Infectious Diseases Watch

September 18, 2022

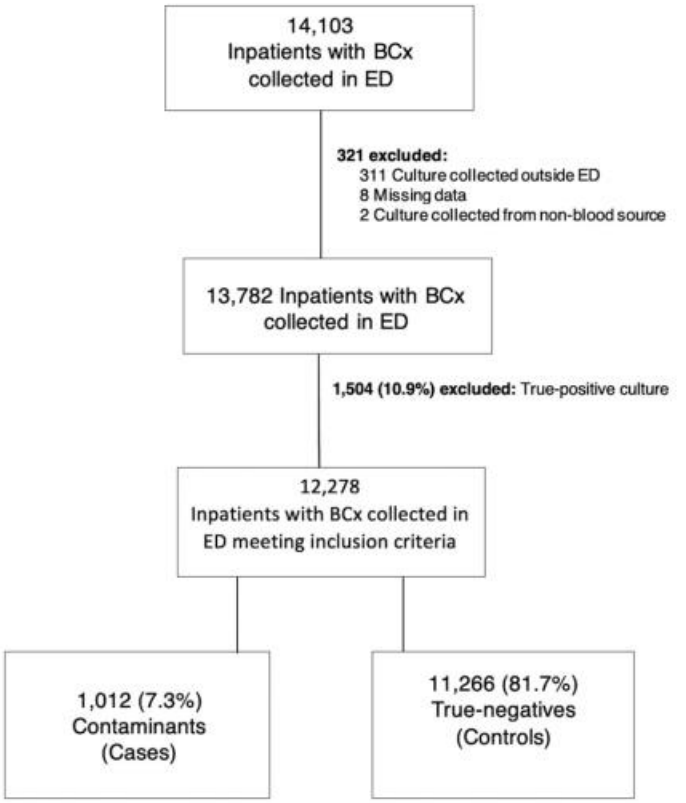
Ed Septimus, MD

Risk factors and clinical outcomes associated with blood culture contamination

ICHE 2022; 43: 291–297,

doi.org/10.1017/ice.2021.111

This study was a retrospective, case-control study at 500 bed academic institution. Electronic medical records of adult inpatients with blood culture collected in the ED between May 2014 and March 2018 were reviewed. The blood culture first performed per admission was defined as a blood-culture episode. Patients with positive blood culture revealing microbial contaminants were considered cases and patients with negative blood culture were considered controls. Patients with positive blood culture not meeting microbial contaminant definition (true positive) were excluded from all analyses. Blood-culture collections on inpatient units were excluded to better evaluate the clinical impact of blood-culture contamination at the time of admission [ED] on the entire hospitalization. Institutional blood-culture collection guidelines recommend the collection of 2 sets of blood samples from 2 peripheral sites, 15 minutes apart. Dedicated phlebotomy teams were not present in the emergency department; therefore, blood culture collection was performed primarily by registered nurses (>97%). Microbial contaminants were defined according to the laboratory guidelines (i.e., 1 of 2 sets positive for an organism rarely pathogenic, such as coagulase negative staphylococci, Micrococcus, Corynebacterium, Bacillus spp nonanthracis, or viridans streptococci) adopted from previously published recommendations. If only 1 set of blood cultures was obtained, positive cultures were considered true positives. [I am not sure I agree-I would exclude] Patient-specific data including age, sex, race, BMI, comorbid conditions, activation of code sepsis, and sepsis status were compared between cases and controls. Risk factors identified as significant ($P < .05$) were included in multivariate analysis. Age and BMI were assessed as continuous variables. The primary outcome was hospital length of stay (LOS). Secondary outcomes included length of antimicrobial therapy (LOT) defined as the number of days that a patient received any systemic antimicrobial agent, total days of antimicrobial therapy (DOT) defined as the aggregate sum of individual antimicrobial days of therapy, infectious disease (ID) consultation, transthoracic echocardiograms (TTEs), transesophageal echocardiograms (TEEs), total hospital charges, vancomycin utilization, acute kidney injury (AKI) defined as an increase in serum creatinine >0.3 mg/dL over a 48-hour period or >1.5× increase over a 7-day period, hospice referral, and in-hospital mortality.



After adjusting for age, race, BMI, comorbidities, and sepsis status, patients with blood-culture contamination had a higher LOS as compared to patients without contaminated blood culture (unadjusted: 7.9 days vs 6.6 days; adjusted: $\beta = 1.24 \pm 0.24$; $P < .0001$). Similarly, patients with contaminated blood culture had higher antibiotic LOT (unadjusted: 6.2 days vs 5.2 days; adjusted: $\beta = 1.01 \pm 0.20$; $P < .001$), hospital charges (unadjusted: $36,008 vs $28,875; adjusted: $\beta = 0.22 \pm 0.03$; $P < .0001$), rate of AKI (unadjusted: 36.7% vs 26.3%; aOR, 1.60; 95% CI, 1.40–1.83), frequency of TTE orders (unadjusted: 27.4% vs 19.2%; aOR, 1.51; 95% CI, 1.30–1.75), and in-hospital mortality (unadjusted: 8.0% vs 4.6%; aOR, 1.69; 95% CI, 1.31–2.16) compared to patients without contaminated blood culture. In univariate analysis, vancomycin was ordered more frequently (81% vs 65%; $P < .0001$) and administered longer (mean DOT, 3.5 days vs 2.5 days; $P < .0001$) in patients with contaminated blood cultures. The patients most at risk for contamination were of older age, black race, higher BMI, and had comorbidities such as CHF, COPD, and paralysis.

Comment: Not surprisingly this study suggests patients with a difficult stick have a higher contamination rate which is consistent with common risk factors previously reported in the literature such as older age, presence of comorbidities, and severity of illness. [PLoS One 2015;10(10):e0137653] As the authors point out “risk are likely due to the difficulty of the venipuncture: the darker skin of black patients makes isolating peripheral veins more difficult visually; obese individuals’ increased subepidermal fat masks peripheral veins; older individuals typically have more tenuous, collapsed, or fragile veins; and patients presenting with shock or severe sepsis have collapsed veins due to low blood pressure, which can create a sense of urgency that could contribute to poor technique or shortcuts in culture collection.”

Since this study was a retrospective, case-control study, and they were unable to standardize or validate every finding. In addition, their data collection was limited to the data recorded in the electronic medical record. A reminder, inpatient units were excluded, and this study only looked at ED which may decrease the generalizability of their conclusions; however, this paper confirms the importance of decreasing blood culture contamination in terms of unnecessary antibiotics, adverse drug effects, and costs. See next article

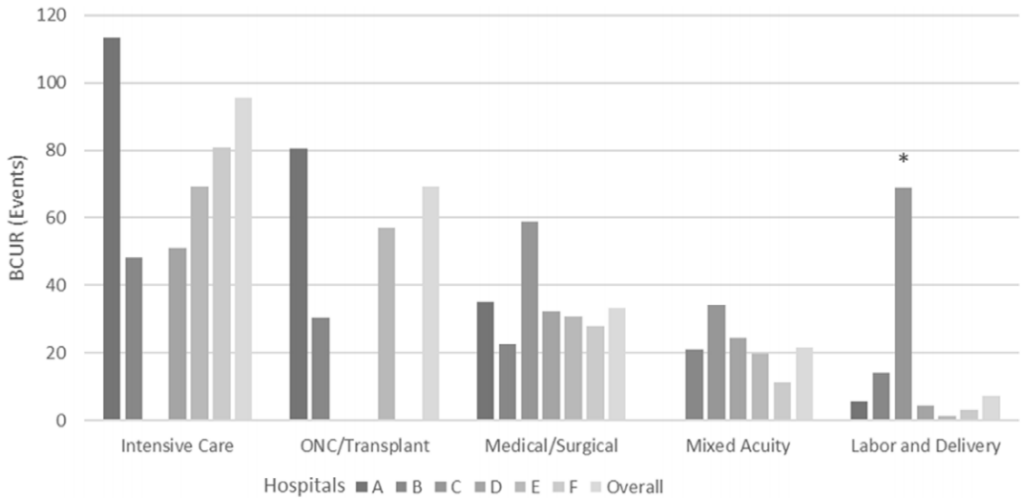
Evaluation of hospital blood culture utilization rates to identify opportunities for diagnostic stewardship

ICHE published online September 8, 2022

doi.org/10.1017/ice.2022.191

The investigators performed a retrospective analysis of blood-culture utilization during adult inpatient or ED encounters in 6 hospitals from May 2019 to April 2020. They investigated 2 measures of blood-culture utilization rates (BCURs): the total number of blood cultures, defined as a unique accession number per 1,000 patient days (BCX) and a new metric of blood-culture events per 1,000 patient days to account for paired culture practices. They defined a blood-culture event as an initial blood culture and all subsequent samples for culture drawn within 12 hours for patients with an inpatient or ED encounter. Cultures were evaluated by unit type, positivity and contamination rates, and other markers evaluating the quality of blood-culture collection.

In total, 111,520 blood cultures, 52,550 blood culture events, 165,456 inpatient admissions, and 568,928 patient days were analyzed. Overall, the mean BCUR was 196 blood cultures per 1,000 patient days, with 92 blood culture events per 1,000 patient days (range, 64–155 among hospitals). Furthermore, 7% of blood-culture events were single culture events, 55% began in the ED, and 77% occurred in the first 3 hospital days. Among all blood cultures, 7.7% grew a likely pathogen, 2.1% were contaminated, and 5.9% of first blood cultures were collected after the initiation of antibiotics.



Comment: Blood-culture utilization varied by hospital and was heavily influenced by ED culture volumes. Their positivity and contamination rates, overall and at the hospital level, are similar to

those of several previous studies, and they fell within expected ranges of 7%–9% and 2%–3%, respectively. [Clin Infect Dis 2018;67:e1–e94; ICHE 2018;39:1353–1359] They did not address blood volumes which can impact percent positivity. Hospital comparisons of blood culture metrics can assist in identifying opportunities to optimize blood-culture collection practices. Earlier this year I reviewed an article in JCM on blood culture utilization in a hospital setting. [J Clin Microbiol 2022; 60:e01005-21] Below are the 2 key tables. These 2 articles highlight opportunities for blood culture diagnostic stewardship.

High diagnostic value of initial blood cultures	**Exceptions**
• Severe sepsis/septic shock • Infections associated with high or intermediate risk of bacteremia	NA
Low diagnostic value of initial blood cultures	**Exceptions**
• Fever ±leukocytosis in stable patients without suspicion for endovascular infection	Patients with splenectomy
• Post-operative fever within 48 hours	Presence of severe sepsis/septic shock
• Infections with low risk of bacteremia (e.g., cystitis, prostatitis, cellulitis, non-severe pneumonia, prosthetic joint infection)	• Endovascular infection suspected • Presence of severe sepsis/septic shock
• Persistent febrile neutropenia in hemodynamically stable patients with two negative sets	• NA

High diagnostic value of *repeat* blood cultures	**Exceptions**
• To document clearance of *S. aureus* bacteremia • To document clearance of *S. lugdunensis* bacteremia • Any organism suspected to be causing infective endocarditis/endovascular infection • Concern for persistent bacteremia • To distinguish contamination from true bacteremia	**NA**
Low diagnostic value of *repeat* blood cultures	**Exceptions**

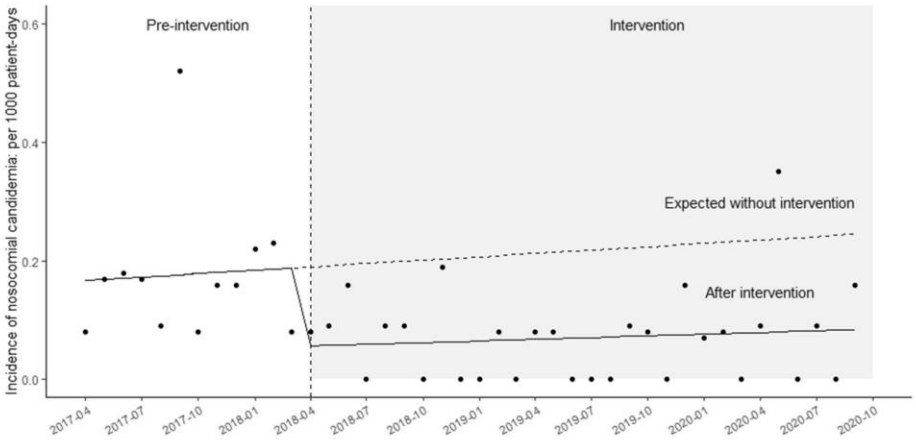
Impact of the antimicrobial stewardship program on hospital-acquired candidemia Scientific Reports 2022 12:15135

doi.org/10.1038/s41598-022-19374-3

This study aimed to evaluate the effect of ASP on the incidence of hospital acquired candidemia. The investigators conducted a retrospective study from April 2017 to September 2020. They reviewed patients that were treated with three broad-spectrum antipseudomonal agents: carbapenem, tazobactam/piperacillin, and cefepime. Monthly aggregated hospital antimicrobial consumption was measured as days of therapy (DOTs) per 1000 patient-days, and the monthly incidence of hospital acquired candidemia was recorded.

