Infectious Diseases Watch

November 28, 2022

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VII: Amoxicillin Shortage: Looking Under the Hood

Amoxicillin is in short supply across the country, alarming pediatricians, and parents as a surge in respiratory illnesses strains hospitals and outpatient facilities, many of which are still trying to recover from the pandemic. The FDA said shortages would likely persist in the coming months.

Public health officials are concerned that holiday travel combined with big family gatherings at Thanksgiving and winter break, may fuel a further rise in respiratory illnesses. So far, experts are not anticipating as big a surge as last winter with Covid-19, but the lifting of mask mandates and other precautions as well as lower immunity to influenza and other respiratory viruses are of concern. Influenza is four to six weeks early, and RSV is usually a January-February virus. In addition, other respiratory illnesses, such as rhinoviruses and adenoviruses, are also circulating. (see below)The seasonal respiratory illnesses have surfaced earlier than usual, and they have spread quickly across the country. Oseltamivir is also in short supple in certain areas in the US.

The shortages highlight the fragility of the nation's drug supply chain, especially for inexpensive generics like amoxicillin. But let is focus on the run-on amoxicillin. This highlights another serious problem that continues to pose a threat to human health. Overprescribing of antibiotics for viral illnesses continues despite numerous attempts to reduce unnecessary antibiotics for upper respiratory infections. The CDC estimates that up to 43% of antibiotic prescriptions are unnecessary. The overuse of antibiotics can accelerate the development of resistance and increase adverse events including dysbiosis a predisposing factor for the development of C. difficile infection.

In a recent article reviewed on June 6, 2022 in ID Watch [Volume 1, Issue 21-JAMA Netw Open 2022;5(5):e2214153] investigators at Pew and the Washington University School of Medicine in St. Louis analyzed a large database containing outpatient insurance claims and outpatient pharmacy-dispensed medications for patients with commercial insurance. Looking at antibiotic prescriptions by diagnosis, the analysis found that 36% of children with sinusitis, 34% of children pharyngitis, and 31% of children with suppurative otitis media received an inappropriate antibiotic. For children with viral infections, the proportion who received an inappropriate antibiotic ranged from 4% for those with influenza to 70% of children with bronchitis. Analysis of adverse events found that, in the children with upper respiratory infections, the increased risk for an adverse event associated with an inappropriate antibiotic prescription was significant. Inappropriate antibiotic selection for pharyngitis was associated with a more than eightfold increase in the risk of *C difficile* infection (hazard ratio [HR], 8.42; 95% confidence interval [CI], 3.09 to 23.0). Children who received the non-guideline recommended antibiotic for suppurative otitis media more had a quadrupled risk of severe allergic reaction (HR, 4.14; 95% CI, 2.48 to 6.92). For children with viral infections, unnecessary antibiotics were associated with higher risk of rash or urticaria. Overuse and misuse of antibiotics for viral respiratory infections is even higher in adults.

This shortage we are seeing is in part the result of poor stewardship and our supply chain. While many clinicians are generally aware of these potential threats, unfortunately despite education and feedback, we have a long way to go. Recent studies confirm that investments, such as dedicated antimicrobial stewardship personnel and initiatives across the continuum of care, could lead to a substantial return on investment. Despite decades of work and discussion, we have not made enough progress. It is time to hold all of us accountable.

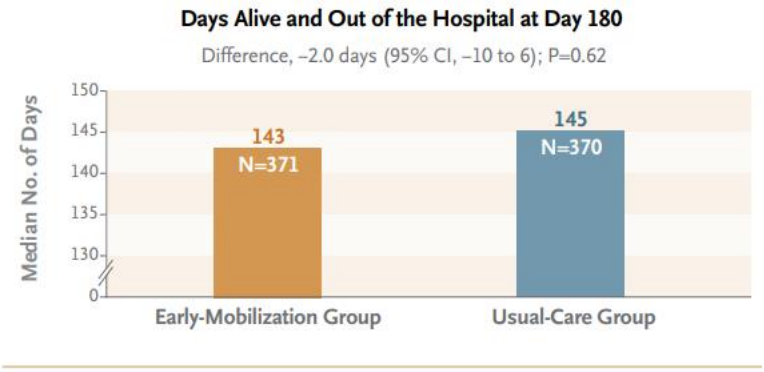
General Infectious Diseases

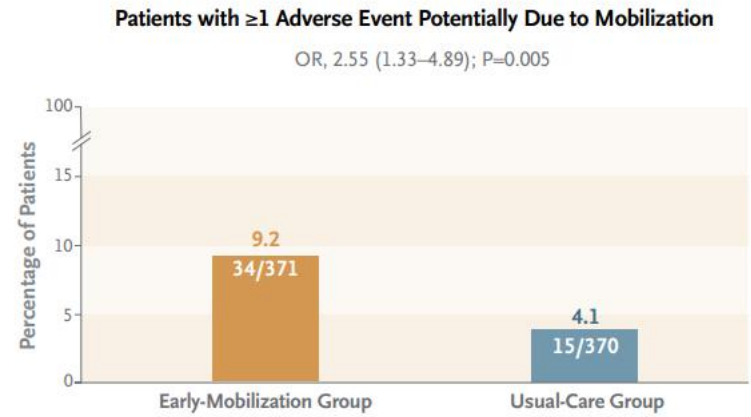
Early Active Mobilization during Mechanical Ventilation in the ICU N Engl J Med 2022; 387:1747-58.

DOI: 10.1056/NEJMoa2209083

Some literature suggests that early mobilization of patients in the ICU may reduce the length of hospital stay, risk of VAP, and increase survival, and reduce disability. The investigators randomly assigned 750 adult patients in the ICU who were undergoing invasive mechanical ventilation to receive increased early mobilization (sedation minimization and daily physiotherapy) or usual care (the level of mobilization that was normally provided in each ICU). They randomly assigned patients in a 1:1 ratio to receive early mobilization or usual care using a centralized Web-based interface. Patients received the trial treatment while they were in the ICU for up to 28 days after randomization. The primary outcome was the number of days that the patients were alive and out of the hospital at 180 days after randomization. Key secondary outcomes were mortality at 180 days, the number of ventilator-free days and days out of the ICU from randomization to day 28, and patient-reported outcome measures, including quality of life and function in survivors at day 180. This trial, which was performed in 49 hospitals across three continents, the ICU population reflected similar patients in other high-income countries

The median number of days that patients were alive and out of the hospital was 143 (interquartile range, 21 to 161) in the early-mobilization group and 145 days (interquartile range, 51 to 164) in the usual-care group (absolute difference, -2.0 days; 95% CI, -10 to 6; P=0.62). The mean (±SD) daily duration of active mobilization was 20.8±14.6 minutes and 8.8±9.0 minutes in the two groups, respectively (difference, 12.0 minutes per day; 95% CI, 10.4 to 13.6). A total of 77% of the patients in both groups were able to stand by a median interval of 3 days and 5 days, respectively (difference, -2 days; 95% CI, -3.4 to -0.6). By day 180, death had occurred in 22.5% of the patients in the early-mobilization group and in 19.5% of those in the usual-care group (odds ratio, 1.15; 95% CI, 0.81 to 1.65). Among survivors, quality of life, activities of daily living, disability, cognitive function, and\ psychological function were similar in the two groups. Serious adverse events were reported in 7 patients in the early-mobilization group and in 1 patient in the usual care group. Adverse events that were potentially due to mobilization (arrhythmias, altered blood pressure, and desaturation) were reported in 34 of 371 patients (9.2%) in the early-mobilization group and in 15 of 370 patients (4.1%) in the usual-care group (P=0.005).





Comment: The findings in this study are at variance with a previous meta-analysis showing that active mobilization in the ICU, particularly when delivered early, significantly increased the number of days that patients were alive and out of the hospital at 180 days. [Intensive Care Med 2017; 43:171-83] However, the findings in this trial are broadly consistent with the results of several other randomized, controlled trials that were conducted recently. [Am J Respir Crit Care Med 2016; 193:1101-1110; JAMA 2016; 315:2694-2702] There are some additional caveats about this trial. The patients received mobilization therapy only while they were in the ICU. However, the ICU may represent only the beginning of a long course of recovery for many of these patients. The high frequency of early mobilization in the usual-care group was also surprising. A physiotherapist assessed the patients on 81% of ICU days in the usual-care group, as compared with 94% of ICU days in the intervention group. Therefore, this may have contributed to the negative results. Lastly, I see no mention of VAPs or VAEs or a detailed description of "usual care". What was their protocol for spontaneous awakening trials, sedation protocols, or oral care?

Antimicrobial resistance in the EU/EEA (EARS-Net) 2021 November 2022

A new report from the European Centre for Disease Prevention and Control (ECDC) suggests that as many as 35,000 residents of the European Union die each year from complications caused by antimicrobial resistance (AMR). The report was based on data collected from 2016 through 2020, with increasing deaths in each year—most notably among antibiotics of last resort. With AMR causing roughly 100 deaths per day in the region, it's more deadly than influenza, tuberculosis, and HIV/AIDS combined! ☹

To gauge the impact of AMR on the region, the authors used annual rates of bloodstream infections (BSI) with antibiotic-resistant bacteria, adjusted the data with population coverage-corrected number of BSIs to other types of infections, and deducted the estimated number of secondary BSIs. Between 2016 and 2020, the annual number of cases of infections with the included bacterium- antibiotic resistance combinations in the EU/European Economic Area ranged from 685,433 (95% uncertainty interval [UI], 589,451 to 792,873) in 2016 to 865,767 (95% UI, 742,802 to 1,003,591) in 2019. The authors said the annual number of attributable deaths ranged from 30,730 (95% UI, 26,935 to 34,836) in 2016 to 38,710 (95% UI, 34,053 to 43,748) in 2019. Of note, 71% of infections with antibiotic-resistant bacteria (95% confidence interval (CI), 68.2 to 74.0%) were healthcare-associated. The largest burden of disease was caused by third-generation cephalosporin-resistant *E coli*, followed by MRSA, and third-generation cephalosporin-resistant *K. pneumoniae.* Greece, Italy, and Romania had the highest burdens, after adjusting for population.

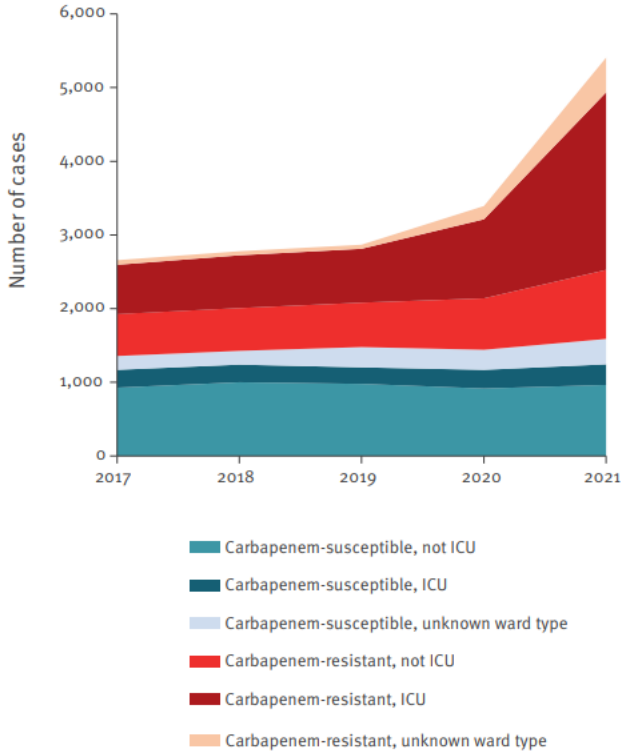
Although the rates of AMR infections and deaths are increasing in Europe, there was a dip in 2020 to 2021, largely because of behavior changes that took place during the first year of the Covid-19 pandemic. There was less community use of antibiotics, and many elective surgeries and inpatient procedures were delayed, leading to a decrease in healthcare-associated infections (HAIs). However, despite the overall decrease in AMR from 2020-2021 infections due to carbapenem resistant *Acinetobacter* spp. (CRAB) increased during the first year of the pandemic. The report predicted that CRAB would continue to grow in 2022 and 2023. (see articles below Eurosurveillance and Lancet)

Comment: In the US there was a substantial increase in both HAIs and AMR during the pandemic. The CDC recently updated the National and State Progress Report on HAIs demonstrating continued challenges in reducing HAIs during the pandemic. [review in ID Watch Volume 2, Issue 12, November 14, 2022] In a recent publication (see article below-ICHE) infection prevention staffing levels and experience correlated with higher HAIs. During the pandemic we have seen burnout and retirements impacting maintaining a stable infection prevention and nursing workforce.

Large increase in bloodstream infections with carbapenem resistant *Acinetobacter* species during the first 2 years of the COVID-19 pandemic, EU/EEA, 2020 and 2021 Eurosurveillance November 17, 2022

Recent data from the European Antimicrobial Resistance Surveillance Network (EARS-Net) show a large increase of +57% in Acinetobacter species bloodstream infections in the European Union and European Economic Area in the first years of the COVID-19 pandemic (2020–2021) compared with 2018–2019. (See report above) Most were resistant to carbapenems, from ICUs, and in countries with≥50% carbapenem resistance in Acinetobacter spp. in 2018–2019.

Acinetobacter species bloodstream infections reported by laboratories that continuously reported data to EARS-Net, by carbapenem susceptibility testing result and type of patient ward, EU/EEA, 2017–2021 (n = 16,626)



US CDC Special Report July 2022

Available data show an alarming increase in resistant infections starting during hospitalization, growing at least 15% from 2019 to 2020.

- Carbapenem-resistant *Acinetobacter* (↑78%)
- Antifungal-resistant *Candida auris* (↑60%)*
- Carbapenem-resistant Enterobacterales (↑35%)
- Antifungal-resistant *Candida* (↑26%)
- ESBL-producing Enterobacterales (↑32%)
- Vancomycin-resistant Enterococcus (↑14%)
- Multidrug-resistant *P. aeruginosa* (↑32%)
- Methicillin-resistant *Staphylococcus aureus* (↑13%)

Comment: In the US there has been an 78% increase in CRAB during the pandemic. Acinetobacter spp. is difficult to eradicate from the hospital environment, colonizing hospital patients and staff and causing outbreaks, particularly in ICUs. These infections are some of the most difficult to treat. Antimicrobial stewardship to decrease overuse and misuse of antibiotics also play a key role in decreasing CRAB. This report highlights the requirement for reinforced Acinetobacter preparedness, infection prevention, and ASP in both the US and Europe.

Infection preventionist staffing levels and rates of 10 types of healthcare-associated infections: A 9-year ambidirectional observation Infect Control Hosp Epidemiol 2022; 43: 1641–1646

doi.org/ 10.1017/ice.2021.507

Standardized NHSN definitions were used for HAIs. Staffing levels were measured in full-time equivalents (FTE) for IPs and total monthly hours worked for nurses. A time-trend analysis using control charts, t tests, Poisson tests, and regression analysis was performed using Minitab and R computing programs on rates and standardized infection ratios (SIRs) of 10 types of HAIs. An additional analysis was performed on 3 stratifications: critically low (2–3 FTE), below recommended IP levels (4–6 FTE), and at recommended IP levels (7–8 FTE) in a 528-bed teaching hospital.

