# Infectious Diseases Watch

January 1, 2023

Ed Septimus, MD

## General Infectious Diseases

### US Facing Shortage of Infectious Disease Physicians

In the recent Match Day, “only 56% of adult and 49% of pediatric infectious disease training programs were filled, even though most other specialties filled all or nearly all their programs.

” Still, the public “recognizes the need for infectious disease doctors,” as “about 91% of respondents to an IDSA-sponsored poll said it’s important to have infectious disease experts in hospitals” and “another 65% said increasing the number of people who focus on managing infectious diseases will better prepare the US for the next pandemic.

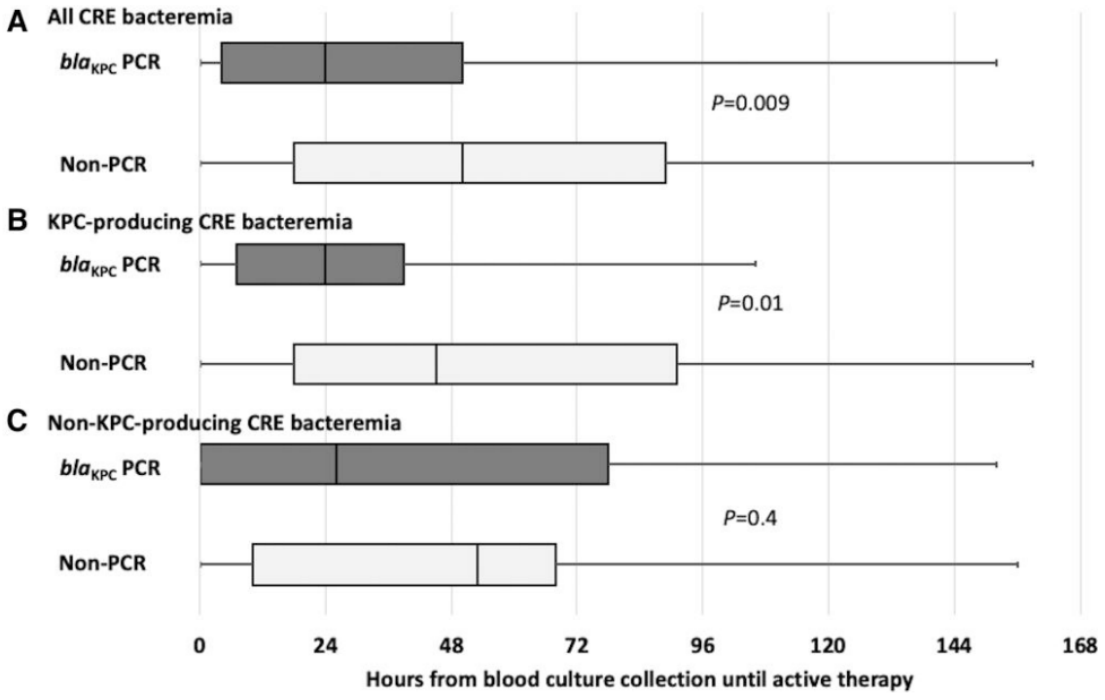
**Comment:** This is a serious issue. IDSA has been on this for over a decade to highlight the value infectious disease (ID) specialists. ID specialists go into research, public health, and clinical practice. They bring a unique perspective in infection prevention and antimicrobial stewardship. Multiple studies have demonstrated that getting an ID consult for serious infections such as invasive MRSA improves outcomes. ID is a cognitive specialty without a procedure, so on salary surveys they are listed in the lowest 4 along with pediatrics, rheumatology, and endocrinology. Hospital administration has been reluctant to pay ID for administrative time and when they do pay, the rates have been low. If as a society we claim we recognize the importance of ID specialists, it is time we not only recognize the value of ID, but we compensate accordingly. This would be a good first step in attracting the best and brightest students and residents into ID. For me ID has been a very professionally rewarding and wonderful specialty.

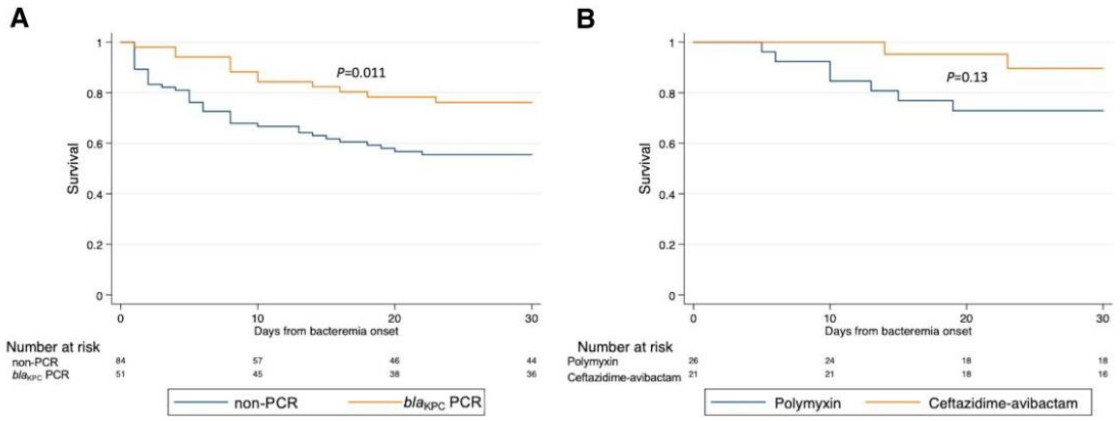
### Impact of a Rapid Molecular Test for Klebsiella pneumoniae Carbapenemase and Ceftazidime-Avibactam Use on Outcomes After Bacteremia Caused by Carbapenem-Resistant Enterobacterales Clin Infect Dis 2022; 75:2066–75

doi.org/10.1093/cid/ciac354

The investigators conducted an observational study of patients with CRE bacteremia from 2016 to 2018 at 8 New York and New Jersey medical centers and assessed center-specific clinical microbiology practices. They compared time to receipt of active antimicrobial therapy and mortality between patients whose positive blood cultures underwent rapid molecular testing for the *K. pneumoniae* carbapenemase (KPC) gene ($bla_{KPC}$) and patients whose cultures did not undergo this test. CRE isolates underwent antimicrobial susceptibility testing by broth microdilution and carbapenemase profiling by whole-genome sequencing. They also assessed outcomes when ceftazidime-avibactam and polymyxins were used as targeted therapies.

Of 137 patients with CRE bacteremia, 89 (65%) had a KPC-producing organism. Patients whose blood cultures underwent *bla*$_{KPC}$ PCR testing (n= 51) had shorter time until receipt of active therapy (median: 24 vs 50 hours; *P*= .009) compared with other patients (n= 86) and decreased 14-day (16% vs 37%; *P*= .007) and 30-day (24% vs 47%; *P*= .007) mortality. *Bla*$_{KPC}$ PCR testing was associated with decreased 30-day mortality (adjusted odds ratio: .37; 95% CI: .16–.84) in an adjusted model. The 30-day mortality rate was 10% with ceftazidime-avibactam monotherapy and 31% with polymyxin monotherapy (*P*= .08).




**Comment:** This study adds to the evidence supporting rapid diagnostic tests' role in antibiotic stewardship and, more importantly, demonstrates improvement in patient outcomes. In a recent comprehensive meta-analysis focusing on molecular rapid diagnostic testing in BSIs the combined odds ratio from 26 studies showed a significantly lower mortality risk (0.66; 95% CI, 0.54–0.80) with rapid diagnostics, especially when the pathogen was gram-negative bacteria

(0.51; 95% CI, 0.33– 0.78) and interventions were combined with antibiotic stewardship support (0.64; 95% CI, 0.51–0.79). [Clin Infect Dis 2017; 64:15–23] Most studies to date are observational studies which may suffer from potential biases. To my knowledge there are only 2 studies which are RCTs. [Eur J Clin Microbiol Infect Dis 2014; 34:831–8; Ther Clin Risk Manag 2008; 4:637] Most trials using rapid diagnostics showed reduced time to pathogen identification and/or targeted antibiotics prescription, unfortunately only one reported patient outcome benefit [Ther Clin Risk Manag 2008; 4:637] until this trial. Reasons for the lack of demonstrating clinical advantage are that study sites may have a low incidence of resistant infections, leading to insufficient power to detect differences in clinical outcomes, and lack of antibiotic stewardship support to prescribing physicians which reduced the benefit of rapid diagnostics. In this trial in the NY area, CREs have been endemic for years which may not be typical of other metropolitan areas. The C-suite will always ask about the business case since the use of molecular testing is an add on, not a replacement for other studies. Trials looking at cost-effectiveness have not been convincing. Remember most molecular studies for BSIs are culture dependent, reliant on conventional laboratory methods for bacterial growth and isolation before the tests can be run. In addition, resistance genes detected by molecular methods may not be expressed phenotypically. To be clear, rapid diagnostics are essential in our battle against antibiotic resistance especially since AR has significantly increased during the pandemic. One size may not fit all. Factors to consider would be local resistance patterns and the effectiveness of the integration of diagnostic and antimicrobial stewardship to assure results are actionable in real-time. In our fight to combat MDROs we need to optimize diagnostics and appropriate use of antibiotics when they are indicated for the right duration, and to assure appropriate cultures are obtained before starting antibiotics to identify the pathogen which will allow for both de-escalation and escalation when appropriate.

## **A case–control study evaluating the unnecessary use of intravenous broad-spectrum antibiotics in presumed sepsis and septic-shock patients in the emergency department** Antimicrobial Stewardship Healthcare Epidemiology published online December 6, 2022

doi:10.1017/ash.2022.341

The investigators retrospectively reviewed electronic medical records of adults who presented to the emergency department between January 2018 and June 2018 with suspected sepsis (defined as having ≥2 systemic inflammatory response syndrome [SIRS] criteria) and received ≥1 dose of intravenous broad-spectrum antibiotic. They evaluated the appropriateness of empiric antibiotic use in the setting of suspected sepsis in the ED, the percentages of bacterial infection and antibiotic-related adverse drug effects were quantified. Code sepsis at the institution was activated when ED providers utilized the ED sepsis order set.

In total, 218 patients were included in the final analysis. Moreover, 19.3% of these patients had confirmed bacterial infections; 44.5% had suspected bacterial infections; and 35.9% did not have bacterial infection. Elevated SIRS score (i.e., ≥2) and Quick Sequential Organ Failure Assessment (qSOFA) score (i.e., ≥2) were not associated with the presence of bacterial infections. They identified 90-day *C. difficile* infections in 7 patients and drug-resistant organism infections in 6 patients, regardless of the presence of bacterial infections.

**Comments:** As other studies have shown, more than one-third of the patients who received IV broad-spectrum antibiotics in the ED for suspected sepsis (SIRS score ≥2) did not have confirmed or suspected bacterial infection supported by positive cultures or clinical findings suggestive of bacterial infection. The current SSC guidelines recommend initiating antimicrobials within 1 hour in adults with possible septic shock or a high likelihood of sepsis (strong, low quality of evidence). The SSC guidelines also recommend using sepsis screening tools, such as SIRS to identify sepsis promptly; however, the guidelines acknowledge the poor specificity of SIRS score or qSOFA score in identifying infection. [Intensive Care Med 2021; 47:1181–1247] In this study elevated SIRS score (i.e., ≥2) and qSOFA score (i.e., ≥2) were not associated with the presence of bacterial infections. SIRS continues to be part of the definitions of severe sepsis and septic shock in the CMS Severe Sepsis and Septic Shock Early Management Bundle (SEP- 1). I must admit, balancing the high mortality risk of sepsis with antimicrobial stewardship is challenging. Studies have shown administering antibiotics within 1 hour for patients with septic shock improves survival, however, this has not been demonstrated for patients without septic shock. Studies have shown that unnecessary and inappropriate antibiotics are strongly associated with antibiotic related ADEs. [JAMA Intern Med 2017; 177:1308–1315] This was retrospective in nature, and the assessment of clinical infection by the investigators was based solely on documentations available in the EMR. The study also lacked a negative control group to appropriately assess SIRS or qSOFA for its ability to predict sepsis or bacterial infection. Nonetheless, this study highlights the unintended consequences the SEP-1 measure, but we also must acknowledge this effort has drawn attention to a very important syndrome where early identification and appropriate interventions can save lives. The question moving forward how can we make the measure better.

## **Association of Follow-up Blood Cultures With Mortality in Patients With Gram-Negative Bloodstream Infections A Systematic Review and Meta-analysis** JAMA Netw Open. 2022;5: e2232576.

doi:10.1001/jamanetworkopen.2022.32576

Obtaining follow-up blood cultures (FUBCs) in patients with *S aureus and Candida* BSI is standard practice, but the utility in patients with gram-negative bacterial BSI (GN-BSI) is unclear. The authors wanted to examine whether obtaining FUBCs is associated with decreased mortality (KQ1) and whether positive vs negative FUBCs are associated with increased mortality for patients with gram-negative BSIs. (KQ2)

The authors used MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Web of Science, and gray literature to March 11, 2022. RCTs or observational studies that matched or statistically adjusted for differences in, at minimum, level of acute illness between patients in the intervention (e.g., FUBCs obtained) and control (e.g., FUBCs not obtained) groups were included in primary analyses. Articles published in languages other than English were excluded. Main outcome was mortality before hospital discharge or up to 30 days from the index blood culture.

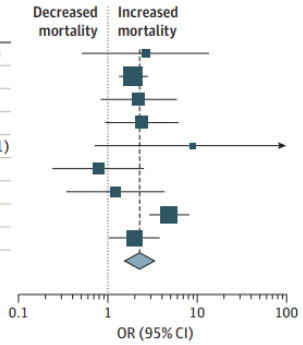
From 3495 studies, 15 were included (all nonrandomized). In the 5 studies (n = 4378 patients) that met criteria for the KQ1 primary analysis, obtaining FUBCs was associated with decreased mortality (hazard ratio, 0.56; 95% CI, 0.45-0.71). For KQ2, 2 studies met criteria for the primary analysis (i.e., matched or statistically adjusted for differences in patients with positive vs negative FUBCs), so an exploratory meta-analysis of all 9 studies that investigated KQ2 (n =

3243 patients) was performed. Positive FUBCs were associated with increased mortality relative to negative blood cultures (odds ratio, 2.27; 95% CI, 1.54-3.34). Limitations of the literature included a lack of randomized studies and few patient subgroup analyses. The overall strength of evidence for the association of obtaining follow-up blood cultures with decreased mortality was only moderate.