Pre-intervention period (From April 2017 to March 2018)	Intervention period (From April 2018 to September 2020)
1. Monitoring antimicrobial use density (carbapenems, tazobactam/piperacillin, cefepime, intravenous quinolones, vancomycin, daptomycin, and linezolid) 2. Therapeutic drug monitoring (vancomycin)	1. Monitoring antimicrobial use density (carbapenems, tazobactam/piperacillin, cefepime, intravenous quinolones, vancomycin, daptomycin and linezolid) 2. Therapeutic drug monitoring (vancomycin) 3. Weekly 1.5 h case conference by antimicrobial stewardship team members indication criteria - Patients treated with broad-spectrum antipseudomonal agents for more than 7 days (carbapenems, tazobactam/piperacillin, cefepime, and intravenous quinolones) - Positive blood culture - Unresponsive to antibiotic treatment 4. Infectious diseases consultations by part-time infectious diseases specialist (once a week)

The median monthly carbapenem-DOTs during pre-intervention and intervention were 28.4 and 10.0, respectively. Time series analysis showed significant level changes after intervention: −10.0 DOTs (p = 0.02). There was a downward trend in the monthly carbapenem-DOTs after intervention. The median hospital acquired candidemia incidence was 0.17 and 0.08 per 1000 patient-days during pre-intervention and intervention periods, respectively. Time-series analysis showed a significant level change after intervention (− 0.16 per 1000 patient-days; p = 0.048).

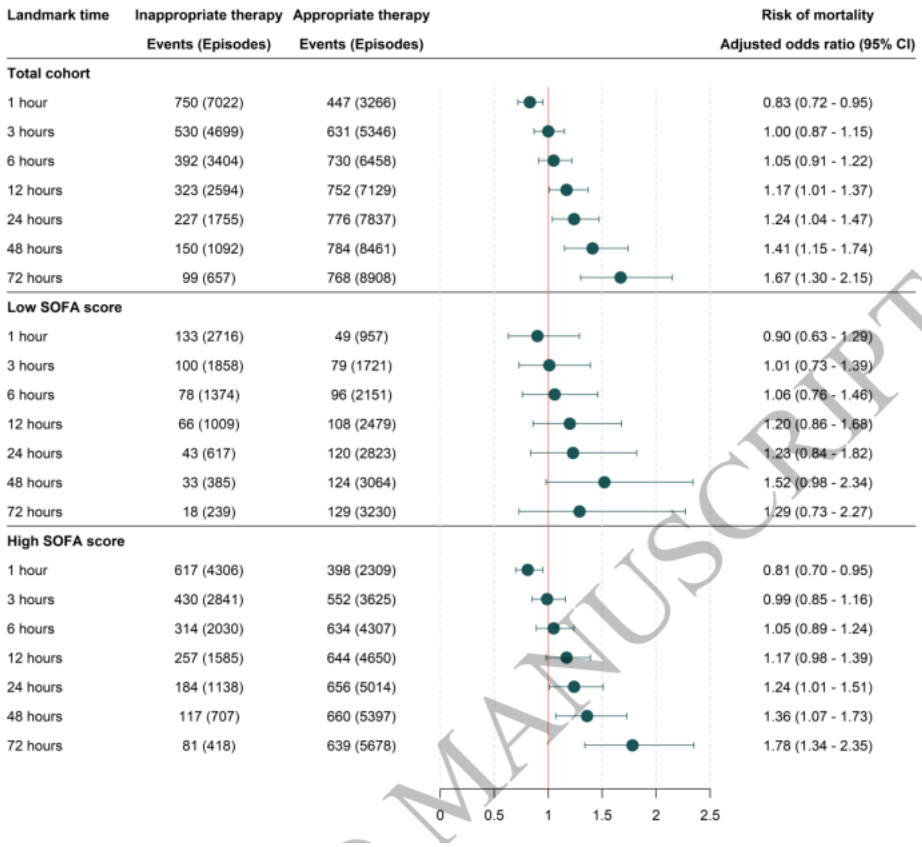


Comment: The decrease in broad-spectrum antibiotic use (especially carbapenems) achieved a sustained clinical impact by reducing the incidence of hospital-acquired candidemia. This was attributed to the education-based antimicrobial stewardship program which was effective in decreasing the incidence and mortality rate of hospital-acquired candidemia and multidrug-resistant infection. One of the weaknesses of this study relate to its retrospective and uncontrolled nature. Second, this study did not measure the 30-day mortality of hospital-acquired candidemia and other hospital-acquired multidrug-resistant BSIs, such as extended spectrum β-lactamase- (ESBL) producing or carbapenem resistant organisms. The impact of other interventions, including improved hand hygiene, infection control, a more detailed analysis on Candida spp., such as antifungal consumption, and resistance ratio between the periods was not evaluated in this study.

Association between time to appropriate antimicrobial treatment and 30-day mortality in patients with bloodstream infections: a retrospective cohort study
Clin Infect Dis published online September 6, 2022

This was a retrospective cohort study using electronic health record data from a large academic center in Sweden. Adult patients admitted between the years 2012-2019, with onset of BSI at the ED or general wards, were included. Pathogen-antimicrobial drug combinations were classified as appropriate or inappropriate based on reported *in vitro* susceptibilities. the association between appropriate therapy and mortality was assessed with multivariable logistic regression analysis at pre-specified landmark times. The first blood culture was regarded as the onset of the BSI and data on all significant pathogens identified within 24 hours from this blood culture was collected. Depending on whether the onset was within or beyond 48 hours after hospital admission, the BSI was classified as community-onset or hospital-onset respectively. They excluded pre-defined contaminants, based on the CDC/National Healthcare Safety Network Patient Safety Component Manual. Most culture results were available to clinicians within 24-72 hours after culture collection. Comorbidities were assessed with the Charlson Comorbidity Index (CCI, categorized as 0, 1-2, 3-4, ≥5) based on ICD-10 codes available from 5 years before admission until 24 hours after admission.

They included 10,628 BSI-episodes, occurring in 9192 unique patients. The overall 30-day 12 mortality was 11.8%. There was no association between appropriate therapy and mortality found at the 1, 3 and 6 hours landmark after blood culture collection. At 12 hours, the risk of death increased with inappropriate treatment (adjusted odds ratio 1.17 [95% confidence interval, 1.01-1.37]) and continued to increase gradually at 24, 48 and 72 hours. Stratifying by high or low SOFA-score generated similar odds ratios, but with wider confidence intervals. The BSI-episodes corresponded to 12223 unique pathogens of which *Escherichia coli*, *Staphylococcus aureus* and viridans streptococci were the most prevalent pathogens. The most common empirical antimicrobials were cefotaxime (46.5%), piperacillin-tazobactam (35.7%) and meropenem (12.1%).



Comment: Due to the relatively small number of septic shock patients, of which most received appropriate treatment within the first hours, the study was underpowered to draw meaningful conclusions in this subgroup. The main limitation relates to its observational nature. Since the study population was large, it was not feasible to assess if adequate source control measures were taken. This is another article that confirms in the absence of septic shock there is time to evaluate your patient up to 3-6 hours before starting antibiotics. The SSC recommends antibiotics should be administered within 3 hours if shock is not present. Several months ago I reviewed an article in CCM which concluded unadjusted rate of death or prolonged length of stay was elevated for patients who received antibiotics within the first hour of hospital presentation[patients who received antibiotics immediately after arrival to the hospital tended to have higher acuity], decreased for those who received antibiotics in the next 3 hours, then increased steadily after 4 hours.[J-Curve] [Crit Care Med 2022; 50:799-809]

Polio Declared State of Emergency for New York

The first polio case in nearly a decade was identified in July in New York State. [see ID Watch in July] Officials said an unvaccinated man in Rockland County was infected with polio that had been shed from someone who received the oral polio vaccine, which has not been administered in the United States since 2000. No other cases have been identified by the state, but officials have been monitoring wastewater for polio. In August, New York City officials said they had identified polio in the city's wastewater. On Friday, state health officials announced that they had identified polio in 57 samples collected from wastewater in several downstate

counties between May and August. The majority of the samples were collected in Rockland County, and 50 of them were genetically linked to the case of the Rockland resident. Thirteen of the wastewater samples were collected in Orange County, six were collected in Sullivan County and one was collected in Nassau County. State health officials have marked seven of the samples containing polio as a particular concern because they have not been linked to the Rockland County case.

The polio vaccination rates in counties where the samples were collected are lower than those in the rest of the state, according to state data published in August. The statewide average rate for polio vaccination among children under 2 years old is around 79 percent. The rate in Rockland County was around 60 percent. The rate in Orange County was around 59 percent. And the rate in Sullivan County was around 62 percent.

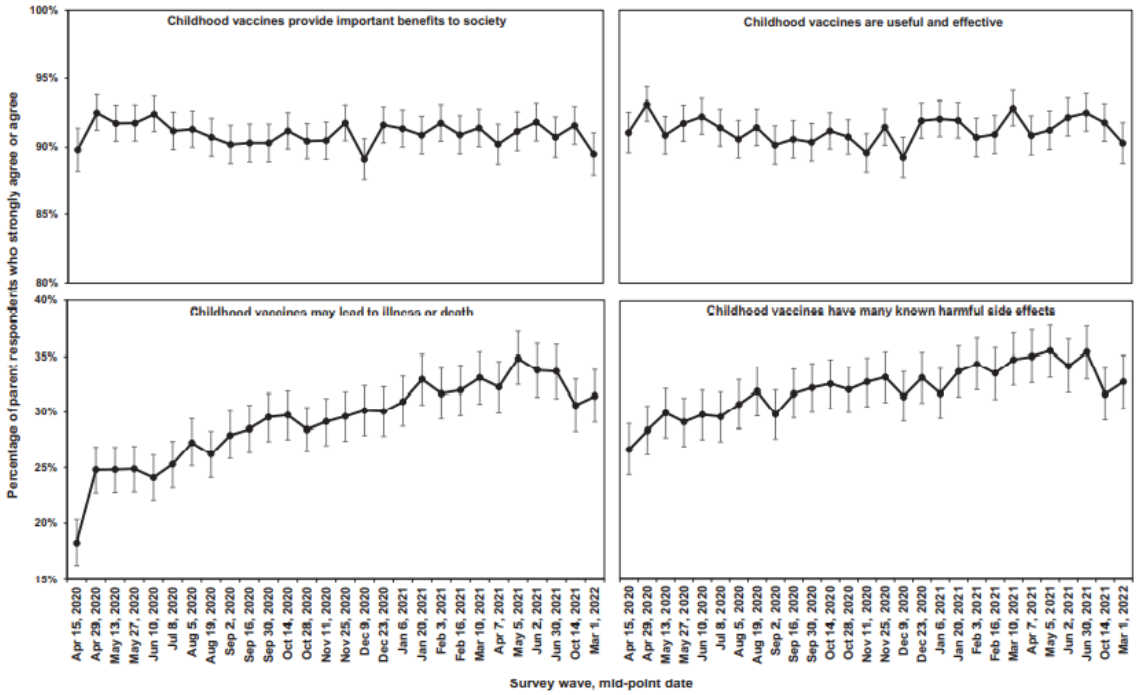
Comment: Orange and Rockland Counties are both home to large numbers of Hasidic Jews and anti-vaccine sentiment has spread among some in that community. We want to see the polio vaccination rate above 90 percent. Wastewater surveillance have also found polio in places like London, meaning there may be more cases circulating around the globe. This is another example of what happens when we let our guard down and allow vaccination rates to decline. See next article

Trends in Parents' Confidence in Childhood Vaccines During the COVID-19 Pandemic Pediatrics 2022:e2022057855

DOI: https://doi.org/10.1542/peds.2022-057855

The investigators analyzed data from the Understanding America Study (UAS), a probability-based Internet panel of 9500 United States adults. America surveys were administered to the UAS panel (in English and Spanish) biweekly from April 1, 2020, to February 16, 2021, then monthly through July 20, 2021, with 2 additional surveys from September 23 to October 1, 2021 and February 1 to March 30, 2022. Respondents were asked whether they agreed with 4 statements (presented in random order) about childhood vaccines: "Childhood vaccines, such as those for measles or chicken pox: 1) provide important benefits to society; 2) may lead to illness or death; 3) have many known harmful side effects; 4) are useful and effective."