The observation covered 1.6 million patient days of surveillance. IP staffing levels fluctuated from ≤2 IP FTE (critically low) to 7–8 IP FTE (recommended levels). Periods of highest CAUTI SIRs, hospital-onset Clostridioides difficile and carbapenem-resistant Enterobacteriaceae infection rates, along with 4 of 5 types of surgical site SIRs coincided with the periods of lowest IP staffing levels and the absence of certified IPs and a healthcare epidemiologist. CLABSIs increased amid lower nursing levels despite the increased presence of an IP and a hospital epidemiologist.

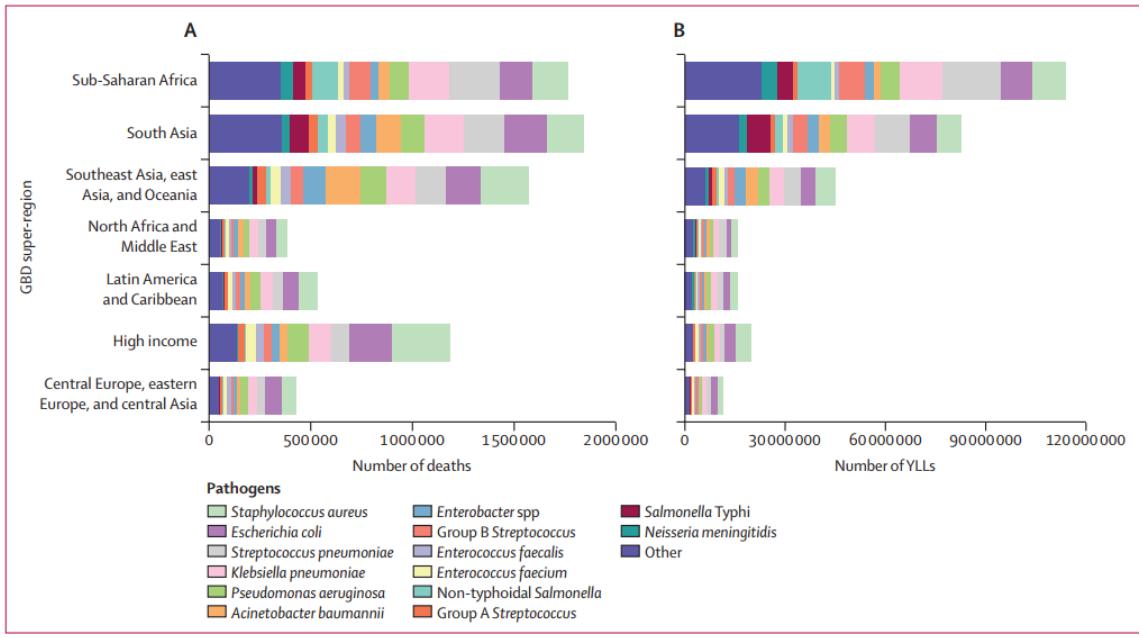
Comment: Of 10 HAIs, 8 had highest incidences during periods of lowest IP staffing and experience. Some HAI rates varied inversely with levels of IP staffing and experience and others appeared to be more influenced by nursing levels or other confounders. These HAI trends are consistent with a recent report from the NHSN showing that HAI rates increased during the pandemic, especially CLABSI rates. Older determinations of optimum IP-to-patient ratios were based on surveys, a Delphi method, or combinations of surveys and task analysis. A ratio of 0.8 to 1.0 ICP for every 100 occupied acute care beds was suggested as adequate staffing by the Delphi panel. In addition, they recommended staffing must not only consider the number of occupied beds (average daily census) but also include the scope of the program, the complexity of the health care facility or system, the characteristics of the patient population, and the unique or urgent needs of the facility and community. [Am J Infect Control 2002; 30:321-33] In this current study no causal relationships can be inferred due to its quasi-experimental design and lack of confounder control. Similarly, it is difficult to differentiate the effect of staffing levels from other influences and confounders. Only a single institution was included, but using SIRs helped adjust for facility level factors and increased generalizability. Surprisingly, surgical decolonization and prophylaxis practices were not standardized across each surgical subspecialty. Despite these limitations, this study provides useful information for resource allocation and patient safety. These data are pertinent given the ongoing shortages of IPs and nurses.

Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019 Lancet published online November 21, 2022

doi.org/10.1016/ S0140-6736(22)02185-7

The investigators estimated deaths associated with 33 bacterial genera or species across 11 infectious syndromes in 2019 using methods from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, in addition to a subset of the input data described in the Global Burden of Antimicrobial Resistance 2019 study. This study included 343 million individual records or isolates covering 11,361 study-location-years. They used three modelling steps to estimate the number of deaths associated with each pathogen: deaths in which infection had a role, the fraction of deaths due to infection that are attributable to a given infectious syndrome, and the fraction of deaths due to an infectious syndrome that are attributable to a given pathogen. Estimates were produced for all ages and for males and females across 204 countries and territories in 2019. 95% uncertainty intervals (UIs) were calculated for final estimates of deaths and infections associated with the 33 bacterial.

From an estimated 13.7 million (95% UI 10.9–17.1) infection-related deaths in 2019, there were 7.7 million deaths (5.7–10.2) associated with the 33 bacterial pathogens (both resistant and susceptible to antimicrobials) across the 11 infectious syndromes estimated in this study. They estimated deaths associated with the 33 bacterial pathogens to comprise 13.6% (10.2–18.1) of all global deaths and 56.2% (52.1–60.1) of all sepsis-related deaths in 2019. Five leading pathogens—*S. aureus, E. coli, S. pneumoniae, K. pneumoniae,* and *P. aeruginosa*—were responsible for 54.9% (52.9–56.9) of deaths among the investigated bacteria. The deadliest infectious syndromes and pathogens varied by location and age. The age-standardized mortality rate associated with these bacterial pathogens was highest in the sub-Saharan Africa super-region, with 230 deaths (185–285) per 100,000 population, and lowest in the high-income super-region, with 52.2 deaths (37.4–71.5) per 100,000 population. *S aureus* was the leading bacterial cause of death in 135 countries and was also associated with the most deaths in individuals older than 15 years, globally. Among children younger than 5 years, *S pneumoniae* was the pathogen associated with the most deaths. In 2019, more than 6 million deaths occurred because of three bacterial infectious syndromes, with lower respiratory infections and bloodstream infections each causing more than 2 million deaths and peritoneal and intra-abdominal infections causing more than 1 million deaths.



YLLs=years of life lost.

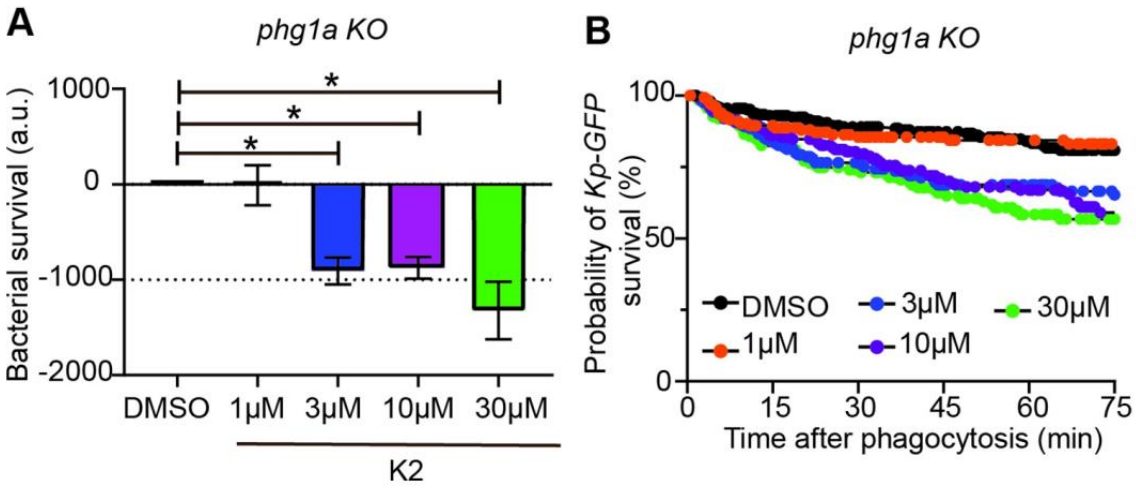
Comment: Strategies need to be developed and implemented to address this substantial burden. First, infection prevention can reduce the burden of HAIs. Community programs that focus on health education, management of malnutrition in LMICs (low-income and middle-income countries, and the core principles of access to clean water, sanitation, and hygiene is critical. Second, vaccination can have a substantial effect on the burden of bacterial infections. Implementation and uptake of vaccines for bacteria like *S pneumoniae* can directly reduce the burden of bacterial infections. Developing bacterial vaccines beyond pneumococcus are needed. Acceptance of vaccines for non-bacterial infections like influenza, where bacterial superinfection is a common complication, can also reduce the burden of bacterial infections. A new strategic approach and increased investment in the development of new and effective antibiotics are essential to face the increasing threat posed by bacterial antimicrobial resistance. Unfortunately, *M tuberculosis* was not included in this analysis. Lastly, inadequate microbiological capacity has substantial effects on both population health estimates and the clinical care of individual patients. There is an urgent need to build microbiology laboratory networks and develop innovative surveillance strategies. Input data for each modelling step has incomplete geographical coverage and is of varying quality for many LMICs, and we did not have data for 61 countries or territories for all three of our modelling steps. The identification of deaths in which infection had a role relied on ICD coded deaths, which did not always correlate with expert chart review.

Predictive mathematical modelling and further advancements in genomic epidemiology of infections will increase insights at the global level and hopefully be used to guide strategies for reducing the burden of bacterial infectious diseases, including infection prevention and control measures, vaccine development and implementation, and the availability of basic acute care services.

5-ethyl-2'-deoxyuridine fragilizes Klebsiella pneumoniae outer wall and facilitates intracellular killing by phagocytic cells PLoS ONE 17: e0269093.

doi.org/10.1371/journal. pone.0269093

K. pneumoniae (KP) pathogenicity relies largely on its ability to escape phagocytosis and intracellular killing by phagocytic cells. Interfering with these escape mechanisms may allow to decrease bacterial virulence and to combat infections. In this study, the investigators used Dictyostelium discoideum(soil-dwelling amoeba) as a model phagocyte to screen a collection of 1,099 chemical compounds. *D*. *discoideum* ingests non-pathogenic KpGE *K*. *pneumoniae* bacteria and can efficiently use them as a food source. On the contrary, *phg1a* KO *D*. *discoideum* mutants kill ingested *K*. *pneumoniae* inefficiently. Phg1A KO D. discoideum cells cannot feed upon KP bacteria, unless bacteria bear mutations decreasing their virulence. They identified 3 non-antibiotic compounds that restored growth of phg1A KO cells on KP, and they characterized the mode of action of one of them, 5-ethyl-2'-deoxyuridine (K2). K2-treated bacteria were more rapidly killed in D. discoideum phagosomes than non-treated bacteria. They were also more sensitive to polymyxin, and their outer membrane was more accessible to a hydrophobic fluorescent probe.



Comment: There are two ways by which intracellular killing can be facilitated: either by stimulating the intracellular killing mechanisms, or by rendering bacteria more susceptible to intracellular killing. K2 clearly falls into the second category, since bacteria grown in the presence of K2 are more easily killed when they are ingested by *D*. *discoideum*, as well as when they are exposed to *D*. *discoideum* extracts *in vitro*. These results suggest that K2 acts by rendering the membrane of KP accessible to antibacterial effectors. K2 was effective on three different KP strains and acted at concentrations as low as 3 μM. Since K2 decreases *K*. *pneumoniae* virulence at a concentration of 3 μM, the investigators speculate that it could be used to treat *K*. *pneumoniae* infections. K2 has previously been used to treat viral infections but its precise molecular mechanism of action in K. pneumoniae needs confirmation. K2 is 5-ethyl-2'-deoxyuridine, also known as edoxudine. It was used until 1998 as a topical antiviral drug, to treat genital herpes simplex infections. Developing non-antibacterial interventions may help improve patient outcomes. Current research has been directed at the host microbiome and phage therapy to name a few.

Clinical Impact of Ceftriaxone Resistance in *Escherichia coli* Bloodstream Infections: A Multicenter Prospective Cohort Study

OFID published online October 27, 2022

doi.org/10.1093/ofid/ofac572

This is a prospective cohort of patients with *E coli* BSI at 14 United States hospitals between November 2020 and April 2021. For each patient with a CRO-R *E coli* BSI enrolled, the next consecutive patient with a ceftriaxone-susceptible (CRO-S) *E coli* BSI was included. Primary outcome was desirability of outcome ranking (DOOR) at day 30, with 50% probability of worse outcomes in the CRO-R group as the null hypothesis. Inverse probability weighting (IPW) was used to reduce confounding.

Notable differences between patients infected with CRO-R and CRO-S *E coli* BSI included the proportion with Pitt bacteremia score ≥4 (23% vs 15%, *P* = .079) and the median time to active antibiotic therapy (12 hours [interquartile range {IQR}, 1–35 hours] vs 1 hour [IQR, 0–6 hours]; *P* < .001). Unadjusted DOOR analyses indicated a 58% probability (95% CI, 52%–63%) for a worse clinical outcome in CRO-R versus CRO-S BSI. In the IPW-adjusted cohort, no difference was observed (54% [95% CI, 47%–61%]). Secondary outcomes included unadjusted and adjusted differences in the proportion of 30-day mortality between CRO-R and CRO-S BSIs

(-5.3% [95% CI, -10.3% to -.4%] and -1.8 [95% CI, -6.7% to 3.2%], respectively), postculture median length of stay (8 days [IQR, 5–13 days] vs 6 days [IQR, 4–9 days]; $P < .001$), and incident admission to a long-term care facility (22% vs 12%, $P = .045$).

Comment: In this prospective cohort study of 300 patients with *E coli* BSI from 14 hospitals across the US, patients infected with CRO-R *E coli* BSI had worse clinical outcomes compared to patients infected with CRO-S *E coli* BSI in unadjusted analyses. However, after adjusting for important confounders, no difference was seen in the primary DOOR analysis. However, patients infected with CRO-R BSI were more likely to have prolonged lengths of hospital stays, to remain in the hospital at day 30, and to be newly transferred to long-term care facilities. Previous studies have demonstrated that infections exhibiting drug-resistant phenotypes are generally associated with increased mortality compared to infections caused by drug susceptible isolates. This investigation was unfortunately not powered to detect a mortality difference. However, all-cause mortality was numerically higher in the CRO-R group, although this difference was not statistically significant. Treating physicians prescribed empiric carbapenem therapy for most patients with CRO-R *E coli.* In an international randomized clinical trial, carbapenem therapy was associated with a significant decrease in 30-day mortality in patients with CRO-R *E coli* BSI. [JAMA 2018; 320:984–94] Patients with CRO-R *E coli* bacteremia who receive early carbapenem therapy may have similar 30-day mortality rates as those with CRO-S *E coli* bacteremia. However, studies have shown a significant delay in escalation without the use of molecular capabilities. [Clin Infect Dis 2021; 73:e39-46] 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., *bla* $_{\text{CTX-M-15}}$, *bla* $_{\text{SHV-12}}$), plasmid-mediated *bla*$_{\text{ampC}}$genes (e.g., *bla*$_{\text{DHA}}$, *bla*$_{\text{FOX}}$), chromosomally derepressed *bla* $_{\text{ampC}}$ genes, and hyperexpressed narrow-spectrum β-lactamase genes with associated mutations in permeability. CLSI does not endorse routine ESBL testing, so it is performed only by a minority of clinical microbiology laboratories. They attempted to mitigate the impact of cofounders on clinical outcomes through IPW propensity score–adjusted analysis. Nonetheless, residual confounding may persist.

