an aerosol generating procedure, conduct in an Airborne Infection Isolation Room (AIIR) when feasible.

Transmission of Carbapenem-resistant *Klebsiella pneumoniae* in US hospitals

Clin Infect Dis published online September 29, 2022

doi.org/10.1093/cid/ciac791

Carbapenem-resistant *Klebsiella pneumoniae* (CRKp), particularly those of sequence type ST258, often cause hospital-acquired antibiotic-resistant infection in the US. Accurate genetic analysis is critical to understanding how these pathogens spread within healthcare facilities. WGS allows categorization of organisms into related clusters. This can be done statically (where relatedness is determined by a fixed cut-off of differences of single nucleotide polymorphisms [SNP]), or dynamically (where sampling times, genetic distance, and rates of SNP accumulation and transmission are considered). Each method has strengths and weaknesses.

To compare static versus dynamic genetic assessment, investigators in the Consortium on Resistance Against Carbapenems in Klebsiella and other Enterobacteriaceae 2 (CRACKLE-2) studied a cohort of 350 US patients who were hospitalized at 42 different institutions for infection with CRKp ST258 from April 30, 2016, through August 31, 2017. Most patients were admitted from home (n=150, 43%) or a long-term care facility (n=115, 33%). Urine (n=149, 43%) was the most common site of isolation. In total, 55 static and 47 dynamics clusters were identified involving 210/350 (60%) and 194/350 (55%) patients, respectively. About half of static clusters were identical to dynamic clusters. Among 55 static clusters involving 2 to 5 patients, 60% of clusters were identified as intra-system (within a hospital) and 40% as inter-system (between hospitals). Similarly, among 47 dynamic clusters of 2 to 4 patients, 68% were defined as intra-system and 32% as inter-system.

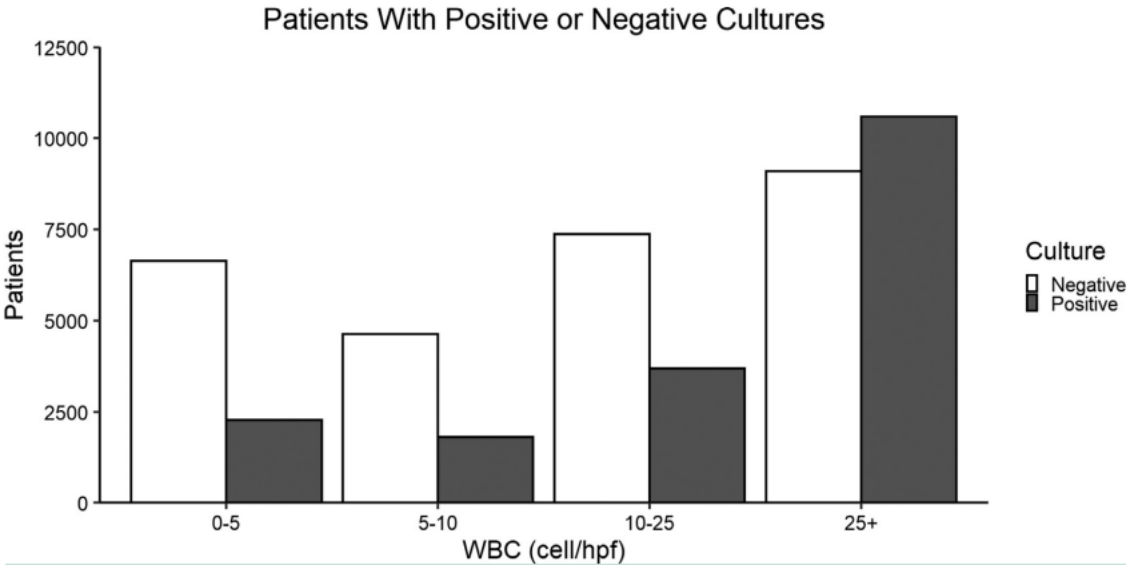
Comment: Widespread intra-system and inter-system transmission of CR*Kp* was identified in hospitalized US patients. Employing different methods for assessing genetic similarity resulted in only minor differences in interpretation. Asymptomatic screening cultures were not included in CRACKLE-2. Therefore, it is likely that the degree of clustering may be underrepresented. Long-term gastrointestinal colonization [Clin Microbiol Infect 2013; 19: E190-6] and environmental reservoirs (e.g., plumbing, surfaces) [Clin Infect Dis 2018; 67: 171-8 39, 40] can contribute to spread of CR*Kp* among healthcare facilities. Further refinement of WGS should provide improved information in understanding spread of these MDROs which hopefully can result in better infection prevention interventions.

Correlation of Pyuria and Bacteriuria in Acute Care Am J Med 2022; 135:e353-e358

doi.org/10.1016/j.amjmed.2022.04.022

Pyuria is common in asymptomatic bacteriuria (ASB) and urinary tract infections (UTIs), but whether degree of pyuria is useful for predicting bacteriuria is unknown. In this cross-sectional study, investigators in a single US health system compared rates of urine culture positivity at four cutoffs of white blood cells per high-power field (WBC/hpf) to define an optimal value for pyuria as a predictor of bacteriuria. Data were drawn from 46,000 hospitalizations of adults (mean age, 57; 80% women) who had both urinalysis and urine culture.

Bacteriuria was defined as any bacterial growth on urine culture, regardless of amount! At WBC/hpf cutoffs of 0 to 5, 5 to 10, 10 to 25, and >25, prevalence of bacteriuria was 25%, 28%, 33%, and 54%, respectively — a statistically significant trend. Positive predictive value across cutoffs ranged from 45% to 55%, and negative predictive value ranged from 70% to 80%. In patients with positive cultures, bacterial growth exceeded 50,000 colony forming units per mL about 80% of the time — even among those with only 0 to 5 WBC/hpf.



Comment: This is a very limited study since there is no information on symptoms which is key in differentiating ASB from UTI. In addition, the relatively low positive and negative predictive values mean the degree of pyuria alone does not provide enough information to reliably predict bacteriuria.

Administration of a β-Lactam Prior to Vancomycin as the First Dose of Antibiotic Therapy Improves Survival in Patients with Bloodstream Infections Clin Infect Dis 2022;75:98–104

doi.org/10.1093/cid/ciab865

The investigators performed a multicenter, observational study including 3,376 patients ≥ 13 years with BSIs to evaluate the sequence of antibiotic administration with 7-day mortality. They

used inverse probability of treatment weighting based on propensity scores using a robust set of variables collected from the EHR. Propensity scores were generated based on demographics, Pitt bacteremia score, intensive care unit status, highest lactate, highest white blood cell count, Charlson comorbidity index, severe immunocompromise, administration of active empiric therapy, combination therapy, and time from emergency department arrival to first antibiotic dose.

Of 3376 eligible patients, 2685 (79.5%) received a β-lactam and 691 (20.5%) received vancomycin as their initial antibiotic. In the IPTW cohort, exposed and unexposed patients were similar on all baseline variables. Administration of a β-lactam agent prior to vancomycin protected against 7-day mortality (adjusted odds ratio [aOR], 0.48 [95% confidence interval {CI}, .33–.69]). Similar results were observed when evaluating 48-hour mortality (aOR, 0.45 [95% CI, .24–.83]). Administration of vancomycin prior to a β-lactam was not associated with improved survival in the subgroup of 524 patients with methicillin-resistant Staphylococcus aureus BSI (aOR, 0.93 [95% CI, .33–2.63]). The patients in this study were sick, with over 41% of them admitted to the ICU within 24 hours, and they still found a reduction in mortality of 52% due to simply administering the β-lactam agent prior to vancomycin.

Comment: The investigators found administration of the β-lactam agent prior to vancomycin protected against 7-day mortality (adjusted OR, 0.48 [95% CI, 0.24-0.83]). Even in their sensitivity analysis restricted to those patients with a BSI from MRSA, there was no harm seen with initial beta-lactam, nor was there a benefit with initial vancomycin. When you consider the predominance of Gram-negative organisms as the underlying cause of sepsis, there is a logical argument for an earlier administration of a broad spectrum β-lactam. In addition, when you take in to account the time it takes to administer a β-lactam (5 minutes for a push or 30 minutes for IV piggyback) vs vancomycin IV (>60 minutes) then you might also see why there may be no harm even in those patients with MRSA BSIs. For patients presenting with a sepsis-like picture, the likelihood that a broad-spectrum β-lactam will provide adequate coverage for the pathogen is higher than for vancomycin. Evaluating 20 years of data from the SENTRY Antimicrobial Surveillance Program, broad-spectrum β-lactam coverage is anticipated to be effective for >90% of all pathogens recovered in blood cultures. [Antimicrob Agents Chemother 2019; 63:e00355–19] In addition, the past two decades there has been a shift to more gram-negative pathogens associated with BSIs. Due to the retrospective nature of our study, the investigators were unable to account for all variables that might impact the decision to prioritize β-lactam or vancomycin administration. They did attempt to mitigate some of the confounding by indication with the development and incorporation of propensity scores. Nonetheless, the small to no downsides, the reported mortality benefit, and the biological plausibility of giving a β-lactam first make this a simple but clinically important intervention to hard wire in clinical practice.

Influenza

2022 National Survey: Attitudes about Influenza and Pneumococcal Disease, and the Impacts of COVID-19 NFID

Overall, most US adults believe annual flu vaccination is the best protection against flu, but many do not plan to get vaccinated against flu during the 2022-2023 flu season

- 69% agree that annual flu vaccination is the best preventive measure against flu-related deaths and hospitalizations but only 49% plan to get a flu vaccine during the 2022-2023 flu season
- 41% are either unsure or do not plan to get vaccinated against flu during the 2022-2023 flu season
- 65% of adults aged 65 years and older plan to get a flu vaccine compared with only 45% of adults age 18-64 years who plan to get a flu vaccine
- Among those who do not plan to get a flu vaccine, top reasons cited include
    - 41% do not think flu vaccines work very well
    - 39% are concerned about potential side effects from the vaccine
    - 28% said that they never get the flu
    - 24% are concerned about getting flu from the vaccine
    - 20% do not think flu is a serious illness

Of concern, about 1 in 5 (22%) who are at higher risk for flu-related complications said they were not planning to get vaccinated this season

Healthcare professionals are the primary and most trusted source of information about flu and flu vaccination

- 76% of US adults trust healthcare professionals a great deal or a lot for flu vaccine information, far more than other sources[3]
- 53% of US adults trust the Centers for Disease Control and Prevention (CDC) a great deal or a lot for flu vaccine information
- Hispanic adults are less trusting of healthcare professionals than White adults (62% vs 79%) and less trusting of the CDC (37% vs 56%)

For most US adults, personal experience with COVID-19 does not change how likely they are to get a flu vaccine this year. Among those who have tested positive for COVID-19:

- 1 in 4 (25%) say it makes them more likely to get vaccinated against flu

US adults are not very confident about the safety of getting flu and COVID-19 vaccines at the same time

- Only 32% are extremely/very confident about the safety of receiving flu and COVID-19 vaccines at the same time
- 37% are not very or not at all confident in the safety of getting a flu and COVID-19 vaccine at the same time, while 30% are only somewhat confident in the safety of getting vaccinated against both flu and COVID-19 at the same time
- 36% say they would receive both vaccines at the same time if offered, 41% say they would not, and 23% are unsure

Confidence in vaccine coadministration differed by race and education levels:

- 48% of both Black and Hispanic adults say they have little or no confidence in the safety of getting vaccinated against flu and COVID-19 at the same time, compared with 35% of White adults

- 42% of US adults without a college degree have little or no confidence in the safety of getting vaccinated against both flu and COVID-19 at the same time, compared with 27% of college graduates

Mask Behaviors During Flu Season

- A majority of US adults (58%) report that they will wear a mask at least sometimes during flu season
  - 40% of US adults will wear a mask if flu and/or COVID-19 activity is high in their community
  - 35% will wear a mask around crowds and large groups of people
  - 22% will wear a mask indoors
  - 21% of US adults will wear a mask only if required and 16% say they will not wear a mask
- Black adults (78%) are more likely than White adults (52%) to wear a mask during flu season
- Women (66%) are more likely than men (50%) to wear a mask during flu season

Among adults aged 65 years and older, or those with an underlying health condition who are at higher risk for pneumococcal disease, there are gaps in awareness and understanding about pneumococcal disease and vaccination

- 45% of those at higher risk are not familiar with pneumococcal disease
- 29% of those at higher risk have been advised to receive a pneumococcal vaccine
- Among those who have been advised to get vaccinated, the majority (74%) have received a pneumococcal vaccine
- Among those who are unsure or do not plan to get a pneumococcal vaccine, the top reason (57%) cited was that their doctor has not recommended it

Comment: Last year, the CDC estimates 51% of Americans 6 months and older got the flu shot, a similar percentage seen in the 2020-2021 season. Among adults, flu shot uptake increased with age, with 37% of adults ages 18 to 49 years getting the shot, 52% for adults age 50 to 64 years, and 74% for adults ages 65 years and older. For children ages 6 months to 17 years, flu vaccination coverage was 58% for the 2021-2022 flu season, down from 64% during the 2019-2020 season. Less than 50% of pregnant women, a group deemed high risk for flu complications, received the flu shot last year!

- The CDC released influenza burden estimates for the 2021-2022 flu season, noting that it was similar to the 2011-2012 season, with 9 million infections, 4 million clinic visits, 100,000 hospitalizations, and 5,000 deaths. Older adults accounted for 83% of deaths, which is similar to recent seasons before the COVID-19 pandemic. These findings continue to highlight the fact that older adults are particularly vulnerable to severe disease with influenza virus infection and that influenza prevention measures such as vaccination are important to reducing the impact of the seasonal epidemics on this population. A key factor continues to come out in all these surveys-trust in CDC: only 53% of US adults trusted the CDC for influenza vaccine information!

US flu activity rises slowly, with H3N2 predominant

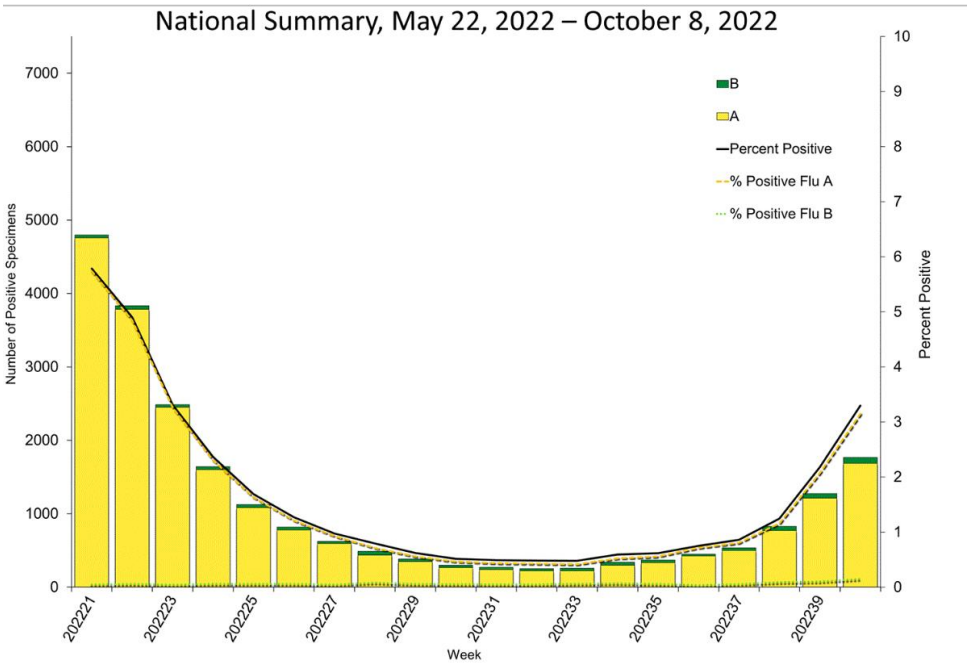
US flu indicators continue to slowly rise, mainly due to the H3N2 influenza A strain, according to the latest weekly update today from the Centers for Disease Control and Prevention (CDC).

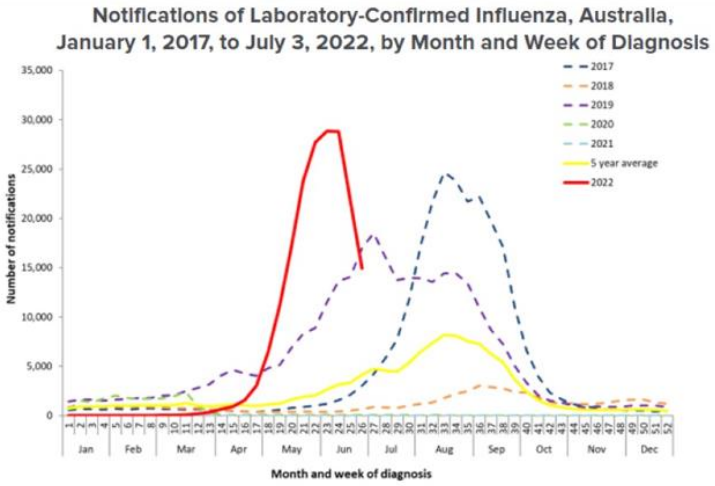
The percentage of respiratory specimens that tested positive for flu at clinical labs rose to 2.5% last week, over 95% of specimens classified as influenza A. At public health labs, 97.6% of respiratory samples that were positive for flu were influenza A, and of subtyped samples, 63.3% were the H3N2 strain.

Outpatient visits for flulike illness rose to 2.4% but are still below the national baseline of 2.5%. The CDC emphasized that the outpatient visit metric can also include people with other respiratory illnesses, including COVID and respiratory syncytial virus. Last week the highest levels of flulike illness visits were in kids ages 0 through 4, followed by those ages 5 to 24 years old.

Four areas reported high flu activity, a metric that also reflects clinic visits for flulike illness. They are Texas, Georgia, the District of Columbia, and the Mariana Islands. Three states reported moderate activity: South Carolina, Tennessee, and Virginia.

One pediatric flu death was reported in a child who died in late March, raising last flu season's total to 40.





Australian Government Department of Health and Aged Care. 2022. Accessed July 11, 2022. https://www1.health.gov.au/internet/main/publishing.nsf/Content/ozflu-surveil-no07-22.htm

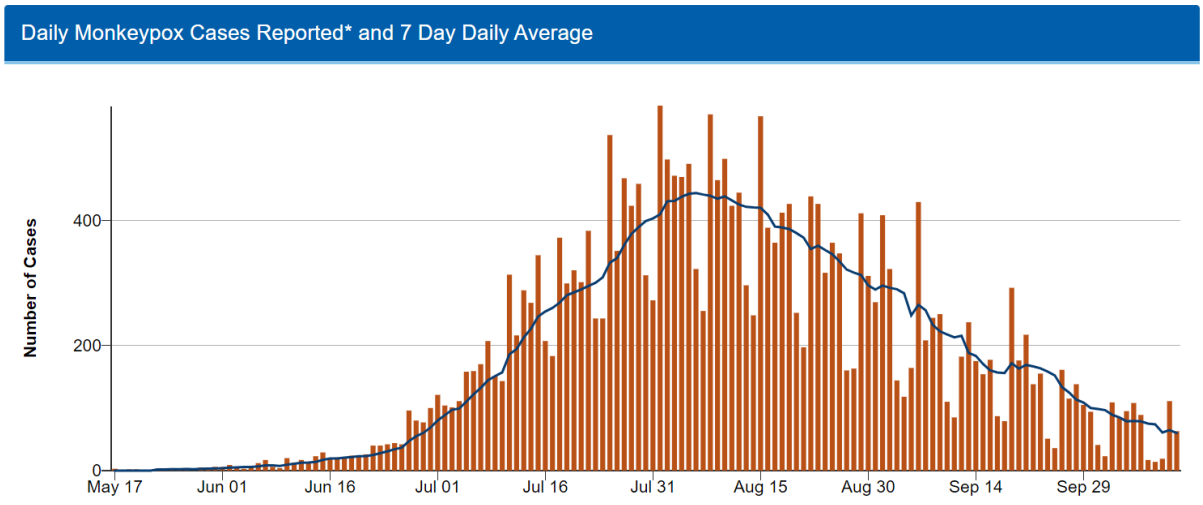
Comment: I included the Australian influenza since looking at the Southern Hemisphere can predict our flu season. Australia had an early and active season, and we are already seeing an uptick in the US. Based on the survey above we need to double down to encourage people to get vaccinated.

Monkeypox

The FDA has issued an EUA for new monkeypox test

Abbott's monkeypox test has receive FDA EUA. This test will offer real-time PCR test results for clinicians. The test relies on swabs of lesions. Positive results are indicative of the presence of monkeypox virus (clade I/II) DNA; clinical correlation with patient history and other diagnostic information is necessary to determine patient infection status.

Comment: This is the first commercial test to be authorized for MPXV detection. This is a welcomed addition.



Comment: At the global level, MPXV cases continue to fall, but levels are rising in 21 countries, mostly in the Americas. Americas account for about 90% of infections reported last week per WHO. More than 2,300 new cases were reported in the region last week, most from the US(27,000 cases to date), but also several from Brazil, Colombia, and Mexico. She added that 95% of cases are in men and 56% have occurred in people who are HIV-positive. More than 70,000 cases have been reported to the WHO.

Risk for monkeypox transmission to health care personnel (HCP) MMWR early release September 16, 2022

The risk for monkeypox transmission to HCP caring for symptomatic patients is thought to be low but has not been thoroughly assessed in the context of the current outbreak. CDC currently recommends that HCP wear a gown, gloves, eye protection, and an N95 (or higher-level) respirator while caring for patients with suspected or confirmed monkeypox to protect themselves from infection.