From April 2020 to March 2022, the percentage of parents who agreed with the "important benefits" and "useful and effective" statements remained stable and high, ranging from 89.5 to 92.5% and from 89.3 to 93.2%, respectively (Fig 1). By contrast, the percentage of parents who agreed with the illness or death and harmful side effects statements increased significantly by 13.2% (95% confidence interval [CI]: 9.4% to 16.9%) and 6.1% (95% CI: 2.2% to 9.9%), respectively.



Comment: In this national sample, the proportion of parents concerned about the safety and side effects of routine childhood vaccines unfortunately increased significantly between April 2020 and March 2022. In contrast, parent confidence in the benefits and effectiveness of childhood vaccines remained high. This survey underscores the important role of physicians who are trusted by parents about vaccinations. This survey had insufficient sample sizes for certain racial and ethnic groups, and inability to determine if concern was higher or lower for specific childhood vaccines or the exact factors causing the observed rise in concern. This increased concern started at the start of the pandemic. We also know during the pandemic pediatric immunizations have declined. This hesitancy and decline in vaccinations can lead to increased risk of vaccine preventable diseases. We must do better. See article above

Severe Respiratory Illnesses Associated with Rhinoviruses and/or Enteroviruses Including EV-D68 – Multistate, 2022 HAN September 9, 2022

Healthcare providers and hospitals in several regions of the US notified CDC during August 2022 about increases in pediatric hospitalizations in patients with severe respiratory illness who also tested positive for rhinovirus (RV) and/or enterovirus (EV). Upon further typing, some specimens have been positive for enterovirus D68 (EV-D68). Concurrently, pediatric acute respiratory illness sentinel surveillance sites are reporting a higher proportion of EV-D68 positivity in children who are RV/EV positive compared to previous years. Although it primarily causes acute respiratory illness, EV-D68 has been associated with acute flaccid myelitis (AFM), a rare but serious neurologic complication involving limb weakness.

RVs and EVs are both part of the *Enterovirus* genus. EVs can cause ARI but are associated with other clinical presentations, such as febrile rash and neurologic illness, including aseptic meningitis, encephalitis, or AFM. EV-D68 has biologic and genomic similarities to RVs;

respiratory symptoms are similar in patients infected with RVs and EV-D68. Common symptoms among hospitalized children with EV-D68 include cough, shortness of breath, and wheezing; fever is reported in approximately half of known cases. On rare occasions, EV-D68 may cause AFM. This rare but serious neurologic condition primarily affects children and typically presents with sudden limb weakness. There are no available vaccines or specific treatments for RV or EV, including EV-D68, and clinical care is supportive.

Comment: EV-D68 is thought to peak in late summer and early fall. The number of detections in July—August 2022 was greater than in the same period of the previous three years (2019, 2020, and 2021). As of August 30, 2022, CDC has not received increased reports of AFM cases with onset in 2022. However, increases in EV-D68 respiratory illnesses have typically preceded cases of AFM, indicating that increased surveillance for AFM in the coming weeks will be crucial.

Monkeypox

Monkeypox presenting as proctitis in men who have sex with men

Clin Infect Dis published online September 6, 2022

doi.org/10.1093/cid/ciac737

This study was a retrospective study which reviewed all patients diagnosed with monkeypox virus (MPV) in Israel between May 5, 20.22 and July 16, 2022. They identified 70 men who have sex with men (MSM) confirmed to have monkeypox. Anal pain was the most common symptom of proctitis . In 11 patients (42.3%), symptoms and signs of proctitis preceded the skin rash, appearing at a median of three days (range, 1 to 7 days) before the rash. In six patients (23%) proctitis was the only clinical manifestation, without them ever developing a rash. Three patients with proctitis (11.5%) were found to have an anal mass protruding from the rectum accompanied by excruciating pain. 15 patients with proctitis (57.6%) were assessed for co-infection with N. gonorrhea and C. 19 trachomatis using PCR from a rectal swab. Of these, two patients were positive for N. gonorrhea, two for C. trachomatis and one patient for both.

Comment: They identified 70 men who have sex with men (MSM) confirmed to have monkeypox. More than a third presented with proctitis, and in two thirds of proctitis patients, there was no typical rash upon presentation, and in one-fifth, there was no rash at all, making diagnosis difficult. This study has confirmed others indicating perineal disease with few if any lesions in MSM.

Single and 2-dose vaccinations with MVA-BN® induce durable B cell memory responses in healthy volunteers that are comparable to older generation replicating smallpox vaccines

medRxiv posted September 9, 2022

doi.org/10.1101/2022.09.07.22279689

In this set of clinical studies, participants who had never been immunized against smallpox were randomized to receive, 4 weeks apart: 2 placebo vaccinations (PBO group, N =181); 1 MVA-BN vaccination followed by placebo (1×MVA group, N =181); or 2 MVA-BN vaccinations (2×MVA group, N = 183). In addition, participants with a history of smallpox vaccination received 1 MVA-BN booster (HSPX+ group, N = 200). The 1×MVA and 2×MVA groups responded with increases in neutralizing antibody (nAb) GMTs at Week 2 (5.1 and 4.8, respectively) that further increased at Week 4 (7.2 and 7.5). All doses were administered subcutaneously with a 24- or 25-gauge needle in the upper arm according to standard clinical practice. Safety and reactogenicity assessments included solicited local and systemic adverse events, unsolicited adverse events, and serious adverse events.

The initial study included a total of 753 participants. Of these, there were 204 participants vaccinated against smallpox in the distant past who were assigned to receive an MVA-BN booster. The other 549 participants, who had never been vaccinated against smallpox, were randomized to receive either placebo, 1 or 2 MVA-BN primary vaccinations. Approximately 2 years later, 306 participants who received MVA-BN primary vaccinations in the initial study were screened for participation in the follow-up study. Of these, 304 participants (92 from the 2×MVA group, 91 from the 1×MVA group, and 121 from the HSPX+ group) provided blood samples to assess antibody persistence. A total of 75 and 77 participants who initially received 2 or 1 MVA primary vaccinations were revaccinated with an MVA-BN booster and included in the 2×MVA BD and 1×MVA BD groups, respectively.

The 1×MVA and 2×MVA groups responded with increases in neutralizing antibody (nAb) GMTs at Week 2 (5.1 and 4.8, respectively) that further increased at Week 4 (7.2 and 7.5). Two weeks after the second primary vaccination in the 2×MVA group (at Week 6), nAb GMT peaked (45.6) before stabilizing 2 weeks thereafter (at Week 8) (34.0). In the HSPX+ group, a rapid anamnestic response was observed with a peak nAb GMT at Week 2 (175.1) that was much larger than the peak responses in either of the primary vaccination (1× or 2×MVA) dose groups of smallpox vaccine-naïve subjects. Persistence of nAbs relative to baseline was observed at 6 months in all groups (highest in HSPX+), with a return to near baseline nAb levels 2 years later. Subsets of ~75 participants each, who received primary vaccinations in the 1×MVA and 2×MVA groups, were administered an MVA-BN booster 2 years later. Both booster dose (BD) groups exhibited rapid anamnestic responses with nAb GMTs that peaked 2 weeks post-booster (80.7 and 125.3). These post-booster titers in the 1×MVA and 2×MVA groups were higher than those observed at any timepoint following primary vaccination, were comparable to HSPX+ subjects who had been administered a booster and remained elevated at 6 months post-booster (25.6 and 49.3). The observed anamnestic responses, in the absence of sustained detectable nAbs, support the presence of durable immunological memory following MVA-BN immunization. No safety concerns were identified, and the most common adverse event following the 2-year MVA-BN booster was injection site erythema in 82.2% of participants.

Comment: MVA-BN booster-induced anamnestic responses support durable immune memory. One or two primary MVA-BN vaccinations induce similar durable B cell memory responses. Anamnestic responses were observed in those immunized with MVA-BN 2 years earlier. No safety concerns were revealed following a 2-year MVA-BN booster. We now need studies with the intradermal administration to compare with the more traditional SQ administration.

Two Cases of Monkeypox-Associated Encephalomyelitis — Colorado and the District of Columbia, July–August 2022 MMWR early released September 13, 2022

Two US monkeypox patients developed encephalomyelitis in the week after symptom onset, one in Colorado and one in Washington, DC, suggesting neurologic complications are a potential outcome of monkeypox infections.

The first case of encephalomyelitis was in an immunocompetent gay man in his 30s in Colorado, with no known monkeypox exposure or international travel. According to the authors, 9 days after symptom onset of fever and rash, the patient developed progressive left arm and leg weakness and numbness, urinary retention, and intermittent priapism, and was hospitalized. MRI of the spine showed multifocal, longitudinally extensive, partially enhancing lesions of the central thoracic spinal cord and gray matter of the conus medullaris, with a single cervical level of canal stenosis with partial cord compression (presumably chronic and not acute). Cerebrospinal fluid (CSF) analysis demonstrated 155 white blood cells/μL with 60% lymphocytes, 30% monocytes, and 10% neutrophils; 9 red blood cells/μL; glucose 64 mg/dL; and protein 273 mg/dL. CSF bacterial cultures and CSF HSV and VZV PCR results were negative. After the onset of neurologic symptoms, the man was treated with tecovirimat. Subsequently, pulsed intravenous (IV) methylprednisolone (for suspected demyelination and spinal cord edema), IV immunoglobulin (IVIG) (for a possible parainfectious autoimmune process), and IV penicillin (for empiric syphilis treatment in case of a latent infection) were added to the patient's regimen, with partial improvement in numbness and weakness over several days. Persistent weakness in the left leg lasted longer than 1 month, and the man required an assistive walking device.

The patient in Washington, DC, was also an otherwise healthy gay man in his 30s who similarly had no known monkeypox virus (MPXV) exposure or recent travel. Five days after typical monkeypox symptoms began, he developed bowel and bladder incontinence and progressive flaccid weakness of both legs and was hospitalized. The patient's condition worsened, and he was intubated and admitted to the intensive care unit. MRI of the brain showed nonenhancing lesions of the pons, cerebellum, and medulla without restricted diffusion. MRI of the spine showed multifocal, partially enhancing lesions in the central cervical and upper thoracic regions. CT imaging of the abdomen and pelvis demonstrated rectal thickening with pelvic lymphadenopathy consistent with proctitis, thought to be related to MPXV infection. CSF analysis demonstrated 30 white blood cells/μL with 89% lymphocytes and 11% monocytes; 4 red blood cells/μL, glucose 65 mg/dL, and protein 60 mg/dL. CSF bacterial cultures and CSF HSV and VZV PCR results were negative. He was treated with oral and intravenous tecovirimat, IVIG, and later rituximab, a monoclonal antibody medication. After 5 weeks he was discharged from the hospital to an acute inpatient rehabilitation, walking with an assistive device.