Evaluation of an Opt-Out Protocol for Antibiotic De-Escalation in Patients With Suspected Sepsis: A Multicenter, Randomized, Controlled Trial. Clin Infect Dis published online September 28, 2022

doi.org/10.1093/cid/ciac787

Patients (N=767) with suspected sepsis were enrolled in a patient-level randomized trial, which was conducted at 10 sites in the US between 2018 and 2020**.** Investigators aimed to determine whether the use of an opt-out protocol decreases unnecessary antibiotic treatment for suspected sepsis. Patients were randomly assigned in a 1:1 fashion to receive either the opt-out protocol (n=383) or usual care (controls; n=384). The protocol included 5 steps that all occurred on the same day: 1. eligibility screen, 2. Safety check, 3. randomization, 4. opt-out procedure, and 5. Guided de-escalation discussion. The intervention involved a pharmacist-led discussion with the clinician to encourage antibiotic discontinuation using opt-out language. Clinicians were asked to provide rationales and de-escalation plans for patients in whom antibiotic treatment was continued as opposed to per-protocol antibiotic cessation. The primary outcome was the number of antibacterial days of therapy (DOT) at 30 days following enrollment.

Among patients included in the intervention and control cohorts, the median age was 63 (IQR, 49-73) and 66 (IQR, 53-76) years, 49% and 45% were women, 49% and 51% were White, 32% and 29% were hospitalized within the past 90 days, and the median Elixhauser comorbidity score was 11 (IQR, 5-19) and 11 (IQR, 4-20), respectively. The most common diagnoses indicating antibiotic treatment among the patients included urinary tract, skin and soft tissue, intra-abdominal, and respiratory infections.

Among 9606 patients screened, 767 (8%) were enrolled. Intervention patients had 32% lower odds of antibiotic continuation (79% vs 84%; odds ratio, 0.68; 95% confidence interval [CI], .47–.98). DOT among those who continued antibiotics were similar (ratio of means, 1.06; 95% CI, .88–1.26). The overall length of hospitalization was shorter among patients in the intervention cohort compared with those in the control cohort (median, 5 vs 6 days, respectively). Fewer intervention patients were exposed to extended spectrum antibiotics (36% vs 44%). Common reasons for continuing antibiotics were treatment of localized infection (76%) and belief that stopping antibiotics was unsafe (31%). Thirty-day safety events were similar

A total of 133 and 157 major safety events occurred among patients in the intervention and control cohorts, respectively. The most common safety signals among patients in the intervention vs control cohorts were hospital (15.9% vs 14.8%), recurrence of suspected sepsis (7.8% vs 7.8%), intensive care unit admission (6.8% vs 8.6%), and reinitiation of inpatient antibiotics after more than 48 hours of no antibiotics (4.2% vs 4.2%). At 30 days, the opt-out protocol was associated with the probability of a better 6-level desirability of outcome ranking (DOOR) and a better treatment response, with adjustments for duration of antibiotic risk (RADAR) profiles (OR, 0.52; 95% CI, 0.48-0.56).

Narrow spectrum	Broad spectrum	Extended spectrum, including MDRO and Pseudomonas	Protected
1	2	3	4
1st- and 2nd-generation cephalosporins Amoxicillin TMP/SMX Nafcillin, Oxacillin Metronidazole Doxycycline Nitrofurantoin Penicillin	Ceftriaxone 3rd-generation oral cephalosporins Azithromycin Clarithromycin Amoxicillin/clavulanate Ampicillin/sulbactam Clindamycin	Anti-pseudomonal penicillins Fluoroquinolones Aminoglycosides Vancomycin Cefepime, Ceftazidime Ertapenem Aztreonam	Anti-pseudomonal Carbapenem Colistin Tigecycline Linezolid, Tedizolid Daptomycin Ceftaroline Ceftazidime/avibactam Ceftolozane/tazobactam

Table 3. DETOURS Desirability of Outcome Ranking (DOOR) Outcome

Outcome	Rank
Alive	1
Readmission, relapse of suspected sepsis, *C. difficile* infection, OR deep venous thrombosis	2
≥2 of items in Rank 2 above	3
Subsequent ICU Admission OR hemodialysis	4
Subsequent ICU Admission AND hemodialysis	5
Death	6

Comment: An antibiotic opt-out protocol that targeted patients with suspected sepsis resulted in more antibiotic discontinuations, similar DOT when antibiotics were continued, and no evidence of harm. Future stewardship interventions must directly address diagnostic uncertainty and perceptions of safety when addressing antibiotic decision-making for patients with suspected sepsis. Diagnostic stewardship is critical to reduce diagnostic uncertainty. This study was limited by the inclusion of patients from both community and academic hospitals with varied resources and antibiotic stewardship practice. Time-related effects were difficult to interpret due to the many changes in care delivery associated with the onset of the pandemic.

Discontinuing MRSA and VRE contact precautions: Defining hospital characteristics and infection prevention practices predicting safe de-escalation

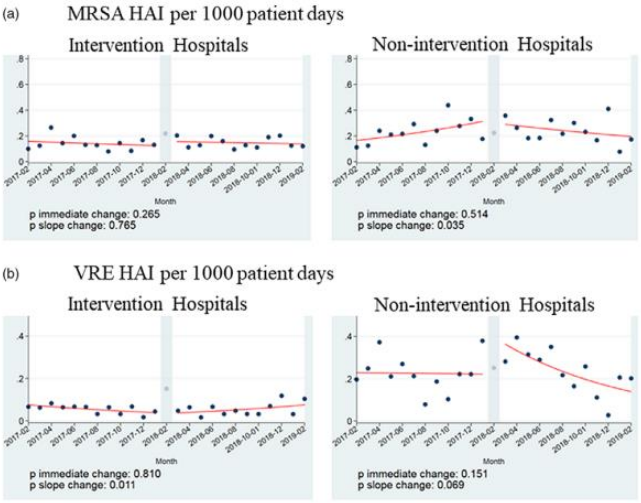
ICHE 2022; 43:1595–1602

doi:10.1017/ice.2021.457

This study is an interrupted time series retrospective, observational, quasi-experimental study comparing the rate of MRSA and VRE HAIs before and after contact precautions were discontinued for endemic MRSA and VRE involving 15 acute care hospitals. Each of the 15 study hospitals independently elected to either to remove contact precautions for MRSA and VRE (intervention hospitals, N = 12) or to continue current practice (nonintervention hospitals, N = 3), based on baseline HAI rates and patient populations at high risk of HAI. All neonatal ICUs and burn units in intervention hospitals continued precautions for MRSA and VRE. Rates of MRSA and VRE HAIs were collected for 12 months before and after. Trends in HAI rates were analyzed using Poisson regression. To predict conditions when contact precautions may be safely discontinued, selected baseline hospital characteristics and infection prevention practice. The primary outcomes were rates of MRSA and VRE HAI per 1,000 patient days and MRSA laboratory-identified (LabID) events per 100 patient admissions using NHSN procedures (2017–2019). LabID events are based on positive clinical isolates, providing a surrogate marker of HAI. The investigators collected data on hospital characteristics and infection prevention practices from hospital records and local infection prevention teams, including number of beds, percent ICU beds, percent private rooms, CHG bathing, hand hygiene adherence, and use of UV disinfection.

Aggregated HAI rates from intervention hospitals before and after discontinuation of contact precautions were 0.14 and 0.15 MRSA HAI per 1,000 patient days (P = .74), 0.05 and 0.05 VRE HAI per 1,000 patient days (P = .96), and 0.04 and 0.04 MRSA laboratory identified (LabID) events per 100 admissions (P = .57). No statistically significant rate changes occurred between intervention and non-intervention hospitals. All successful hospitals had low baseline MRSA and VRE HAI rates and high hand hygiene adherence. We observed no correlations between rate

changes after discontinuation and the assessed hospital characteristics and infection prevention factors, but the rate improved with higher proportion of semiprivate rooms (P = .04).



Comments: They detected no associations with (1) status as a community or a tertiary-care facility, (2) bed size, (3) percentage ICU population, or (4) the change in rates of MRSA or VRE HAI per 1,000 patient days. There was no association between the hospital's percentage of private rooms and the change in the rate of VRE HAI per 1,000 patient days, although there was an increase in MRSA HAI per 1,000 patient days in hospitals with a higher percentage of private rooms (ρ, 0.659; P = .04). There was no association between the use of CHG bathing and change in rate of MRSA or VRE HAI after removing contact precautions. In addition, there were no correlations between hand hygiene compliance or UV disinfection and rates of MRSA and VRE HAI after precautions were removed. The overall conclusion from this study was discontinuing contact precautions for MRSA/VRE did not result in increased HAI rates. This suggests that contact precautions can be safely removed from diverse hospitals, including community hospitals and those with lower proportions of private rooms, but good hand hygiene and low baseline HAI rates should be conditions necessary in considering safely discontinue contact precautions for patients with MRSA and VRE. Although this study had an interrupted time series design with control hospitals, it was still observational, and assignment to either an intervention or control group was based on self-selection, not random assignment. Although this was a large study of the discontinuation of contact precautions, they only included data from 12 hospitals with 1 year of follow-up. Data regarding compliance with infection prevention factors other than hand hygiene were not available. They only assessed UV disinfection primarily at time of patient discharge and not the quality of daily and post discharge room cleaning. Because some populations will likely benefit from contact precautions, further data on how to target these populations and how to mitigate the potential harms of contact precautions should be evaluated in future research.

Respiratory Viruses

Association between influenza vaccination and risk of stroke in Alberta, Canada: a population-based study Lancet Public Health 2022; 7: e914–22

Doi.org/10.1016/S2468-2667(22)00222-5

The investigators obtained administrative data from the Alberta Health Care Insurance Plan (which covers all residents of Alberta, Canada) beginning on Sept 30, 2009, or May 15 of the year in which residents were recorded as being 18 years of age. Individuals were censored at the earliest of three events: death, recorded outmigration, or December 31, 2018. The outcome of interest was any stroke event, comprising acute ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and transient ischemic attack. They used Andersen-Gill Cox models to analyze the hazard of any stroke event for individuals with recent (<182 days) influenza vaccination compared with those without recent influenza vaccination, with adjustment for age, sex, anticoagulant use, atrial fibrillation, chronic obstructive pulmonary disease, diabetes, hypertension, income quintile, and rural or urban home location. Two-way interaction terms between each individual covariate and vaccination status were used to assess for effect modification by risk factor. The association between vaccination and risk of each type of stroke was also modelled, adjusting for baseline covariates.

The study sample consisted of 4,141,209 adults (29,687,899 person-years of observation time) registered under the provincial health-care system between Sept 30, 2009, and Dec 31, 2018. 1 769,565 (42-73%) individuals received at least one vaccination during the study period, and 38,126 stroke events were recorded. Adjusted for demographics and comorbidities, recent influenza vaccination significantly reduced the hazard of stroke (hazard ratio 0·775 [95% CI 0·757–0·793]). This association persisted across all stroke types. They found effect modification by each covariate examined except for home location; however, vaccination was associated with a reduced risk of stroke overall across all ages and risk profiles except for individuals without hypertension.

Comment: This study provides substantial evidence of a reduction in hazard of stroke among those recently vaccinated against influenza in Canada. Influenza vaccination could be a public health strategy for the prevention of stroke of all types in adults of all ages. These data originated from a single province in a high-income country with a publicly funded health-care system; as such, wide generalizability to other areas globally might be limited. Although it is biologically plausible that the influenza vaccine might be associated with reduced stroke risk, it is also plausible that individuals seeking seasonal immunizations have higher health literacy and healthier lifestyles, leading to a reduced stroke risk. See next article

Influenza vaccine to reduce adverse vascular events in patients with heart failure: a multinational randomised, double-blind, placebo-controlled trial Lancet Glob Health 2022; 10: e1835–44

doi.org/10.1016/s2214-109w(22)0043-6

This is a large RCT was conducted in 10 countries in Asia, Africa, and the Middle East. Heart failure patients were matched 1:1 to receive either an annual flu shot for up to 3 years or a placebo injection of saline.

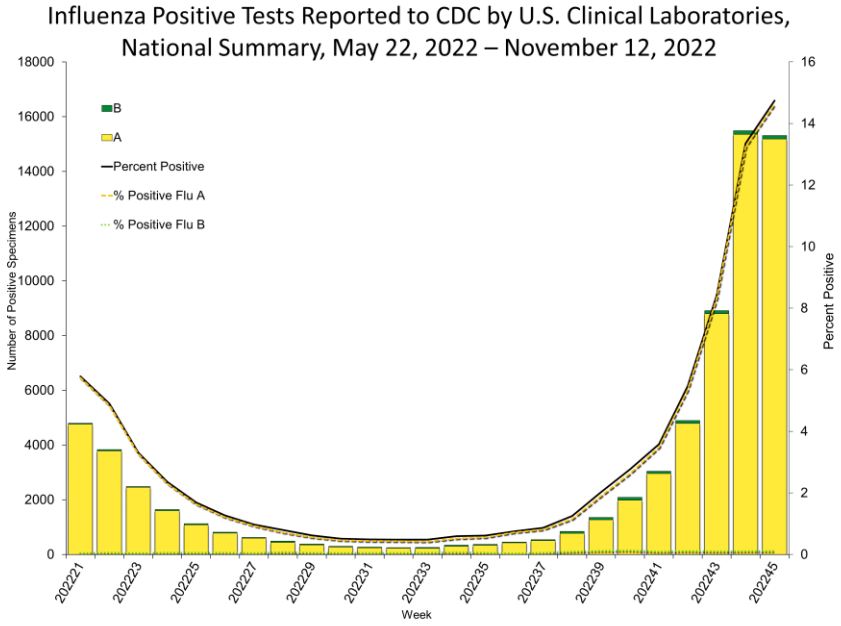
A total of 5,129 patients were involved in the study, which ran from 2015 to 2021. Over half of participants (51.4%) were women, and the mean age was 57.2 years. A total of 20.7% of participants had a previous myocardial infarction, and 8.0% had had a previous stroke.