**Figure 3. Association of Positive Follow-up Blood Cultures (FUBCs) With Mortality in Patients With Gram-Negative Bloodstream Infection**

| Source | OR (95% CI) |
|---|---|
| Amipara et al,[9] 2021 | 2.64 (0.51-13.55) |
| Maskarinec et al,[5] 2020 | 1.93 (1.33-2.80) |
| Chan et al,[11] 2021 | 2.22 (0.83-5.93) |
| Wiggers et al,[8] 2016 | 2.40 (0.93-6.19) |
| Groft et al,[32] 2021 | 9.00 (0.71-113.81) |
| Spaziante et al,[28] 2020 | 0.78 (0.24-2.53) |
| Mitaka et al,[29] 2020 | 1.21 (0.34-4.31) |
| Kim et al,[30] 2022 | 4.87 (2.90-8.17) |
| Kang et al,[31] 2013 | 1.98 (1.03-3.81) |
| Total | 2.27 (1.54-3.34) |

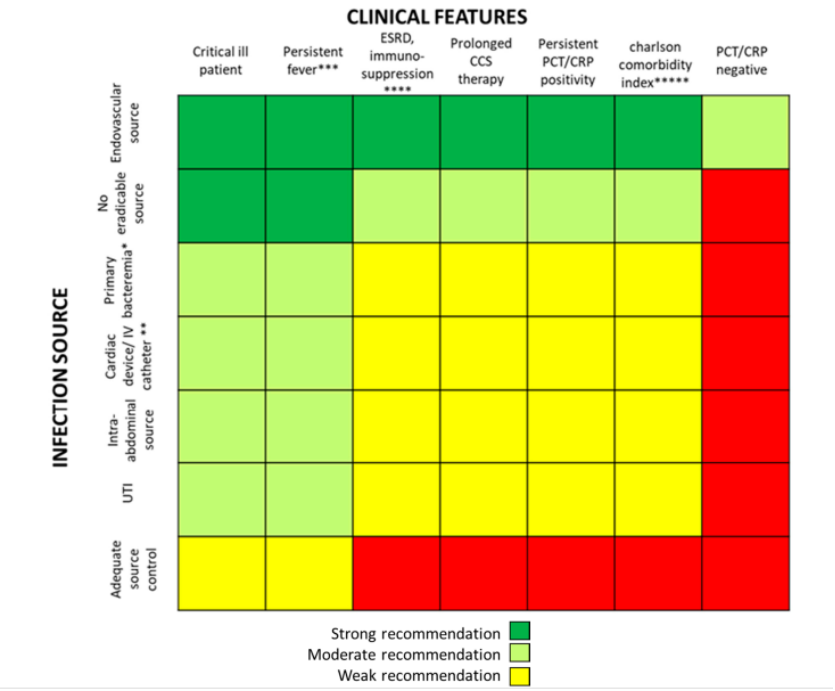
Heterogeneity: $\chi^2_8 = 14.48$ ($P = .07$); $I^2 = 45\%$




The mortality odds ratio (OR) associated with positive FUBCs, relative to negative FUBCs, is presented.

**Comment:** The findings of this study suggest that observational studies support the use of FUBCs in patients with gram-negative BSIs; however, subgroup analyses that identify patients who do not require follow-up blood cultures are lacking. Put another way, the study did not identify groups with GN-BSIs that did not require FUBCs. Another limitation of the literature review was a lack of randomized studies and few patient subgroup analyses. The study did not directly address the mechanism why obtaining FUBCs influence mortality. However, finding of persistent positive BCs was associate with increased morality compared to negative FUBCs make sense since this could point towards inadequate source control or inappropriate therapy.

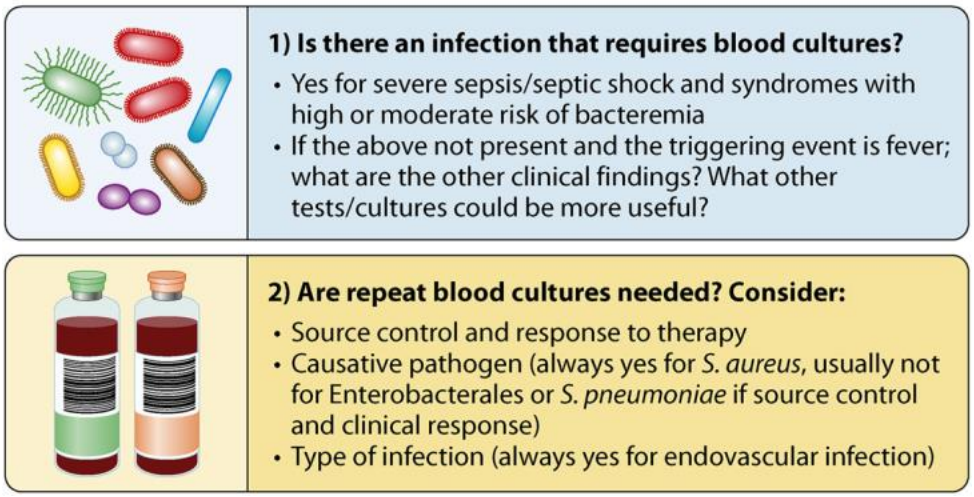
The results of another review demonstrated that critically ill patients, endovascular and/or non-eradicable source of infection, isolation of a multi-drug resistant pathogen, end-stage renal disease, and immunodeficiencies are some factors that may predispose patients to persistent gram-negative bacteremia. An analysis of the different burdens that each of these factors have in this clinical setting allowed the investigators to suggest which patients' FUBCs have the potential to modify treatment choices, prompt an early source control, and finally, improve clinical outcome. [Antibiotics 2020; 9:895] See below




Last year I reviewed an article in JCM on blood culture utilization in a hospital setting. [J Clin Microbiol 2022; 60: e01005-21]. First which patients should have initial blood cultures drawn. Many blood cultures are drawn who have a low risk of bacteremia. See below

| Diagnostic value of initial blood cultures | Exception |
|---|---|
| High diagnostic value | |
| Severe sepsis/septic shock | NA |
| Infections associated with high or intermediate risk of bacteremia | NA |
| Low diagnostic value | |
| Fever ± leukocytosis in stable patients without suspicion for endovascular infection | Patients with splenectomy |
| Postoperative fever within 48 h | 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<br>Presence of severe sepsis/ septic shock |
| Persistent febrile neutropenia in hemodynamically stable patients with 2 negative sets | NA |

They classified high diagnostic value for repeat blood cultures-see figure below for some reason they did not list candida.




In a recent article the authors investigate the value of repeat blood cultures. They analyzed 500 episodes of bacteremia to determine frequency of FUBCs and identify risk factors for persistent bacteremia. They found FUBC added little value in the management of GNB bacteremia. Patients with diabetes mellitus, intravenous central lines, or ESRD had significantly increased rates of positive FUBC for GPC but not GNB. [Clin Infect Dis 2017; 65:1776–9]

What can we learn from this series of articles as to when to obtain FUBCs for gram-negative BSIs (GN-BSI)? Here are my recommendations.

1. FUBC are generally not indicated in Enterobacterales bacteremia of urinary or abdominal source
2. FUBCs should be considered in critically ill ICU patients depending on clinical response and source. These patients often have risk factors for resistant or persistent GN-BSIs including IV catheters and inadequate source control.
3. Consider FUBCs for patient who are immunosuppressed.
4. For suspected cardiac/intravascular source, FUBCs are recommended
5. Patients with a MDR GN-BSI consider FUBCs depending on response and source control.

Expert clinicians and a correct selection of high-risk patients make a difference in terms of the effectiveness of FUBCs. The results of FUBCs should be actionable. A targeted and optimized selection of the occasions where to draw FUBCs should result in a positive impact on patients' management and outcomes.

A more overarching issue is the need for serious blood culture stewardship. We draw too many blood cultures where yield is very low, and contaminants are more common than true bacteremia. We still have patients who only have one set of blood cultures drawn and we have inconsistent volumes being drawn. An example, 80% of blood culture cultures are inadequately filled and we still have single set blood cultures being drawn. We know total volume influences yield. Single sets miss 10 to 40% of bacteremias, depending on the organism. 30 to 50% of blood cultures in low-risk patients grow contaminants that are associated with several unintended consequences such as, including unnecessary antibiotics, especially vancomycin, which can cause nephrotoxicity, additional testing (e.g., additional blood cultures, echocardiography), unnecessary removal of vascular catheters, longer hospital stay, and of

course increased health care costs. Blood cultures that grow contaminants may also lead to patients meeting the NHSN surveillance definition for CLABSI without actually having a CLABSI. One study indicated that 30% of CLABSIs were due to blood culture contaminants. [Infect Control Hosp Epidemiol 34:1042–1047] Blood cultures should be drawn by separate sticks with adweuate volume and labeled appropriately. Efforts to improve both the blood culture collection process and blood culture indications are essential to ensure detection of true bacteremia and minimize unintended consequences.

**Increase in Pediatric Invasive Group A Streptococcal Infections.** CDC HAN December 22, 2022

CDC issued this Health Alert Network (HAN) Health Advisory to notify clinicians and public health authorities of a recent increase in pediatric invasive group A streptococcal (iGAS) infections. In November 2022, CDC was notified of a possible increase in iGAS infections among children at a hospital in Colorado. Potential increases in pediatric iGAS cases in other states were subsequently noted by contributors to the IDSA's provider-based Emerging Infections Network and by certain jurisdictions participating in CDC's Active Bacterial Core Surveillance System (ABCs). This increased number of pediatric iGAS cases in some jurisdictions has occurred in the setting of increased circulation of RSV, influenza viruses, SARS-CoV-2, and other respiratory viruses. While the overall number of cases has remained relatively low and iGAS infections remain rare in children, CDC is investigating these reports.

**Comment**: Like other agents which primarily spread by the respiratory route, cases of GAS, including both iGAS and streptococcal pharyngitis, tend to have a pronounced seasonal pattern with a peak in December through April in the US. Strep throat is most common among school-aged children (i.e., 5–15 years of age), and exposure to someone with strep throat is a risk factor for iGAS infection. In addition, increased rates of iGAS infection have been noted during times of increased influenza activity. Seasonal influenza activity is currently high in the US and above the levels seen in recent years.

<u>Recommendations for Healthcare Providers</u>

1. Offer prompt vaccination against influenza and varicella to all eligible persons who are not up to date.
2. Consider iGAS as a possible cause of severe illness, including in children and adults with concomitant viral respiratory infections. Illness due to iGAS in persons with known viral infections may manifest as persistent or worsening symptoms following initial improvement.
3. Educate patients, especially those at increased risk, on signs and symptoms of iGAS requiring urgent medical attention, especially necrotizing fasciitis, cellulitis and toxic shock syndrome.
4. Obtain culture for suspected iGAS infections, including blood, wound, and pleural fluid cultures, as clinically indicated.
5. Follow clinical practice guidelines for diagnosis and treatment of GAS pharyngitis.
6. Be mindful of potential alternative agents for treating confirmed GAS pharyngitis in children due to the shortage of amoxicillin suspension.

7. Notify appropriate local or state public health departments as soon as possible about unusually aggressive or severe iGAS cases affecting children younger than 18 years of age or clusters of iGAS infections in persons of any age.
8. Ask laboratories to hold iGAS isolates or send them to the state public health laboratory for temporary storage.

**Association of Adverse Events With Antibiotic Treatment for Urinary Tract Infection** Clin Infect Dis 2022; 74:1408-1418

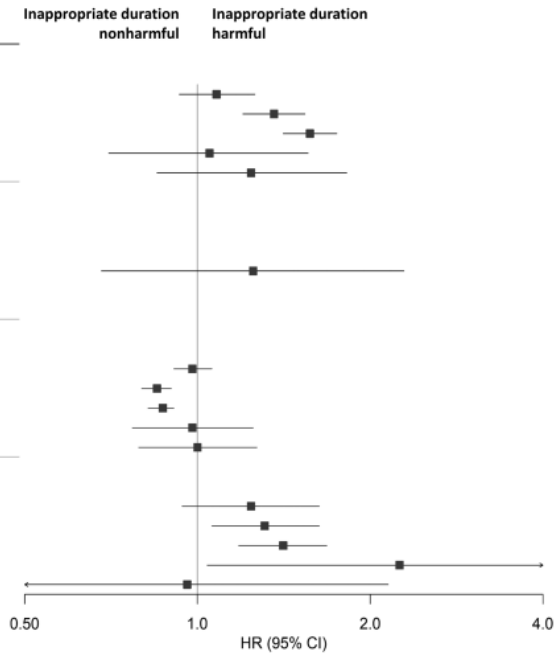
Doi.org/10.1093/cid/ciab637

Uncomplicated UTI (uUTI) is among the most common indications for antibiotics in the outpatient setting. Nitrofurantoin and TMP/ SMX are recommended as first-line agents; FQ and β-lactams are non–first-line agents. [Clin Infect Dis 2011;52:e103-120] For nitrofurantoin, resistance among uropathogens is uncommon. Resistance rates to TMP/SMX have been rising. FQ are highly efficacious but like TMP/SMX resistance has been rising. Guidelines suggest reserving them for important uses other than uUTI. β-Lactam agents, particularly amoxicillin and ampicillin (AMX/AMP), have lower efficacy and a higher prevalence of antibiotic resistance versus other UTI antibiotics. Estimates on the comparative safety of antibiotic agents to treat uUTI remain limited.

Using data from the IBM®MarketScan® Commercial Database, the authors identified 1,169, 033 otherwise healthy, nonpregnant women aged 18–44 years with uncomplicated UTI who initiated an oral antibiotic with activity against common uropathogens from 1 July 2006 to 30 September 2015. They used propensity score–weighted Kaplan-Meier methods and Cox proportional hazards regression models to estimate the association between antibiotic agent and adverse events. Using this large administrative claim database, they compared the risk of several adverse events associated with commonly used antibiotic agents for outpatient treatment of uUTI among young women in the US. They classified adverse events into 2 categories: (1) adverse drug events (i.e., specific to drugs but not specific to antibiotics) and (2) potential microbiome-related adverse events (i.e., specific to antibiotics due to the pathophysiology of antibiotic-induced microbiome disruption). For microbiome-disruption–related adverse event outcomes, they evaluated the association between each outcome and treatment duration, stratified by antibiotic agent.