Neither patient had been vaccinated against either smallpox or monkeypox.

Comment: The underlying pathology behind this is unclear but might represent either MPXV invasion of the CNS or a parainfectious autoimmune process triggered by systemic MPXV infection. Though rare, such outcomes were seen during smallpox outbreaks. The symptom presentation was indicative of acute disseminated encephalomyelitis (ADEM), and inflammation in the brain and spinal cord that damages myelin. For severe MPXV disease, tecovirimat is recommended as first-line antiviral therapy, although the degree of CNS penetration is unknown. For significant edema, demyelination, or an ADEM-like presentation, corticosteroids can be considered, although benefits should be weighed against the immunosuppressive risks during an active infection. In addition, for a suspected parainfectious autoimmune CNS process or ADEM-like presentation, empiric IVIG or PLEX (or PLEX followed by IVIG) can be considered. The role for anti-B–cell therapies such as rituximab is not known.

LA County man died from monkeypox

A severely immunocompromised man died from MPXV in Los Angeles County, officials announced today. County officials made the confirmation in cooperation with the CDC.

Though his death was the second death in the country reportedly linked to MPXV, this is the first confirmed death due to the virus. Texas health officials are still investigating monkeypox role in the Houston patient's death late last month, but believe it was caused by MPXV also in an immunocompromised patient.

Comment: Although the clade II MPXV has a very low risk of death, patients who are immunocompromised are at higher risk of dying. In addition, as we are learning of severe complications such as encephalomyelitis. Currently laboratory testing has indicated that the current outbreak is associated with the Clade IIb of MPVX. See above Behavioral changes and vaccinations are the key to controlling this outbreak.

Guidance for Tecovirimat Use Under Expanded Access Investigational New Drug Protocol during 2022 U.S. Monkeypox Outbreak CDC September 15, 2022

For most patients with healthy immune systems, supportive care and pain control is usually enough. However, there are some instances where tecovirimat could be beneficial, and today CDC has updated guidance to reflect this.

Specifically, tecovirimat should be considered for use in people who have:

- Severe disease — meaning that someone has a condition such as hemorrhagic disease, confluent lesions (individual sores have joined into one larger sore), sepsis, encephalitis, eye infections, or other infections that require hospitalization
- Involvement of anatomic areas which might result in serious disease including scarring

Tecovirimat should also be considered for use in people who are at high risk for severe disease, including:

- People with immunocompromising conditions
- Children, particularly patients younger than 8 years of age
- People who are pregnant or breastfeeding
- People with certain skin infections

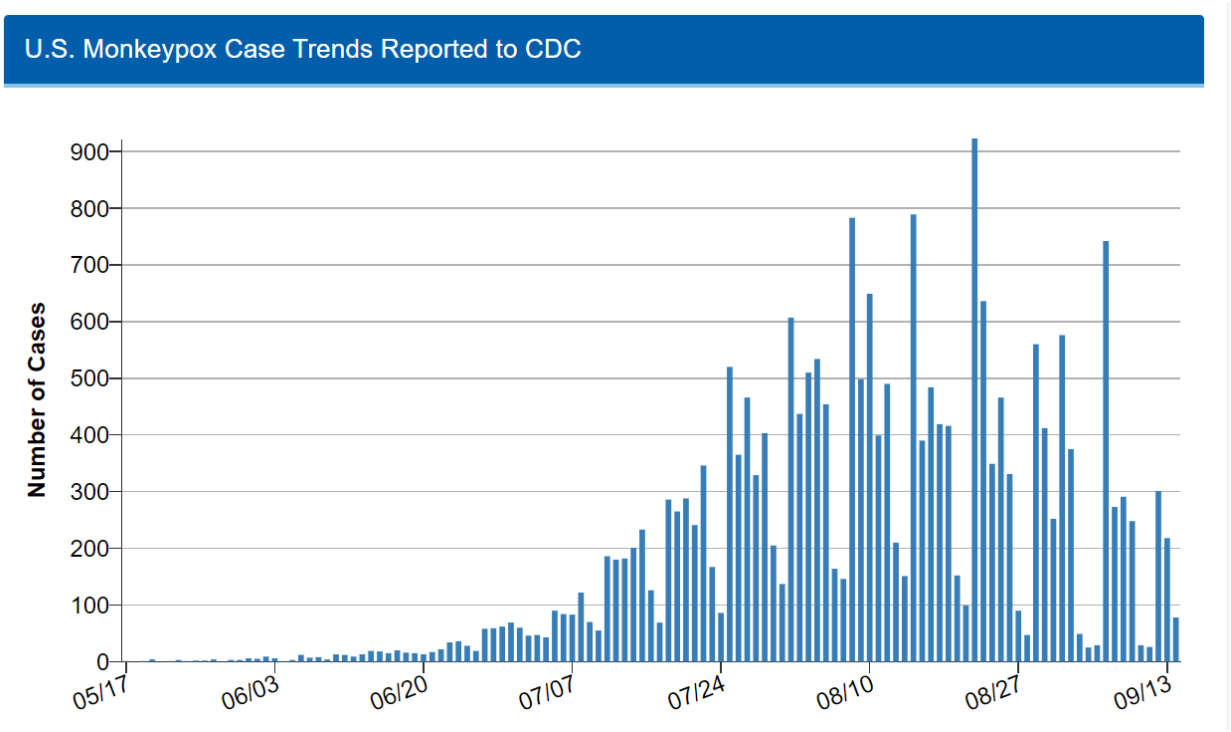
FDA Warns Monkeypox Virus May Develop Resistance To Tecovirimat

The monkeypox virus is only one mutation away from evading a key antiviral drug being used to treat at-risk patients, federal health officials are now warning – and they're urging [physicians] to be 'judicious' in prescribing the sought-after treatment."

Comment: Tecovirimat works by inhibiting a viral protein, called VP37, that all orthopoxviruses (e.g., smallpox virus, monkeypox virus, vaccinia virus) share. However, as noted in the drug

label, tecovirimat has a low barrier to viral resistance. This means small changes to the VP37 protein could have a large impact on the antiviral activity of tecovirimat.

CDC is actively monitoring for changes in the monkeypox virus that could make the virus less susceptible to tecovirimat. Fortunately, the incidence of MPXV infection has declined (see below), but we have confirmed two deaths in highly immunocompromised individuals. See above. Our current strategy to test and contact-trace our way out of this epidemic has had only limited effect, so we need a strategy to vaccinate those at risk (especially sexually active MSM in the US with HIV and STDs). See next article Given vaccine supply, we may want to hold off on vaccinating those who have had smallpox vaccination (which ended around 1970 in the US), since these individuals will likely still have some protection against monkeypox. Then, when vaccine supplies increase, we can extend doses to every MSM who wants to be vaccinated and other high-risk individuals. Behavior modification is still a key strategy in addition to vaccination.



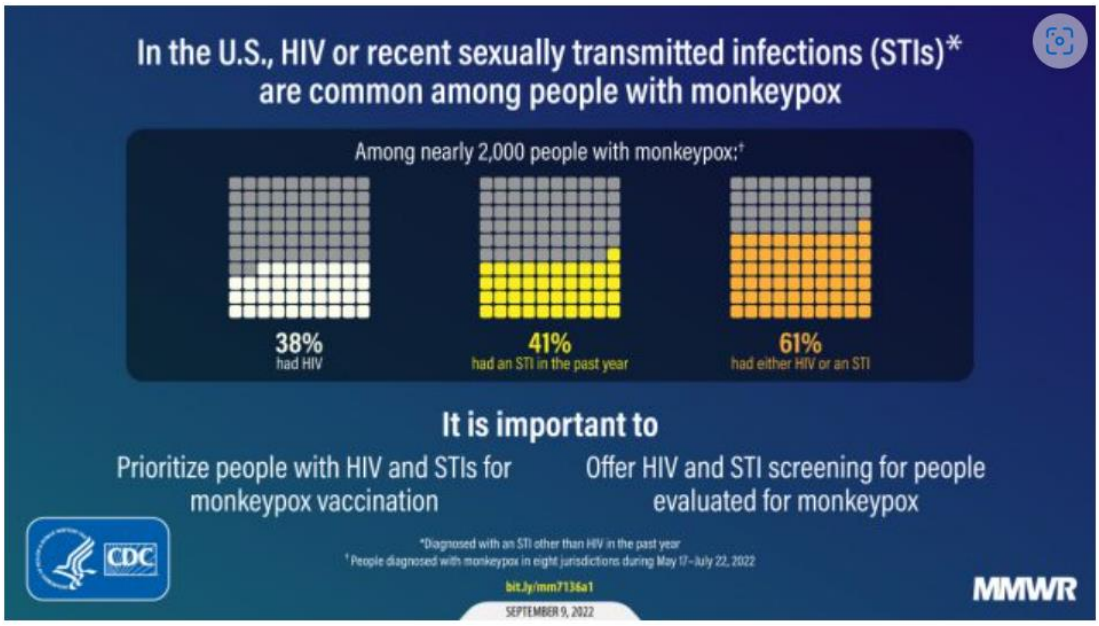
HIV and Sexually Transmitted Infections Among Persons with Monkeypox — Eight U.S. Jurisdictions, May 17–July 22, 2022 MMWR 2022 / 71;1141–1147

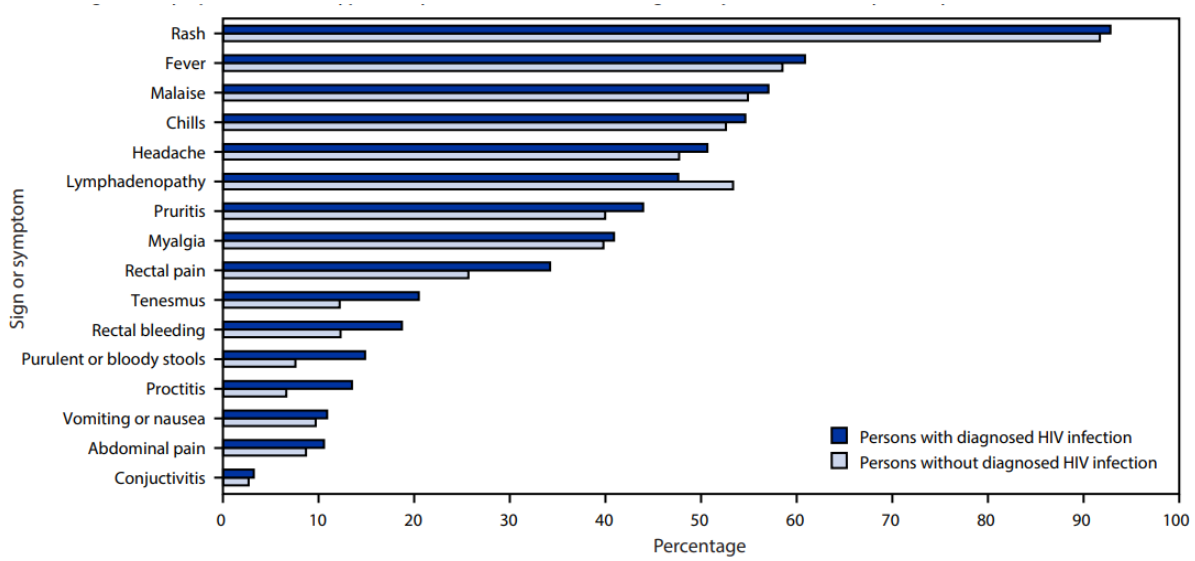
The present study used surveillance data for HIV, monkeypox, and other STIs from eight jurisdictions of the United States to analyze and correlate HIV infection and STI diagnoses within the preceding year to individuals with monkeypox (MPXV) infections. The data were also used to assess the severity of MPXV cases related to HIV infection status.