Colorado Department of Public Health and Environment (CDPHE) evaluated HCP exposures and personal protective equipment (PPE) use in health care settings during care of patients who subsequently received a diagnosis of Orthopoxvirus infection (presumptive monkeypox determined by a polymerase chain reaction [PCR] DNA assay) or monkeypox (real-time PCR assay and genetic sequencing performed by CDC). During May 1–July 31, 2022, a total of 313 HCP interacted with patients with subsequently diagnosed monkeypox infections while wearing various combinations of PPE; only 23% wore all recommended PPE during their exposures. 28% of exposed HCP were considered to have had high- or intermediate-risk exposures and were therefore eligible to receive PEP with the JYNNEOS vaccine; among those, 48% (12% of all exposed HCP) received the vaccine. During May 1–July 31, 2022, a total of 313 HCP were exposed to 55 patients with monkeypox, including 20 high-risk, 67 intermediate-risk, and 226 low- or uncertain-risk exposures. Seven HCP had exposure during aerosol-generating procedures; three of whom wore an N95 respirator during their exposure. Overall, 273 (87%) exposures to patients with monkeypox rash or lesions occurred, and 161 (59%) included direct contact with the patient's skin or lesions (gloves were worn in 125 exposures, were not worn in 30 exposures, and use of gloves was unknown for six exposures). Twenty-six (8%) exposed HCP reported handling linens; 23 (88%) of whom were wearing gloves. Approximately two thirds of encounters with monkeypox patients (215; 69%) lasted 5–30 minutes. Only one health care worker was exposed for >3 hours; this HCP wore an N95 respirator and all other recommended PPE for the duration of the exposure. HCP in sexually transmitted infection (STI) clinics and community health centers reported the highest adherence to recommended PPE use, and primary and urgent care settings reported the lowest adherence. In all no HCP developed a monkeypox infection during the 21 days after exposure.

Comment: This report suggests that the risk for transmission of monkeypox in health care settings is low. These findings are consistent with literature review from previous U.S. outbreaks [ICHE 2022; 43:920–4] and internationally imported cases, with one case report of transmission to a health care worker after contact with contaminated patient linens in the UK during a previous outbreak [Emerg Infect Dis 2020;26:782–5], and one case of transmission to a health care worker in

the US during the current outbreak. Data on exposures to contaminated materials were incomplete, limiting the ability to draw conclusions regarding this potential route of transmission. In addition, information about whether patients had covered lesions or worn facemasks during their health care visits was unavailable.

Epidemiological and clinical characteristics of patients with monkeypox in the GeoSentinel Network: a cross-sectional study Lancet Infect Dis published online October 7, 2022

doi.org/10.1016/ S1473-3099(22)00651-X

The investigators analyzed data for patients with confirmed monkeypox who were included in the GeoSentinel global clinical-care-based surveillance system between May 1 and July 1 2022, across 71 clinical sites in 29 countries. Data collected included demographics, travel history including mass gathering attendance, smallpox vaccination history, social history, sexual history, monkeypox exposure history, medical history, clinical presentation, physical examination, testing results, treatment, and outcomes. They did descriptive analyses of epidemiology and sub analyses of patients with and without HIV, patients with CD4 counts of less than 500 cells per mm^3 or 500 cells per mm^3 and higher, patients with one sexual partner or ten or more sexual partners, and patients with or without a previous smallpox vaccination.

226 cases were reported at 18 sites in 15 countries. Of 211 men for whom data were available, 208 (99%) were gay, bisexual, or men who have sex with men (MSM) with a median age of 37 years (range 18–68; IQR 32–43). Of 209 patients for whom HIV status was known, 92 (44%) men had HIV infection with a median CD4 count of 713 cells per mm^3. Of 219 patients for whom data were available, 216 (99%) reported sexual or close intimate contact in the 21 days before symptom onset; MSM reported a median of three partners (IQR 1–8). Of 195 patients for whom data were available, 78 (40%) reported close contact with someone who had confirmed monkeypox. Overall, 30 (13%) of 226 patients were admitted to hospital; 16 (53%) of whom had severe illness, defined as hospital admission for clinical care rather than infection control. No deaths were reported. Compared with patients without HIV, patients with HIV were more likely to have diarrhea ($p=0{\cdot}002$), perianal rash or lesions ($p=0{\cdot}03$), and a higher rash burden (median rash burden score 9 [IQR 6–21] for patients with HIV vs median rash burden score 6 [IQR 3–14] for patients without HIV; $p<0.0001$), but no differences were identified in the proportion of men who had severe illness by HIV status. A significant proportion of patients reported attending large mass gatherings before developing monkeypox symptoms. Of 161 patients with available information, 37 (23%) met their sexual partners at such gatherings.

Comment: These data from GeoSentinel are notable for the predominance of sexual or close intimate contact as a mode of transmission, which was previously only suspected. Many patients report fewer lesions than in past outbreaks, and the sexual transmission component is relatively new.

COVID-19

COVID-19 News

APIC Response to CDC Lifting Universal Masking in Health Care

The Association for Professionals in Infection Control and Epidemiology (APIC)urges all infection preventionists to maintain mandatory mask requirement policies for all healthcare employees in patient care areas despite the CDC's recent guidance shift.

In September, the CDC lifted the mandatory masking recommendation for healthcare workers, instead recommending facilities use its community transmission levels to determine when masking should be required. According to the release, the seven-day lag in CDC COVID-19 testing data limits the ability to detect surges in real time.

APIC recommends maintaining mask requirements for the following reasons:

- We are entering what is predicted to be a severe flu season with COVID-19 surges.
- Indicators like wastewater surveillance and rising case counts overseas point to a new wave of COVID-19 cases in the coming months.
- Shifting back and forth between universal masking is confusing and erodes trust.
- Rising COVID-19 cases could lead to healthcare worker shortages.

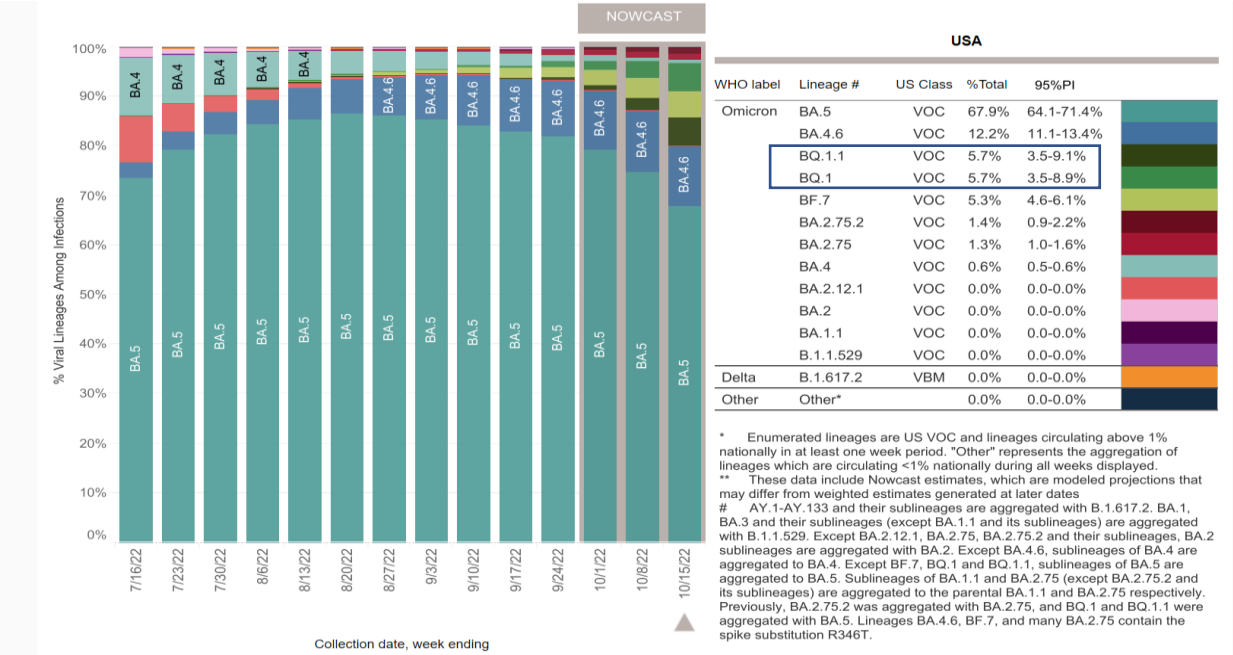
Comment: ACIP's view is consistent with view in the last ID Watch. Given increase in influenza and the increase Covid-19 in NE, this is not the time to eliminate universal masking in health care.

Variant Updates

Two new Omicron subvariants, both related to the BA.5 version are contributing to the most recent US uptick, called BQ.1 and BQ.1.1. They were estimated to represent a combined 11.4% of US Covid-19 cases by mid-October, according to estimates per CDC update released October 15th.

BA.5 remains the dominant version of the virus circulating in the US at about 68% of recent cases, according to CDC estimates. But the subvariant landscape has become busier as the virus that causes Covid-19 continues to mutate. Another version virus experts are watching because of its potential to spread easily, called BA.2.72.2, represented an estimated 1.4% of cases in the latest CDC report.

United States: 7/10/2022 – 10/15/2022	United States: 10/9/2022 – 10/15/2022 NOWC



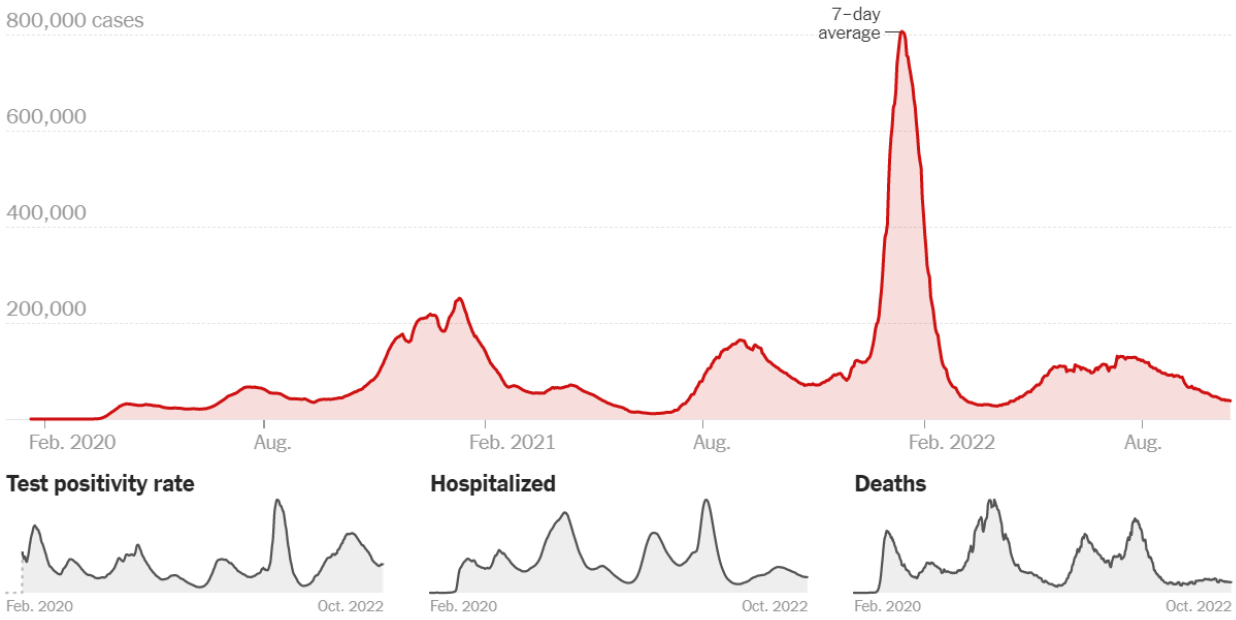
USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	67.9%	64.1-71.4%
	BA.4.6	VOC	12.2%	11.1-13.4%
	BQ.1.1	VOC	5.7%	3.5-9.1%
	BQ.1	VOC	5.7%	3.5-8.9%
	BF.7	VOC	5.3%	4.6-6.1%
	BA.2.75.2	VOC	1.4%	0.9-2.2%
	BA.2.75	VOC	1.3%	1.0-1.6%
	BA.4	VOC	0.6%	0.5-0.6%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
	BA.1.1	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%	0.0-0.0%

* 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
# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. 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 aggregated to BA.4. Except BF.7, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Sublineages of BA.1.1 and BA.2.75 (except BA.2.75.2 and its sublineages) are aggregated to the parental BA.1.1 and BA.2.75 respectively. Previously, BA.2.75.2 was aggregated with BA.2.75, and BQ.1 and BQ.1.1 were aggregated with BA.5. Lineages BA.4.6, BF.7, and many BA.2.75 contain the spike substitution R346T.