Of 2 first-line agents, TMP/SMX (vs nitrofurantoin) was associated with higher risk of several adverse drug events(ADE) including hypersensitivity reaction (hazard ratio, 2.62; 95% confidence interval, 2.30–2.98), acute renal failure (2.56; 1.55–4.25), skin rash (2.42; 2.13–2.75), urticaria (1.37; 1.19–1.57), abdominal pain (1.14; 1.09–1.19), and nausea/vomiting (1.18; 1.10–1.28), but a similar risk of potential microbiome-related adverse events. Compared with nitrofurantoin, non–first-line agents were associated with higher risk of several ADEs and potential microbiome-related adverse events including non–*C. difficile* diarrhea, *C. difficile* infection, vaginitis/vulvovaginal candidiasis, and pneumonia. Treatment duration modified the risk of potential microbiome-related adverse events.

| Outcome | No. of events (Rate per 10,000 person-days) Appropriate Duration | Inappropriately Long Duration | Weighted HR (95% CI) |
|---|---|---|---|
| Non-*C. difficile* diarrhea | | | |
| Nitrofurantoin | 174 (1.39) | 823 (1.46) | 1.08 (0.93-1.26) |
| TMP/SMX | 266 (1.24) | 1,001 (1.64) | 1.36 (1.20-1.54) |
| Fluoroquinolone | 345 (1.21) | 1,908 (1.85) | 1.57 (1.41-1.75) |
| Broad-spectrum β-lactam | 35 (2.48) | 50 (2.78) | 1.05 (0.70-1.56) |
| Narrow-spectrum β-lactam | 123 (2.26) | 65 (2.72) | 1.24 (0.85-1.82) |
| *C. difficile* infection | | | |
| Nitrofurantoin | 1 (0.00) | 7 (0.00) | NE |
| TMP/SMX | 1 (0.00) | 4 (0.00) | NE |
| Fluoroquinolone | 11 (0.01) | 49 (0.02) | 1.25 (0.68-2.29) |
| Broad-spectrum β-lactam | 2 (0.05) | 1 (0.02) | NE |
| Narrow-spectrum β-lactam | 3 (0.02) | 0 (0.00) | NE |
| Vaginitis / vulvovaginal candidiasis | | | |
| Nitrofurantoin | 696 (6.00) | 3,128 (5.97) | 0.98 (0.91-1.06) |
| TMP/SMX | 1,246 (6.26) | 3,076 (5.40) | 0.85 (0.80-0.90) |
| Fluoroquinolone | 1,600 (6.07) | 5,215 (5.44) | 0.87 (0.82-0.91) |
| Broad-spectrum β-lactam | 98 (7.48) | 124 (7.40) | 0.98 (0.77-1.25) |
| Narrow-spectrum β-lactam | 381 (7.38) | 168 (7.43) | 1.00 (0.79-1.27) |
| Pneumonia | | | |
| Nitrofurantoin | 53 (0.16) | 294 (0.20) | 1.24 (0.94-1.63) |
| TMP/SMX | 89 (0.16) | 339 (0.21) | 1.31 (1.06-1.63) |
| Fluoroquinolone | 129 (0.17) | 640 (0.23) | 1.41 (1.18-1.68) |
| Broad-spectrum β-lactam | 8 (0.22) | 27 (0.58) | 2.25 (1.04-4.85) |
| Narrow-spectrum β-lactam | 34 (0.24) | 15 (0.24) | 0.96 (0.43-2.15) |



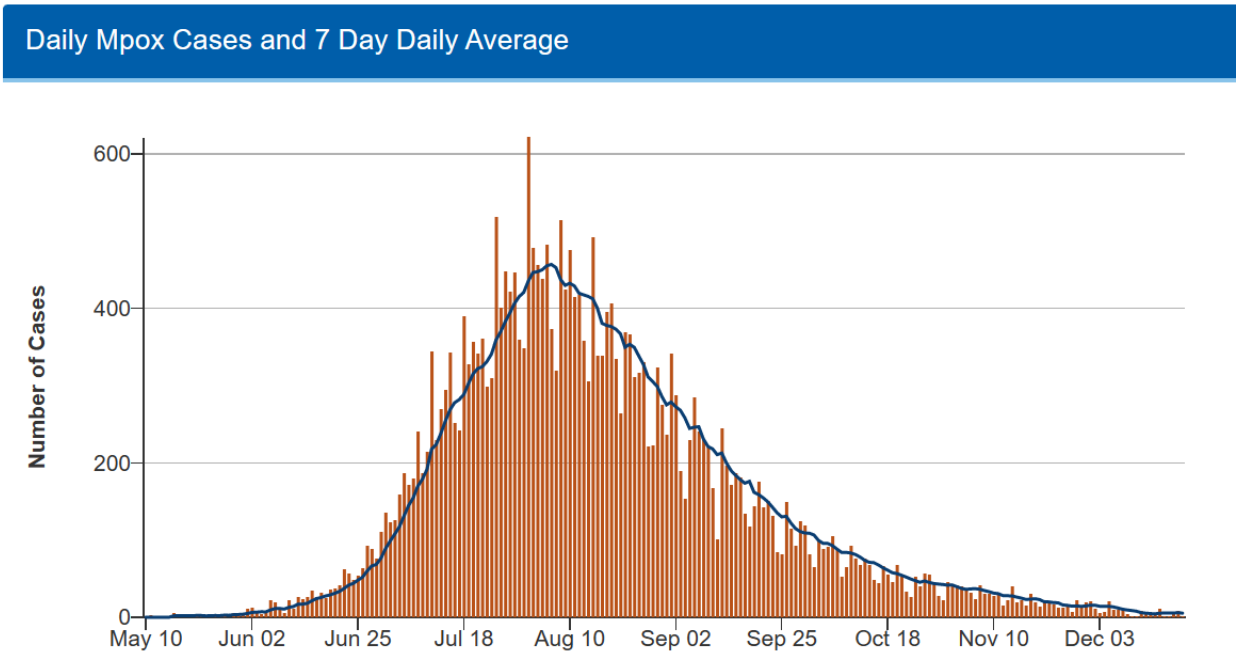

**Comment:** The results are consistent with previous studies. They demonstrate differences in the safety of first-line agents, wherein TMP/SMX is associated with higher risks of additional adverse events (acute renal failure, rash, nausea/ vomiting, abdominal pain) versus nitrofurantoin. Given increased resistance to TMP/SMX IDSA now recommends nitrofurantoin as first line therapy for uUTI. The findings also confirm previous reports on FQ safety, demonstrating increased risk of certain adverse events (e.g., *C. difficile* infection, tendinopathy). They also observed that broad-spectrum β-lactams are associated with higher risks of ADEs than narrow-spectrum agents, which validates ASP principles to use narrow-spectrum agents, when possible, to treat bacterial infections. The study also demonstrated that antibiotic duration increases risk of potential microbiome-related adverse events, likely due to antibiotic-induced disruption of the microbiota. These findings are consistent with the well-established association between longer treatment duration and increased risk of *C. difficile* infection. This study was an observational study, the exposure was not randomized; therefore, effect estimates are potentially subject to confounding by unobserved differences between exposure groups. They did use a propensity score methods to account for demographic and clinical covariates, but residual confounding may still exist. Using billing claims data are advantageous for studying events because of the large sample size, but they lack important clinical information such as laboratory results, which may result in missing or misclassified adverse event outcomes. Finally, they did not require confirmation of true bacterial UTI due to the absence of data on urine testing results or signs and symptoms of infection. I included this article to stress that antibiotics are not without sides effects and that urine stewardship is important to make sure we do not treat asymptomatic bacteriuria and only obtaining a urine with an indication.

# Mpox

## WHO: Surveillance, case investigation and contact tracing for mpox (monkeypox): interim guidance, 22 December 2022

The WHO updated its mpox guidance. Quarantine or exclusion from work are not necessary as long as no symptoms develop but known contacts should avoid sexual contact with others during the 21 days monitoring period, regardless of their symptoms given that transmission may occur before symptom onset.

**Comment:** Mpox has caused 83,497 cases, 72 of them fatal, in 110 countries since May. Most cases (95.8%) have occurred as a result of sexual transmission between men who have sex with men (MSM). See US graph of cases below. Fortunately, the mpox outbreak appears to be coming to an end.




## Clinical features and management of individuals admitted to hospital with monkeypox and associated complications across the UK: a retrospective cohort study. Lancet Infect Dis published online December 22, 2022

doi.org/10.1016/ S1473-3099(22)00806-4

In this cohort study, the investigators undertook a retrospective review of electronic clinical records and pathology data for all individuals admitted between May 6, and August 3, 2022, to 16 hospitals from the Specialist and High Consequence Infectious Diseases Network for mpox. Inclusion criteria were clinical signs consistent with mpox and MPXV DNA detected from at least one clinical sample by PCR testing. Patients admitted solely for isolation purposes were excluded from the study. Key outcomes included admission indication, complications (including

pain, secondary infection, and mortality) and use of antibiotic and anti-viral treatments. Routine biochemistry, hematology, microbiology, and virology data were also collected. Outcomes were assessed in all patients with available data.

Almost all (153 of 156) patients were men; the median age was 35. Approximately 71% were White, and 47 of 155 (30%) were living with HIV. Rectal and perianal pain was the most common indication for hospitalization, with severe pain reported in 89 of 156 (57%) and secondary bacterial infection in 82 of 142 (58%) individuals with available data. The median hospital stay was 5 days. No deaths were reported, but 10 patients required surgery, and two cases of encephalitis were reported. 38 (24%) of the 156 individuals received tecovirimat. Almost a third of the patients had intercurrent sexually transmitted infections, which is higher than that reported for outpatient populations.

**Comment:** Although they report no deaths, they highlight the substantial burden of complex morbidity in immunocompetent individuals admitted to hospital with mpox. Based on few data in selected populations, advanced HIV infection and other causes of severe immunocompromise might significantly increase morbidity and case fatality. Further prospective studies are required to identify risk factors associated with severe mpox and specific complications. This data also suggest that secondary bacterial infection is common, and that studies of antimicrobial prophylaxis and treatment may be required in individuals diagnosed with mpox. This analysis supports most global estimates that overall mortality in mpox caused by clade IIb virus is low.

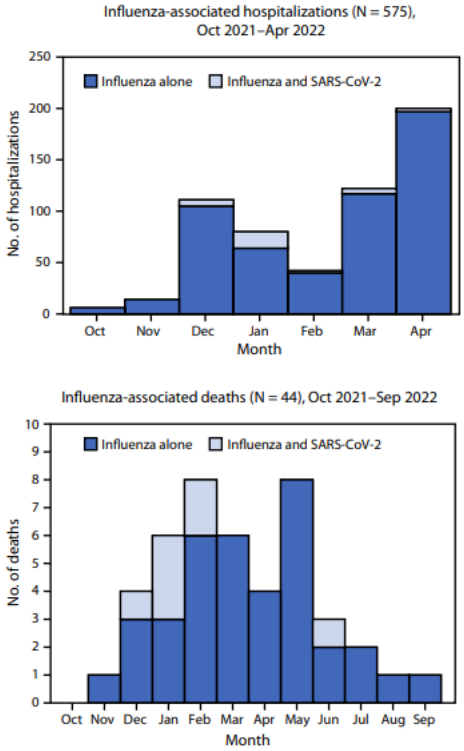
## Respiratory Viruses(not SARS-Cov-2)

### Prevalence of SARS-CoV-2 and Influenza Coinfection and Clinical Characteristics Among Children and Adolescents Aged MMWR 2022; 71:1589-1596

This report describes characteristics and prevalence of laboratory-confirmed influenza virus and SARS-CoV-2 coinfections among patients aged <18 years who had been hospitalized or died with influenza as reported to three CDC surveillance platforms during the 2021–22 influenza season. Data from two Respiratory Virus Hospitalizations Surveillance Network (RESP-NET) platforms (October 1, 2021–April 30, 2022), and notifiable pediatric deaths associated with influenza virus and SARS-CoV-2 coinfection (October 3, 2021–October 1, 2022) were analyzed.

SARS-CoV-2 coinfections occurred in 6% (32 of 575) of pediatric influenza-associated hospitalizations and in 16% (seven of 44) of pediatric influenza-associated deaths. Compared with patients without coinfection, a higher proportion of those hospitalized with coinfection received invasive mechanical ventilation (4% versus 13%; p = 0.03) and bilevel positive airway pressure or continuous positive airway pressure (BiPAP/ CPAP) (6% versus 16%; p = 0.05).

Among seven coinfected patients who died, none had completed influenza vaccination, and only one received influenza antivirals.



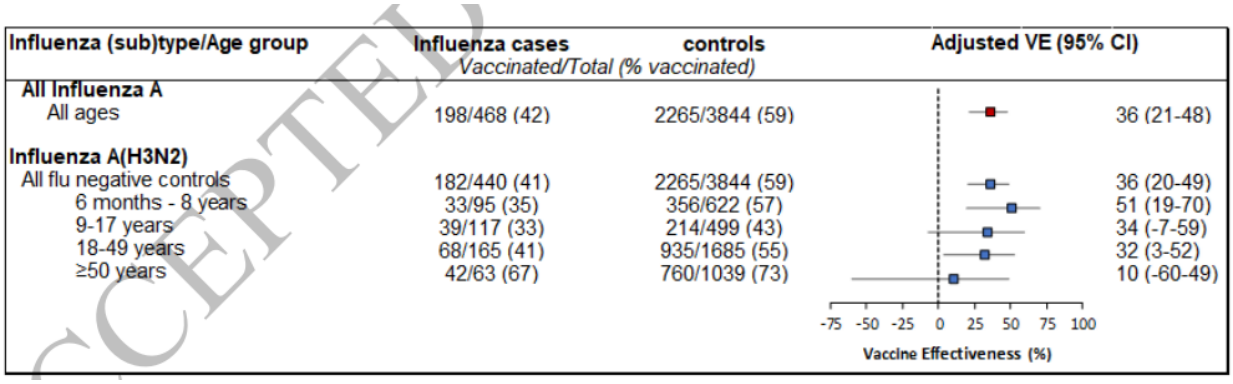

**Comment**: This report identified increased use of invasive and noninvasive mechanical ventilation among coinfected patients, indicating potentially more severe disease among children and adolescents with influenza and SARS-CoV-2 coinfection. These findings also highlight the underuse of influenza antivirals and seasonal influenza vaccines, particularly among persons aged <18 years with influenza virus and SARS-CoV-2 coinfections who died. Influenza and SARS-CoV-2 coinfections were infrequent (representing 6% of hospitalizations and 16% of deaths within these populations), likely in part because of lower-than-usual influenza virus circulation. [? viral interference]  Viral testing was performed at the clinician's discretion or according to hospital policy and might have been influenced by factors including clinical presentation, severity of illness, and previous testing. Information on Covid-19 vaccination and SARS-CoV-2 antiviral treatment was not included because this information could not be systematically ascertained for patients across all data sources. FluSurv-NET and COVID-NET catchment areas include approximately 9%–10% of the U.S. population, limiting the generalizability of results. These findings represent a small number of cases of influenza and SARS-CoV-2 coinfection, further limiting the ability to draw firm conclusions. The high degree of cocirculation of multiple respiratory viruses [SARS-CoV-2, influenza, and RSV] during the current season, and the higher-than-usual early-season influenza activity, underscore the importance of increasing awareness among parents and providers that influenza and SARS-CoV-2 coinfections occur in pediatric patients and that coinfection can potentially cause more severe illness. For pediatric patients with acute respiratory illness symptoms with suspected severe illness, testing for both influenza and SARS-CoV-2, and other respiratory viruses is critical to facilitate early detection of coinfections and help guide clinical treatment and management.