The study found that HIV prevalence was 38% among the 1,969 MPXV patients diagnosed between May 17 and July 22, 2022. The prevalence of one or more reportable STIs among the diagnosed MPXV patients was 41%. The percentage of MPXV-infected persons with HIV and one or more STIs diagnosed in the preceding year was 18. The incidence of hospitalization with

MPXV was higher among persons with HIV infection (8%) compared to persons without HIV (3%). Among the MPXV patients with diagnosed HIV infections, 82% showed indications of viral suppression, 92% had received HIV care in the previous year, and 78% showed CD4 counts of 350 or higher. The prevalence of HIV in MPXV patients varied according to demographic factors. Individuals between 18 and 24 had a lower HIV incidence than those aged 55 or above. Race and ethnicity were also factors in varying the prevalence of HIV among MPXV patients. African American MSM had the highest prevalence (63%), followed by Hispanic persons (41%), non-Hispanic White persons (28%), and non-Hispanic Asians (22%).

Additionally, some MPXV symptoms, such as rectal pain and bleeding, tenesmus, proctitis, and bloody stools, were reported more by patients with HIV infection than those without HIV. Unsuppressed HIV load in MPXV patients was also associated with symptoms such as lymphadenopathy, pruritis, rectal bleeding, and bloody stools. Low CD4 levels (<350) in MPXV patients with concurrent HIV infection were linked to a higher incidence of fever and generalized pruritis.





Comment: It is important to prioritize persons with HIV infection and STIs for vaccination. Screening for HIV and other STIs and other preventive care should be considered for persons evaluated for MPXV, with HIV care and HIV preexposure prophylaxis offered to eligible persons.

COVID-19

COVID-19 News

COVID-19 Updates

1. As of September 7th, the nation's seven-day case average was 70,488, an 18.8 percent decrease from the previous week's average. This marks the seventh week of decline.

2. As of Sept. 8, 17.2 percent of counties, districts or territories had high COVID-19 community levels, an 8.6 percentage point decrease from the week prior.

3. Another 43.1 percent had medium community levels, marking a 2.3 percentage point decrease from the week prior.

4. The seven-day hospitalization average for August 31st to September 6th was 4,620, a 10.5 percent decrease from the previous week's average. Hospitalization rates are 10X higher in unvaccinated persons. See article below

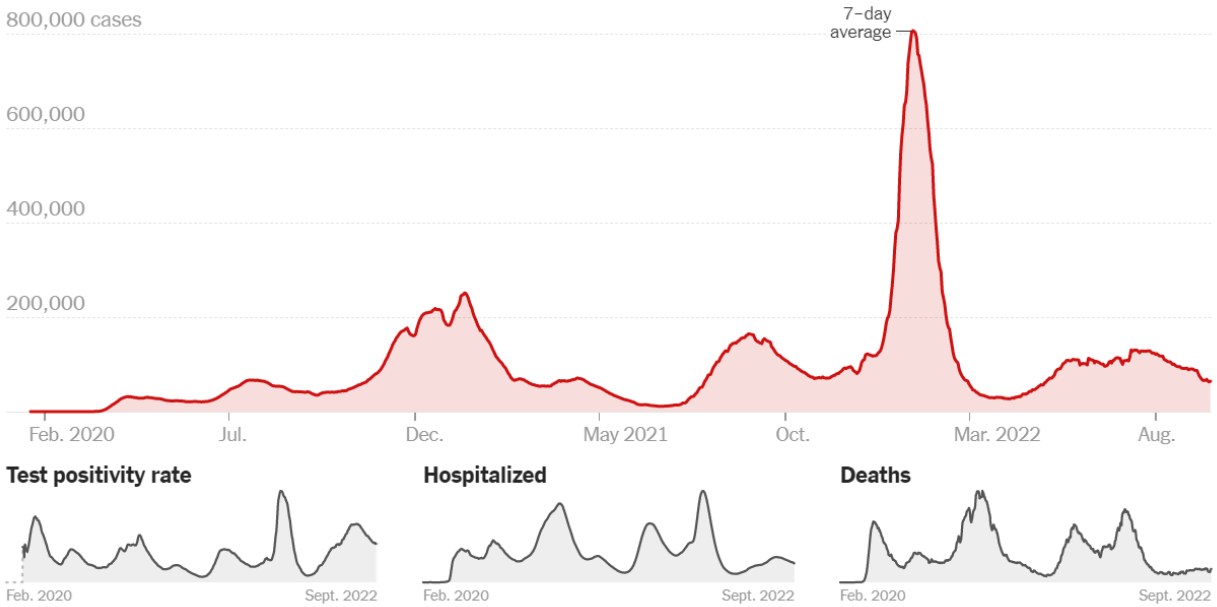
5. The current seven-day death average is 314, down 28.1 percent from the previous week's average. ~85% of death at in people >65.

6. As of September 7th, about 263.1 million people — 79.2 percent of the U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 224.4 million people,

or 67.6 percent of the population, have received both doses. In addition, ~30% of fully vaccinated persons over age 65 haven't received their first booster.

7. About 109 million additional or booster doses in fully vaccinated people have been reported. However, 50 percent of people eligible for a booster dose have not yet gotten one, the CDC said.

8. Based on projections for the week ending September 10th, the CDC estimates the omicron subvariant BA.5 accounts for 87.5 percent of US COVID-19 cases, while BA.4.6 accounts for 9.2 percent and BA.4 makes up 2.2 percent. Other omicron subvariants make up the rest.



Comment: Cases falling in nearly every state, and in many places, the declines are significant. Hospitalizations have also seen sustained improvement. Fewer than 35,000 people are currently in American hospitals with the coronavirus each day, a decrease of 11 percent over the past two weeks. Deaths today are far lower than they were a year ago. See MMWR article on mortality

COVID-19 Journal Review

The Lancet Commission on lessons for the future from the COVID-19 pandemic.

Lancet published online September 14, 2022

doi.org/10.1016/ S0140-6736(22)01585-9

The report is aimed at UN member states and agencies and intergovernmental groups such as the G20 and G7. The commission included 28 experts from around the world.

It details national negligence in prevention, rationality, public health practices, and international cooperation, as well as "excessive nationalism" that led to unequal access to resources such as personal protective equipment (PPE), vaccines, and treatments.

The report details 10 failures:

- A lack of timely notification of the initial outbreak of COVID-19
- Delays in acknowledging that SARS-CoV-2 spreads by aerosols and to implement appropriate public health mitigation measures at national and international levels
- An absence of coordination among countries to suppress viral transmission
- Government failures to examine evidence and adopt best practices for controlling the pandemic and managing economic and social spillovers from other countries
- A lack of global funding for low- and middle-income countries (LMICs)
- A failure to ensure adequate supplies and equitable distribution of key resources such as PPE, diagnostic tests, drugs, medical devices, and vaccines—particularly for LMICs
- A dearth of timely, accurate, systematic data on infections, deaths, viral variants, health system responses, and indirect health consequences
- Poor enforcement of appropriate levels of biosafety regulations leading up to the pandemic, raising the possibility of a lab leak
- A failure to combat systematic disinformation
- The lack of global and national safety nets to protect vulnerable populations

The report proposes the five pillars of fighting infectious diseases, including prevention strategies such as vaccination, containment, health services, equity, and global innovation and diffusion.

Level of implementation	Qualities, frameworks, and crucial stakeholders for prosocial behaviour and decision making
Global • Well coordinated and collaborative multilateral system • Transparent communication between countries • Sharing resources (eg, personal protective equipment, therapeutics, vaccines, and intellectual property) • Financing • Public health messaging and communication	• Cooperation among national governments, including major powers • Oversight mechanisms to hold countries accountable when they act against collective action • Collaboration among public health organisations, scientific and academic organisations, civil society organisations, national and regional leadership facilitated by the multilateral system • Collaboration among international financial institutions, multilateral development banks, and countries for emergency financing • Collaboration between international financial institutions, multilateral development banks, global health funders, and countries to ensure equitable access to necessary finance and health-related diagnostics and countermeasures, especially vaccines
Regional • Research and development and countermeasure pooling • Vaccines and therapeutics procurement • Sharing resources (eg, personal protective equipment, therapeutics, vaccines, and intellectual property) • Financing for commodity procurement and socioeconomic protection	• Consistent and transparent cooperation among scientific and academic organisations, civil society organisations, regional leadership, and multisectoral national leadership • Consistent and transparent collaboration among scientific and academic organisations to pool research and development and facilitate technology transfer and knowledge • Collaboration among regional leadership, including multilateral development banks and national leadership, to procure pandemic-related resources (eg, personal protective equipment, therapeutics, and vaccines) for equitable distribution • Collaboration between multisectoral national leadership and multilateral development banks to make necessary financing available to support socioeconomic safety nets • Previous experience with highly infectious and dangerous respiratory pathogens
National • National health system response • Surveillance and warning systems • Public health capacity • Health-care systems capacity • Research and development pooling • Financing for social and economic protection and countermeasure procurement and delivery • Public health messaging and communication	• Agreeing to and obeying international norms • Low politicisation of public health measures • Oversight mechanisms to hold provinces and municipalities accountable when they act against collective action • Consistent and transparent collaboration among provincial and municipal leadership, multisectoral national leadership, and civil society organisations • Consistent and transparent collaboration among scientific and academic organisations to pool research and development and facilitate technology transfer and knowledge • Health-care systems centred around primary health care and universal health coverage • Collaboration between national leaders, public health officials and hospital administrators to ensure routine health services are maintained and health systems receive adequate emergency funding to support quality care provision • Previous experience with highly infectious and dangerous respiratory pathogens
Provincial and municipal • Health-care systems capacity • Public health capacity • Surveillance • Protection of vulnerable communities • Social, economic, and humanitarian assistance programmes • Public health messaging and communication	• Collaboration among public health departments, trusted local organisations and individuals, and media outlets to provide public with clear public health messaging and communication • Collaboration between provincial and municipal leadership and local civil society organisations to provide individuals, businesses, and communities with social, economic, and humanitarian support • Health-care systems centred around primary health care, to ensure non-pandemic-related health services are maintained • Previous experience with highly infectious and dangerous respiratory pathogens
Individual • Public health and social measures to protect the community (eg, masking and isolating) • Vaccination • Public health messaging and communication	• Trust between individuals • High social cohesion • Trust in institutions or government • Measures in place to hold accountable individuals who share false information and to limit the sharing of misinformation on social media • Previous experience with the spread of highly infectious and dangerous respiratory pathogens

Comment: This is a scathing report on the international Covid-19 pandemic response. This report calls it "a massive global failure on multiple levels" and spares no one. The report offers the best opportunity to learn from our failures. We should constructively and quickly build more resilient health systems and stronger political systems that support the health and wellbeing of people for the rest of the 21st century. We must insist that the failures and lessons from the past 3 years are not wasted. In the end this Commission report aims to contribute to a new era of multilateral cooperation based on strong UN institutions to reduce the dangers of Covid-19, forestall the next pandemic, and enable the world to achieve the agreed goals of sustainable development, human rights that governments are committed to pursue as members of the UN. We can do better and we must do better.