Comment: Recent changes in the mix of variants in the US do not appear to have significantly affected the pandemic's trajectory in the US so far, but it may can take time before a subvariant is prominent enough to have such an impact. The BQ subvariants' quick rise suggests that they either have increased transmissibility and/or increased immune escape compared with BA.5. Nationally, key measures such as hospitalizations have continued a downward trajectory since late July, but with some recent signs of wavering. Wastewater reports in recent weeks have shown a rise in the NE. The NE has also seen a recent rise in new Covid-19 hospital admissions. [See below] In order to keep ahead of the rapidly mutating coronavirus, the US approved bivalent boosters targeting the BA.4 and BA.5 subvariants on August 31. Yet only 7.6 million Americans have received the Omicron booster since it became widely available on Labor Day. A survey from the Kaiser Family Foundation found that two-thirds of Americans are either putting off getting the new booster or saying they won't get it at all!

COVID-19 by the Numbers



Comment: New reported cases have fallen by about 20 percent nationally in the past two weeks, to an average of fewer than 40,000 cases per day. Cases are falling in nearly every state, with the Midwest and South seeing some of the largest declines. Hospitalizations are also decreasing in most states, though they have ticked up in recent weeks in much of the NE. (see above) Test positivity has increased in recent days and remains relatively high, after falling consistently since July. If that trend continues, it could be an early sign of another wave in the US, similar to the ones seen this month in Canada and some parts of Europe. The number of deaths remains persistently flat at just under 400. [still too high]

Three more COVID-19 updates:

1. Cases are expected to jump 10 percent over the next two weeks, according to modeling from Rochester, Minn.-based Mayo Clinic. The forecast suggests daily average cases will increase from 43,071 on September 28 to 47,594 by October 12th.

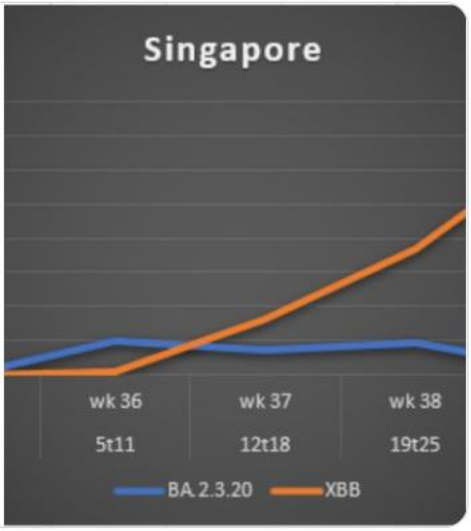
2. The CDC has dropped country-by-country travel advisories, The agency said it will no longer maintain the list of or advisories for foreign countries because "fewer countries are testing or reporting COVID-19 cases," limiting its ability to assess risks. The CDC said it will now limit travel health notices for "a concerning COVID-19 variant."

3. The CDC revised its "up to date" COVID-19 vaccination term September 30th to include the primary series and the recently authorized omicron-targeting booster.

What is XBB?

The XBB strain is causing a small surge in cases in countries like Bangladesh and Singapore. The latter has recorded a daily average of about 5,500 cases over the past week, compared to a daily average of 2,000 cases a month ago. Experts are paying close attention to the XBB strain, which combines two different Omicron strains. The

new strain may be the most immune-evasive yet due to its combination of mutations from other strains. Experts are also concerned that monoclonal antibody treatments might be less effective against newer variants like XBB, BA.2.75.2, and BA.4.6. [see above]



Comment: This new strain bears watching over the next 2-4 weeks along with the BQ subvariants' discussed above.

FDA says Evusheld antibody treatment likely inactive against Omicron BA.4.6

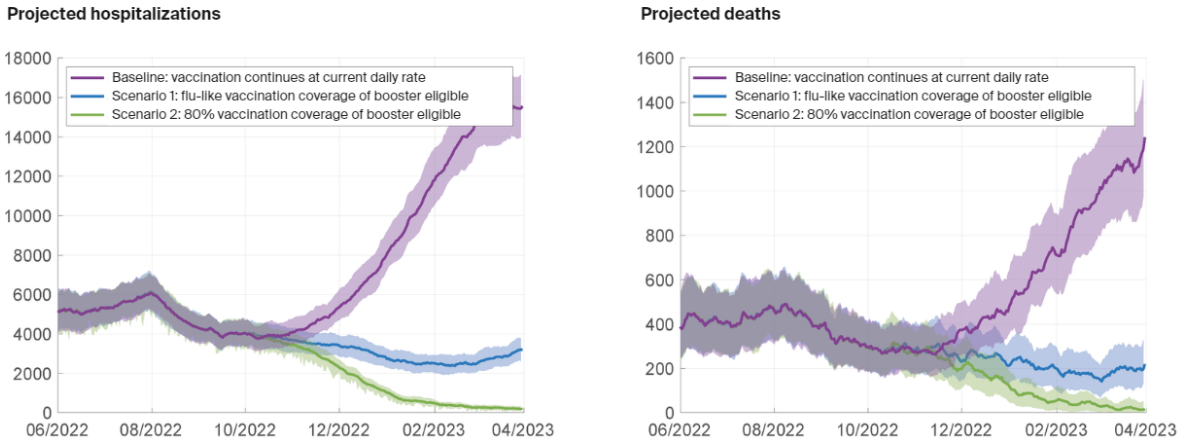
The FDA has updated the Fact Sheet for Evusheld (tixagevimab co-packaged with cilgavimab), warning that the monoclonal antibody combination appears unlikely to be active against the emerging Omicron BA.4.6 subvariant. virus-like particles (VLPs) pseudotyped with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike of Omicron BA.4.6 showed reduced susceptibility to tixagevimab (>1000-fold) and to cilgavimab (>1000-fold) In contrast, VLPs pseudotyped with the SARS-CoV-2 spike of Omicron BA.1 or BA.1.1 also showed reduced neutralizing activity, but to a lesser extent (132- to 183-fold or 424- fold, respectively), while Omicron BA.2 showed no change in neutralizing activity (3.2-fold). VLPs pseudotyped with the spike of the Omicron BA.2.12.1, BA.2.75, BA.3, or BA.4/BA.5 subvariants exhibited 5- fold, 2.4- to 15-fold, 16-fold, and 33- to 65-fold reductions, respectively. The FDA said authentic Omicron BA.1, BA.1.1, BA.2, or BA.5 viruses showed 12- to 30-fold, 176-fold, 5.4-fold, or 2.8- to 16-fold reductions in susceptibility, respectively.

Comment: Evusheld currently remains the only option for pre-exposure prophylaxis of COVID-19 and is authorized under EUA in immunocompromised individuals who may not mount an adequate response to COVID-19 vaccination, and for people who are not suitable candidates for COVID-19 vaccination due to a history of a severe adverse reaction. Evusheld still offers protection against many of the currently circulating variants and may offer protection against future variants, however if BA.4.6 continues to increase this poses some challenges for this patient population. We still have Paxlovid, remdesivir, and molnupiravir for early treatment.

The Commonwealth Fund Analysis on Boosters

They estimated a fall booster vaccination campaign that reaches coverage similar to the 2020–2021 influenza vaccination (scenario 1) would prevent more than 75,000 deaths and more than 745,000 hospitalizations and generate savings of $44 billion associated with direct medical costs by the end of March 2023, compared to the baseline. An even more successful campaign (scenario 2) would prevent approximately 90,000 deaths, more than 936,000 hospitalizations, and avert $56 billion in direct medical costs over the course of the next six months, compared with the baseline scenario.

Projected Seven-Day Rolling Average of COVID-19 Hospitalizations and Deaths in the U.S., Under Different Booster Vaccination Coverage Scenarios



Comment: They did not consider the rise of yet another immune-evasive variant in their analysis, since the estimated magnitude of the surge is primarily driven by waning immunity. With the rise of new Omicron subvariants, or an entirely new variant, the surge could be significantly larger, and their results may in fact be an underestimate of the benefits of bivalent booster vaccination in terms of cases, hospitalizations, deaths, and medical costs averted. Second, CDC has recently updated guidance regarding isolation of individuals with COVID-19 and quarantine of those who have been exposed. We do not yet have concrete data regarding adherence to previous guidance or behavioral changes in the wake of the update, so they did not include this element in their projections. My perspective if we do see a surge this fall/winter relaxed measures are likely to increase a fall/winter surge if one occurs. Third, they did not incorporate holiday-driven contact into their simulations. Many people celebrated fall and winter holidays modestly in 2020 and 2021, but this may not hold true for 2022.

Preliminary Data on Pfizer's New Omicron-Targeting Booster Bivalent Vaccine

In the study, investigators measured neutralizing antibody responses by examining blood samples taken one week after subjects got the bivalent vaccine. They compared subjects who received the booster with those who got an additional shot of the original vaccine.

Among people 55 years and older, those who received a bivalent shot showed a stronger immune response against the BA.4 and BA.5 than those in the same age group who received a fourth dose of the original vaccine.

Comment: This is encouraging and expected. It is too early to determine durability of protection since we know neutralizing antibodies decline over time. We do not know yet if the new vaccine is better at VE and if it is any better at preventing severe disease and death compared to standard booster. Uptake of the new booster has been disappointing. More than 11 million Americans have received an updated booster shot, or 4.5% of the eligible population of those age 12 and older, according to the CDC. See above