**Influenza Vaccine Effectiveness Against Influenza A(H3N2)- Related Illness in the United States During the 2021–2022 Influenza Season** Clin Infect Dis published online December 12, 2022

DOI: 10.1093/cid/ciac941

Between October 2021 and April 2022, investigators across 7 sites enrolled patients aged ≥6 months seeking outpatient care for acute respiratory illness with cough. Using a test-negative design, they assessed VE against influenza A(H3N2). Due to the correlation between influenza and SARS-CoV-2 vaccination, participants who tested positive for SARS-CoV-2 were excluded from vaccine effectiveness estimations. Estimates were adjusted for site, age, month of illness, race/ethnicity and general health status. Participants were considered vaccinated with receipt of one or more doses of any 2021–2022 seasonal influenza vaccine ≥14 days prior to illness onset.

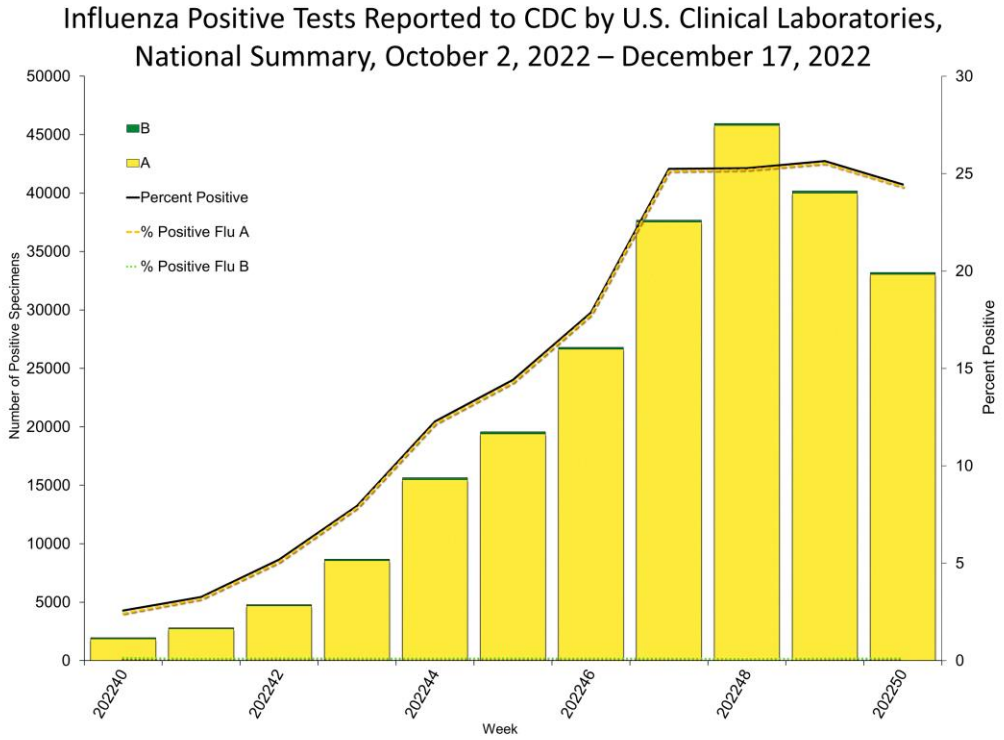
Among 6,260 participants, 468 (7%) tested positive for influenza only, including 440 (94%) for A(H3N2). All 206 sequenced A(H3N2) viruses were characterized as belonging to genetic group 3C.2a1b subclade 2a.2, which has antigenic differences from the 2021–2022 season A(H3N2) vaccine component that belongs to clade 3C.2a1b subclade 2a.1. After excluding 1,948 SARS-CoV-2 positive patients, 4,312 patients were included in analyses of influenza VE; only 2,463 (57%) were vaccinated against influenza. Effectiveness against A(H3N2) for all ages was 36% (95%CI, 20-49%) overall; however, VE against A(H3N2) varied by age from 51% (95%CI, 19%–70%) among patients aged 6 months – 8 years, 32% (95%CI, 3%–52%) among adults aged 18–49 years, and 10% (95%CI, -60%–49%) among adults aged ≥50 years. The study was underpowered to detect a statistically significant VE of 30% in all age groups. Numbers of cases among older adults aged ≥50 years was particularly small. Compared to unvaccinated participants, participants who received influenza vaccine were older, more likely to be non-Hispanic white, more likely to have received 3 or more Covid-19 vaccinations, and more likely to report having at least one high-risk medical condition.




**Comment:** Influenza vaccines were 36% effective against A(H3N2)-related illnesses among all participants less than 50 years of age. Lower VE among older adults compared with younger persons has been observed in previous seasons, especially against A(H3N2) viruses [Lancet Infect Dis 2016; 16(8): 942-51]. Healthcare behavior has changed during the Covid-19 pandemic, and enrollment of patients with outpatient illness from Covid-19 testing sites might have affected results in uncertain ways. VE estimates in this report are specific to the prevention of outpatient influenza illness rather than to more severe influenza outcomes (e.g.,

hospitalization, ICU admission or death), which other study designs may be able to address Despite these limitations, influenza vaccination in 2021–2022 did reduce outpatient medically attended acute respiratory illness with cough due to influenza A(H3N2) viruses by approximately one-third overall. There is no mention if elderly patients received a high dose or adjuvant vaccine Clearly, we need better vaccines against influenza.

## Respiratory Viruses by the Numbers



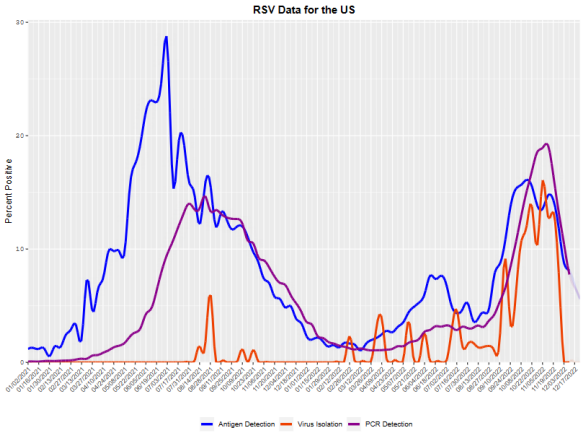

**Comment:**

- Seasonal influenza activity remains high but is declining in most areas.
- Of influenza A viruses detected and subtyped during week 50, 77.8% were influenza A(H3N2) and 22.2% were influenza A(H1N1)
- The majority of influenza viruses tested are in the same genetic subclade as and antigenically similar to the influenza viruses included in this season's influenza vaccine.

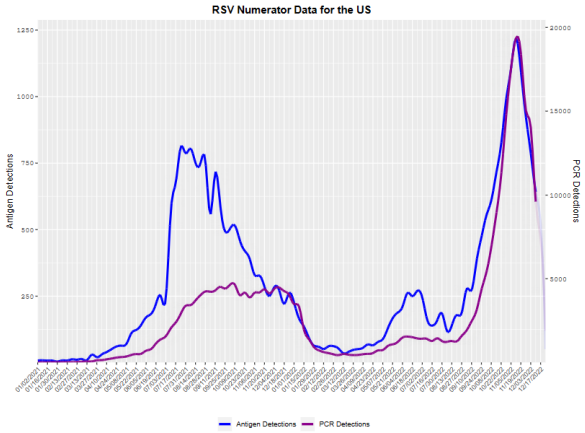
## Other Respiratory Viruses

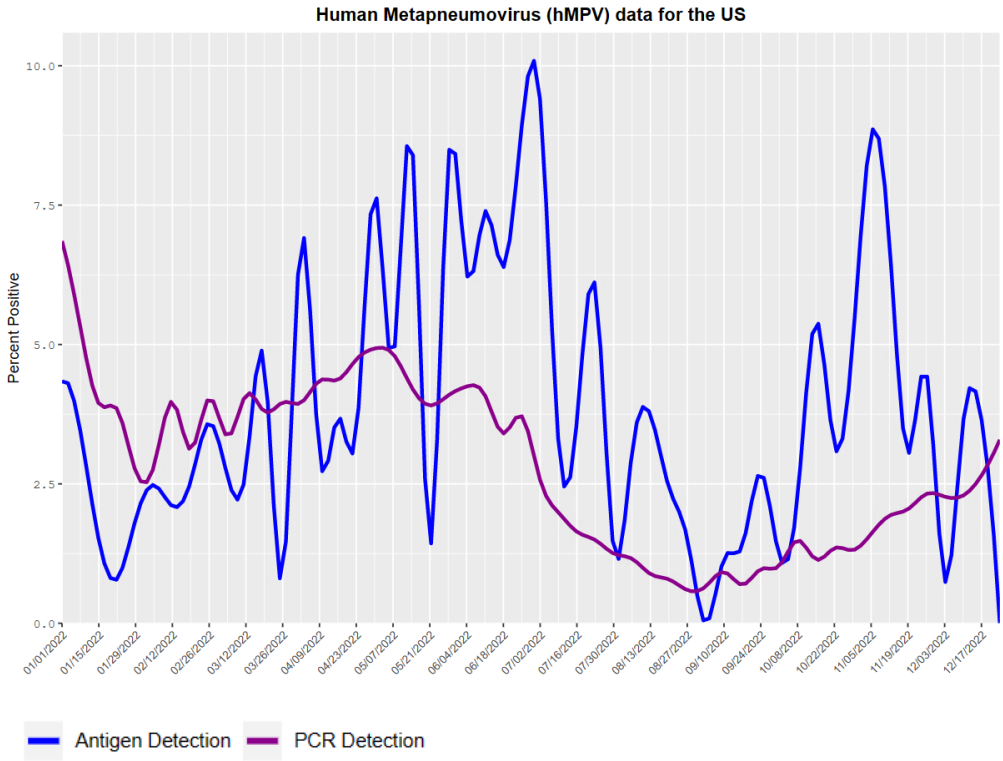
### Respiratory Syncytial Virus (RSV)