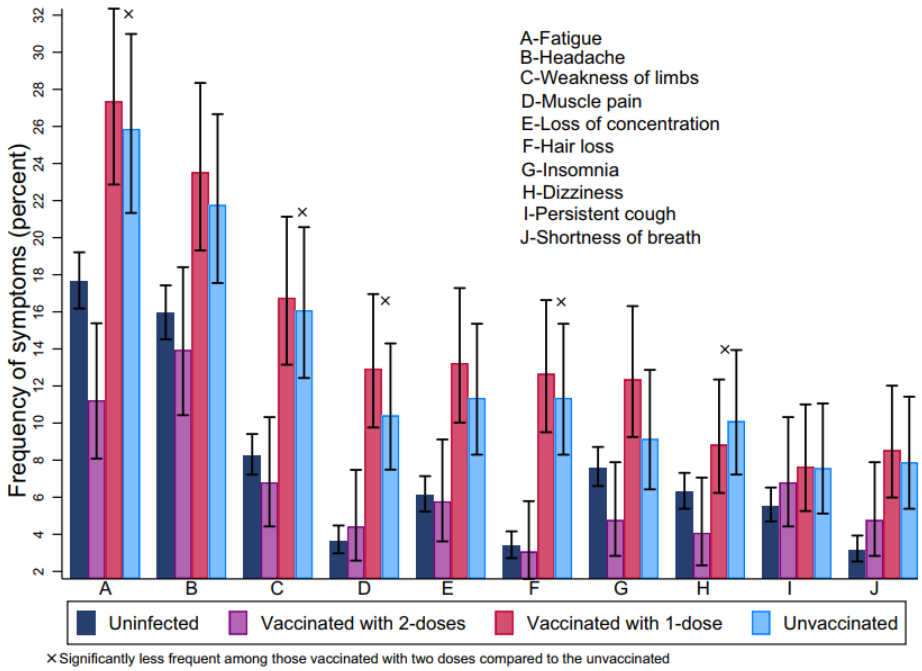
Association between BNT162b2 vaccination and reported incidence of post-COVID-19 symptoms: cross-sectional study 2020-21, Israel Vaccines published online August 26, 2022

doi.org/10.1038/s41541-022-00526-5

The investigators invited individuals PCR-tested for SARS-CoV-2 infection at participating hospitals between March 2020 and November 2021 to fill an online questionnaire that included

information about demographics, acute COVID-19 episode and symptoms they were currently experiencing. Using binomial regression, we compared vaccinated individuals with those unvaccinated and those uninfected, in terms of post-acute self-reported symptoms.

Of the 951 infected, 637(67%) were vaccinated. In the study population, the most prevalent symptoms were: fatigue (22%), headache (20%), weakness of limbs (13%), and persistent muscle pain (10%). After adjusting for age, time from beginning of symptoms to responding to the survey, and baseline symptoms, those who received two vaccine doses were less likely than unvaccinated individuals to report any of these symptoms (fatigue, headache, weakness of limbs, persistent muscle pain) by 62%, 50%, 62%, and 66% respectively, (Risk ratios 0.38, 0.50, 0.38, 0.34, $p < 0.04$ in the listed sequence). Compared to the 2447 included individuals who never reported SARS-CoV-2 infection, double-vaccinated participants were no more likely to report any of the mentioned symptoms. Vaccination with 2+ doses of Pfizer was associated with a reduced risk of reporting most of the common post-acute Covid-19 symptoms.



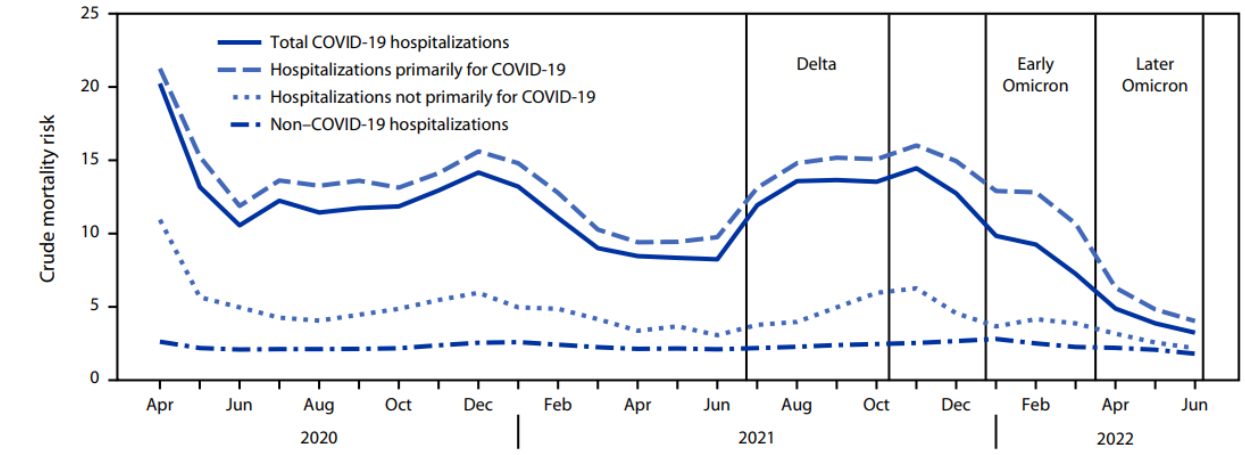
Comment: These results suggest that vaccination appears to have a protective effect against long Covid-19. All ten of the most common long Covid-19 symptoms were reduced by at least 50 percent among people who had at least two vaccine shots. The reduction in shortness of breath, for example, was 80%. The reporting of fatigue was 62% lower among the vaccinated, headaches were 50% lower, weakness of limbs 62%, and persistent muscle pain 66%.

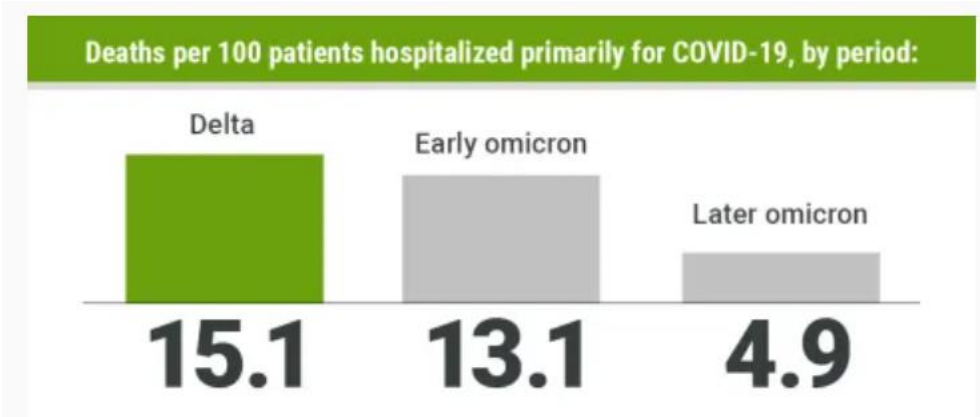
We have known for a long time that vaccination reduces the severity of Covid-19 illness. We are now starting to see evidence there is even more benefit, namely protection against long Covid-19 symptoms. So, there is now an extra reason to get vaccinated.

Mortality Risk Among Patients Hospitalized Primarily for COVID-19 During the Omicron and Delta Variant Pandemic Periods — United States, April 2020–June 2022 MMWR 2022; 71:1182-1189

Using a large hospital administrative database,[Premier Healthcare Database Special Covid-19 Release (PHD-SR)] CDC assessed in-hospital mortality risk overall and by demographic and clinical characteristics during the Delta (July–October 2021), early Omicron (January–March 2022), and later Omicron (April–June 2022) variant periods among patients hospitalized primarily for COVID-19. Model-estimated adjusted mortality risk differences (aMRDs) (measures of absolute risk) and adjusted mortality risk ratios (aMRRs) (measures of relative risk) for in-hospital death were calculated comparing the early and later Omicron periods with the Delta period.

Crude mortality risk (cMR) (deaths per 100 patients hospitalized primarily for COVID-19) was lower during the early Omicron (13.1) and later Omicron (4.9) periods than during the Delta (15.1) period ($p<0.001$) Adjusted mortality risk was lower during the Omicron periods than during the Delta period for patients aged ≥18 years, males and females, all racial and ethnic groups, persons with and without disabilities, and those with one or more underlying medical conditions, as indicated by significant aMRDs and aMRRs ($p<0.05$) During the later Omicron period, 81.9% of in-hospital deaths occurred among adults aged ≥65 years and 73.4% occurred among persons with three or more underlying medical conditions.





Comment: During the period of Omicron variant predominance, the crude mortality risk among patients hospitalized primarily for COVID-19 decreased to 4.9% during April–June 2022, which is lower than any previous time in the pandemic and approximately one third of what it was during the period of Delta variant predominance. A few limitations to be aware. First, the definition of hospitalizations primarily for Covid-19 might be subject to misclassification, which could vary over time with changing patient and contextual factors. In addition, vaccination status and previous Covid-19 were not ascertained in PHD-SR; thus, the effect of SARS-CoV-2 immunity on mortality risk could not assessed. Finally, although PHD-SR captures approximately 25% of annual U.S. hospital admissions, these findings might not be nationally generalizable. [but appears to be consistent with other publications]

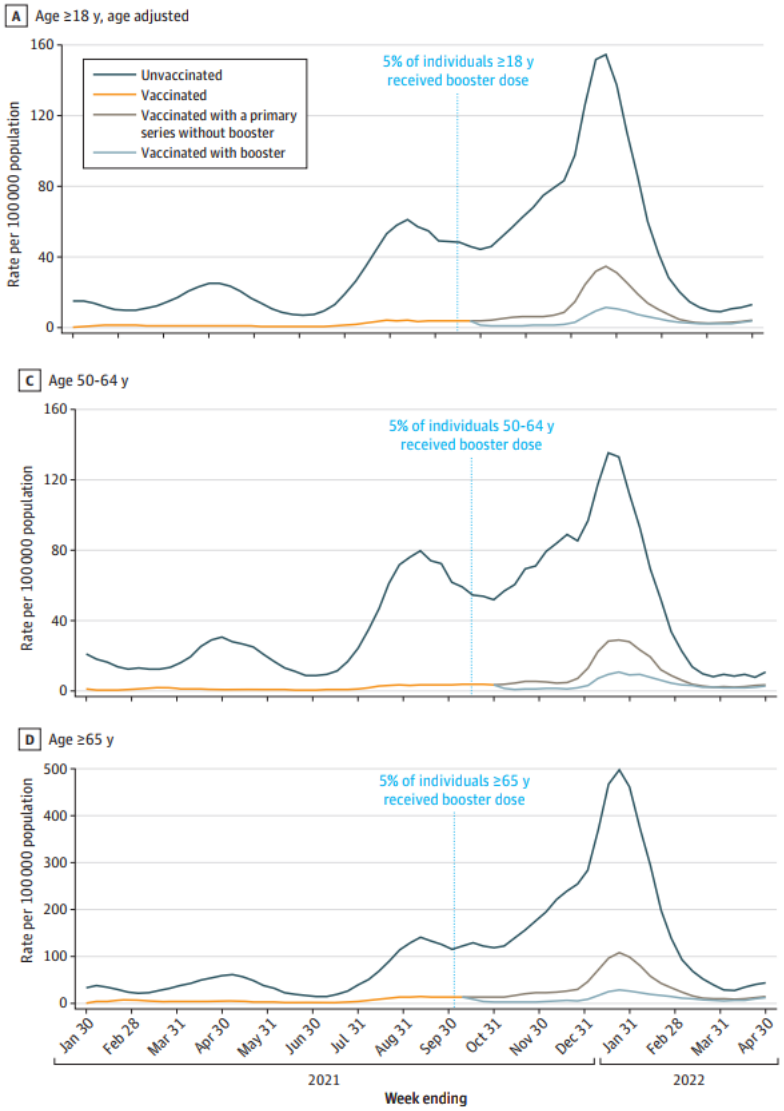
Vaccination, early treatment, and appropriate nonpharmaceutical interventions remain important public health priorities for preventing Covid-19 deaths, especially among persons at high- risk.

COVID-19-Associated Hospitalizations Among Vaccinated and Unvaccinated Adults 18 Years or Older in 13 US States, January 2021 to April 2022 JAMA Intern Med published online September 8, 2022

doi:10.1001/jamainternmed.2022.4299

From January 1, 2021, to April 30, 2022, patients 18 years or older with laboratory-confirmed SARS-CoV-2 infection were identified from more than 250 hospitals in the population-based Covid-19–Associated Hospitalization Surveillance Network. State immunization information system data were linked to cases, and the vaccination coverage data of the defined catchment population were used to compare hospitalization rates in unvaccinated and vaccinated individuals. Vaccinated and unvaccinated patient characteristics were compared in a representative sample with detailed medical record review; unweighted case counts and weighted percentages were calculated. Laboratory-confirmed Covid-19–associated hospitalization, defined as a positive SARS-CoV-2 test result within 14 days before or during hospitalization. The main outcome was Covid-19–associated hospitalization rates among vaccinated vs unvaccinated persons and factors associated with Covid-19–associated hospitalization in vaccinated persons were assessed.