Novavax COVID-19 booster dose October 12, 2022

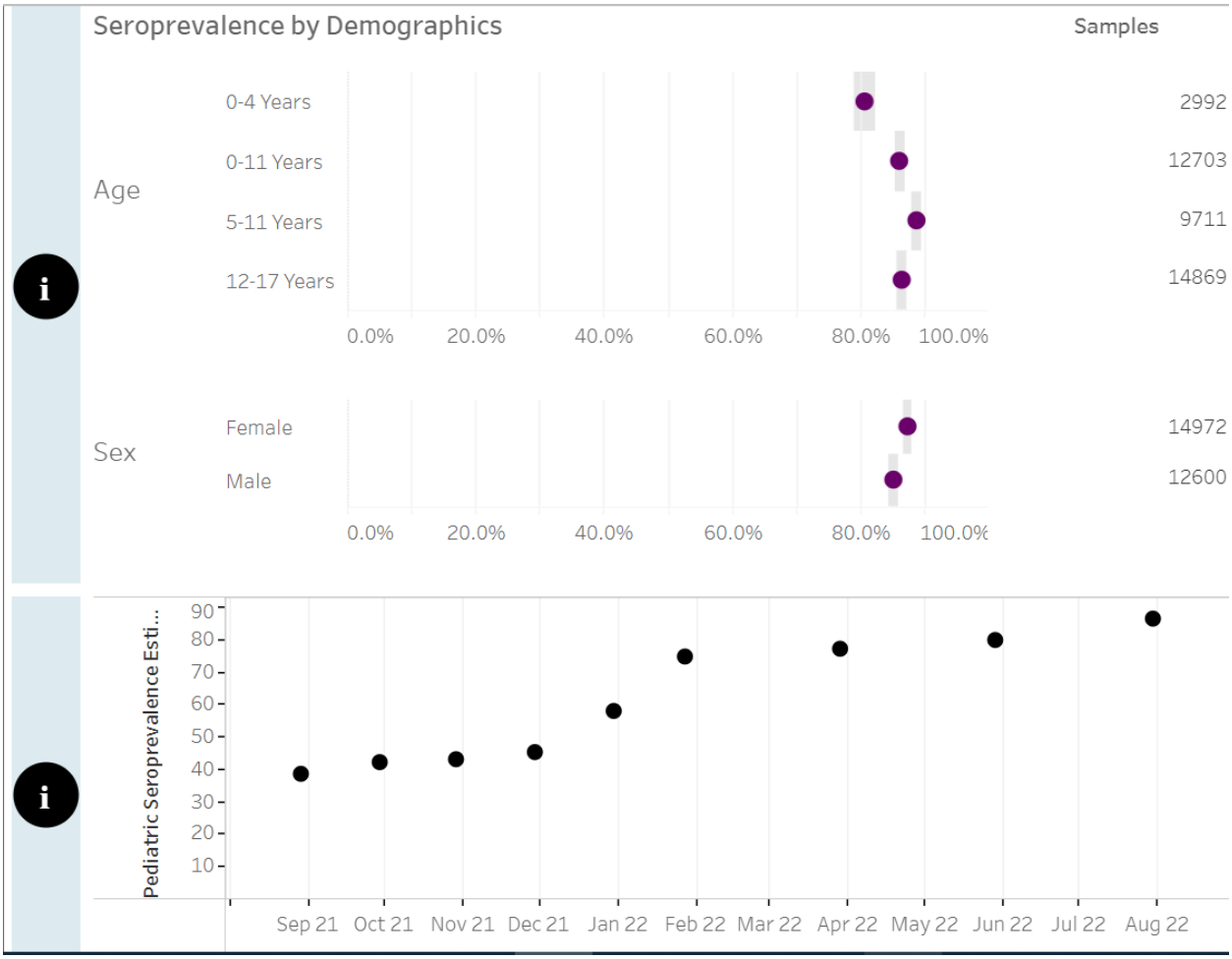
Novavax reported that studies in adults and adolescents showed that the booster dose of its COVID vaccine produced robust antibodies against several Omicron variants, including BA.1, BA.2 and BA.5.

The data was from two studies - a late-stage study evaluating the booster in adults and adolescents who had received Novavax primary vaccination and another study testing it in those aged 18 to 49 who had received primary series of Novavax vaccine or other authorized or approved vaccines. The company said ongoing trials are studying the efficacy of the vaccine against variants including BA.4 and BA.5.

Comment: Like the Pfizer announcement we need real world studies on VE and duration.

Nationwide Commercial Lab Pediatric Antibody Seroprevalence

This nationwide seroprevalence survey provides estimates of the proportion of the U.S. pediatric population (ages 6 months to 17 years) with evidence of at least one resolving or past infection with SARS-CoV-2, the virus that causes COVID-19. Reinfections are not included. Starting in March 2022, estimates covered 8-week information collection periods; historical monthly data for the US pediatric population between September 2021 and February 2022 are provided for context. This survey estimates the percentage of children and adolescents with detectable antibodies showing past infection with SARS-CoV-2, but not the total amount of antibody against SARS-CoV-2 in their blood.



Comment: This analysis shows that as of August, 86% of children between 6 months and 17-years-old have had at least one COVID infection since the pandemic began. The figure shows an increase from data in April, when the" agency found 75% of people under the age of 17 had been infected with the virus. This together with estimates from adults indicate that ~85-90% of the US population now has antibodies thanks in large part to Omicron!

FDA authorizes bivalent COVID-19 boosters for children ages 5 to 11

Children ages 5 to 11 are now eligible to receive a COVID-19 booster aimed at both the original virus that causes COVID-19 and the omicron BA.4 and BA.5 variants.

The FDA authorized the boosters October 12th from both Pfizer and Moderna, and the director of the CDC gave a thumbs up on the shots several hours later. The Moderna booster is approved for kids as young as 6 years old, and the Pfizer version is now authorized for kids down to 5 years old.

Comment: Children are less likely than adults to become severely ill and die of COVID-19 infections or to suffer from long COVID-19. But that risk isn't zero. Because COVID-19 vaccines have been found to be extremely safe, pediatricians strongly recommend that nearly all children receive the two-dose primary series as well as a booster. The AAP said COVID cases in children for the week ending October 6th were up slightly from the previous week, with nearly 40,700 cases reported. Unfortunately, the uptake of vaccination has been disappointing.

COVID-19 Journal Review

Clinical, Virologic, and Immunologic Evaluation of Symptomatic Coronavirus Disease 2019 Rebound Following Nirmatrelvir/Ritonavir Treatment

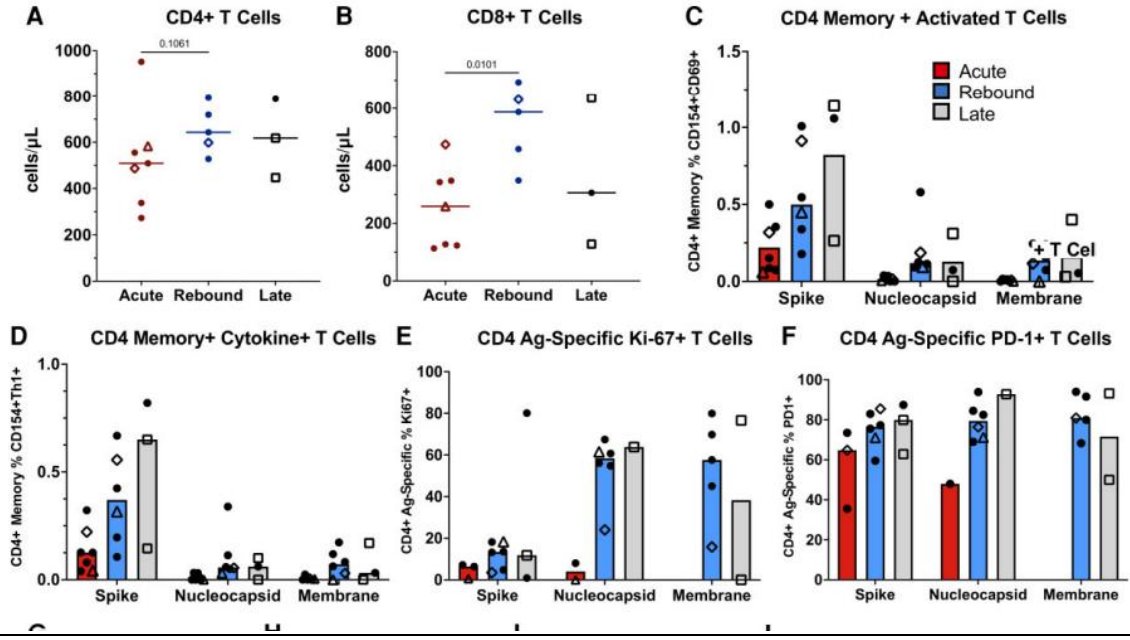
Clin Infect Dis published online October 6, 2022

doi.org/10.1093/cid/ciac663

Some patients who received Nirmatrelvir/Ritonavir (NMV-r) demonstrated a rise in viral load between day 10 and day 14, and clinical rebound after completing NMV-r has now been reported. [Research Square [Preprint]. May 23, 2022]

Six individuals with relapse of COVID-19 symptoms after treatment with nirmatrelvir/ritonavir, 2 individuals with rebound symptoms without prior antiviral therapy and 7 patients with acute Omicron infection (controls) were studied. Soluble biomarkers and serum SARS-CoV-2 nucleocapsid protein were measured. Nasal swabs positive for SARS-CoV-2 underwent viral isolation and targeted viral sequencing. SARS-CoV-2 anti-spike, anti–receptor-binding domain, and anti-nucleocapsid antibodies were measured. Surrogate viral neutralization tests against wild-type and Omicron spike protein, as well as T-cell stimulation assays, were performed.

High levels of SARS-CoV-2 anti-spike immunoglobulin G (IgG) antibodies were found in all participants. Antinucleocapsid IgG and Omicron-specific neutralizing antibodies increased in patients with rebound. Robust SARS-CoV-2–specific T-cell responses were observed, higher in rebound compared with early acute COVID-19 patients. Inflammatory markers mostly decreased during rebound. Two patients sampled longitudinally demonstrated an increase in activated cytokine producing CD4+ T cells against viral proteins. No characteristic resistance mutations were identified. SARS-CoV-2 was isolated by culture in only 1 of 8 rebound patients; Polybrene addition increased this to 5 of 8. [The infected cells were incubated at 37°C with 5% carbon dioxide in Dulbecco’s minimum essential medium (DMEM) supplemented with 2% heat-inactivated fetal bovine serum (HI-FBS) and observed daily for cytopathic effects (CPEs). Upon observation of CPEs, the virus supernatant was harvested and sequenced. This culture technique was subsequently repeated with the addition of 5 µg/mL of Polybrene (headimethrine bromide) to DMEM supplemented with 2% HI-FBS] None of the rebound patients required additional treatment or hospitalization.



Comment: In this study clinical rebound corresponds to development of a robust antibody and T-cell immune response, arguing against a high risk of disease progression. These findings suggest that a more robust immune response rather than uncontrolled viral replication characterizes these clinical rebounds. However, the presence of infectious virus supports the need for isolation and assessment of longer treatment courses especially in immunocompromised individuals where the immune response may be ineffective. The sample size for each group was small in the late group, as patients who were 8–15 days from symptom onset and not exhibiting rebound symptoms were not actively recruited in this protocol. Longitudinal data were only available for 2 patients. Studies in larger cohorts is required to assess the incidence, clinical, and, importantly, epidemiologic implications of rebound COVID-19.

Diagnostic accuracy of covid-19 rapid antigen tests with unsupervised self-sampling in people with symptoms in the omicron period: cross sectional study.

BMJ published online September 14, 2022 [378:e071215]

doi.org/10.1136/bmj-2022-071215

Unsupervised SARS-CoV-2 rapid antigen testing with three commercial kits had 70% to 81% sensitivity during the period when Omicron emerged and became predominant in the Netherlands.

Rapid antigen testing for COVID-19 has largely replaced PCR testing in the ambulatory setting, but accuracy data are limited. Dutch investigators performed a prospective assessment of rapid antigen testing at public testing facilities using self-collected nasal or nasal plus oropharyngeal swabs; three commercial kits were compared with PCR.

In all, 6497 individuals were enrolled from December 21, 2021, to February 10, 2022, a period when the proportion of SARS-CoV-2 infections caused by Omicron rose from 29% to 99% in the

Netherlands. The sensitivities for nasal samples with the three kits ranged from 77%–86% over the entire study period, but this range fell to 70%–81% when Omicron became predominant. For the two assays with combined oropharyngeal and nasal testing, the samples had up to 10% higher sensitivity over nasal samples alone. Subset analysis found an increase in sensitivity for individuals having a confirmatory rapid antigen test secondary to a prior positive test, and a slight decrease in sensitivity for individuals with previous COVID-19.