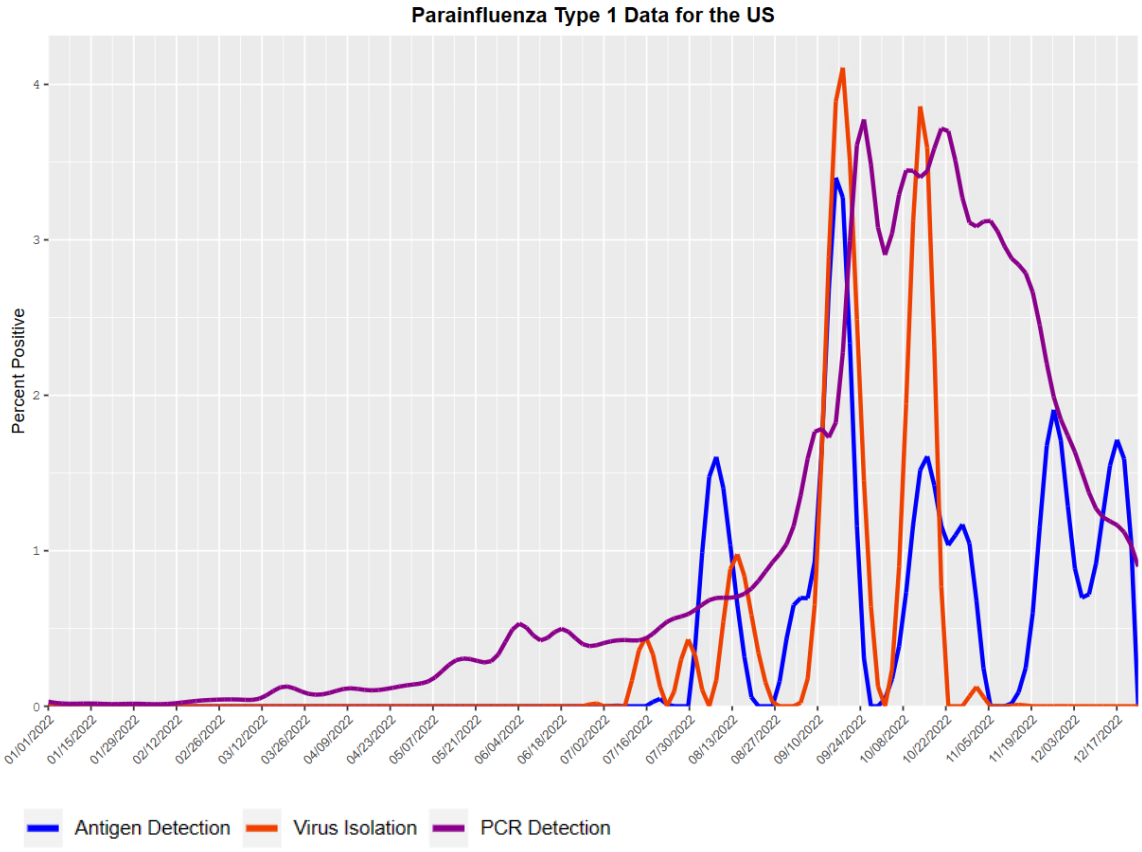
#### Percent Positive

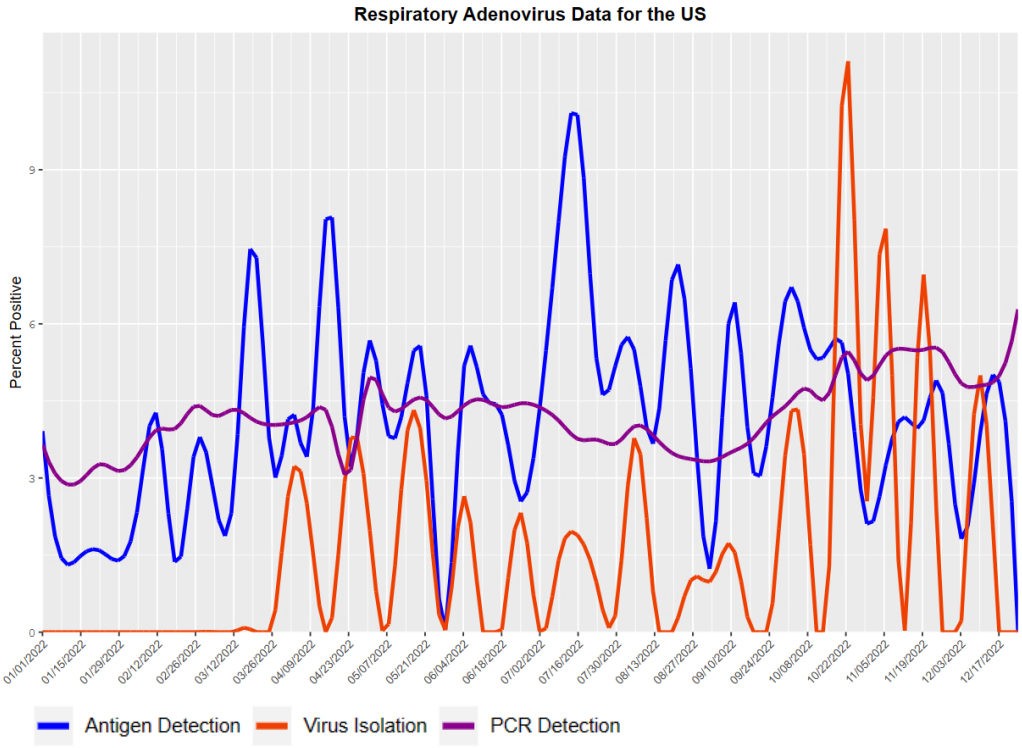



#### Detections



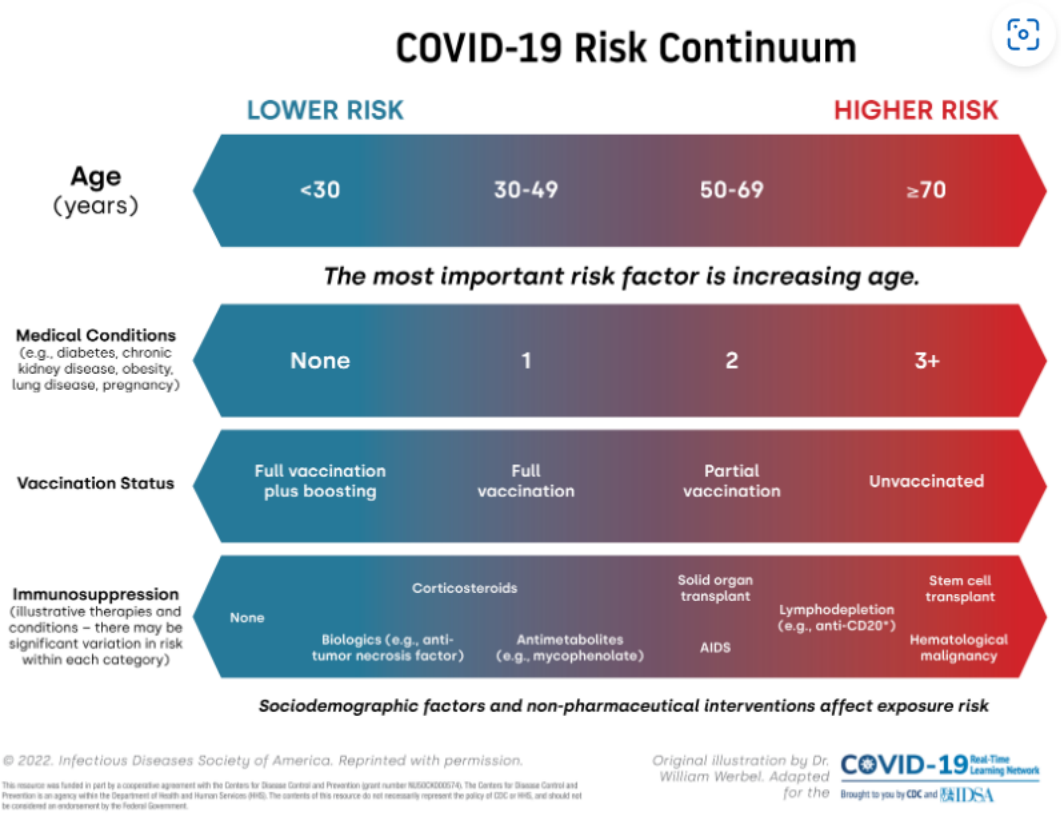

Parainfluenza Type 1 Data for the US
Percent Positive
0
1
2
3
4
01/01/2022
01/15/2022
01/29/2022
02/12/2022
02/26/2022
03/12/2022
03/26/2022
04/09/2022
04/23/2022
05/07/2022
05/21/2022
06/04/2022
06/18/2022
07/02/2022
07/16/2022
07/30/2022
08/13/2022
08/27/2022
09/10/2022
09/24/2022
10/08/2022
10/22/2022
11/05/2022
11/19/2022
12/03/2022
12/17/2022
Antigen Detection
Virus Isolation
PCR Detection


Respiratory Adenovirus Data for the US
Percent Positive
0
3
6
9
01/01/2022
01/15/2022
01/29/2022
02/12/2022
02/26/2022
03/12/2022
03/26/2022
04/09/2022
04/23/2022
05/07/2022
05/21/2022
06/04/2022
06/18/2022
07/02/2022
07/16/2022
07/30/2022
08/13/2022
08/27/2022
09/10/2022
09/24/2022
10/08/2022
10/22/2022
11/05/2022
11/19/2022
12/03/2022
12/17/2022
Antigen Detection
Virus Isolation
PCR Detection

**Comment:** For the most part except for adenovirus there is a general downward trend for other respiratory viruses.

# COVID-19

## COVID-19 Real Time Learning Network




**Comment:** I included this graph which lays out risk based on age, medical conditions, and vaccination status.

## US Offers Free At-Home Covid-19 Tests Again

The Biden administration will resume providing free Covid-19 tests to Americans, part of a wider effort to combat the virus during the holiday season as the number of reported cases and hospitalizations are on the rise. Households can order a total of four at-home tests that will be mailed to them. Orders for the tests began shipping the week of December 19th. The plan also includes offering governors help with mobile and pop-up vaccination sites and releasing a pandemic playbook for nursing homes.

**Comment:** Reported Covid-19 cases and hospitalizations increased after the Thanksgiving holiday, according to data from the CDC. There were almost 3,000 reported deaths from the virus for the week that ended December 7, agency data show. Hospitalization rates are lower than they were during this time last year, when the Omicron variant rapidly swept the US, however, with the emergence of XBB we are now seeing a rise again.

## US to Require Negative Covid Tests for Travelers Coming From China. December 28, 2022

The US, fearful that a surge of Covid-19 infections in Beijing could create a new and more dangerous variant, announced on Wednesday that it will require travelers from China, including Hong Kong and Macau, to present negative Covid-19 tests (either PCR or rapid antigen) within 48 hours before entering the US. The requirement will take effect on January 5th, according to the CDC, which made the announcement. [not sure the delay] CDC is concerned over China's lack of transparency about its outbreak — and its failure to track and sequence variants and subvariants that are circulating within its borders. CDC said the requirement for testing will apply to air passengers regardless of their nationality and vaccination status. It will also apply to travelers coming from China who enter the United States through a third country, or who connect through the United States to other destinations.

**Comment:** After three years of insisting on a "zero Covid-19" policy, China made an abrupt turnabout in early December and lifted that policy. Since then, there has been a dramatic uptick in the number of cases in Beijing. A major concern among public health officials is that the Chinese population has little natural immunity [in part due to the lockdowns], vaccination rates are inadequate, and they are using vaccines with lower VE than the mRNA vaccines all these factors has allowed the virus to spread rapidly. Scientists in Hong Kong have reported that an Omicron subvariant BF.7 has been responsible for the Beijing outbreak. That variant is a sublineage of BA.5, which had until recently been dominant in the US. BF.7, while present in the US for months(only 2.1%), has not shown signs of outcompeting other Omicron variants in this country. See variant update below We have tried testing and travel restrictions in the past with questionable success. Testing may give some a false sense of security. In the end I hope China will be more transparent.

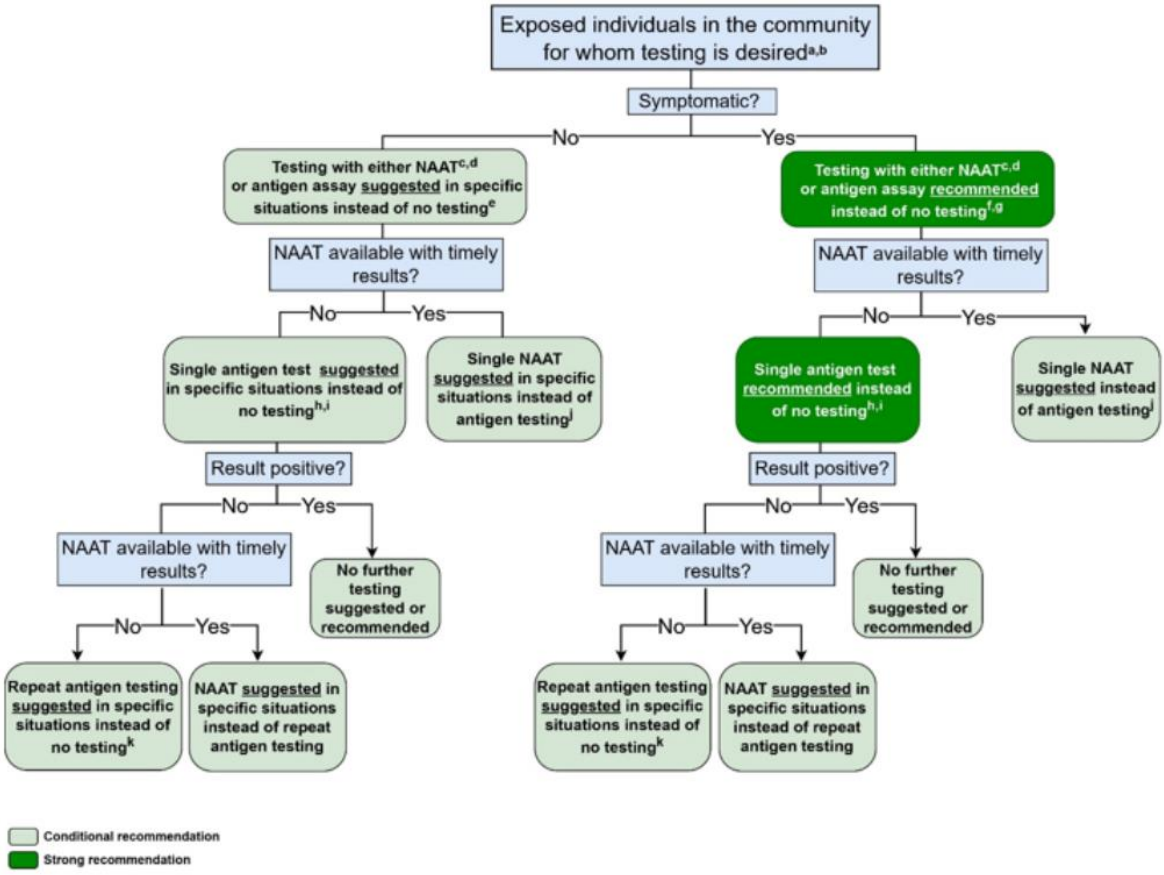
## IDSA Update on Antigen Testing December 20, 2022

Most SARS-CoV-2 Ag tests in clinical use are point-of-care (POC) lateral flow devices that generate results in approximately 15 minutes. The overall specificity of SARS-CoV-2 Ag tests g was ≥99% compared to standard PCR. Therefore, routine confirmation of positive Ag results by a reference molecular method is not necessary in most settings. In contrast, Ag test sensitivity was low or moderate and was dependent on the presence or absence of Covid-19 symptoms and the time of testing after symptom onset. Pooled Ag test sensitivity was 81% (95% CI: 78% to 84%) for symptomatic individuals and 89% (95% CI: 83% to 93%) if testing occurred within the first five days of illness; after 5 days, sensitivity fell to 54%. Testing patients within 3 days of

symptom onset yielded results similar to testing within 5 days. Among asymptomatic individuals, pooled sensitivity of Ag testing was 63%. Ag tests performed similarly in adults and children.

Despite the widespread use of Ag testing to guide individual attendance at school, work, and large social gatherings, the panel identified no clinical trials or observational studies that directly informed these testing applications, and so it was unable to make recommendations about Ag testing in these situations. Similarly, the panel found no clinical trials or observational studies that compared risk of onward transmission of SARS-CoV2 from patients who were released from isolation based on time from symptom onset *versus* results of an Ag test. Therefore, the panel was unable to make a recommendation about the utility of Ag testing to guide discontinuation of isolation.

The value of serial *versus* single sample testing compared to molecular testing, results of serial testing were estimated using mathematical modeling; results of this analysis suggested that repeat testing would improve sensitivity. The panel stated an evidence gaps included the performance of Ag tests in vaccinated individuals or those previously infected with SARS-CoV-2.




**Recommendation 1:** For symptomatic individuals suspected of having Covid-19, the IDSA panel recommends a single Ag test over no test *(strong recommendation, moderate certainty evidence)*

**Recommendation 2:** For symptomatic individuals suspected of having Covid-19, the IDSA panel suggests using standard NAAT (i.e., rapid RT-PCR or laboratory-based NAAT) over a rapid Ag test *(conditional recommendation, low certainty evidence)*.

**Recommendation 3:** For symptomatic individuals suspected of having Covid-19, the IDSA panel suggests using a single standard NAAT (i.e., rapid RT-PCR or laboratory-based NAAT) rather than a strategy of two consecutive rapid Ag tests *(conditional recommendation, very low certainty evidence)*.

**Recommendation 4:** For asymptomatic individuals with known exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single (i.e., one-time) Ag test over no testing in specific situations *(conditional recommendation, moderate certainty evidence)*.

**Recommendation 5:** For asymptomatic individuals with known exposure to SARS-CoV-2 infection, the IDSA panel suggests using a single standard NAAT (i.e., rapid RT-PCR or laboratory-based NAAT) over a single rapid Ag test *(conditional recommendation, low certainty evidence)*.

**Recommendation 6:** In asymptomatic individuals with a known exposure to SARS-CoV-2, if standard NAAT testing or results are not available in a timely manner and a first Ag test is negative, the IDSA panel suggests repeat Ag testing *(conditional recommendation, very low certainty evidence)*.