Using representative data from 192 509 hospitalizations, monthly Covid-19–associated hospitalization rates ranged from 3.5 times to 17.7 times higher in unvaccinated persons than vaccinated persons regardless of booster dose status. From January to April 2022, when the Omicron variant was predominant, hospitalization rates were 10.5 times higher in unvaccinated persons and 2.5 times higher in vaccinated persons with no booster dose, respectively, compared with those who had received a booster dose. Among sampled cases, vaccinated hospitalized patients with Covid-19 were older than those who were unvaccinated (median [IQR] age, 70 [58-80] years vs 58 [46-70] years, respectively; $P < .001$) and more likely to have 3 or more underlying medical conditions (1926 [77.8%] vs 4124 [51.6%], respectively; $P < .001$).



Three-Week Moving Average Population-Based Rates of Covid-19–Associated Hospitalizations

Comment: This study demonstrates that Covid-19 vaccines are strongly associated with prevention of serious Covid-19 illness. This study taken together with the above study confirm higher risk to patients over age 65, and patients with 3 or more high-risk underlying medical conditions.

Resistance of SARS-CoV-2 Omicron Subvariant BA.4.6 to Antibody Neutralization

bioRxiv posted online September 6, 2022

doi.org/10.1101/2022.09.05.506628

Compared to BA.5, these new subvariants harbor a mutation at R346 residue in the spike glycoprotein, raising concerns for further antibody evasion. We compared the viral receptor binding affinity of the new Omicron subvariants with BA.5 by surface plasmon resonance. We also performed VSV-based pseudovirus neutralization assays to evaluate their antigenic

properties using sera from individuals who received three doses of a COVID-19 mRNA vaccine (boosted) and patients with BA.1 or BA.2 breakthrough infection, as well as using a panel of 23 monoclonal antibodies (mAbs). Compared to the BA.5 subvariant, BA.4.6, BA.4.7, and BA.5.9 showed similar binding affinities to hACE2 and exhibited similar resistance profiles to boosted and BA.1 breakthrough sera, but BA.4.6 was slightly but significantly more resistant than BA.5 to BA.2 breakthrough sera. Moreover, BA.4.6, BA.4.7, and BA.5.9 showed heightened resistance over to a class of mAbs due to R346T/S/I mutation. Notably, the authorized combination of tixagevimab and cilgavimab completely lost neutralizing activity against these three subvariants. The loss of activity of tixagevimab and cilgavimab against BA.4.6 leaves us with bebtelovimab as the only therapeutic mAb that has retained potent activity against all circulating forms of SARS-CoV-2. As the virus continues to evolve, our arsenal of authorized mAbs may soon be depleted, thereby jeopardizing the wellbeing of millions of immunocompromised persons who cannot robustly respond to COVID-19 vaccines.

Comment: If combination tixagevimab cilgavimab becomes less effective, this will leave our immunocompromised population at greater risk.

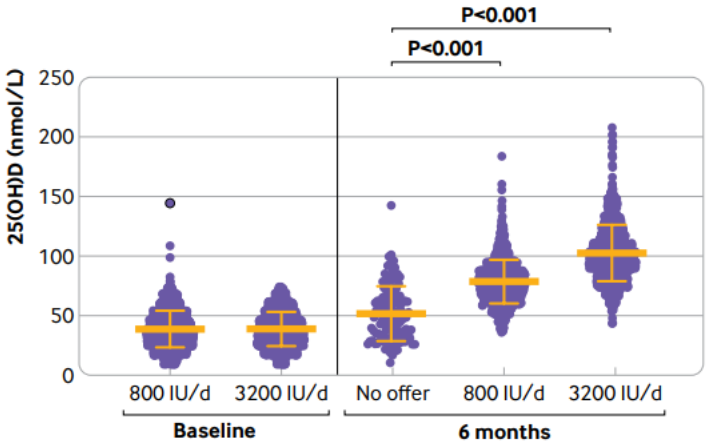
Effect of a test-and-treat approach to vitamin D supplementation on risk of all cause acute respiratory tract infection and covid-19: phase 3 randomised controlled trial (CORONAVIT)

BMJ 2022;378:e071230

doi.org/10.1136/ bmj-2022-071230

This study was a phase 3 open label randomized controlled trial. 6200 people aged ≥16 years who were not taking vitamin D supplements at baseline were eligible. Offer of a blood 25(OH)D concentration with provision of a six-month supply of lower dose vitamin D (800 IU/day, n=1550) or higher dose vitamin D (3200 IU/day, n=1550) to those with blood 25(OH)D concentration <75 nmol/L, compared with no offer of testing or supplementation (n=3100). Follow-up was for six months. The primary outcome was the proportion of participants with at least one swab test or doctor confirmed acute respiratory tract infection of any cause. A secondary outcome was the proportion of participants with swab test confirmed Covid-19. Logistic regression was used to calculate odds ratios and associated 95% confidence intervals. The primary analysis was conducted by intention to treat.

Of 3100 participants offered a vitamin D test, 2958 (95.4%) accepted and 2674 (86.3%) had 25(OH) D concentrations <75 nmol/L and received vitamin D supplements (n=1328 lower dose, n=1346 higher dose). Compared with 136/2949 (4.6%) participants in the no offer group, at least one acute respiratory tract infection of any cause occurred in 87/1515 (5.7%) in the lower dose group (odds ratio 1.26, 95% confidence interval 0.96 to 1.66) and 76/1515 (5.0%) in the higher dose group (1.09, 0.82 to 1.46). Compared with 78/2949 (2.6%) participants in the no offer group, 55/1515 (3.6%) developed covid-19 in the lower dose group (1.39, 0.98 to 1.97) and 45/1515 (3.0%) in the higher dose group (1.13, 0.78 to 1.63).



Comment: Among people aged 16 years and older with a high baseline prevalence of suboptimal vitamin D status, implementation of a population level test-and-treat approach to vitamin D supplementation was not associated with a reduction in risk of all cause acute respiratory tract infection or Covid-19. Vitamin D metabolites have long been recognized to support innate immune responses to respiratory viruses and bacteria and regulate immunopathological inflammation. [D. Nutrients 2015;7:4240-70; Nat Immunol 2022;23:62-74] Studies investigating potential associations between higher vitamin D status or vitamin D supplement use and reduced risk of SARS-CoV-2 infection have shown mixed results. Clinical trials of prophylactic vitamin D to reduce the incidence and severity of Covid-19 are lacking, as are studies comparing the effectiveness of different doses of vitamin D supplements for the prevention of acute respiratory tract infections of any cause among adults. Participants randomized to the no offer of supplementation group reported taking a vitamin D supplement on one or more occasions during follow-up. This could have led to increases in 25(OH) D concentrations in the no offer arm over the course of the study. This trial was designed to investigate the effectiveness of a pragmatic test-and-treat approach to boosting population vitamin D status, rather than evaluating the biological efficacy of vitamin D to prevent acute respiratory tract infections. The proportion of those randomized to the no offer arm who experienced the primary outcome (4.6%) was lower than the 20% anticipated in the sample size calculation, possibly reflecting the impact of public health measures to control transmission of SARS-CoV-2. Men, people from ethnic minorities, and those with lower educational status were relatively underrepresented among study participants compared with the general population, which may have compromised the generalizability of their findings.

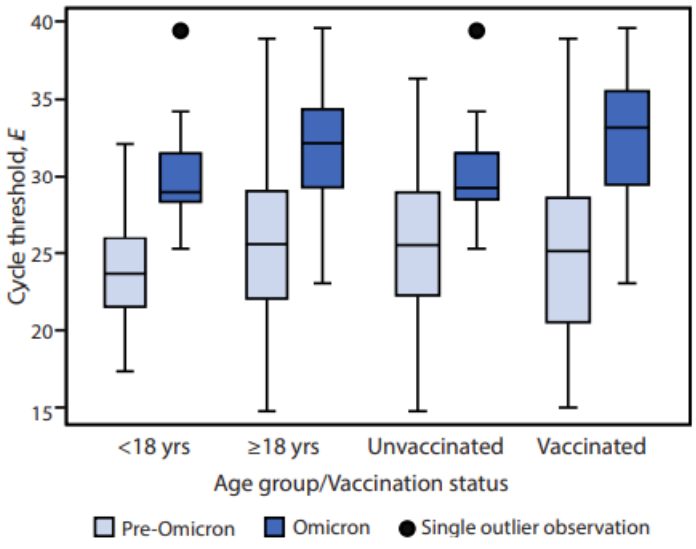
Detection of Higher Cycle Threshold Values in Culturable SARS-CoV-2 Omicron BA.1 Sublineage Compared with Pre-Omicron Variant Specimens — San Francisco Bay Area, California, July 2021—March 2022 MMWR 2022; 71:1151-1154

As part of an ongoing longitudinal cohort study, persons with documented SARS-CoV-2 infection (based on a positive clinical real-time RT-PCR test result) and their household members were recruited within 5 days of the first symptom onset in the household (or first RNA-positive test result if the infected person was asymptomatic). All participants self-collected nasal swab specimens [see next article] once daily for 2 weeks from the first onset in the household;

some participants also provided a serum specimen at enrollment to identify evidence of previous infection. Real-time RT-PCR targeting SARS-CoV-2 nucleocapsid (*N*) and envelope protein (*E*) genes was used to detect RNA and to determine Ct values, whole genome sequencing was used to identify the infecting variant strain and sublineage, and the presence or absence of culturable virus was assessed by cytopathic effect observed in tissue culture. Enrollment sera were tested for the presence or absence of anti-N immunoglobulin G (IgG).

A total of 1,147 nasal swab specimens from 124 participants were analyzed; among 17 participants infected with Omicron variants (all BA.1 sublineages) and 107 infected with pre-Omicron variants, 149 and 998 specimens, respectively, were collected. Timing of specimen collection after onset (in each participant) was similar in both groups (median = 8 days; IQR = 6–11 days). Among the 17 participants with Omicron BA.1 infections, nine (53%) were adults and 10 (59%) were fully vaccinated. Among 107 participants with pre-Omicron infections, 92 (86%) were adults and 35 (33%) were fully vaccinated. Nearly all participants were symptomatic (16 of 17 participants with Omicron BA.1 infection and 100 of 107 with pre-Omicron infection). No participants reported previous infection, and among 58 participants with available sera, none had detectable anti-N IgG at enrollment.

Accounting for age group and vaccination status, *E*-specific Ct values in all specimens were significantly higher in Omicron specimens than in pre-Omicron specimens (Ct difference = 4.45, p<0.001). When analysis was limited to RNA-positive specimens, a similar trend was observed (Ct difference = 3.90, p<0.001). Despite these higher Ct values in Omicron than in pre-Omicron specimens, culturable virus was detected in specimens from a similar percentage of participants in both variant groups (Omicron = 76%; pre-Omicron = 71%), a similar percentage of total specimens (Omicron = 26%; pre-Omicron: 30%), and was detected for a similar duration following onset (median = 6 days, IQR = 5–8 days for both Omicron and pre-Omicron specimens). Among virus-positive specimens, *E*-specific Ct values were significantly higher in Omicron specimens than pre-Omicron specimens (Ct difference = 5.77, p<0.001).This difference was observed as early as day 3 after onset through day 8 after onset. When stratified by age group or vaccination status, virus-positive Omicron specimens were associated with higher *E*-specific Ct values than were virus-positive pre-Omicron specimens (p<0.01). Similar findings were observed in the *N*-specific analysis (p<0.001).



Comment: Virus-positive (i.e., potentially infectious) specimens from participants infected with SARS-CoV-2 Omicron variants had significantly higher Ct values than did virus-positive specimens from participants infected with pre-Omicron variants. These data show that Ct values may not provide a consistent proxy for infectiousness across SARS-CoV-2 variants. Inoculum size capable of transmitting infection is unknown. This is a single-site study with a small number of participants infected with the Omicron BA.1 sublineage; thus, these findings might not be representative of all infected persons or BA.5. Replication of these findings with additional participants is necessary and is ongoing. In addition, approximately one half of the participants did not provide an enrollment serum specimen; thus, it was not possible to confirm the incidence of previous infection.