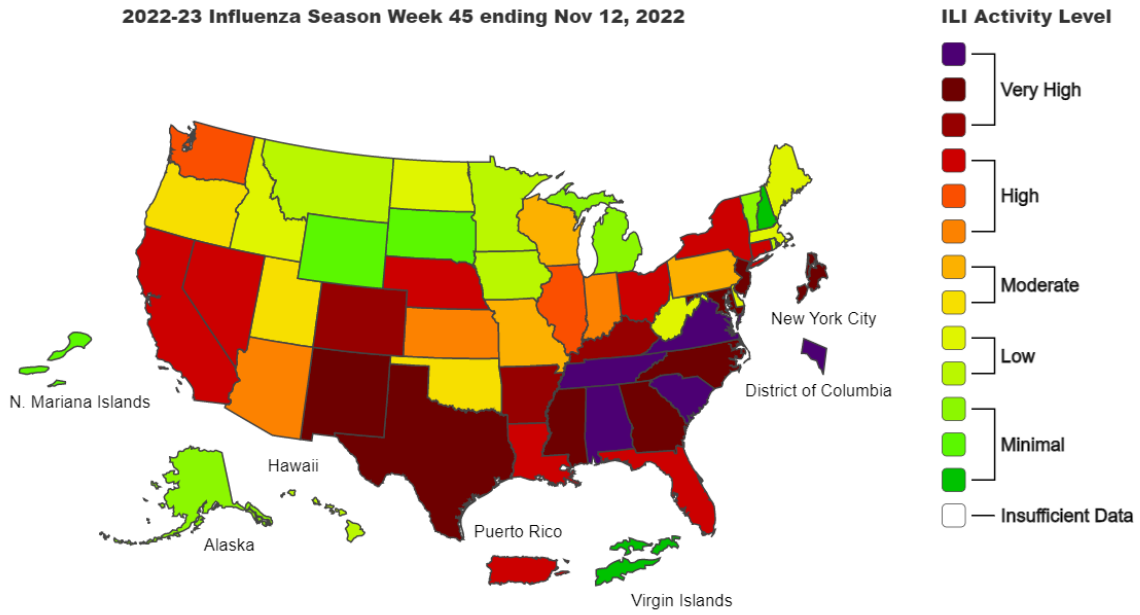
Over the course of 1 year, a flu vaccine reduced pneumonia by 40% and hospitalization by 15% in patients with heart failure. During influenza season in the fall and winter, the vaccine reduced deaths by 20% in these patients.

Most important, fewer study participants had all-cause hospitalization in the vaccine group than in the placebo group (388 participants [15.2%] vs 455 participants [17.7%]; hazard ratio [HR], 0.84 [95% confidence interval [CI], 0.74 to 0.97]), and there were fewer recurrent all-cause hospitalizations in the vaccine group than in the placebo group (557 participants [21.8%] vs 671 participants [26.1%]; HR, 0.84 [95% CI, 0.75 to 0.94]).

Comment: An estimated 1 billion people get flu annually around the world, with 5 million of those cases severe. More than 1 in 5 patients with heart failure have a recurrent cardiovascular event during an influenza infection. In this study, the vaccine reduced all-cause hospitalization by 16% and reduced community acquired pneumonia by 42%. Taken in conjunction with previous trials and a systematic review and meta-analysis of observational studies of influenza vaccine in patients with heart failure suggest benefit and the importance of vaccinating patients with heart failure against influenza. [Heart Fail Rev 2019; 24: 109–14.]

Influenza by the numbers

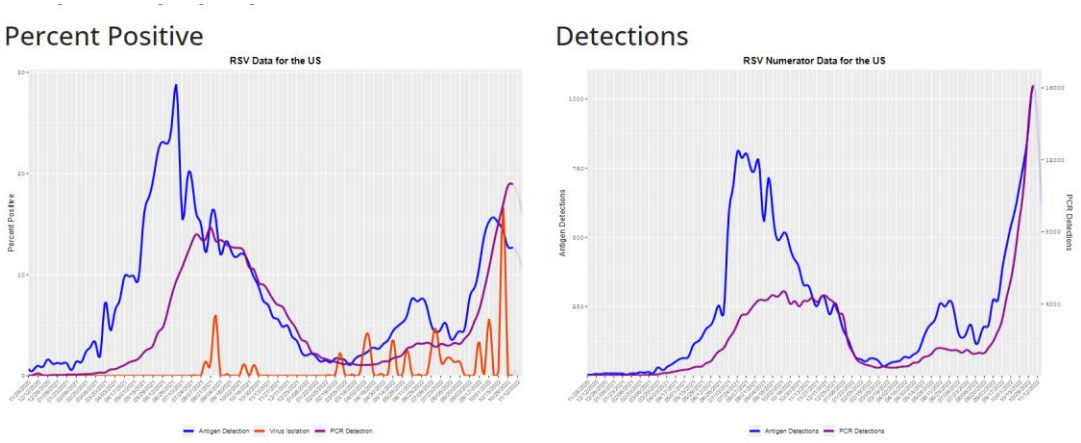




Comment: Seasonal influenza activity is elevated across the country. The majority of influenza viruses detected this season have been influenza A(H3N2) viruses, but the proportion of subtyped influenza A viruses that are A(H1N1) is increasing slightly. Two more influenza-associated pediatric deaths were reported this week, for a total of seven pediatric flu deaths reported so far this season. CDC estimates that, so far this season, there have been at least 4.4 million illnesses, 38,000 hospitalizations, and 2,100 deaths from influenza.

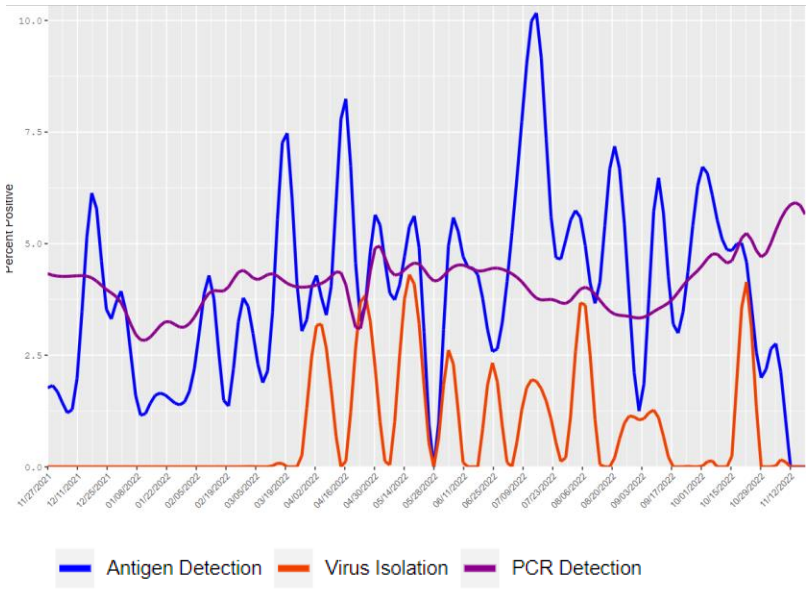
Other Respiratory Viruses by the numbers Graphs last undated November 17th

RSV

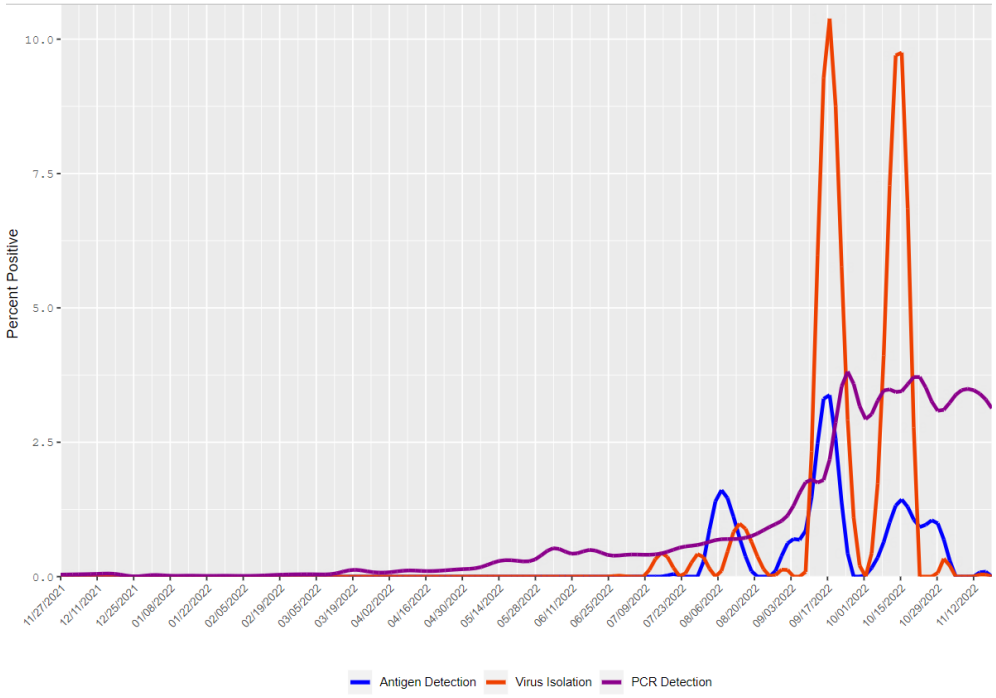


Comment: RSV continues to be a significant player in many regions, but some regions are now seeing a leveling off and a decline in cases. This hopefully will continue across the US over the next few weeks. Other respiratory viruses are also circulating -see graphs below

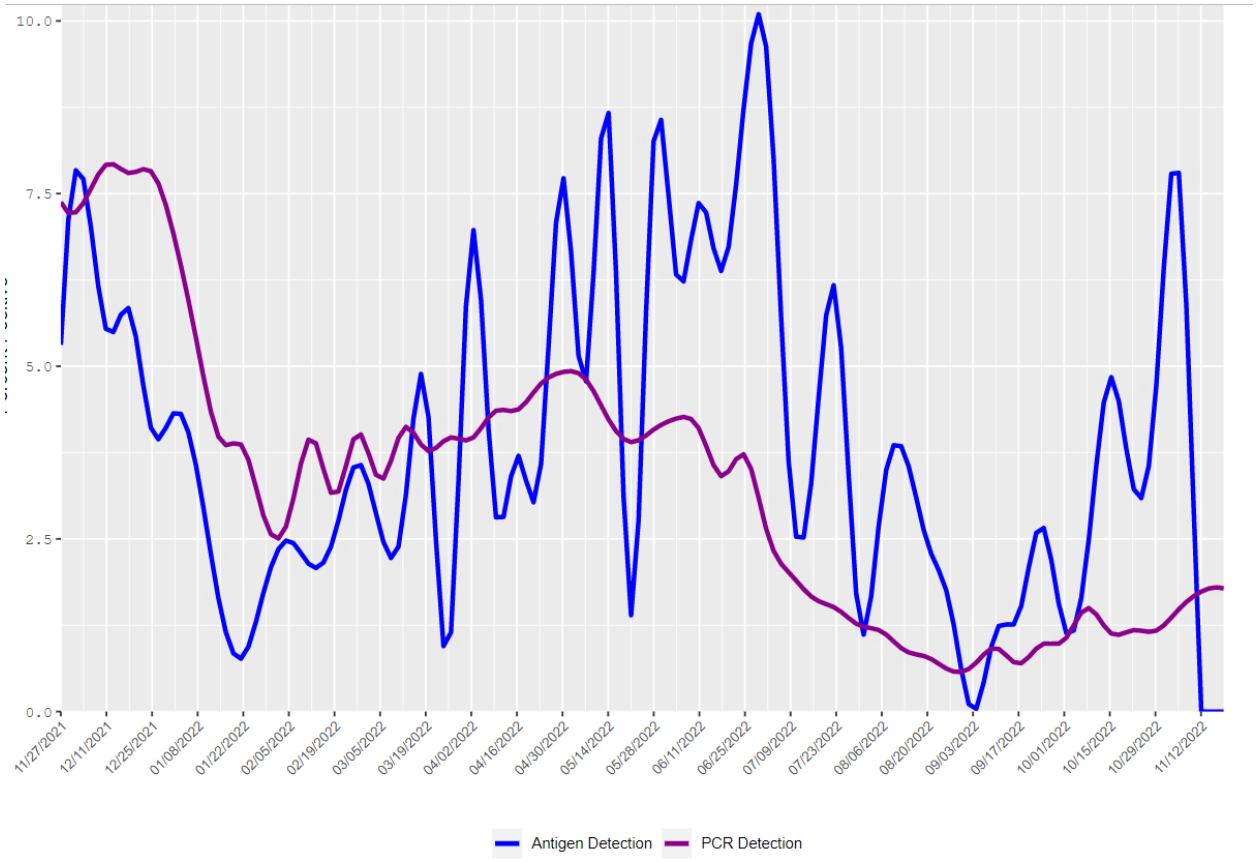
Adenovirus



Parainfluenza



Metapneumovirus

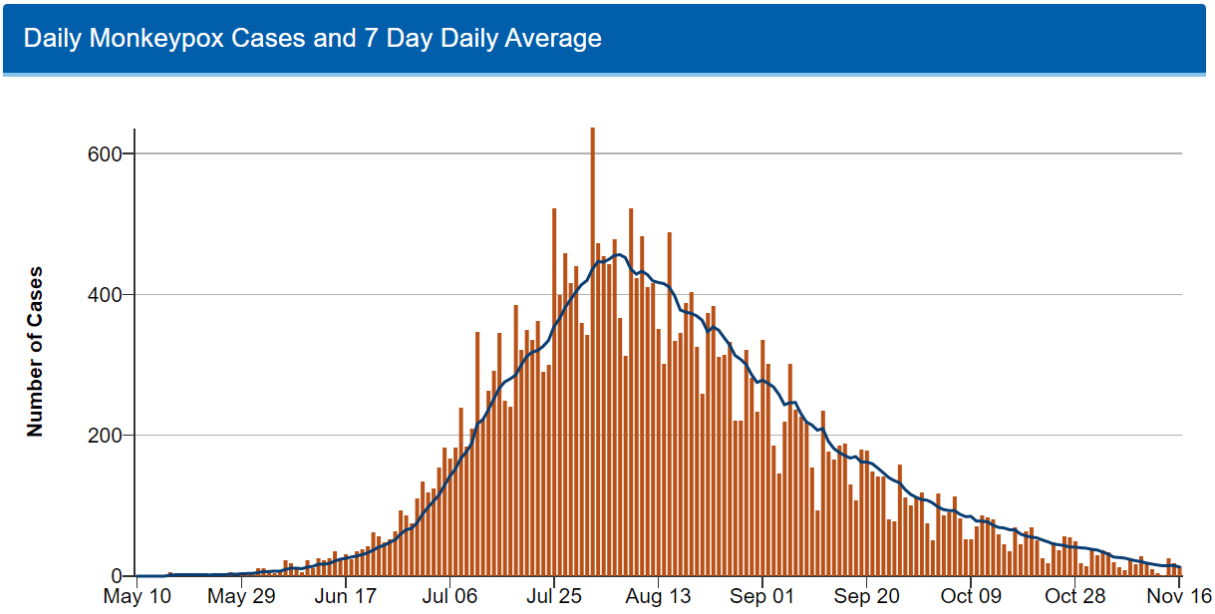


Monkeypox

WHO renames monkeypox November 22, 2022

The WHO will rename monkeypox "MPOX" in an effort to destigmatize the virus. The Biden administration was concerned the stigma surrounding the virus's name was negatively impacting the vaccination campaign that started over the summer.

The US has recorded nearly 30,000 infections of MPOX,[80,000 cases globally] according to the CDC. But with the availability of vaccinations, cases have fallen from a high of more than 400 cases per day over the summer to fewer than 20 cases per day nationally. There have been 14 deaths.



Comment: We have made considerable progress through vaccinations and behavior changes; however, we need to do more to protect our most vulnerable. We have treatment with tecovirimat (Tpoxx), but the CDC has just warned about the development of resistance especially in immunocompromised persons. The best approach remains prevention.