**Recommendation 7:** Among students in educational settings or employees in workplaces for whom SARS-CoV-2 testing is desired, the IDSA panel suggests neither for nor against two consecutive Ag tests over no testing for the diagnosis of SARS-CoV-2 infection (evidence gap).

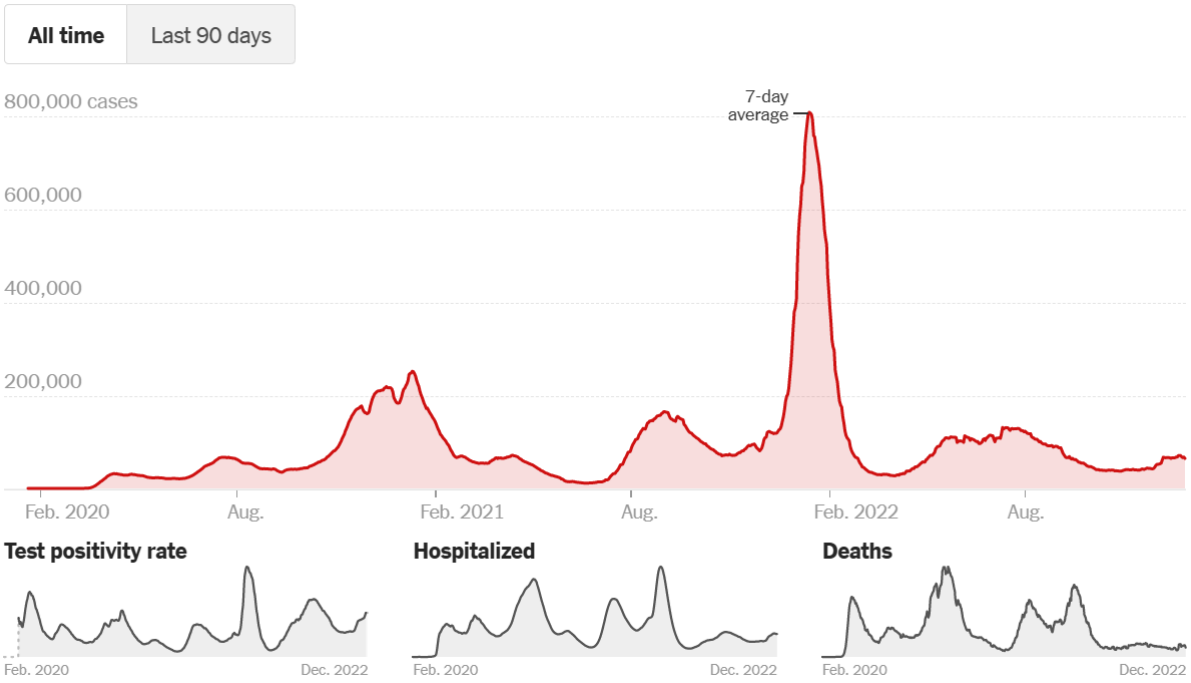
**Recommendation 8:** For asymptomatic individuals planning to attend a large gathering (e.g., concert, conference, party, sporting event), the IDSA panel suggests neither for nor against Ag testing over no testing (evidence gap).

**Recommendation 9:** For individuals for whom Ag testing is desired, the IDSA panel suggests for either point-of-care or laboratory-based Ag testing *(conditional recommendation, low certainty evidence)*.

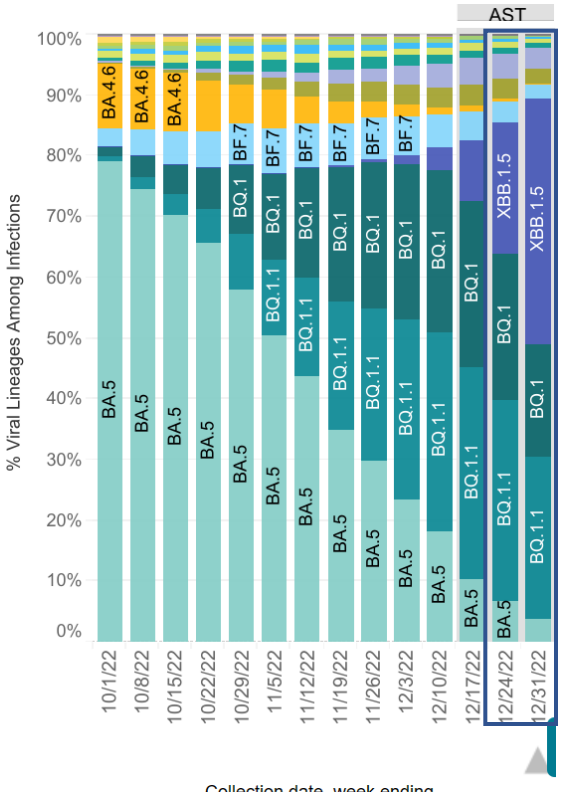
**Recommendation 10:** The IDSA panel suggests either observed or unobserved self-collection of swab specimens for Ag testing if self-collection is performed *(conditional recommendation, low certainty evidence)*.

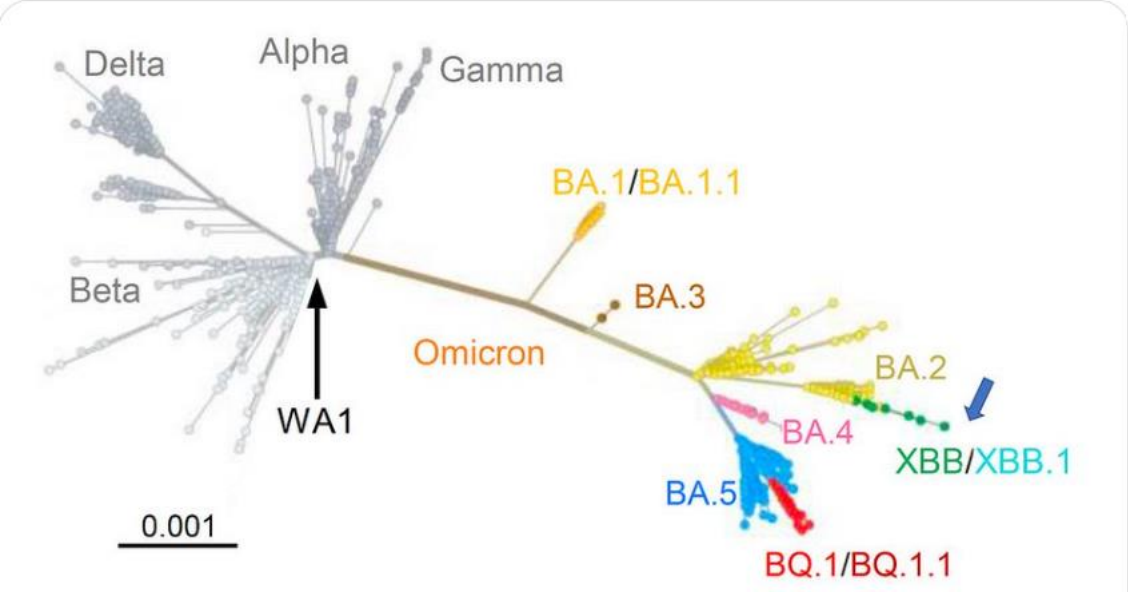
**Comment:** This is a thoughtful review which provides recommendations based on the current level of evidence. The Guidelines also identifies knowledge gaps. Given the widespread availability of home rapid antigen tests and the government again providing free home testing it is prudent we educate the public about the limitations of rapid Ag testing compared to standard PCR. I agree with the Guidance which suggests using a single (i.e., one-time) Ag test over no testing in specific situations. Although they do not take a stance for doing an Ag test for asymptomatic individuals planning to attend a large gathering (e.g., concert, conference, party, sporting event) I do not see much downside except to remind the user the limitation of rapid Ag and the test should not give the user a false sense of security. I also agree if the first Ag test is negative, the IDSA panel suggests repeat Ag testing.

## COVID-19 by the Numbers

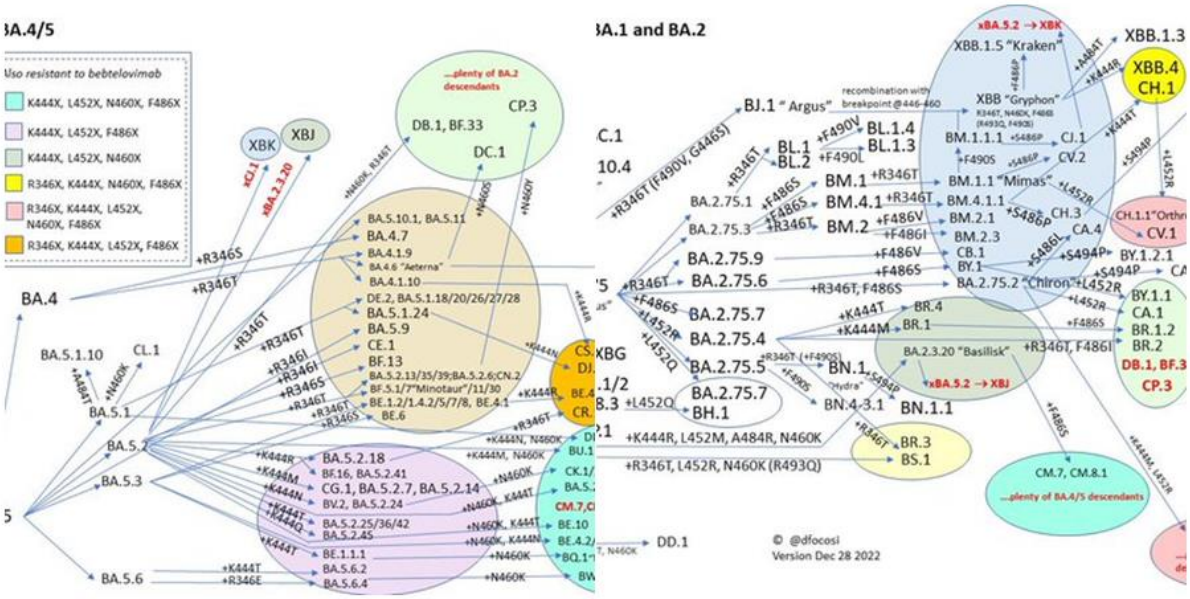



| WHO label | Lineage # | US Class | %Total | 95%PI |
|---|---|---|---|---|
| Omicron | XBB.1.5 | VOC | 40.5% | 22.7-61.0% |
| | BQ.1.1 | VOC | 26.9% | 18.9-36.5% |
| | BQ.1 | VOC | 18.3% | 12.5-25.9% |
| | BA.5 | VOC | 3.7% | 2.6-5.2% |
| | XBB | VOC | 3.6% | 2.5-5.0% |
| | BN.1 | VOC | 2.4% | 1.6-3.5% |
| | BF.7 | VOC | 2.1% | 1.4-3.1% |
| | BA.2.75 | VOC | 0.9% | 0.5-1.4% |
| | BA.5.2.6 | VOC | 0.6% | 0.4-0.9% |
| | BA.4.6 | VOC | 0.3% | 0.2-0.5% |
| | BA.2 | VOC | 0.3% | 0.2-0.5% |
| | BF.11 | VOC | 0.3% | 0.2-0.4% |
| | BA.2.75.2 | VOC | 0.1% | 0.1-0.2% |
| | BA.4 | VOC | 0.0% | 0.0-0.0% |
| | BA.1.1 | VOC | 0.0% | 0.0-0.0% |
| | B.1.1.529 | VOC | 0.0% | 0.0-0.0% |
| | 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* | | 0.0% | 0.0-0.0% |

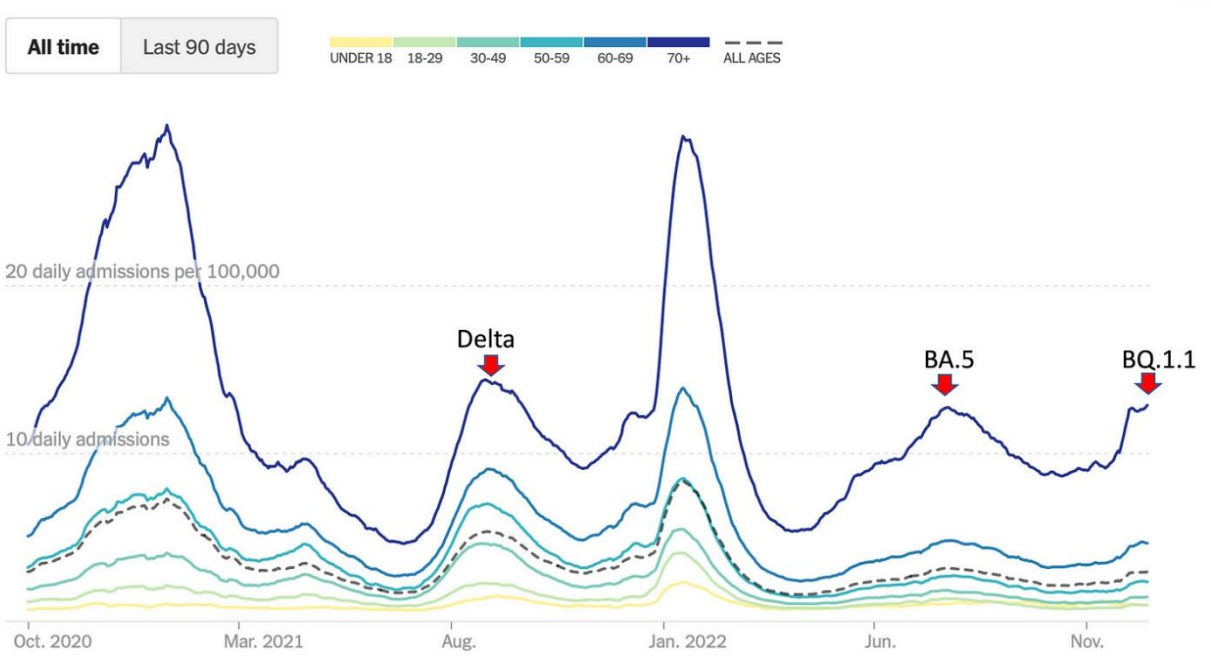





**Evolution of Omicron**




**Comment:** XBB.1.5 has more than doubled and now is outcompeting other variants. XBB now accounts for 40% with BQ.1.1. and BQ.1 combined are down to 45%. Cases are rising in some states especially in the Northeast where XBB accounts for >50% of variants. Percent positivity is rising in many areas of the country as well. Hospitalizations in some areas have seen a rise and varies with age-see below Hospitalizations are now over 44,000 the highest in months.