An Antibody from Single Human VH-rearranging Mouse Neutralizes All SARS-CoV-2 Variants Through BA.5 by Inhibiting Membrane Fusion Science Immunol published online August 11, 2022

DOI: 10.1126/sciimmunol.add5446

The investigators describe a mouse model in which the primary B cell receptor (BCR) repertoire is generated solely through V(D)J recombination of a human VH1-2 heavy chain(HC) and, substantially, a human Vκ1-33 light chain (LC). Thus, primary humanized BCR repertoire diversity in these mice derives from immensely diverse HC and LC antigen-contact complementarity-region-3 (CDR3) sequences generated by non-templated junctional modifications during V(D)J recombination. Immunizing the human VH1-2/Vκ1-33-rearranging mouse model with SARS-CoV-2 (Wuhan-Hu-1) spike protein immunogens elicited several VH1-2/Vκ1-33-based neutralizing antibodies that bound RBD in a different mode from each other and from those of many prior human patient-derived VH1-2-based neutralizing antibodies. Of these, SP1-77 potently and broadly neutralized all SARS-CoV-2 variants through BA.5. Cryo-EM studies revealed that SP1-77 bound RBD away from the receptor-binding-motif via a CDR3-dominated recognition mode. Latticelight-sheet-microscopy-based studies showed that SP1-77 did not block ACE2-mediated viral attachment or endocytosis, but rather blocked viral-host membrane fusion. The broad and potent SP1-77 neutralization activity and non-traditional mechanism of action suggest this antibody might have therapeutic potential. Likewise, the SP1-77 binding epitope may further inform on vaccine strategies. Finally, the general class of humanized mouse models we have described may contribute to identifying therapeutic antibodies against future SARSCoV-2 variants and other pathogens.

A

Pseudotyped Virus Neutralization of Monoclonal Antibodies (IC_{50}: ng/ml)

		Alpha	Beta	Gamma	Epsilon	Iota_ K484E	Iota	Delta	Omicron				
	G614	B.1.1.7	B.1.351	P.1	B.1.429	B.1.526. K484E	B.1.526	B.1.617. 2	BA.1	BA.2	BA.3	BA.4/ BA.5	BA.2.12. 1
SP1-77	20	28	16	15	36	19	11	76	6.5	33	7	16	8
VHH7-5-82	38	20	>10,000	>10,000	>10,000	26	>10,000	>10,000	>10,000	-	-	-	-
VHH7-7-53	68	43	>10,000	>10,000	62	43	>10,000	96	>10,000	-	-	-	-

Neutralization titer IC_{50} (ng/ml)
<10
10-100
100-1,000
1,000-10,000
>10,000

Pseudotyped Virus Neutralization of Monoclonal Antibodies (IC_{80}: ng/ml)

		Alpha	Beta	Gamma	Epsilon	Iota_ K484E	Iota	Delta	Omicron				
	G614	B.1.1.7	B.1.351	P.1	B.1.429	B.1.526. K484E	B.1.526	B.1.617. 2	BA.1	BA.2	BA.3	BA.4/ BA.5	BA.2.12. 1
SP1-77	47	166	35	81	213	37	29	327	26	82	28	56	37
VHH7-5-82	201	109	>10,000	>10,000	>10,000	128	>10,000	>10,000	>10,000	-	-	-	-
VHH7-7-53	423	363	>10,000	>10,000	315	284	>10,000	792	>10,000	-	-	-	-

Neutralization titer IC_{80} (ng/ml)
<10
10-100
100-1,000
1,000-10,000
>10,000

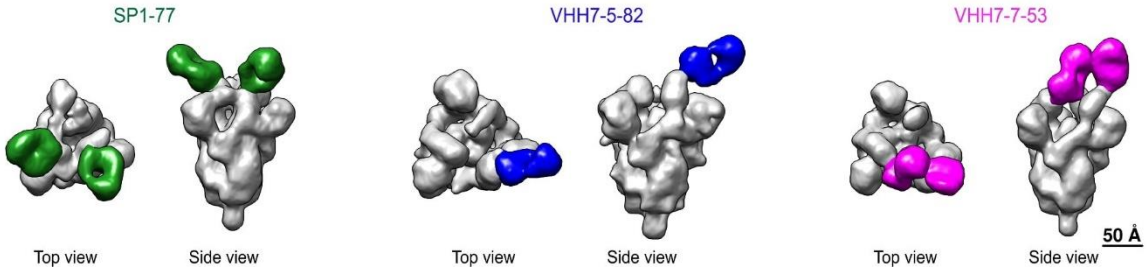
B

PRNT Live Virus Neutralization of Monoclonal Antibodies (ng/ml)

	WA1		B.1.1.7		B.1.351		P.1		B.1.617.2	
	Prototype		Alpha		Beta		Gamma		Delta	
	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}	IC_{50}	IC_{90}
SP1-77	1.1	2.4	1.1	1.3	0.8	1.1	0.8	1.2	9.7	12.1
VHH7-5-82	910.5	1128.0	111.6	1436.0	>10,000	>10,000	>10,000	>10,000	>10,000	>10,000
VHH7-7-53	136.3	2365.0	58.4	172.6	>10,000	>10,000	>10,000	>10,000	149.3	409.6

Neutralization titer (ng/ml)
<10
10-100
100-1,000
1,000-10,000
>10,000

C



Comment: This study demonstrated the generation of a broadly neutralizing monoclonal antibody developed using a humanized mouse model carrying single V_H1-2 heavy chain (HC) and $V_κ$1-33 light chain (LC) segments. The SP1-77 antibody differs from previous monoclonal antibodies in the mechanism of SARS-CoV-2 inhibition, as well as the SARS-CoV-2 RBD epitope of binding. Overall, the study has established a successful prototype for using humanized mouse models carrying V_H and $V_κ$ segments to generate a diversity of antibodies and demonstrated the potential of using mouse models to develop humanized antibodies against various pathogens. The SP1-77 neutralization mechanism they describe provides further insight into how a non-ACE2 blocking antibody can potently neutralize SARS-CoV-2. Future mutagenic studies are required to understand the specific residues that determine SP1-77 binding to the RBD.

COVID-19 Vaccines in Infants, Children, and Adolescents Pediatrics published online September 3, 2022 [2022:e2022058700]

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Recommendations

- The American Academy of Pediatrics (AAP) recommends coronavirus disease 2019 (COVID-19) vaccination for all infants, children, and adolescents 6 months of age and older who do not have contraindications to receiving a COVID-19 vaccine authorized or approved for use for their age. This includes primary series and/or booster doses as recommended by the CDC.
- Any COVID-19 vaccine, appropriate by age and health status, authorized through emergency use authorization or approved through a biologics license application by the FDA and recommended by the CDC, is recommended for COVID-19 vaccination according to CDC guidelines for infants, children, and adolescents.
- Individuals ≥6 months of age with a previous asymptomatic infection or symptomatic disease caused by severe acute respiratory syndrome coronavirus 2 should receive COVID-19 vaccination, according to CDC guidelines.
- Given the importance of routine vaccination and the need for rapid uptake of COVID-19 vaccines, the AAP supports coadministration of routine childhood and adolescent immunizations with COVID-19 vaccines (or vaccination in the days before or after) for infants, children, and adolescents who are behind on or due for immunizations (based on the CDC/AAP Recommended Child and Adolescent Immunization Schedule) and/or at increased risk from vaccine- preventable diseases.
- Pediatricians are encouraged to promote vaccination and vaccine confidence through ongoing, proactive messaging (i.e., reminder recall, vaccine appointment/clinics), and to use existing patient visits as an opportunity to promote and provide COVID-19 vaccines.
- Pediatricians' role in promoting vaccination among their patient population and in their community is critical, especially among those at highest risk for severe illness, hospitalization, and death from COVID-19, as well as their household contacts. Parents, caregivers, and patients might have questions that need to be addressed related to the vaccines. Pediatricians play an essential role in helping answer these questions, as well as in reducing existing disparities and addressing any barriers to accessing Covid-19 vaccines in their community.

Comment: These are common sense recommendations from the AAP and should help primary care physicians who care for children. The uptake of Covid-19 vaccines has been very disappointing especially in children < age 5. The publication does not specifically discuss the bivariant booster approved for children 12 and older.

Effectiveness and Durability of the BNT162b2 Vaccine against Omicron Sublineages in South Africa N Engl J Med published online September 14, 2022

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In this analysis, the investigators separately assessed the effectiveness and durability of the BNT162b2 vaccine against BA.1 or BA.2 and against BA.4 or BA.5 among members of Discovery Health, a medical care organization that provides health insurance to 3.7 million

persons in South Africa. During the period from November 15, 2021, to June 24, 2022, a total of 32,883 patients who had been hospitalized for medical treatment underwent PCR testing for SARS-CoV-2, a period that spanned the BA.1–BA.2 and BA.4–BA.5 omicron waves.

In this population, they assessed the effectiveness of two doses and three doses (i.e., the original two-dose series plus a booster) of the Pfizer vaccine against hospital admission for the treatment of possible sequelae of Covid-19 according to whether the BA.1 and BA.2 sublineages were dominant (November 15, 2021, to February 28, 2022) or whether the BA.4 and BA.5 sublineages were dominant (April 15 to June 24, 2022). In this analysis, we used a logistic regression model after adjustment for covariates to estimate vaccine effectiveness as 1 minus the odds of vaccination among positive cases. Vaccination status was analyzed according to the time that had elapsed since the administration of the most recent dose of vaccine (not vaccinated, 0 to 13 days, 14 to 27 days, 1 to 2 months, 3 to 4 months, 5 to 6 months, 7 to 8 months, or ≥9 months).

Among the patients who had received two doses of vaccine, waning of effectiveness against hospitalization was evident as early as 3 to 4 months after vaccination during both periods when the omicron sublineages were dominant. The vaccine effectiveness was 56.3% (95% CI, 51.6 to 60.5) during the BA.1–BA.2 wave and 47.4% (95% CI, 19.9 to 65.5) during the BA.4–BA.5 wave. Although boosting with a third dose-maintained vaccine effectiveness against severe disease caused by all four sublineages at 1 to 2 months, the vaccine effectiveness had decreased by 3 to 4 months to an effectiveness of 50.0% (95% CI, 4.4 to 73.9) during the BA.1–BA.2 wave and 46.8% (95% CI, 35.3 to 56.2) during the BA.4–BA.5 wave.

Table 1. BNT162b2 Vaccine Effectiveness against Hospitalization for Covid-19 in South Africa, According to the Dominant Omicron Sublineage.*

Time since Most Recent Vaccine Dose	VE of Dose 2		VE of Dose 3	
	BA.1–BA.2 Omicron Wave	BA.4–BA.5 Omicron Wave	BA.1–BA.2 Omicron Wave	BA.4–BA.5 Omicron Wave
	percent (95% CI)			
0–13 days	66.7 (38.3–82.0)	—	—	—
14–27 days	80.3 (62.8–89.5)	—	81.6 (68.1–89.4)	—
1–2 mo	61.3 (54.7–66.9)	—	66.4 (53.7–75.6)	68.8 (59.5–76.0)
3–4 mo	56.3 (51.6–60.5)	47.4 (19.9–65.5)	50.0 (4.4–73.9)	46.8 (35.3–56.2)
5–6 mo	45.6 (39.3–51.3)	26.3 (7.1–41.6)	—	—
7–8 mo	38.4 (16.9–54.4)	23.6 (11.1–34.3)	—	—
≥9 mo	—	19.3 (6.3–30.5)	—	—

Comment: They found rapid waning of vaccine effectiveness against the current sublineages of the omicron variant with respect to protection against hospitalization. Their data indicate that boosting maintains vaccine effectiveness against severe disease caused by the current omicron sublineages, although the evidence of rapid waning of durability indicates the need for regular boosting as early as 4 months after the last dose or the need for vaccines to incorporate variants of concern to maintain protection. The bivariant vaccine currently available is a way to address the waning vaccine effectiveness for high-risk individuals. We need to take into

account individuals who had natural infection this summer when BA.5 was the predominant variant. They did not report on mortality.