Mutations in the monkeypox virus replication complex: Potential contributing factors to the 2022 outbreak J Autoimmunity 2022; 133:102928

doi.org/10.1016/j.jaut.2022.102928

To assess if mutations in the MPXV DNA replication complex (RC) contribute to the outbreak, the investigators conducted a temporal analysis of available MPXV sequences to identify mutations, generated a DNA replication complex (RC) using structures of related viral and eukaryotic proteins, and structure prediction method AlphaFold. The sequences used in the analysis were acquired from the NCBI nucleotide sequence database through the NCBI Virus portal. As of June 28, 2022, all available and complete MPXV nucleotide sequences were downloaded from the portal.

Ten mutations within the RC were identified and mapped onto the RC to infer role of mutations. Two mutations in F8L (RC catalytic subunit), and two in G9R (a processivity factor) were ~100% prevalent in the 2022 sequences. F8L mutation L108F emerged in 2022, whereas W411L emerged in 2018, and persisted in 2022. L108 is topologically located to enhance DNA binding affinity of F8L. Therefore, mutation L108F can change the fidelity, sensitivity to nucleoside inhibitors, and processivity of F8L. Surface exposed W411L likely affects the binding of regulatory factor(s). G9R mutations S30L and D88 N in G9R emerged in 2022 and may impact the interaction of G9R with E4R (uracil DNA glycosylase). The remaining six mutations that appeared in 2001, reverted to the first (1965 Rotterdam) isolate. Two nucleoside inhibitors brincidofovir and cidofovir have been approved for MPXV treatment. Cidofovir resistance in vaccinia virus is achieved by A314T and A684V mutations. Both A314 and A684 are

conserved in MPXV. Therefore, resistance to these drugs in MPXV may arise through similar mechanisms. See next report below

Mutations in MPXV over various periods.

Gene	Residue	1965	2001	2018	2022	Epitope[a]
F8L	108	L	L	L	**F**	**ISPDGCYSL**
MPXV						**(epitope 1)**
DNA	411	W	W	**L**	**L**	**LTFDYVVTF**
Polymerase	428	I	**T**	I	I	**(epitope 2)**
	484	A	**S**	A	A	
	501	I	**V**	I	I	
	785	N	**D**	N	N	
A22R	313	I	**S**	I	I	–
Processivity factor						
E5R	454	D	**N**	D	D	–
Helicase (NTPase)						
E4R	–	–	–	–	–	–
Uracil Glycosylase						
G9R	30	S	S	S	**L**	-
PCNA ortholog	88	D	D	D	**N**	-

Comment: The investigators presented the components of the MPXV replication complex and identified mutations in this complex that likely contribute to the 2022 MPX outbreak. Mutation L108F in F8L, which appeared in the 2022 outbreak, is close to the 'flipped' template nucleotide and will enhance F8L processivity, whereas W411L likely enhances the binding of a component of the replication complex by altering the surface exposed region. The evolution of resistance mutations remains possible since critical functional pathways have already been susceptible to functional mutations within the viral proteins. See next report below

CDC warns of Tecovirimat resistance

CDC sent a Health Alert Network notice on November 17th to health providers about two cases of Tpoxx resistance in people treated for monkeypox. Both had underlying immunocompromising conditions.

Resistance to tecovirimat (Tpoxx) has been rare and mostly associated with long courses of use. The two patients had, "progressive monkeypox infection despite prolonged treatment (>14 days) with tecovirimat. Both patients required inpatient treatment. These are the first known cases of monkeypox with laboratory-confirmed tecovirimat resistance in the United States

Comment: Tecovirimat is a virostatic agent that targets a major envelope protein conserved across orthopoxviruses (VP37 in monkeypox virus). While naturally circulating tecovirimat-resistant monkeypox viruses have not been observed, previous cell culture experiments performed during drug development and independent studies performed prior to the current outbreak have demonstrated induction of resistance following tecovirimat exposure. Furthermore, experimental data have highlighted a relatively low barrier to resistance, with

single amino acid substitutions at various locations in the F13L gene coding VP37 conferring substantial reductions in tecovirimat's antiviral activity. Isolates from this patient, sequenced by the state laboratory, demonstrated genotypic changes in F13L associated with tecovirimat resistance. In addition, CDC confirmed phenotypic resistance to tecovirimat in cell culture. CDC has analyzed sequences from more than 4,000 specimens from across the world, and only 13 changes in the F13L protein were found, including the two cases included in this HAN.

In patients who have severe disease or certain patients who are at high risk for progression to severe disease, such as patients with HIV and CD4 counts <350 cells/mm3 or other severely immunocompromising conditions, the use of two or more therapeutics should be considered based on the individual clinical situation. In addition to tecovirimat (oral and intravenous), available therapeutics include cidofovir (intravenous), brincidofovir (oral), and VIGIV. Cidofovir is commercially available; intravenous tecovirimat, brincidofovir, and VIGIV are only available via CDC or FDA approval for release from the Strategic National Stockpile (SNS).

Comment: These last two reviews highlight the complexity of the MPXV outbreak. Reports like this will help sort out the circumstances that lead top this outbreak and hopefully help us understand how to prevent and treat future outbreaks.

Human monkeypox virus infection in women and non-binary individuals during the 2022 outbreaks: a global case series Lancet published online November 17, 2022

doi.org/10.1016/ S0140-6736(22)02187-0

The current case study looks at 136 case-patients with monkeypox virus infection diagnosed between May 11 and Oct 4, 2022, across 15 countries.

The overall median age was 34 years (range, 19 to 84), and the case-patients included 62 trans women, 69 cis women, and 5 nonbinary individuals who were born female.

A total of 121 out of 139, or 89%, of the case-patients reported having sexual intercourse with men before contracting the virus; sexual transmission was suspected in 55 (89%) of the trans women and 45 (61%) cis women and nonbinary individuals. The remaining cases in trans and cis women had an unknown route of transmission. Only cis and nonbinary women reported non-sexual routes of transmission, including household and occupational exposure. In total, 74% of cases in women were likely caused by sexual contact, compared to 95% to 100% reported in the authors' case series on men. Similar to men, a high proportion of females in the case study were also HIV positive, with 37 (27%) of all individuals living with HIV and a higher proportion among trans women (31 of 62; 50.0%) than among cis women and nonbinary individuals (6 of 74; 8.1%). In cis women, genital rash and mucosal lesions were often misdiagnosed as other sexually transmitted infections: 25 (34%) of 74 cis women and nonbinary individuals in the case series were initially misdiagnosed. The clinical features of monkeypox in women and non-binary individuals were similar to those described in men, including the presence of anal and genital lesions with prominent mucosal involvement. Anatomically, anogenital lesions were reflective of sexual practices: vulvovaginal lesions predominated in cis women and non-binary individuals and anorectal features predominated in trans women.

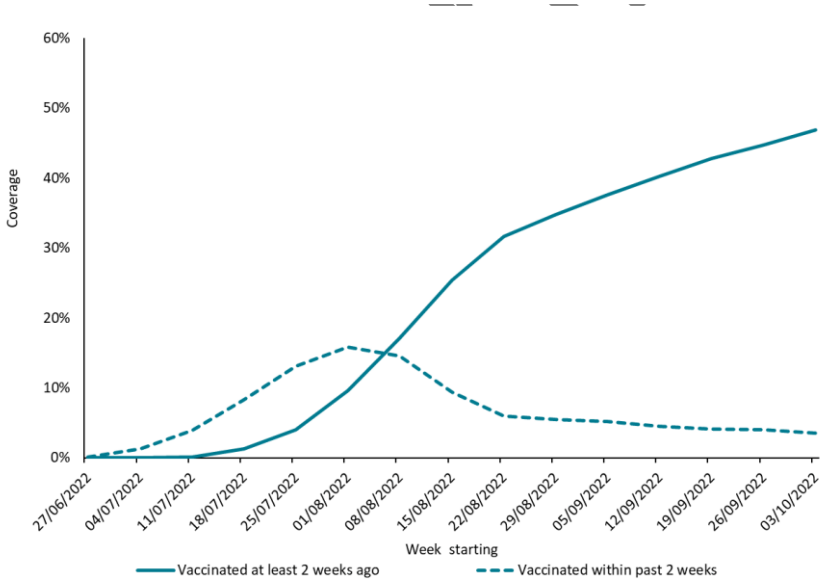
Comment: The evidence available to date indicates that women represent a small but important part of the overall population infected with monkeypox virus during the 2022 outbreaks. In this

case series, characteristic clinical findings typically included a self-limiting genital and anal vesiculopustular rash, often involving the mucosa, with or without systemic symptoms before the onset of rash. In trans women and cis women and non-binary people, the site of the lesions largely corresponded to the type of sexual activity reported. Clinicians need to be made aware of the differing clinical presentations according to gender identity and sexual practices.

Effectiveness of one dose of MVA-BN smallpox vaccine against monkeypox in England using the case-coverage method pre-print posted November 22, 2022

This study was conducted by the UK Health Security Agency (HSA) data scientists and their UK colleagues analyzed monkeypox cases in England from July 4th to November 3rd involving men who have sex with men at high risk for the disease. A recent, yet unpublished, Israeli study estimated 79% vaccine effectiveness after one dose in high-risk GBMSM (gay, bisexual and other men who have sex with men) [Res Sq posted September 23rd-reviewed ID Watch Volume 2, Issue 9, October 2, 2022] , while a US study reported unvaccinated individuals to be 14 times more likely to develop monkeypox disease than vaccinated persons. Of the 363 monkeypox patients during this period, 8 had been vaccinated at least 14 days before, and 32 had been vaccinated between 0 to 13 days before. The other 323 had not received a Jynneos vaccine. They sent questionnaires collecting information on demographics, vaccination history and symptoms. Returned questionnaires with a rash onset date (or alternative proxy) between 4 July and 9 October 2022 were included. Females, heterosexual men, and those with missing vaccination information were excluded.

The investigators estimated vaccine effectiveness (VE) 14 or more days after a single dose was 78% (95% confidence interval [CI], 54% to 89%). For men vaccinated 13 days or less, VE was -4% (95% CI, -50% to 29%).



Comment: This study and the study from Israel are encouraging. However, we need to acknowledge some weaknesses. First the questionnaire return rate was low (about 33%) and, potentially, if vaccinated cases are more likely to return completed questionnaires, VE would be

underestimated and vice versa. Vaccine information was obtained only from self-reported data, there is no national vaccination registry with identifiable data for this program [we need a national vaccine registry!]. Given the aggregated nature of the vaccine coverage data, they were also unable to adjust for other potential confounders other than time period. Lastly, behavioral changes post-vaccination may also have affected VE estimates. For example, if vaccinated individuals were less likely to abstain from high-risk sexual activity because of having received the vaccine. Despite these weaknesses one dose of vaccine appears effective if given at least two weeks before exposure.

COVID-19

Moderna bivalent COVID-19 booster

The booster, mRNA-1273.222, targets the BA.4 and BA.5 subvariants and is one of two boosters Moderna has been testing against its original vaccine. Both mRNA-1273.222 and the company's other bivalent booster vaccine, mRNA-1273.214, which is aimed at the Wuhan strain of SARS-CoV-2 and the BA.1 subvariant, outperformed the original vaccine booster, according to a press release from Moderna.

Study participants received Moderna's original COVID-19 vaccine as a booster shot about 4 1/2 months after initial vaccination and the updated booster, mRNA-1273.222, about 9 1/2 months after initial vaccination. Although pre-booster titer levels were similar between the groups, the updated mRNA-1273.222 bivalent booster triggered a 15.1-fold increase in titer levels. Participants without a previous SARS-CoV-2 infection saw a 26.4-fold increase in titer levels and participants who had a previous infection saw a 9.8-fold increase in titer levels.

Moderna also reported that an exploratory analysis of 40 participants using research assays demonstrated "robust neutralizing activity" against BQ.1.1, though the response was about five-fold lower than the booster's effects against BA.4 and BA.5. see next report

Pfizer bivariant against BQ.1.1

Pfizer says its updated booster, which was designed to target Omicron BA.4 and BA.5, also protects against surging Omicron subvariants like BQ.1.1 and BQ.1. A month after getting the bivalent booster, adults 55 and over were found to have a nine-fold increase in antibodies against BQ.1.1, Pfizer said in a news release. People who got another dose of the original vaccine showed a two-fold increase in antibodies against BQ1.1.

Comment: When the updated booster was developed, BA.5 was the dominant strain of Covid-19 in the US, but that has changed in recent months. According to information posted by the CDC recently, BA.5 now accounts for about 19% of cases while BQ.1.1 accounts for 29% and its cousin BQ.1 for 28%.(see below) Moderna reported on November 14th that its bivalent booster provides protection against BQ.1.1 but not as much as against the BA.5 variant.(see above)

Covid-19 by the numbers

Key Updates

Variants

1. Based on projections for the week ending November 26th , the CDC estimates that BQ.1 accounts for 28% of cases, while BQ.1.1 accounts for 29%.

2. BQ.1 and BQ.1.1, which have been dubbed "escape variants" because of their evasiveness to some Covid-19 treatments, surpassed BA.5 to become the nation's dominant strain. Accounting for 19% of cases, BA.5 is now behind BQ.1. BF.7, another omicron subvariant experts are closely monitoring, slimmed down from 8.2 percent to 7% of cases. Other omicron subvariants, each hovering between 0 percent and 5 percent, make up the rest. See below

Cases and Hospitalization

3. Cases have risen modestly in the past two weeks, to around 42,000 per day nationwide, while hospitalizations and deaths have been roughly flat, but some regions are seeing a slight uptick.

Deaths

4. The current seven-day death average is 317, down 5.3 percent from the previous week's average, which was 335.

Vaccinations

5. As of November 16th, about 267.5 million people — 80.6 percent of the U.S. population — have received at least one dose of the COVID-19 vaccine, and about 228.2 million people, or 68.7 percent of the population, have received both doses. But uptake of the bivalent vaccine is <15%. About 113.9 million people have received a booster dose, and more than 35.4 million people have received an updated omicron booster. However, 48.7 percent of people eligible for a booster dose have not yet gotten one, per CDC.

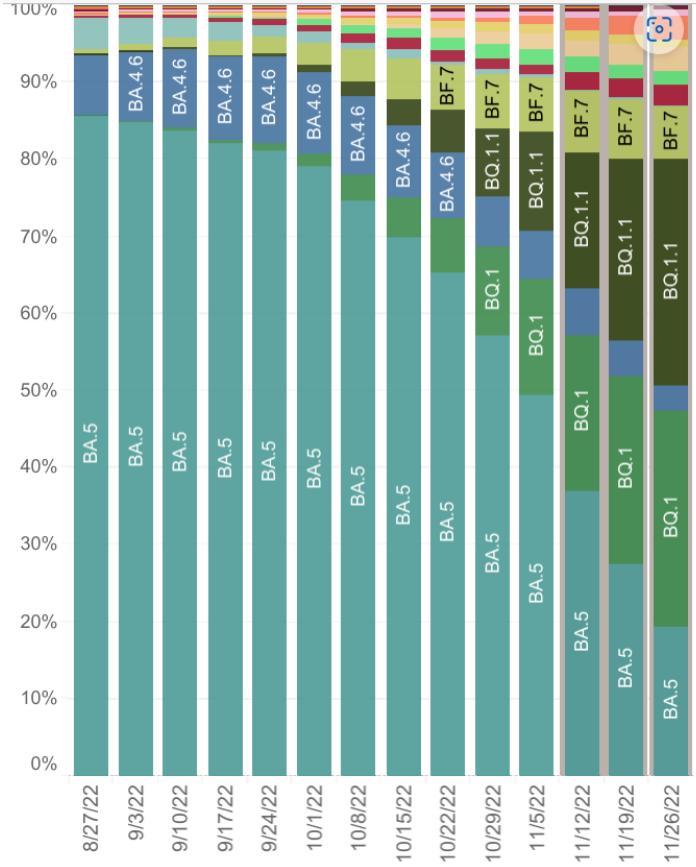
Wastewater surveillance

6. About 48 percent of the U.S. is reporting moderate to high virus levels in wastewater. Of these surveillance sites, 17 percent are seeing some of the highest levels since December 1, 2021.