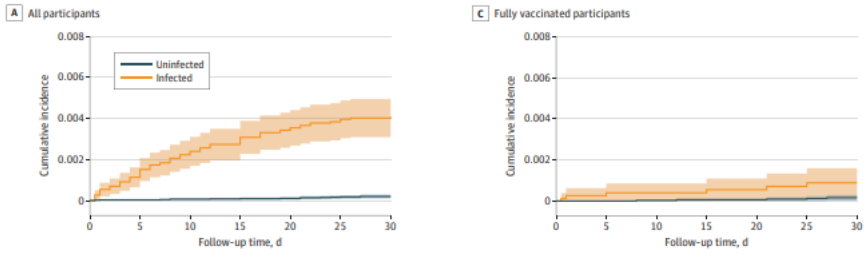
Comment: Unsupervised SARS-CoV-2 rapid antigen testing with three commercial kits had 70% to 81% sensitivity during the period when Omicron emerged. 20-30% of infections were missed with a single test is consistent with other studies. Based on these observations the FDA advised individuals who have Covid-19 symptoms should perform 2 or 3 RATs over ~48 hours if initial test is negative. The investigators also found lower sensitivity in persons with prior infection. This may be due to a lower viral load in subsequent infections.

Clinical and Genetic Risk Factors for Acute Incident Venous Thromboembolism in Ambulatory Patients With COVID-19 JAMA Intern Med 2022; 182:1063-1070

DOI: 10.1001/jamainternmed.2022.3858

Evidence is mixed about risk for venous thromboembolism (VTE) among patients with ambulatory SARS-CoV-2 infections [JAMA Intern Med 2021; 181:997 and BMJ 2022; 377:e069590]. In this U.K. population-based cohort study, investigators set out to determine the 30-day risk for VTE (i.e., deep venous thrombosis or pulmonary embolism) among 19,000 outpatients (mean age, 64) with ambulatory COVID-19.

In 18,818 outpatients with COVID-19 (10 580 women [56.2%]; mean [SD] age, 64.3 [8.0] years) and 93,179 matched uninfected participants (52 177 women [56.0%]; mean [SD] age, 64.3 [7.9] years), Covid-19 infection was associated with an increased risk of VTE in 30 days (incidence rate of 50.99 and 2.37 per 1000 person-years for infected and uninfected people, respectively; HR, 21.42; 95% CI, 12.63-36.31). However, risk was substantially attenuated among the fully vaccinated (HR, 5.95; 95% CI, 1.82-19.5; interaction P = .02). In patients with COVID-19, older age, male sex, and obesity were independently associated with higher risk, with adjusted HRs of 1.87 (95% CI, 1.50-2.33) per 10 years, 1.69 (95% CI, 1.30-2.19), and 1.83 (95% CI, 1.28-2.61), respectively. Further, inherited thrombophilia was associated with an HR of 2.05 (95% CI, 1.15-3.66) for post-COVID-19 VTE.



Comment: Although residual confounders cannot be ruled out in this observational study, this study suggests that ambulatory patients with COVID-19, present a clinically relevant increased risk for VTE during the acute phase, especially if unvaccinated. The risk is also increased by factors of older age, male sex, obesity, incomplete vaccination, and factor V Leiden thrombophilia. Although participants with COVID-19 were from nonhospital settings, they were

tested likely because of the presence of typical symptoms of COVID-19. The extent to which purely asymptomatic infection is associated with VTE risk needs further investigation. The VTE in this study appeared to be clinically relevant events that trigger ICD-10 coding. However, the diagnoses themselves did not necessarily reflect VTE status and severity (e.g., asymptomatic, incidental, or symptomatic. In an earlier small RCT, enoxaparin prophylaxis did not reduce risk of hospitalization and death, but this trial was underpowered. [Lancet Haematol 2022; 8:e585]

Peripartum Outcomes Associated With COVID-19 Vaccination During Pregnancy A Systematic Review and Meta-analysis JAMA Pediatr published online October 3, 2022

doi:10.1001/jamapediatrics.2022.3456

Investigators performed an analysis of nine observational studies comparing the pregnancy outcomes of 81,349 women who received at least one COVID-19 vaccine dose with those of 255,346 unvaccinated peers through April 5, 2022. Average age was 32 to 35 years in the vaccinated group and 29.5 to 33 years in the unvaccinated group.

Among vaccinated women, 98.2% had received an mRNA vaccine (Pfizer, Moderna, or unstipulated), while 1.1% received a viral vector vaccine (AZ or J&J), and 0.7% were undocumented. In the six studies that reported the number of doses, 85.4% of women received two doses of an mRNA vaccine. Seven studies reported the timing of the first dose, with 5.9%, 46.3%, and 47.8% of women receiving their first dose during the first, second, and third trimester, respectively.

COVID-19 vaccination during pregnancy was tied to lower risk of NICU admission (odds ratio [OR], 0.88), stillbirth (OR, 0.73), and maternal SARS-CoV-2 infection (OR, 0.46) and no significant additional risk of preterm birth (OR, 0.89), SGA (OR, 0.99), low Apgar score (indicator of newborn needing medical attention; OR, 0.94), cesarean delivery (OR, 1.05), postpartum hemorrhage (OR, 0.95), or chorioamnionitis (infection of the placenta or amniotic fluid; OR, 0.95).

Four studies separately reported rates of preterm birth and SGA according to the timing of the first vaccine dose. The incidence of preterm birth and SGA was not significantly different between women vaccinated during the first trimester and their unvaccinated counterparts (ORs, 1.81 and 1.09, respectively). Vaccination during the second or third trimester relative to no vaccination, however, was tied to a lower risk of preterm birth (OR, 0.80) and SGA (OR, 0.94).

Comment: In summary, COVID-19 vaccination during pregnancy was linked to a lower risk of NICU admission, stillbirth, and maternal SARS-CoV-2 infection and no additional risk of preterm birth, small for gestational age (SGA), low Apgar score, cesarean delivery, postpartum hemorrhage, or chorioamnionitis. But despite accumulating evidence of the safety and effectiveness of COVID-19 vaccination in pregnancy for mothers and babies, vaccination rates in this group remain inadequate.

Protective Effect of Previous SARS-CoV-2 Infection against Omicron BA.4 and BA.5 Subvariants N Engl J Med published online October 5, 2022

DOI: 10.1056/NEJMc2209306

Led by researchers from Weill Cornell Medicine-Qatar in Doha, the investigators analyzed data on COVID-19 lab testing, clinical infection, vaccination, and demographic factors from an

integrated nationwide digital-health information platform, which includes all results of PCR and RAT results from healthcare facilities.

The study spanned May 7 to July 28, 2022, a period of BA.4/BA.5 dominance in Qatar. Qatar has an unusually young and diverse population, with only 9% of its residents aged 50 years and older, and 89% expatriates from more than 150 countries. Each case-patient was matched with an uninfected control.

Pre-Omicron infection at least 90 days before reinfection was 35.5% (95% confidence interval [CI], 12.1% to 52.7%) effective against symptomatic BA.4/BA.5 reinfection and 27.7% (95% CI, 19.3% to 35.2%) effective against symptomatic or asymptomatic BA.4/BA.5 reinfection.

Omicron infection offered greater protection (76.2%; 95% CI, 66.4% to 83.1%) against symptomatic BA.4/BA.5 reinfection and 78.0% (95% CI, 75.0% to 80.7%) protection against symptomatic or asymptomatic infection. Pre-Omicron infections occurred a median of 518 days before symptomatic BA.4/BA.5 infections, compared with a 189-day interval between the initial Omicron infection and the BA4/BA.5 reinfection—or a difference of 329 days. For any BA.4 or BA.5 reinfection, the difference was 309 days (490 vs 181).

An analysis of effectiveness stratified according to time since previous infection revealed waning protection over time, and analyses classified by COVID-19 vaccination status suggested that previously infected vaccine recipients could have slightly higher protection against reinfection.

Protection from a previous SARS-CoV-2 infection against BA.4 or BA.5 reinfection was modest when the previous infection had been caused by a pre-Omicron variant but strong when it had been caused by a post-omicron subvariant (including BA.1 or BA.2).

Comment: Protection of a previous infection against reinfection with a BA.4 or BA.5 subvariant was lower than that against reinfection with a BA.1 or BA.2 subvariant because of more waning of immune protection over time and a greater capacity for immune-system evasion with the BA.4 and BA.5 subvariants. The study results may not generalize to other countries with an older population. In addition, the number of severe, critical, and fatal COVID-19 cases was too small to estimate the effectiveness of previous infection against hospitalization or death from reinfection.

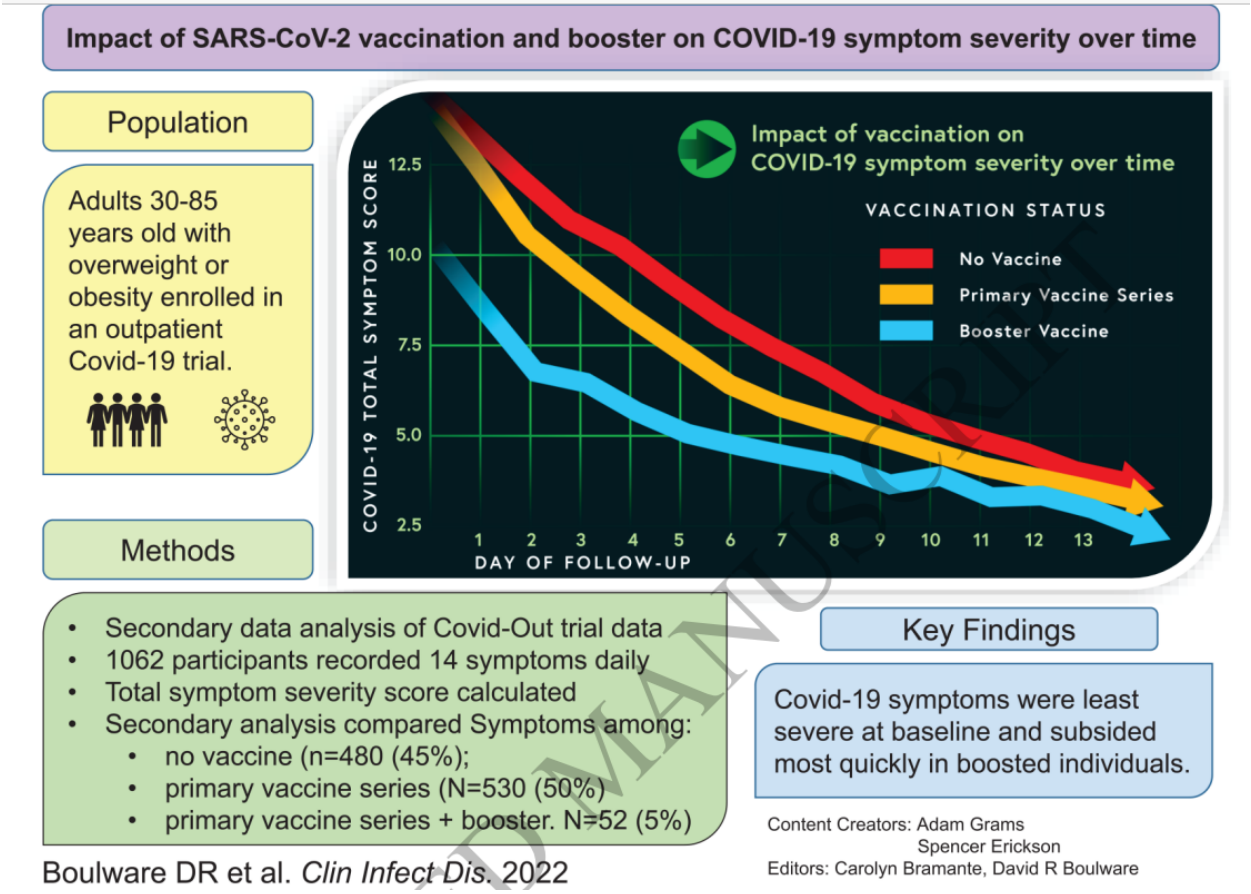
Impact of SARS-CoV-2 vaccination and booster on COVID-19 symptom severity over time in the COVID-OUT trial Clin Infect Dis published online September 17, 2022

doi:10.1093/cid/ciac772

Investigators used patient data from the COVID-Out trial on early outpatient COVID-19 therapy testing metformin, ivermectin and/or fluvoxamine**. [**Reviewed in ID Watch last month] According to the study, participants were given a paper symptom diary which allowed them to rate the severity of symptoms as none, mild, moderate or severe. The researchers then used generalized estimating equations and compared those data between unvaccinated, vaccinated with primary vaccine series only, or vaccine-boosted study participants to provide a secondary analysis of clinical trial data on symptom severity over time.