**Comment:** New data for bivalent vaccine protection demonstrates for age >65 there was a 90% reduction and 2.5% lower hospitalization than without the bivalent booster through the end of November. (See articles below) There is also some cross-reactive immunity of BA.5 bivalent vaccine versus XBB.1.5.

**Association of Time to Surgery After COVID-19 Infection With Risk of Postoperative Cardiovascular Morbidity** JAMA Netw Open 2022;5(12):e2246922.

doi:10.1001/jamanetworkop

This study evaluated the association between time to surgery after COVID-19 diagnosis and the risk of major postsurgical cardiovascular events within 30 days among 3,997 previously infected adult patients at Vanderbilt from January 1, 2020, to December 6, 2021. Major complications included deep vein thrombosis (DVT; blood clot), pulmonary embolism (blood clot in the lungs), stroke, heart attack, acute kidney injury (AKI), and death. Median patient age was 51.3 years, 16.7% were Black, 74.8% were White, and 8.5% were of other races. Median time from Covid-19 diagnosis and surgery was 98 days, and 34.9% of patients underwent surgery within 7 weeks of COVID-19 diagnosis. At the time of testing, 2,350 patients (58.8%) had symptomatic infections, and 1,539 (38.5%) were symptom-free; the symptom status of the remaining 108 cases (2.7%) was unknown. Vaccination did not alter results.

A total of 485 patients (12.1%) had major postoperative cardiovascular complications. Increased time between infection and surgery was tied to a lower rate of complications (adjusted odds ratio [aOR], 0.99), a trend that persisted for the 1,552 patients who had received one or more COVID-19 vaccine doses (aOR, 0.98 per 10 days). The incidence of any adverse cardiovascular event fell steeply at first, from approximately 18% to 10% over the first 100 days

after COVID-19 diagnosis, then steadily declined over the next 10 months, reaching roughly 8% after 400 days, regardless of vaccination status.

Factors associated with elevated risk of an adverse cardiovascular event were older age (aOR, 1.13), male sex (aOR, 1.51), Black race (aOR, 2.01 [vs White race]), higher ASA classification (aOR, 2.43), ASA emergency status (aOR, 1.49), urologic procedure (aOR, 1.98), and any of eight Elixhauser comorbidities (cardiac rhythm abnormalities, neurodegenerative disorders, kidney failure, lymphoma, solid tumor, coagulopathy [tendency toward blood clots], weight loss, and fluid and electrolyte disorders.

Based on recent data suggesting a higher death rate for patients who undergo surgery within 6 weeks of infection, the ASA and the Anesthesia Patient Safety Foundation recommend postponing surgery for 4 to 12 weeks after diagnosis, depending on Covid-19 severity and vaccination status. [last updated February 2022] See below

1. Any delay in surgery needs to be weighed against the time-sensitive needs of the individual patient
2. Elective surgery should be delayed for 7 weeks after a SARS-CoV-2 infection in unvaccinated patients that are asymptomatic at the time of surgery.
3. The evidence is insufficient to make recommendations for those who become infected after Covid-19 vaccination. Although there is evidence that, in general, vaccination reduces postinfection morbidity, the effect of vaccination on the appropriate length of time between infection and surgery/procedure is unknown. [this is partially addressed in the study above]

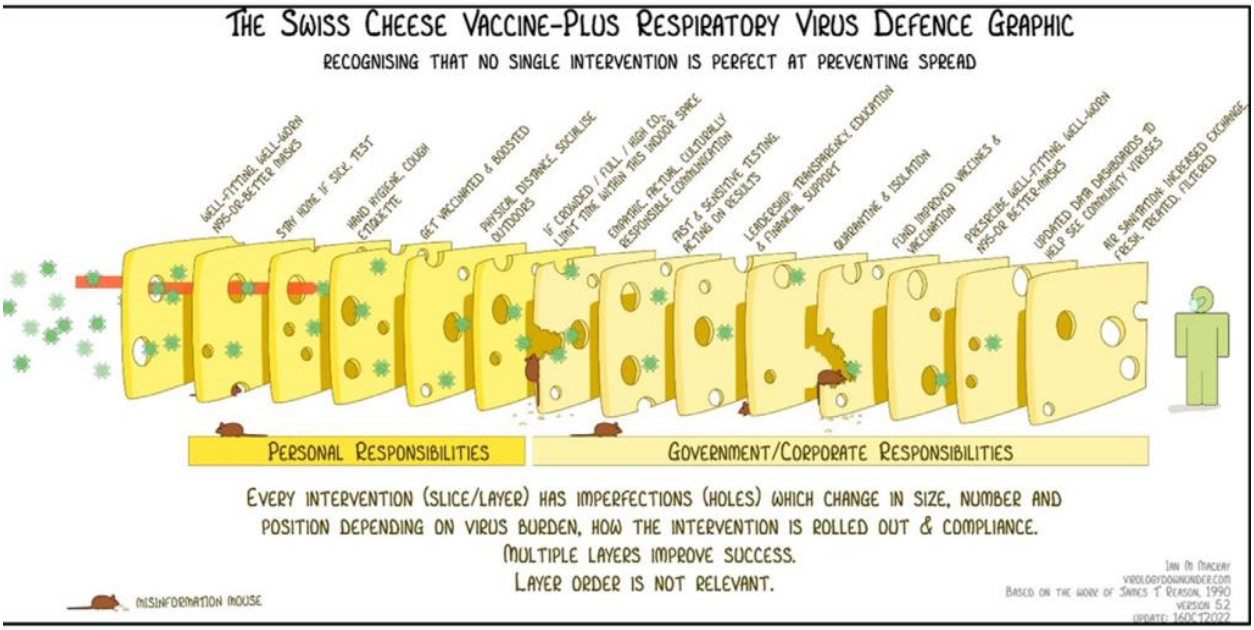
**Comment:** Their findings provide a more granular information of the time-dependent association between Covid-19 infection and outcomes after surgery, estimating a 1% reduction in the risk of our composite outcome for every 10 days after diagnosis. The study lacked the data to stratify patients based on partial vs full vaccination course or type of vaccine received. They were not able to investigate different strains of the virus as their hospital does not perform variant testing and were not sufficiently powered to study temporal trends in their data set. They were able to stratify between asymptomatic and symptomatic infections. They did not find a statistically significant temporal association between the timing of surgery and postoperative outcomes among patients who were asymptomatic at the time of preoperative testing (aOR, 0.98 [per 10 days]; 95% CI, 0.96-1.00; *P* = .06), although their results did show a trend toward reducing rates of complications with delaying time to surgery. See next article

## **Asymptomatic screening for severe acute respiratory coronavirus virus 2 (SARS-CoV-2) as an infection prevention measure in healthcare facilities: Challenges and Considerations.** Infect Control Hosp Epidemiol. published online December 21, 2022

doi:10.1017/ice.2022.295

This guidance acknowledges the logistical challenges and costs of screening programs and data on the lack of substantial aerosol production during elective controlled intubation, extubations, and other procedures. It also cites research showing that Covid-19 testing added 1.9 hours to emergency department visits in one health system and cost a hospital more than $12,500 to identify one asymptomatic infection. Therefore, SHEA recommends against routine

asymptomatic screening for SARS-CoV-2 in most healthcare facilities. The paper acknowledged that Covid-19 screening at facility admission may help curb spread in areas with limited infection-control strategies, such as behavioral health, congregate care, or shared patient rooms. They also acknowledge that infection prevention should analyze specific patients, procedures, and environment of an individual facility to identify situations where the risk of pathogen transmission is increased. Using this approach with asymptomatic screening, one should examine specific factors to consider when weighing the need for such testing. Because healthcare-associated transmission risk can be related to changes in the community incidence of disease, infection prevention interventions may need adjusting in relation to community infection rates. In addition to the community-transmission level, other measures that can signal an increased risk or likelihood of healthcare-associated transmission of SARS-CoV-2, such as the increase incidence of healthcare-onset Covid-19, increased wastewater detection of SARS-CoV-2 RNA, and HCW absenteeism (either related to Covid-19 infection or as a measure of staffing shortages), should be considered. In addition, populations with high risk for complications from Covid-19 or who cannot mount a protective immune response to vaccination may merit screening such as admissions to stem cell transplant or hematologic malignancy units. As an alternative approach, healthcare facilities should consider the use of N95 respirators for staff performing high-risk procedures, clinician screening, reduction of shared patient spaces, and better ventilation.



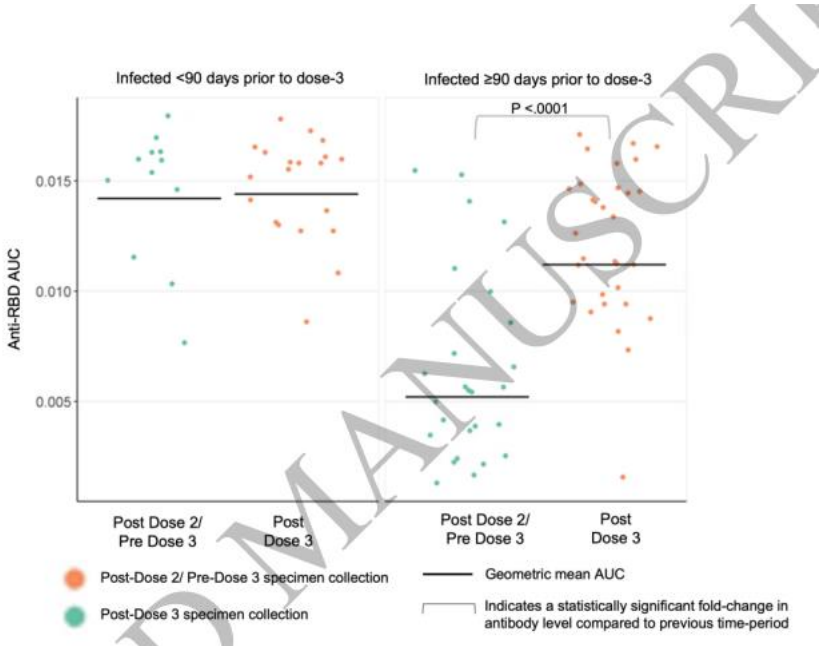

**Comment:** This is a thoughtful document which serves as a guide to screening asymptomatic persons for Covid-19. The key is to do an infection prevention assessment to determine risk and be flexible to move up or down depending on risk. The document recommends prior to implementation of a large-scale asymptomatic screening program, strengthening existing layers of protection (e.g., move to universal N95 respirator use when performing certain procedures on any patient, active versus passive screening of HCW for signs of Covid-19, reducing higher-risk unit layouts to remove semiprivate areas, enhanced ventilation) may be a more reasonable approach. The EIN is doing a survey to gauge practices in the US.

**SARS-CoV-2 infection history and antibody response to three COVID-19 mRNA vaccine doses** Clin Infect Dis published online December 29, 2022

doi.org/10.1093/cid/ciac976

Participants submitted sera every three months, after SARS-CoV-2 infection, and after each Covid-19 vaccine dose. Sera were tested for antibodies and reported quantitatively as area under the serial dilution curve (AUC). Changes in the AUC values over time were compared as fold-changes using a linear mixed model.

Analysis included 388 participants who received dose-3 by November 2021. Three comparison groups: (1) vaccine only with no known prior SARS-CoV-2 infection (n=224); (2) infection prior to dose-1 (n=123); and (3) infection after dose 2 and before dose-3 (n=41). The interval from dose 2 and dose 3 was approximately 8-months. After dose-3, antibody levels rose 2.5-fold (95%CI=2.2-3.0) in group 2, and 2.9-fold (95%CI=2.6-3.3) in group 1. Those infected within 90 days before dose-3 (and median 233 days (IQR=213-246) after dose-2) did not increase significantly after dose-3.





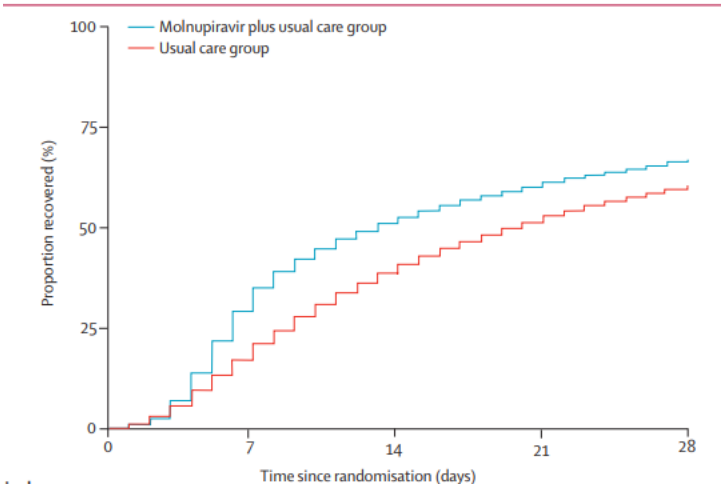

**Comment:** A third dose of mRNA vaccine typically elicited a robust humoral immune response among those with primary vaccination regardless of SARS-CoV-2 infection >3 months prior to boosting. Those with infection < 3 months prior to boosting did not have a significant increase in antibody concentrations in response to a booster. Overall, the study demonstrated a clear benefit from a third vaccine dose, regardless of previous infection status. These data support previous studies that suggest waiting at least three months post-infection to maximize the boost in antibody titers. This data flies in the face of recent CDC who recommended getting the bivalent vaccine soon as 2 months from either infection and/or recent vaccination.

**Molnupiravir plus usual care versus usual care alone as early treatment for adults with COVID-19 at increased risk of adverse outcomes (PANORAMIC): an open-label, platform adaptive randomised controlled trial** Lancet published online December 22, 2022

doi.org/10.1016/ S0140-6736(22)02597-1

PANORAMIC was a UK-based, national, multicenter, open-label, multigroup, prospective, platform adaptive randomized controlled trial. Eligible participants were aged 50 years or older—or aged 18 years or older with relevant comorbidities—and had been unwell with confirmed Covid-19 for 5 days or fewer in the community. Participants were randomly assigned (1:1) to receive 800 mg molnupiravir twice daily for 5 days plus usual care or usual care only. The study was stratified by age (<50 years vs ≥50 years) and vaccination status (yes vs no). Covid-19 outcomes were tracked via a self-completed online daily diary for 28 days after randomization. The primary outcome was all-cause hospitalization or death within 28 days of randomization, which was analyzed using Bayesian models in all eligible participants who were randomly assigned. Average patient age was 56.6 years, and 94% were White. Patients were considered high risk because they were either 50 years and older or had underlying health conditions.