7. About 50 percent of sites are reporting an increase in virus levels, and 44 percent of sites are seeing a decrease. Houston is seeing an increase.

Comment: Daily COVID-19 hospital admissions are projected to increase nationwide over the next four weeks, with 2,000 to 9,000 new daily admissions likely reported on December 9th , according to the CDC's ensemble forecast from 15 modeling groups. mABs have limited activity against the BQ variants which is of concern especially for immunocompromised people. See article below Lancet Infect Dis
Wastewater surveillance has been a very good predictor of activity over the next two weeks.

United States: 8/21/2022 – 11/26/2022



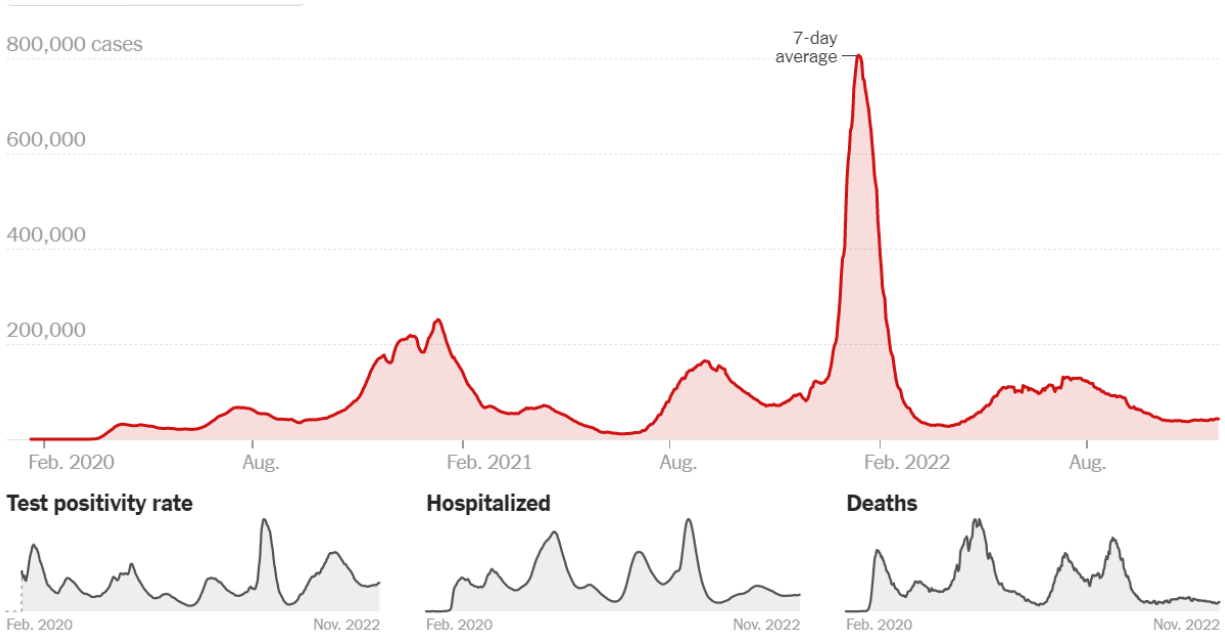
United States: 11/20/2022 – 11/26/2022 NOWCA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BQ.1.1	VOC	29.4%	27.0-31.9%
	BQ.1	VOC	27.9%	25.5-30.5%
	BA.5	VOC	19.4%	17.1-21.9%
	BF.7	VOC	7.0%	6.2-8.0%
	BA.4.6	VOC	3.3%	2.9-3.8%
	XBB	VOC	3.1%	1.5-6.0%
	BN.1	VOC	2.9%	2.3-3.8%
	BA.2.75	VOC	2.6%	2.0-3.5%
	BA.5.2.6	VOC	1.8%	1.5-2.2%
	BF.11	VOC	1.1%	0.8-1.4%
	BA.2	VOC	0.8%	0.5-1.1%
	BA.2.75.2	VOC	0.6%	0.4-0.7%
	BA.4	VOC	0.0%	0.0-0.1%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

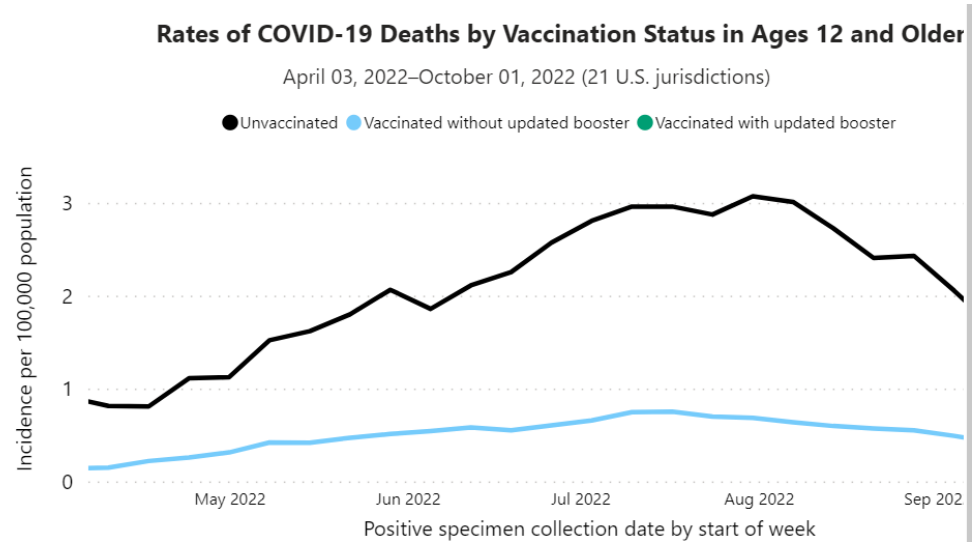
* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** 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, BN.1,XBB and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6,



Rates of COVID-19 Cases and Deaths by Vaccination Status CDC



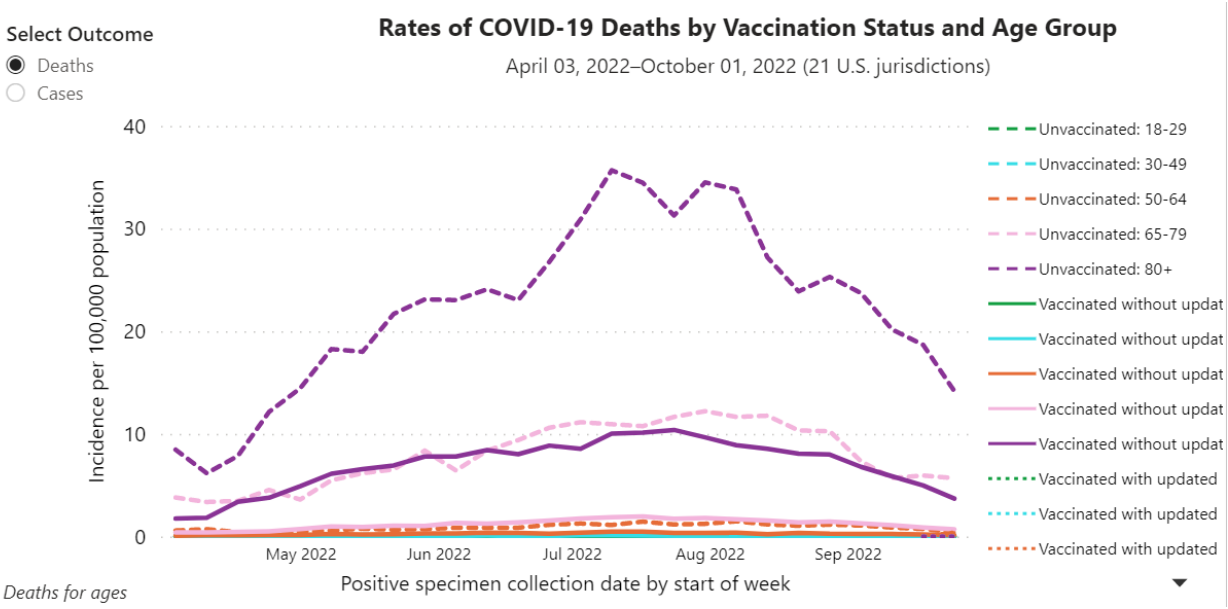
People aged 12 and older vaccinated with an updated (bivalent) booster had:

14.9X
lower risk of dying from COVID-19

in September 2022, and

3.2X
lower risk of testing positive for COVID-19

in October 2022, compared to unvaccinated people.



Covid-19 is no longer mainly a pandemic of the unvaccinated. Washington Post November 23, 2022

Fifty-eight percent of coronavirus deaths in August were people who were vaccinated or boosted, according to an analysis conducted for The Health 202 by at the Kaiser Family Foundation**.** For the first time since the beginning of the pandemic, a majority of Americans dying from Covid-19 were at least partially vaccinated, according to a new analysis of federal and state data.

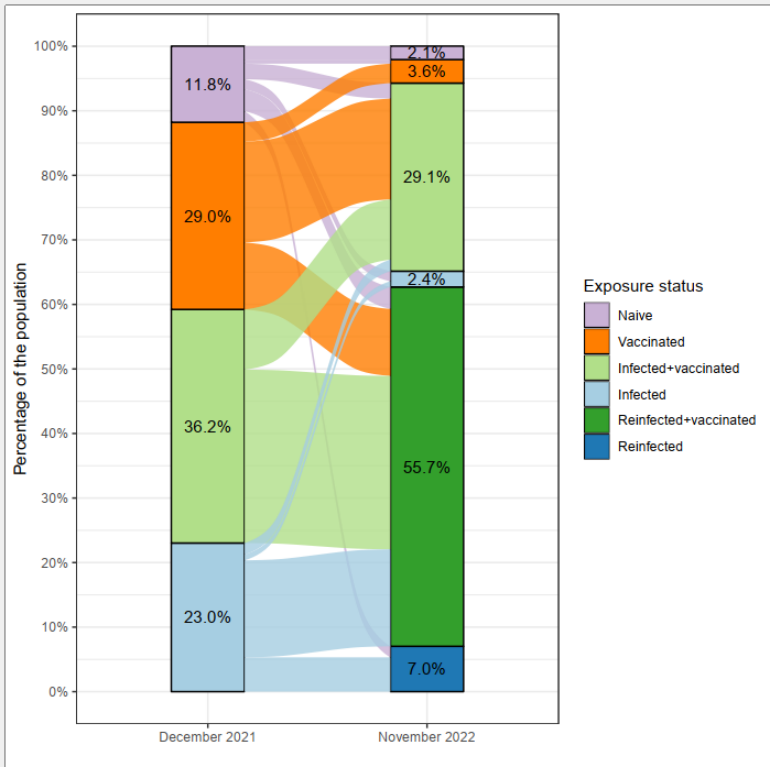
Comment: The waning efficacy of COVID-19 vaccines, the increased transmissibility of the new variants, and the immune evasiveness have all added to spread to elderly and immunocompromised people which has resulted in more deaths among those who have taken at least one vaccine dose. The Washington Post described a "troubling trend" as the share of deaths of people who were vaccinated has been "steadily rising" over the past year. In September 2021, vaccinated people made up just 23 percent of Covid-19 fatalities. In January and February this year, it was up to 42 percent. We can no longer say this is a pandemic of the unvaccinated. Putting this into perspective you are still 15X lower risk of dying if you are up to date with vaccination. See article below

Changes in population immunity against infection and severe disease from SARS-CoV-2 Omicron variants in the United States between December 2021 and November 2022. medRxiv posted online November 20, 2022

doi.org/10.1101/2022.11.19.22282525

The investigators set out to estimate changes in population immunity against infection and severe disease due to circulating SARS-CoV-2 Omicron variants in the United States from December 2021 to October 2022, and to quantify the protection against a potential 2022-2023 winter SARS-CoV-2 wave. They used a Bayesian evidence synthesis of reported COVID-19 data (diagnoses, hospitalizations), vaccinations, and waning patterns for vaccine- and infection acquired immunity, based on a mathematical model of COVID-19 natural history. The main outcome was population immunity against infection and severe disease from SARS-CoV-2 Omicron variants in the United States, by location (national, state, county) and week.

By November 10, 2022, 94% (95% CrI, 79%–99%) of the US population were estimated to have been infected by SARS-CoV-2 at least once. Combined with vaccination, 97% (95%–99%) were estimated to have some prior immunological exposure to SARS-CoV-2. Between December 1, 2021, and November 10, 2022, protection against a new Omicron infection rose from 22% (21%–23%) to 63% (51%–75%) nationally, and protection against an Omicron infection leading to severe disease increased from 61% (59%–64%) to 89% (83%–92%). Increasing first booster uptake to 55% in all states (current US coverage: 34%) and second booster uptake to 22% (current US coverage: 11%) would increase protection against infection by 4.5 percentage points (2.4–7.2) and protection against severe disease by 1.1 percentage points (1.0–1.5).



Comments: Effective protection against SARS-CoV-2 infection and severe disease in October 2022 was substantially higher than in December 2021. I am cautiously optimistic that the combination of natural infections and vaccinations have created enough community immunity that we will not going to see a repeat of what we saw last year at this time. However, despite this high level of protection, a more transmissible or a more immune evasive variant, changes in behavior, or ongoing waning of immunity could lead to a new SARS-CoV-2 wave. Lastly increased travel and indoor gatherings for the holidays could accelerate the spread of Covid-19 and other respiratory viruses.

Effectiveness of Bivalent mRNA Vaccines in Preventing Symptomatic SARS-CoV-2 Infection — Increasing Community Access to Testing Program, United States, September–November 2022 MMWR early release November 22, 2022

In this study, effectiveness of the bivalent (Omicron BA.4/BA.5–containing) booster formulation against symptomatic SARS-CoV-2 infection was examined using data from the Increasing Community Access to Testing (ICATT) national SARS-CoV-2 testing program. During September 14–November 11, 2022, a total of 360,626 NAATs performed at 9,995 retail pharmacies for adults aged ≥18 years, who reported symptoms consistent with COVID-19 at the time of testing and no immunocompromising conditions, were included in the analysis. Relative vaccine effectiveness (rVE) of a bivalent booster dose compared with that of ≥2 monovalent vaccine doses among persons for whom 2–3 months and ≥8 months had elapsed since last monovalent dose was 30% and 56% among persons aged 18–49 years, 31% and 48% among persons aged 50–64 years, and 28% and 43% among persons aged ≥65 years, respectively.