Overall, the parent clinical trial prospectively enrolled 1,323 people, of whom 1,062 (80%) prospectively recorded daily symptom data. Of these, 480 (45%) were unvaccinated, 530 (50%) were vaccinated with their primary series only and 52 (5%) were vaccine-boosted. The study showed that overall symptoms were the least severe for the vaccine-boosted group and most severe for participants who were unvaccinated at baseline and over 14 days. According to the data, average symptom severity was 1.2 points lower (95% CI, 0.6-1.8 points) among vaccinated participants compared with unvaccinated participants, and three points lower (95% CI, 2.1-3.9 points) among boosted participants compared with unvaccinated participants.

The investigators added that individual symptoms including cough, chills, fever, nausea, fatigue, myalgia, headache and diarrhea, and changes in smell and taste, were also the least severe in the vaccine-boosted group. The results were consistent across delta and omicron variant.



Comment: One of the limitations of this study was this was an observational study. In addition, because the trial completed enrollment on January 26, 2022, only 4 months after vaccine boosters were widely available they could not study the durability of boosters against symptom severity over time. The study population comes from a large, randomized trial of US adults over age 30 years with a body mass index of > 25 kg/m^2 (i.e., overweight or obese) who were enrolled predominantly during 2021 with a majority of persons infected with the delta variant or omicron variant. VE from any SARS-CoV-2 infection wanes over time, yet the vaccine-booster was strongly associated with less severe symptoms at baseline as well as over 14-days of illness, even when adjusting for viral variants.

Association Between Vaccination Status and Mortality Among Intubated Patients With COVID-19–Related Acute Respiratory Distress Syndrome JAMA Netw Open published online October 7, 2022

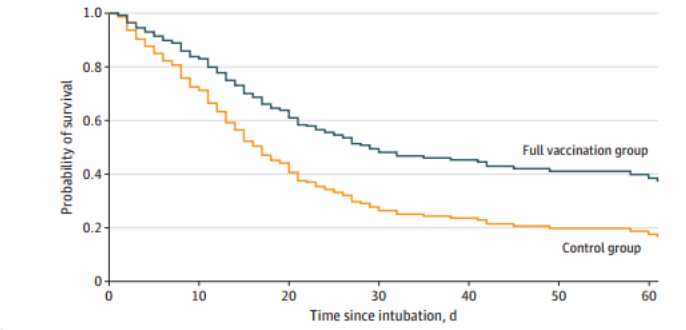
doi:10.1001/jamanetworkopen.2022.35219

The study tracked outcomes among 265 consecutive COVID patients seen in ICUs who underwent invasive mechanical ventilation due to acute respiratory distress syndrome from June 7, 2021, to February 1, 2022.

The investigators analyzed outcomes in a full vaccination group, who completed the primary COVID-19 vaccination series more than 14 days but less than 5 months prior to intubation. The other patients were either unvaccinated or partially vaccinated or had completed their full vaccination series more than 5 months earlier. The primary outcome was time from intubation to all-cause ICU mortality.

The median age of intubated patients was 66, and 64.2% were men. Twenty-six (9.8%) in the full vaccination group required ventilation. Patients in the full vaccination group were older (72.5 vs 66.0 years) and had a higher rate of significant comorbidities (92.3% vs 66.9%) than the unvaccinated group. Despite this the investigators found full vaccination status was significantly associated with lower mortality compared with controls (16 of 26 patients [61.5%] died in the full vaccination group vs 163 of 239 [68.2%] in the control group; hazard ratio, 0.55 [95% CI, 0.32 to 0.94]; *P* = .03).

Figure 1. Survival Curves of Patients Included in the Full Vaccination and Control Groups



Comment: These findings suggest that the total benefits associated with vaccination against COVID-19 may exceed those previously estimated from the prevention of invasive mechanical ventilation alone. The full vaccination group included only 26 patients. Therefore, it did not allow for stable estimates of the characteristics for the full vaccination group. Also, this number did not allow for the performance of direct comparisons of the effectiveness of different vaccine doses (2 vs 3) or different vaccine types among our population of critically ill patients requiring intubation. Given the observational cohort design of this study, they could not rule out residual confounding.

Effectiveness and durability of BNT162b2 vaccine against hospital and emergency department admissions due to SARS-CoV-2 omicron sub-lineages

BA.1 and BA.2 in a large health system in the USA: a test-negative, case-control study Lancet Respir Med published online October 7, 2022

doi.org/10.1016/ S2213-2600(22)00354-X

This test-negative case-control study, by Kaiser Permanente and Pfizer scientists involved 16,994 COVID-19 members of Kaiser Permanente Southern California who were admitted for an acute respiratory infection. Of those, 7,435 (43.8%) had BA.1, 1,056 (6.2%) had BA.2, and 8,503 (50.0%) did not have SARS-CoV-2.

The researchers noted that two-dose Pfizer VE was 40% (95% confidence interval [CI], 27% to 50%) for hospitalization and 29% (95% CI, 18% to 38%) for ED admission against Omicron BA.1 and 56% (95% CI, 31% to 72%) for hospitalization and 16% (95% CI, –3% to 33%) for ED admission against BA.2.

Three-dose VE was 79% (74% to 83%) for hospitalization and 72% (67% to 77%) for ED visit against BA.1 and 71% (55% to 81%) for hospitalization and 21% (1% to 37%) for ED visit against BA.2. VE 3 months or more after the third dose was 76% (69% to 82%) against BA.1-related hospitalization and 65% (56% to 73%) against BA.1-related ED visit. Against BA.2, VE 3 or more months after the third dose was 70% (53% to 81%) for hospitalization and 5% (−21% to 25%) for ED admission. Also, VE 3 months or more after the third dose remained high except for BA.2 ED admission

Comment: In this study, boosters restored vaccine protection to a higher level for at least several months, even against the immune-evasive omicron subvariants, but durable protection from the current generation of vaccines increasingly appears to be an elusive goal. It is hoped that the newly available bivalent boosters should help especially in high-risk individuals at least short term. [see below]

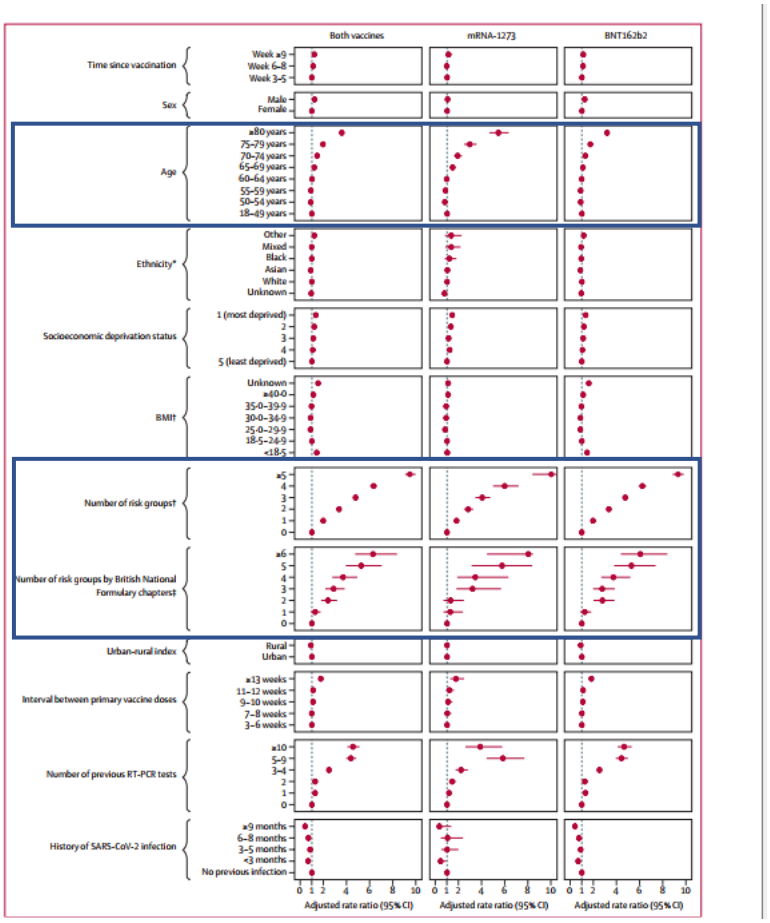
Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales Lancet 2022; 400: 1305–20

Investigators studied 16,208,600 people who completed their primary COVID-19 vaccination series with the Pfizer or AZ vaccines from December 8, 2020, to February 28, 2022, and 13,836,390 who received a Pfizer or Moderna booster from December 20, 2021, to February 28, 2022. [during the omicron wave] Participants lived in England, Northern Ireland, Scotland, and Wales.

A total of 0.4% of primary vaccine recipients and 0.2% of those who received a booster had severe COVID-19 outcomes from December 20, 2021, through February 2022, with booster-associated risk falling from 8.8 to 7.6 events per 1,000 person-years compared with people who didn't receive boosters. The risk of severe outcomes remained elevated in older adults (absolute risk reduction [aRR] for 80 years or older *vs* 18 to 49 years, 3.60), those with chronic conditions (aRR for 5 or more vs no comorbidities, 9.51), men (aRR, 1.23), those taking immunosuppressant drugs (aRR, 5.80), and those with chronic kidney disease (aRR for stage 5, 3.71). Previously COVID-infected people were at lower risk (aRR for infected at least 9 months before booster, 0.41). In addition, they found an increased risk of severe COVID-19 outcomes beginning 10 weeks after completing the primary vaccination with this risk reducing after the first

booster dose. This study also found that previous SARS-CoV-2 infection was associated with a reduced risk of severe COVID-19.