Comment: Bivalent mRNA booster doses provide additional protection against symptomatic SARS-CoV-2 in immunocompetent persons who previously received monovalent vaccine only, with relative benefits increasing with time since receipt of the most recent monovalent vaccine dose. Staying up to date with COVID-19 vaccination, including getting a bivalent booster dose when eligible, is critical to maximizing protection against COVID-19. Vaccination status, previous infection history, and underlying medical conditions were self-reported and might be subject to recall bias. Important data including SARS-CoV-2 exposure risk and mask use were not collected, which might result in residual confounding. Lastly, the circulating variants in the US continue to change. In fact, the result of this study is limited by the fact that the Omicron subvariant that accounted for the largest number of infections during the period of this study, BA.5, has receded and now accounts for only a quarter of cases in the US. It is also difficult to measure how well the updated boosters were working because so many people now have some immunity from earlier infections, including people who were never vaccinated or boosted. [see articles below] At best the new bivalent vaccine appears to provide only moderate protection against symptomatic disease and that while such protection would help in the short term, it was unclear how long it would last. It is also clear that due to T-cell immunity most are still protected against severe disease regardless of variant.

Paxlovid Associated with Decreased Hospitalization Rate Among Adults with COVID-19 — United States, April–September 2022 MMWR early release November 22, 2022 article suggested by Josh Septimus

To examine the benefit of Paxlovid in adults aged ≥18 years in the United States, a large electronic health record (EHR) data set (Cosmos[†]) was analyzed to assess the association

between receiving a prescription for Paxlovid and hospitalization with a COVID-19 diagnosis in the ensuing 30 days. A Cox proportional hazards model was used to estimate this association, adjusted for demographic characteristics, geographic location, vaccination, previous infection, and number of underlying health conditions.

As a reminder, EUA was approved by the FDA on December 22, 2021 (*1*), for use in patients with mild-to-moderate COVID-19 at high risk for progression to severe illness. Eligibility for Paxlovid includes 1) receipt of a positive SARS-CoV-2 test result (including home antigen test), 2) symptoms consistent with mild-to-moderate COVID-19, 3) symptom onset within the past 5 days, 4) age ≥18 years (or age ≥12 years and weight ≥40 kg), 5) one or more risk factors for progression to severe COVID-19, 6) no known or suspected severe renal or hepatic impairment, 7) no history of clinically significant reactions (e.g., toxic epidermal necrolysis or Stevens-Johnson syndrome) to the active ingredients (nirmatrelvir or ritonavir) or other components of the product, and 8) no contraindicated medications.

Among 699,848 adults aged ≥18 years eligible for Paxlovid during April–August 2022, 28.4% received a Paxlovid prescription within 5 days of COVID-19 diagnosis. Being prescribed Paxlovid was associated with a lower hospitalization rate among the overall study population (adjusted hazard ratio [aHR] = 0.49), among those who had received ≥3 mRNA COVID-19 vaccines (aHR = 0.50) and across age groups (18–49 years: aHR = 0.59; 50–64 years: aHR = 0.40; and ≥65 years: aHR = 0.53).

Comment: This study counters the conclusion of another observational retrospective cohort study from Israel, in which patients ages 40 to 64 had little benefit for hospitalization with Paxlovid compared with untreated patients (aHR 0.74, 95% CI 0.35-1.58).[N Engl J Med 2022; 387:790-798-reviewed in ID Watch Volume 2, Issue 6, August 29, 2022] This new study demonstrates that Paxlovid provides protection against severe COVID-19–associated outcomes among persons for whom it is recommended, including those with vaccine-conferred immunity. and that it is underutilized among eligible persons with COVID-19. Notably in the new study, young adults appeared to benefit almost as much as older adults. Unfortunately, Paxlovid is underutilized among eligible persons with COVID-19. In this analysis, only 28% of eligible persons were prescribed Paxlovid. This study used receipt of a Paxlovid prescription is a proxy for use of Paxlovid. Paxlovid course completion and/or compliance could not be verified. In addition, underlying health conditions and immunocompromise were approximated using ICD-10 codes or medical record fields and might not capture the exact prevalence of these conditions. This study did not address how often Covid symptoms rebounded after people finished the five-day treatment. Lastly, Paxlovid should depend on how vulnerable a patient is to progress, not on the severity of initial symptoms. Despite the weaknesses of this study and the Israel study I believe Paxlovid should be considered to everyone eligible, but especially older adults[especially ≥75] and people with multiple underlying high-risk conditions[DM, obesity, renal disease, cardiopulmonary disease, and immunocompromised]. See next article

Prevalence of Contraindications to Nirmatrelvir-Ritonavir Among Hospitalized Patients With COVID-19 at Risk for Progression to Severe Disease JAMA Net Open. 2022;5:e2242140. (November 15, 2022)

doi:10.1001/jamanetworkopen.2022.42140

The authors applied individual medical contraindications listed by the US FDA for nirmatrelvir-ritonavir to a large sample of patients hospitalized with COVID-19, ascertained by a positive

PCR test, in 36 greater Paris University hospitals from January 24, 2020, to November 30, 2021. No patients received nirmatrelvir-ritonavir. They examined the proportion of patients with contraindications to nirmatrelvir-ritonavir in this sample and in those who died within 28 days of hospital admission, who thereby would have needed therapy other than nirmatrelvir-ritonavir in the ambulatory setting. They then stratified the analysis by sex, age (≤65 y vs >65 y), and comorbidity based on ICD-10.

Of 63,656 inpatients with COVID-19, 1131 patients (1.8%) were excluded because of missing data for sex or age. Of the 62,525 remaining patients (median [IQR] age, 52.8 [33.8-70.5] years, 31,561 [50.5%] women), 9136 (14.6%) had a medical contraindication to nirmatrelvir-ritonavir, with higher rates in men (5568 [18.0%]) than in women (3577 [11.3%]), in older patients (5398 of 20,064 [26.9%]) than in younger ones (3738 of 42,461 [8.8%]), and in those with comorbidities (>37.0% for most comorbidities) than without comorbidities (1475 of 37,748 [3.9%]). Among 4861 patients who died, 2463 (50.7%) had a contraindication, with similar rates in men and women as well as older and younger patients but higher rates in patients with vs without comorbidities. The most prevalent contraindications were severe kidney impairment and use of medications dependent on CYP3A for clearance.

Table 1. Prevalence of Possible Medical Contraindications to Nirmatrelvir-Ritonavir in a Sample of Patients Hospitalized With COVID-19

	Patients, No. (%)									
	Full sample of hospitalized patients					Subsample of patients who died within 28 d of hospital admission				
Medical contraindications listed by the US FDA[a]	Total (N = 62 525)	Women (n = 31 561)	Men (n = 30 964)	Age ≤65 y (n = 42 461)	Age >65 y (n = 20 064)	Total (n = 4861)	Women (n = 1882)	Men (n = 2979)	Age ≤65 y (n = 768)	Age >65 y (n = 4093)
Use of medications dependent on CYP3A for clearance[b]										
Any	3233 (5.15)	1218 (3.86)	2015 (6.51)	548 (1.29)	2685 (13.4)	1340 (27.6)	558 (29.6)	782 (26.3)	85 (11.1)	1255 (30.7)
α1-Adrenoreceptor antagonist: alfuzosin	789 (1.26)	72 (0.23)	717 (2.32)	202 (0.48)	587 (2.93)	127 (2.61)	8 (0.43)	119 (3.99)	9 (1.17)	118 (2.88)
Antiarrhythmic: amiodarone, dronedarone, flecainide, propafenone, quinidine	734 (1.17)	319 (1.01)	415 (1.34)	84 (0.20)	650 (3.24)	198 (4.07)	91 (4.84)	107 (3.59)	12 (1.56)	186 (4.54)
HMG-CoA reductase inhibitors: lovastatin, simvastatin	389 (0.62)	155 (0.49)	234 (0.76)	73 (0.17)	316 (1.57)	67 (1.38)	19 (1.01)	48 (1.61)	2 (0.26)	65 (1.59)
Other medications[c]	206 (0.33)	94 (0.30)	112 (0.36)	65 (0.15)	141 (0.70)	23 (0.47)	8 (0.43)	15 (0.50)	3 (0.39)	20 (0.49)
Use of medications that induce CYP3A[b,d]	145 (0.23)	68 (0.22)	77 (0.25)	55 (0.13)	90 (0.45)	18 (0.37)	7 (0.37)	11 (0.37)	5 (0.65)	13 (0.32)
Severe hepatic impairment[e,f]	832 (1.33)	303 (0.96)	529 (1.71)	334 (0.79)	498 (2.48)	282 (5.80)	97 (5.15)	183 (6.14)	92 (12.0)	188 (4.59)
Severe kidney impairment[f,g]	3958 (6.33)	1453 (4.60)	2505 (8.09)	1259 (2.97)	2699 (13.5)	1243 (25.6)	398 (21.1)	845 (28.4)	266 (34.6)	977 (23.9)
Age <12 y	1684 (2.69)	729 (2.31)	955 (3.08)	1684 (3.97)	Not applicable	7 (0.14)	3 (0.16)	4 (0.13)	7 (0.91)	Not applicable
At least 1 medical contraindication to nirmatrelvir-ritonavir[h]	9136 (14.6)	3577 (11.3)	5568 (18.0)	3738 (8.80)	5398 (26.9)	2463 (50.7)	922 (49.0)	1538 (51.6)	381 (49.6)	2082 (50.9)

Comment: Not surprisingly, contradictions to nirmatrelvir-ritonavir were prevalent in individuals hospitalized with COVID-19. These findings also should alert researchers to the risk of confounding by contraindication in observational studies focused on nirmatrelvir-ritonavir, which may overestimate treatment efficacy if not excluding patients with contraindications to this treatment. In addition, some of the contraindicated medications listed here could be temporarily held while taking nirmatrelvir-ritonavir. Even if not contraindicated, treatment may not have been given to some patients due to symptom duration of longer than 5 days. In addition, information about vaccination, race and ethnicity, and weight was unavailable.

Diagnostic accuracy of SARS-CoV-2 rapid antigen self-tests in asymptomatic individuals in the Omicron period: cross sectional study Clin Microbiol Infect published online November 11, 2020

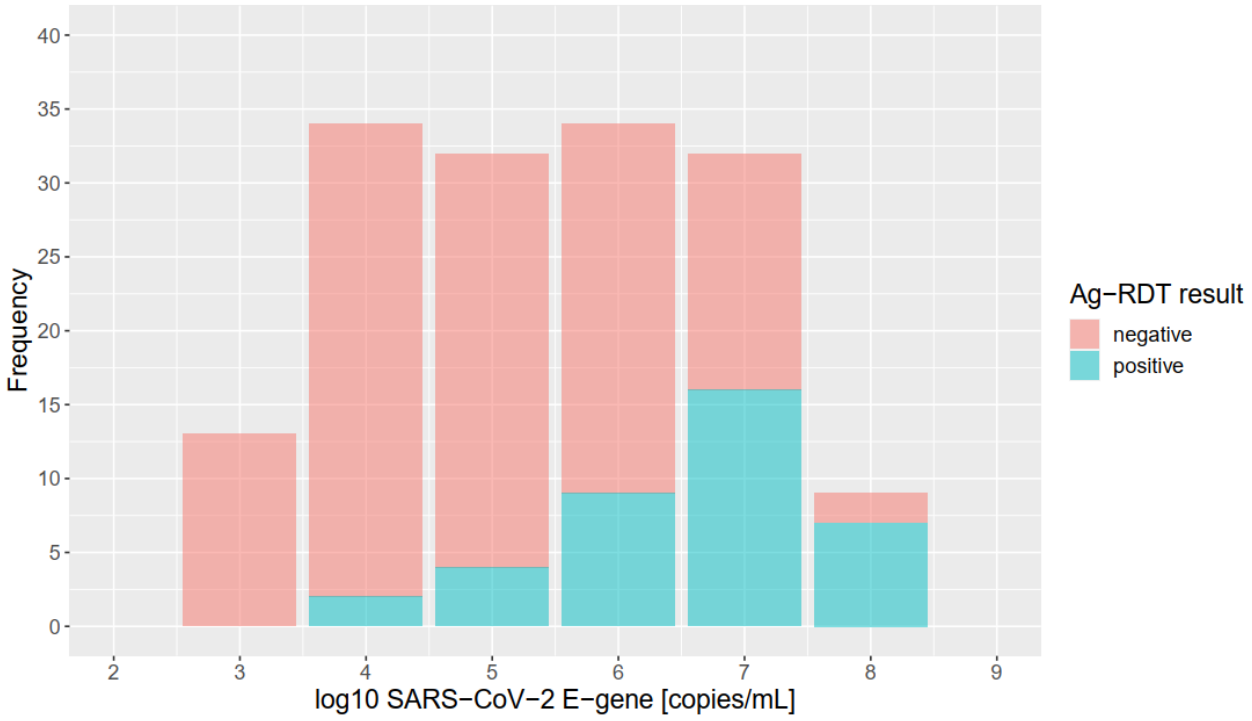
doi.org/10.1016/j.cmi.2022.11.004

The study was conducted between January 2 to March 30, 2022, when Omicron accounted for 90% to 99.5% of all cases in the Netherlands. A total of 3,600 asymptomatic people with suspected COVID-19 were tested using one of three at-home rapid antigen tests(RAT) and a PCR test. Home tests were provided within 3 hours of taking a PCR test.

Overall sensitivities for the three home tests were 27.5% (95% confidence interval [CI], 21.3% to 34.3%) for Flowflex, 20.9% (95% CI, 13.9% to 29.4%) for MPBio, and 25.6% (95% CI, 19.1% to 33.1%) for Clinitest. Viral load distributions in RT-PCR positive individuals show especially false-negative RAT test results in the lower viral load range. After applying a viral load cut-off, sensitivities increased to 48.3% (95% CI, 37.6% to 59.2%), 37.8% (95% CI, 22.5% to 55.2%), and 40.0% (95% CI, 29.5% to 51.2%), respectively.

Participants with negative tests also filled out a questionnaire, which showed 54.8% retested in the 10 days following a negative test, with 24.6% testing positive.

The positive predictive values were greater than 92%, and negative predictive values were greater than 88% for all self-tests. The authors said previous studies on self-tests conducted before Omicron yielded better sensitivities, at 52.5% in asymptomatic individuals.



Comment: They conclude that SARS-CoV-2 self-testing has limited value for asymptomatic individuals wishing to protect vulnerable persons and may even lead to a false sense of security. The high SARS-CoV-2 infection rate within 10 days of a negative PCR test that they

found in this study emphasizes the importance of re-testing over time, especially when symptoms develop. The FDA has long recommended when using a RAT, that you should retest if the first test in negative if symptomatic. RAT generally have even lower sensitivity in detecting asymptomatic disease.

COVID-19 and Excess All-Cause Mortality in the US and 20 Comparison Countries, June 2021-March 2022 JAMA Netw Op published online November 18, 2022

doi:10.1001/jama.2022.21795

The investigators compared the US overall, the 10 most- and least-vaccinated states, and the 20 OECD(Organization for Economic Co-operation and Development) countries with 2021 population exceeding 5 million and greater than $25,000 per capita gross domestic product. US Covid-19 mortality, all-cause mortality, and vaccination data were obtained from the CDC. For other countries, Covid-19 mortality data were obtained from the WHO all-cause mortality data from OECD databases, and vaccination data from Our World in Data. Each location's Covid-19 mortality rate per capita was calculated over 2 periods: (1) Delta from June 27, 2021 (week 26), to December 25, 2021 (week 51), and (2) Omicron from December 26, 2021 (week 52), to March 26, 2022 (week 12). Some mortality data from 2021 and 2022 were provisional.