Figure 3: Pooled analyses of Poisson-adjusted rate ratios for specific clinical risk factors associated with COVID-19-related hospitalisation or death among individuals who received booster doses of mRNA-1273 or BNT162b2



Comment: The study demonstrated that older adults, men, people with underlying medical conditions, and those with suppressed immunity remained at elevated risk for hospitalization and death. This study also highlighted additional risk factors, such as chronic kidney disease, neurological disorders, heart failure, and COPD. I did not see obesity. Most importantly, they demonstrate a substantive increased risk associated with individuals with multiple comorbidities. Increased clinical risk within older people [over age 75 and especially over 80] is not unexpected and is likely to reflect underlying frailty, comorbidity, and immune senescence. Chronologically, most of the population were completing their primary vaccination schedule during two peaks of infection, whereas booster doses were rolled out when infection numbers were falling and the emerging omicron variant was less likely to cause severe outcomes in infected people. As the pandemic enters a new phase, vaccination programs and mitigation strategies need to evolve to prioritize those at highest risk of severe COVID-19 outcomes.

New symptoms and prevalence of postacute COVID-19 syndrome among nonhospitalized COVID-19 survivors Sc Reports published online October 8, 2022

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This is a retrospective single-center cohort study involved 125 nonhospitalised COVID-19 survivors (mean age, 39.3 years) and 347 healthy controls (40.8 years). Most of the COVID-19 patients were infected > 12 months before the interview (43.2%), whereas 28.8% and 28.0% of

the patients were infected < 6 months and 6–12 months before the time of the assessment, respectively.

The primary outcomes were quality of life assessed by the EuroQol five-dimension five-level assessment (EQ-5D-5L), general health status assessed by the EuroQol Visual Analogue Scale (EQ-VAS), cognitive function assessed by the Montreal Cognitive Assessment, and tic symptoms and respiratory symptoms assessed by the Breathlessness, Sputum and Cough Scale (BCSS) and Modified Medical Research Council scale scale, respectively. The secondary outcomes were PTSD assessed by the Impact of Event Scale, anxiety assessed by the Generalized Anxiety Disorder 7-item scale scale, and depression assessed by the Patient Health Questionnaire 9.

In the multivariate regression analysis, the COVID-19 survivor group had a significantly higher prevalence of PTSD than the non-COVID-19 survivor group (odds ratio [OR] 3.99; 95% confidence interval [CI] 2.08–7.64; *P* = 0.000), anxiety (OR 2.40; 95% CI 1.41–4.45; *P* = 0.001), depression (OR 4.11; 95% CI 2.25–7.48; *P* = 0.000), tics (OR = 4.90; 95% CI 2.16–11.12; *P* = 0.000) and cognitive deficit (OR 3.61; 95% CI 2.00–6.28; *P* = 0.000). In addition, the COVID-19 survivor group had a significantly higher EQ-5D-5L assessment score (B = 1.81; 95% CI 1.10–2.92; *P* = 0.000) and BCSS score (B = 0.56; 95% CI 0.15–0.97; *P* = 0.000) than the non-COVID-19 survivor group. However, COVID-19 infection was significantly associated with a lower EQ-VAS score (B = −8.31; 95% CI −12.26 to −4.52; *P* = 0.000).

Stratification of COVID-19 survivors into groups based on the duration between infection and the time of the interview showed that depression, cognitive deficit, tics, impaired quality of life and general health impairment were significantly more prevalent among COVID-19 survivors at < 6 months, 6–12 months and > 12 months than in the non-COVID-19 cohort. However, respiratory symptoms were significantly more prevalent among COVID-19 survivors only in the first 6 months after infection. Meanwhile, PTSD and anxiety were significantly more prevalent in the COVID-19 survivors' group than the non-COVID-19 survivors' group at 6–12 months and > 12 months, whereas the odds of both anxiety and PTSD were not significantly different at < 6 months.

In the comparison according to vaccination status for the odds of developing postacute COVID-19 syndrome (PACS) outcomes in the COVID-19 survivor cohort, only cognitive deficit and EQ-5D-5L assessment scores were significantly different between the vaccinated and non-vaccinated groups. The cognitive deficit prevalence (OR 0.15; 95% CI 0.03–0.87; *P* = 0.034) and the EQ-5D-5L assessment scores (B = −2.11; 95% CI −4.21 to −0.20; *P* = 0.034) were significantly lower in the vaccinated group than in the non-vaccinated group.

Comment: More than 1 year after the onset of COVID-19 infection, nonhospitalised COVID-19 survivors were still suffering from a higher prevalence of posttraumatic stress disorder (PTSD), anxiety, depression, cognitive deficit, and tics as well as lower quality of life and general health status than non-COVID-19 controls.

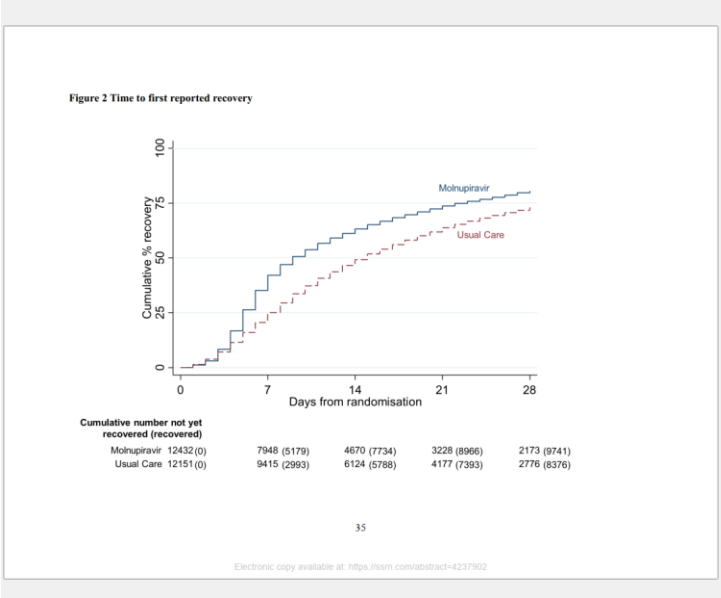
Most of the symptoms reached their highest prevalence in the 6–12-month period and declined after the 12-month period. In addition, the respiratory symptoms were not different between the two study groups 6 months after the infection. Moreover, COVID-19 vaccination was shown to significantly decrease the prevalence of cognitive deficit and quality of life impairment among COVID-19 survivors.

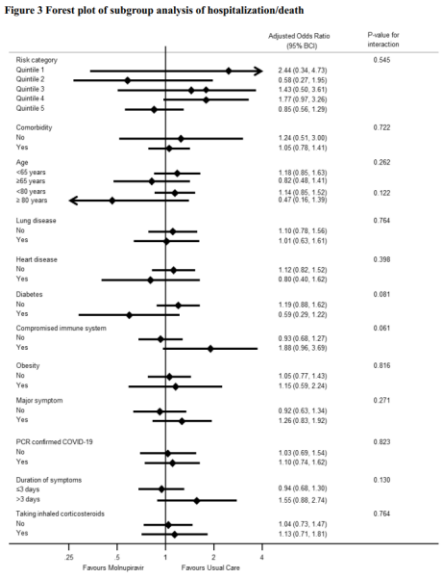
Longitudinal studies with long follow-up periods are needed to establish the time that should elapse after COVID-19 infection for the symptoms of PACS to subside and to better characterize the nature of PACS with a focus on tics. Additionally, RCTs are needed to assess the possibility that COVID-19 vaccines might relieve PACS symptoms.

Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): preliminary analysis from the United Kingdom randomised, controlled open-label, platform adaptive trial SSRN posted October 4, 2022 article suggested by Josh Septimus

This is an open-label, adaptive, multi-arm, platform, RCT involving individuals aged ≥50, or ≥18 years with comorbidities, and symptoms ≤5 days with confirmed COVID-19 in the community. Subjects were randomized to usual care or usual care plus molnupiravir (800mg twice daily for 5 days). The primary outcome measure was all-cause hospitalization/death within 28 days, analyzed using Bayesian models. The main secondary outcome measure was time to first self-reported recovery. A sub-set of participants in each group were assessed for the virology primary outcome measure of day seven SARS-CoV-2 viral load.

Between December 8, 2021, and April 27, 2022, 25,783 participants were randomized to molnupiravir plus usual care (n=12,821) or usual care alone (n=12,962). Mean (range) age of participants was 56·6 years (18 to 99), 58·6% were female, and 99% had at least one dose of a SARS-CoV-2 vaccine. The median duration of symptoms prior to randomization was two days (IQR 1 – 3), the median number of days from symptom onset to starting to take the medication was three days (IQR 3 – 4), 87% (11,109/11,997) received their medication within five days of symptom onset, and 95·4% (n=11857) of participants randomized to molnupiravir reported taking molnupiravir for five days. Primary outcome measure data were available in 25,000 (97%) participants and included in this analysis. 103/12,516 (0·8%) hospitalizations/deaths occurred in the molnupiravir group versus 96/12,484 (0·8%) in usual care alone with a posterior probability of superiority of 0·34 (adjusted odds ratio 1·061 (95% Bayesian credible interval [BCI]) 0·80 to 1·40). Estimates were similar for all subgroups. The observed median (IQR) time-to-first recovery from randomization was 9 (5–23) days in molnupiravir and 15 (7–not reached) days in usual care. There was an estimated benefit of 4·2 (95% BCI: 3·8 – 4·6) days in time-to-first-recovery (TTR) giving a posterior probability of superiority of >0·999 (estimated median TTR 10·3 [10·2 – 10·6] days vs 14·5 [14·2 – 14·9] days respectively; hazard ratio [95% BCI], 1·36 [1·3–1·4] days), which met the pre-specified superiority threshold. On day 7, SARS-CoV-2 virus was below detection levels in 7/34 (21%) of the molnupiravir group, versus 1/39 (3%) in the usual care group (p=0.039), and mean viral load was lower in the molnupiravir group compared with those receiving usual care [(SD) of log10(viral load) 3·82 (1·40) in the molnupiravir group and 4.93 (1·38) in the usual care group, (P<0·001)]. 59 (0·4%) participants experienced serious adverse events in the molnupiravir group and 52 (0·4%) in usual care.





Comment: In this analysis, they found that molnupiravir did not reduce already low hospitalizations/deaths among higher risk, vaccinated adults with COVID-19 in the community, but resulted in faster time to recovery, and reduced viral detection and load. Prior to PANORAMIC, MOVe-OUT was the largest randomized trial of molnupiravir. [N Engl J Med 2022; 386: 509-20] In the MOVe-OUT trial investigators found that molnupiravir statistically significantly reduced the risk of hospitalization or death compared with placebo (risk difference, -3·0 %; 95% CI: -5·9 % to -0·1%). In addition, in the MOVe-OUT trial, molnupiravir statistically significantly increased sustained recovery from anosmia (hazard ratio 1·20; 95% CI: 1·01 to 1·43) and fatigue (hazard ratio 1·15; 95% CI: 1·01 to 1·31), but not other symptoms. In PANORAMIC, molnupiravir helped alleviate all of symptoms measured, including fever, cough, fatigue, muscle ache, diarrhea, headache, loss of taste and smell, dizziness and feeling generally unwell, and shortened the time to self-reported. Molnupiravir may have shortened the time to resumption of normal activities, since the time that normal activities are affected is closely related to the duration of feeling unwell, but they did not measure this outcome directly. The proportion experiencing adverse events was similar in PANORAMIC and MOVe-OUT. Lastly, participants in MOVe-OUT were unvaccinated, while most UK adults are now vaccinated. Clearing virus faster may be of benefit to decreasing transmission and faster time to recovery may still be a benefit worth exploring.