The US reported 370 298 Covid-19 deaths (112 per 100,000) during the Delta and Omicron waves (61/100,000 and 51/100,000, respectively). Covid-19 deaths per capita in the US overall and in both state subgroups significantly exceeded those of all peer countries during the study period (see below). However, there were significantly fewer Covid-19 deaths in the top 10 states by vaccination uptake (73% coverage) at 75 deaths/100,000 compared with the bottom 10 (52% coverage) at 146 per 100,000 ($P < .001$). US excess all-cause mortality exceeded Covid-19 mortality at 145/100,000 and exceeded peer countries in all periods, as did excess all-cause mortality in the least-vaccinated states. From June 27, 2021, to March 26, 2022, the US would have averted 122 304 deaths if Covid-19 mortality matched that of the 10 most-vaccinated states and 266,700 deaths if US excess all-cause mortality rate matched that of the 10 most vaccinated states.

Country	Vaccination rate, %	COVID-19 mortality per 100 000			Potential US deaths averted, No. (%)		
		Delta	Omicron	Total	Delta	Omicron	Total
New Zealand	75	0.5	3.3	3.7	200 663 (99)	157 236 (94)	357 899 (97)
Japan	80	3	7.4	10.4	192 278 (95)	143 443 (85)	335 721 (91)
Australia	76	4.9	14.2	19.2	185 819 (92)	120 894 (72)	306 713 (83)
Republic of Korea	82	6.1	18.2	24.3	181 927 (90)	107 650 (64)	289 577 (78)
The Netherlands	67	16.6	7.9	24.5	147 061 (73)	141 898 (84)	288 959 (78)
Norway	73	10	18.6	28.7	168 899 (84)	106 280 (63)	275 179 (74)
Canada	77	10.2	20.2	30.4	168 351 (83)	101 049 (60)	269 401 (73)
Switzerland	67	16.4	15.5	31.9	147 757 (73)	116 511 (69)	264 268 (71)
Sweden	70	6.3	31.3	37.6	181 286 (90)	64 167 (38)	245 453 (66)
Ireland	78	20.5	17.2	37.7	134 206 (66)	110 857 (66)	245 063 (66)
France	74	14.6	27.6	42.2	153 765 (76)	76 453 (45)	230 218 (62)
Israel	64	19.4	24.9	44.3	137 898 (68)	85 326 (51)	223 224 (60)
Spain	80	17.7	26.7	44.5	143 348 (71)	79 372 (47)	222 720 (60)
Finland	74	12	35.2	47.2	162 449 (80)	51 097 (30)	213 546 (58)
Belgium	76	25.3	22.5	47.7	118 390 (59)	93 526 (56)	211 916 (57)
Denmark	78	10.9	41.2	52.2	166 026 (82)	31 182 (19)	197 208 (53)
Germany	71	29.6	22.7	52.3	104 041 (51)	92 750 (55)	196 792 (53)
Italy	76	15.2	39	54.2	151 867 (75)	38 609 (23)	190 476 (51)
UK	71	30.1	28.9	59	102 324 (51)	72 176 (43)	174 500 (47)
Austria	74	40.4	24.6	65	68 040 (34)	86 582 (52)	154 622 (42)
US							
10 most-vaccinated states	73	28.1	46.6	74.7	108 916 (54)	13 388 (8)	122 304 (33)
Overall	63	60.9	50.6	111.6			
10 least-vaccinated states	52	86.6	59.4	146	−85 080 (−42)	−29 058 (−17)	−114 138 (−31)

Comment: The US continues to experience significantly higher Covid-19 and excess all-cause mortality compared with peer countries during 2021 and early 2022, a difference accounting for 150 000 to 470 000 deaths. Two limitations need to be highlighted. First, they used of some provisional mortality estimates and second they did not adjust by age and comorbidities.

Omicron sublineage BQ.1.1 resistance to monoclonal antibodies Lancet Infect Dis published online November 18, 2022

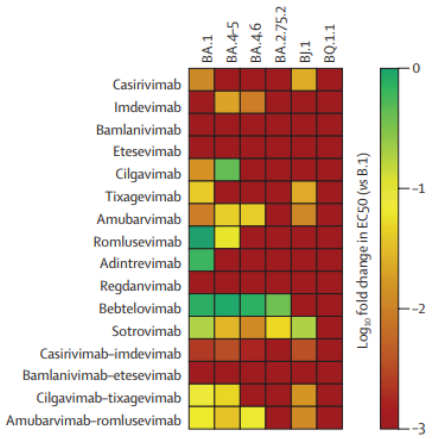
doi.org/10.1016/ S1473-3099(22)00733-2

They used pseudovirus particles (pp) that represent a suitable model to investigate SARS-CoV-2 cell entry and its neutralization. As we expected, pseudovirus particles bearing the BA.1 S protein (BA.1pp) were efficiently neutralized by bebtelovimab, adintrevimab, a n d c i l g a v i m a b – t i x a g e v i m a b (50% effective concentration [EC50] <100 ng/ml), moderately neutralised by tixagevimab, romlusevimab, sotrovimab, and a m u b a r v i m a b – r o m l u s e v i m a b (EC50 100–1000 ng/ml), and poorly neutralised by casirivimab, cilgavimab, amubarvimab, and casirivimab–imdevimab (EC50 1000–10 000 ng/ml). BA4–5pp were efficiently neutralized by bebtelovimab and cilgavimab, moderately neutralised by imdevimab and cilgavimab–tixagevimab, and poorly neutralized by amubarvimab, r o m l u s e v i m a b , s o t r o v i m a b , c a s i r i v i m a b – i m d e v i m a b , a n d a m u b a r v i m a b – r o m l u s e v i m a b , in line with expectations. mAbs, in line with expectations. For BA.4.6pp, bebtelovimab caused efficient neutralization, whereas poor neutralization was noted for imdevimab, amubarvimab, casirivimab–imdevimab, cilgavimab– tixagevimab, and amubarvimab–romlusevimab. With BA.2.75.2pp, bebtelovimab caused efficient neutralization, whereas regdanvimab and sotrovimab caused poor neutralization. For BJ.1pp, none of the tested mAbs

or mAb cocktails caused high neutralization, whereas casirivimab, tixagevimab, sotrovimab, a n d c i l g a v i m a b – t i x a g e v i m a b showed moderate neutralization, and amubarvimab, casirivimab– imdevimab, and amubarvimab– r o m l u s e v i m a b c a u s e d p o o r neutralization. Finally, none of the tested mAbs or mAb cocktails caused appreciable neutralization of BQ.1.1

		B.1	BA.1	BA.4-5	BA.4.6	BA.2.75.2	BJ.1	BQ.1.1
Single mAbs	Casirivimab	21	1890	>50000	>50000	>50000	880	>50000
	Imdevimab	19	>50000	994	2109	>50000	>50000	>50000
	Bamlanivimab	16	>50000	>50000	>50000	>50000	>50000	>50000
	Etesevimab	53	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab	37	2658	88	24200	>50000	>50000	>50000
	Tixagevimab	7	173	10090	27740	>50000	304	>50000
	Amubarvimab	53	5641	1234	1290	>50000	4762	>50000
	Romlusevimab	852	866	8279	>50000	>50000	>50000	>50000
	Adintrevimab	14	23	>50000	>50000	>50000	>50000	>50000
	Regdanvimab	7	>50000	>50000	>50000	6336	>50000	>50000
	Bebtelovimab	5	7	6	7	14	>50000	>50000
Cocktails of mAbs	Sotrovimab	157	833	5554	13000	3239	825	>50000
	Casirivimab–imdevimab	9	3642	2611	5395	>50000	2456	>50000
	Bamlanivimab–etesevimab	18	>50000	>50000	>50000	>50000	>50000	>50000
	Cilgavimab–tixagevimab	7	97	155	7131	>50000	482	>50000
	Amubarvimab–romlusevimab	64	657	1819	1015	>50000	5359	>50000

EC50 (ng/ml)



Comment: Their data reveal that emerging omicron sublineages are resistant to most (ie, BA.4.6, BA.2.75.2, and BJ.1) or all (BQ.1.1) clinically used mAbs. As a consequence, in patients at high risk, treatment with mAbs alone might not provide a therapeutic benefit in regions of the globe in which BQ.1.1 is spreading, suggesting that additional treatment options (e.g., Paxlovid, RDV, or molnupiravir) should be considered.

Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgicencephalomyelitis/chronic fatigue syndrome

Front Immunol
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Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a chronic disease considered to be triggered by viral infections in many cases. Symptoms overlap largely with those of post-acute sequelae of COVID- 19/long-COVID implying common pathogenetic mechanisms. SARS-CoV-2 infection is risk factor for sustained latent virus reactivation that may account for the symptoms of post-viral fatigue syndromes.

Anti-SARS-CoV-2 antibodies were analyzed in plasma and saliva from non-vaccinated ME/CFS (n=95) and HDs (n=110) using soluble multiplex immunoassay. Reactivation of human herpesviruses 1-6 (HSV1, HSV2, VZV, EBV, CMV, HHV6), and human endogenous retrovirus K (HERV-K) was detected by anti-viral antibody fingerprints in saliva.

At 3-6 months after mild/asymptomatic SARS-CoV-2 infection, virusspecific antibodies in saliva were substantially induced signifying a strong reactivation of latent viruses (EBV, HHV6 and HERV-K) in both cohorts. In patients with ME/CFS, antibody responses were significantly

stronger, in particular EBV-encoded nuclear antigen-1 (EBNA1) IgG were elevated in patients with ME/CFS, but not in HDs. EBV-VCA IgG was also elevated at baseline prior to SARS-infection in patients compared to HDs.

Comment: This article caught my eye since we have all struggled with patients with long Covid-19. The pathogenesis of this syndrome has been elusive. The result in this trial perhaps provides a clue. SARS-CoV-2 may cause an altered and chronically aroused anti-viral profile against latent viruses in ME/CFS. SARS-CoV-2 infection even in its mild/asymptomatic form is a potent trigger for reactivation of latent herpesviruses (EBV, HHV6) and endogenous retroviruses (HERV-K), as detected by antibody fingerprints locally in the oral mucosa (saliva samples). This has not been shown before because the antibody elevation is not detected systemically in the circulation/plasma. In this study, 42% of the patients with ME/CFS and 31% of HDs were found to be asymptomatically infected. A more pronounced local mucosal antibody-specific response against SARS-CoV-2 was observed in patients with ME/CFS compared to HDs even though, total IgG levels in saliva were similar. This is consistent with the hypothesis of a hyperinflammatory response to pathogen-associated molecular patterns (PAMPs), including SARS-CoV-2 spike protein-1, in patients with multiple chronic diseases (Science 2021; 373: eabe4832). Their findings demonstrate that SARS-CoV-2 infection even in its mild/asymptomatic form is a potent trigger for reactivation of latent herpesviruses and endogenous retroviruses. This is particularly relevant for individuals suffering from ME/CFS, since they have elevated immune responses against latent viruses. Furthermore, SARS-CoV-2 infection in ME/CFS imposes both a unique and an augmented antibody fingerprint, adding further evidence for altered immune responses in the syndrome. The results suggest that treatment options directed to boost antiviral immune responses, may benefit patients with ME/CFS by tuning the fine balance between latent virus reactivation and an appropriate immune response. More research is needed to confirm these findings.

Vaccine effectiveness against SARS-CoV-2 reinfection during periods of Alpha, Delta, or Omicron dominance: A Danish nationwide study

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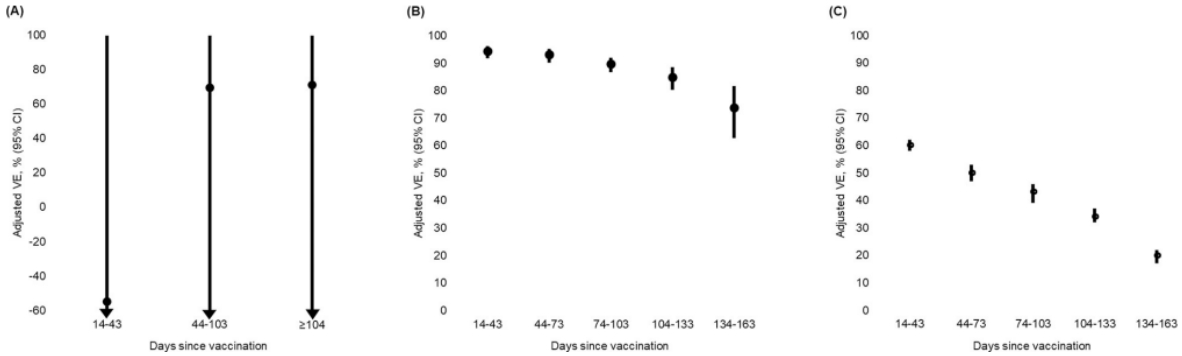
This study used a nationwide cohort design including all individuals with a confirmed SARS-CoV-2 infection, who were alive, and residing in Denmark between 1 January 2020 and 31 January 2022. Using Danish nationwide registries, we obtained information on SARS-CoV-2 infections, COVID-19 vaccination, age, sex, comorbidity, staying at hospital, and country of origin. The study population included were individuals with prior SARS-CoV-2 infection. Estimates of VE against SARS-CoV-2 reinfection with 95% confidence intervals (CIs) were calculated using a Poisson regression model and adjusted for age, sex, country of origin, comorbidity, staying at hospital, calendar time, and test incidence using a Cox regression model. The VE estimates were calculated separately for three periods with different dominant SARS-CoV-2 variants (Alpha (B.1.1.7), Delta (B.1.617.2), or Omicron (B.1.1.529)) and by time since vaccination using unvaccinated as the reference. In total, 148,527 person years and 44,192 SARS-CoV-2 infections were included for the analysis regarding reinfections. The study population comprised of 209,814 individuals infected before or during the Alpha period, 292,978 before or during the Delta period, and 245,530 before or during the Omicron period.

Of these, 40,281 individuals had completed their primary vaccination series during the Alpha period (19.2%), 190,026 during the Delta period (64.9%), and 158,563 during the Omicron period (64.6%). VE against reinfection following any COVID-19 vaccine type administered in

Denmark, peaked at 71% (95% CI: -Inf to 100%) at 104 days or more after vaccination during the Alpha period, 94% (95% CI: 92% to 96%) 14 to 43 days after vaccination during the Delta period, and 60% (95% CI: 58% to 62%) 14 to 43 days after vaccination during the Omicron period. Waning immunity following vaccination was observed and was most pronounced during the Omicron period.



(A) Alpha variant (B.1.1.7), 20 February–15 June 2021. (B) Delta variant (B.1.617.2), 4 July–20 November 2021. (C) Omicron variant (B.1.1.529), 21 December 2021–31 January 2022.

Comment: This study shows that in previously infected individuals, completing a primary vaccination series was associated with a significant protection against SARS-CoV-2 reinfection compared with no vaccination. Even though vaccination seems to protect to a lesser degree against reinfection with the Omicron this study demonstrated that previously infected individuals still benefit from COVID-19 vaccination in all three variant periods. This confirms other studies. Insight into VE in individuals with natural immunity is important to help decision makers plan vaccination strategies. Due to too few events, it was not possible to estimate VE for hospitalization and death. Unmeasured biases such as changes in risk behavior might influence the result.