26,411 participants were randomly assigned, 12,821 to molnupiravir plus usual care, 12,962 to usual care alone. [December 8, 2021 to April 27, 2022] A total of 105 molnupiravir recipients (0.8%) were hospitalized or died, compared with 98 (0.8%) in the control group (adjusted odds ratio, 1.06), demonstrating no benefit, but the molnupiravir group recovered, on average, 4.2 days sooner than controls (9 vs 15 days). In a substudy, the drug also reduced viral detection and load. Seven control patients hadn't recovered by 28 days. A slightly lower number of molnupiravir patients than controls visited their physician after the trial ended (20% vs 24%). Fifty molnupiravir patients (0.4%) had serious adverse events, compared with 45 (0.3%) in the usual-care group. No adverse events were considered related to molnupiravir. 24,290 (94%) of 25,708 participants had had at least three doses of a SARS-CoV-2 vaccine.




**Comment:** Molnupiravir did not reduce hospitalizations or deaths in a community-based vaccinated adult population with Covid-19(Omicron) who were at increased risk of an adverse outcome, either overall or in any patient subgroups. However, molnupiravir was associated with reduced time to recovery overall and for key individual symptoms, reduced healthcare seeking for some primary care services, and reduced viral load. Trials of molnupiravir have previously been done in largely unvaccinated participants before the emergence of the omicron variant. The study findings may not apply to the highest-risk Covid-19 patients. The shortened and sustained symptom reduction, together with the effects on viral clearance, could be an important consideration in high-risk settings, such as nursing homes, in terms of potentially minimizing the spread of infection among high-risk persons. The largest trial of molnupiravir had been the MOVe-OUT, a placebo-controlled, industry-funded phase 3 trial in unvaccinated, non-hospitalized patients with Covid-19 at high risk of adverse outcomes. The results suggest a 30% reduction in hospital admissions and deaths with molnupiravir treatment compared with placebo. [ N Engl J Med 2022; 386: 509–20] The effectiveness of molnupiravir in vaccinated patients in the community at increased risk of morbidity and mortality from Covid-19 had not been done until this trial.

## **VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19** N Engl J Med published online December 28, 2022

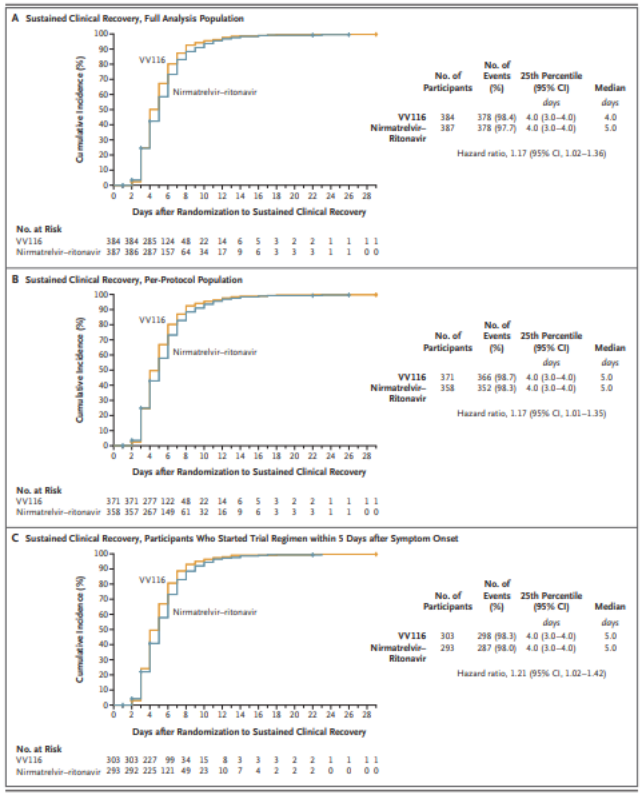
DOI: 10.1056/NEJMoa2208822

Currently, nirmatrelvir–ritonavir is recommended by WHO and NIH for treating mild-to-moderate Covid-19 in high risk patients at risk for progression. Nirmatrelvir is an oral inhibitor of the SARS-CoV-2 3-chymotrypsin–like cysteine protease enzyme that can be dispensed at community pharmacies and has been authorized for emergency use by many countries. However, access to nirmatrelvir is limited worldwide, and its effectiveness depends on ritonavir, which has multiple drug–drug interactions warranting specialized assessment before prescription. Remdesivir is also recommended but needs to be administered intravenously for 3 days, which limits its widespread use. Therefore, several oral analogues of remdesivir have been developed to address this issue. VV116 is a deuterated remdesivir hydrobromide with oral bioavailability and potent activity against SARS-CoV-2 in studies in animals and satisfactory safety and side-effect profiles in phase 1 trials. A preliminary small-scale study has shown a

shorter viral shedding time in patients with Covid-19 who received VV116 within 5 days after the first positive test than in those who received regular care. [Emerg Microbes Infect 2022;11:1518-23]

In this paper, the investigators conducted a phase 3, noninferiority, observer-blinded, randomized trial during the outbreak caused by the B.1.1.529 (omicron) variant of SARS-CoV-2. After written informed consent was obtained, participants from seven hospitals in Shanghai, China were enrolled. Symptomatic adults with mild-to-moderate Covid-19 with a high risk of progression were assigned to receive a 5-day course of either VV116 or nirmatrelvir–ritonavir. The most common risk factor for progression to severe Covid-19 at baseline was an age of 60 years or older (37.7%), followed by cardiovascular disease (including hypertension) (35.1%), a body-mass index (weight in kilograms divided by the square of the height in meters) of 25 or higher (32.9%), current smoking (12.5%), and diabetes (10.1%). The primary end point was the time to sustained clinical recovery through day 28. A total of 822 participants underwent randomization, and 771 received VV116 (384 participants) or nirmatrelvir–ritonavir (387 participants). The noninferiority of VV116 to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery was established in the primary analysis (hazard ratio, 1.17; 95% confidence interval [CI], 1.01 to 1.35) and was maintained in the final analysis (median, 4 days with VV116 and 5 days with nirmatrelvir–ritonavir; hazard ratio, 1.17; 95% CI, 1.02 to 1.36). In the final analysis, the time to sustained symptom resolution (score of 0 for each of the 11 Covid-19–related target symptoms for 2 consecutive days) and to a first negative SARS-CoV-2 test did not differ substantially between the two groups. No participants in either group had died or had progression to severe Covid-19 by day 28. The incidence of adverse events was lower in the VV116 group than in the nirmatrelvir–ritonavir group (67.4% vs. 77.3%).

In summary, among adults with mild-to-moderate Covid-19 who were at risk for progression, VV116 was noninferior to nirmatrelvir–ritonavir with respect to the time to sustained clinical recovery, with fewer safety concerns.

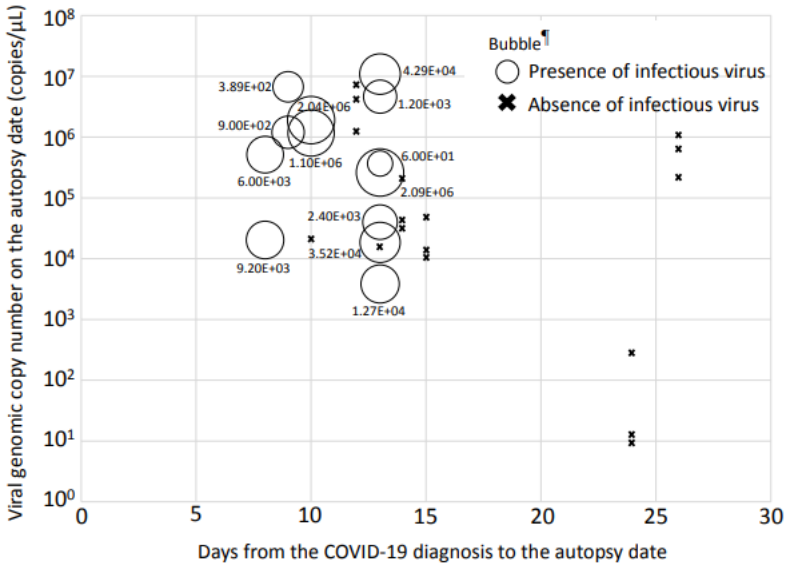



**Comment:** This trial showed that in symptomatic adults hospitalized with mild to-moderate Covid-19 who were at high risk for severe disease, a 5-day course of oral treatment with VV116 was noninferior to nirmatrelvir–ritonavir in shortening the time to sustained clinical recovery. 75.7% of the participants had been vaccinated against SARS-CoV-2, which reflects the current reality of community immunity. In this trial, fewer adverse events occurred in the VV116 group than in the nirmatrelvir–ritonavir Unlike nirmatrelvir–ritonavir, which has drug–drug interactions with multiple medications, VV116 does not inhibit or induce major drug-metabolizing enzymes or inhibit major drug transporters, so interaction with concomitant medications is uncommon. They were not able to conduct this trial with a double-blind and double-dummy design because the production of the placebo tablet for nirmatrelvir–ritonavir was not completed before the trial began owing to the omicron outbreak. Second, the trial involved Chinese adults infected with omicron subvariants in a single geographic area, so the results require validation in more heterogeneous populations with greater diversity of viral variants. Data on rebound was very limited and was not part of their analysis in this trial. Nonetheless, if verified in additional trials, VV 116 would be a welcomed addition to combat SARS-CoV-2 progression in high-risk people.

**High titers of infectious SARS-CoV-2 in COVID-19 corpses** medRxiv posted October 11, 2022

doi.org/10.1101/2022.10.11.22280868

They collected 11 nasopharyngeal swabs and 19 lung tissue specimens from 11 autopsy cases with COVID-19 in 2021. We then investigated the viral genomic copy number by real-time reverse transcription-polymerase chain reaction and infectious titers by cell culture and virus isolation. Results: Infectious virus was present in 6 of 11 (55%) cases, 4 of 11 (36%) nasopharyngeal swabs, and 9 of 19 (47%) lung specimens. The virus titers ranged from 6.00E + 01 plaque-forming units (PFU)/mL to 2.09E + 06 PFU/g. In all cases in which an infectious virus was found, the time from death to discovery was within 1 day and the 53 longest postmortem interval was 13 days.



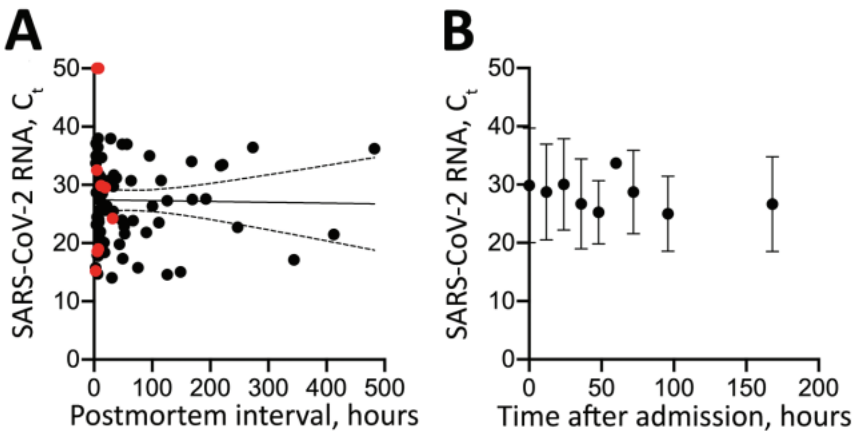

**Comment**: Covid-19 corpses may have high titers of infectious virus after a long 55 postmortem interval (up to 13 days). Therefore, appropriate infection control measures must be taken when handling corpses. See the next 3 articles

**Postmortem Stability of SARS-CoV-2 in Nasopharyngeal Mucosa** Emerg Inf Dis 2021; 329-331

To analyze postmortem stability of SARS-CoV-2 RNA, the investigators selected 11 corpses with short postmortem intervals for a detailed observation over 7 days (168 hours). The median postmortem interval was 5.7 (range 2.9–32.0 [IQR 6.9]) hours. The median cycle threshold (Ct ) of SARS-CoV-2 RNA in swab samples taken at admission was 29.52 (range 15.2– 50.0 [IQR 22.5]).

They determined viral load in a series of 9 sequential pharyngeal swab samples (time points 0, 12, 24, 36, 48, 60, 72, 96, and 168 hours after admission). They consistently detected SARS-CoV-2 RNA at constant levels at all time points analyzed, except for patient 7 at 0, 12, and 24 hours after admission and patient 8 at admission.

They then demonstrated maintained infectivity of SARS-CoV-2 in tissues of deceased patients. SARS-CoV-2 RNA persisted over time at constantly high titers. Taken together, their data indicate potentially high infectivity of human corpses, requiring hazard assessments in professional fields concerned and careful and conscious handling.




**Comment:** Their infectivity study relies on a limited number of cases and patients with severe immunosuppression. Further research should investigate viral persistence in corpses with longer postmortem intervals (>1 week) and corpses exhibiting lower initial viral loads. We recommend all work on corpses be conducted according to guidelines recently published by the WHO.

**Infectivity of deceased COVID-19 patients** International Journal of Legal Medicine (2021) 135:2055–2060

During autopsy, swabs and organ samples were taken and examined by PCR for the detection of SARS-CoV-2 ribonucleic acid (RNA). Determination of infectivity was performed by means of virus isolation in cell culture. In two cases, virus isolation was successful for swabs and tissue samples of the respiratory tract (PMI 4 and 17 days). The two infectious cases showed a shorter duration of Covid-19 until death than the two non-infectious cases (2 and 11 days, respectively, compared to > 19 days), which correlates with studies of living patients, in which infectivity could be narrowed to about 6 days before to 12 days after symptom onset. Most notably, infectivity was still present in one of the Covid-19 corpses after a post-mortem interval of 17 days and despite already visible signs of decomposition.

**Comment:** The infectivity is mainly dependent on the time interval between initial disease symptoms and the occurrence of death as well as the viral load and may be present even after the onset of decay. Medical personnel (as well as other professional groups in the field) are therefore exposed to a certain risk of infection with SARS-CoV-2 during postmortem handling

and examination of Covid-19 corpses—thus, adequate protective measures have to be enforced to reduce the risk of infection with SARS-CoV-2.

## SARS-CoV-2 infection and persistence in the human body and brain at autopsy.

Nature published online December 14, 2022

doi.org/10.1038/s41586-022-05542-y

Scientists from the NIH tested samples from autopsies that were performed from April 2020 to March 2021. An analysis of tissue samples from the autopsies of 44 people who died with Covid-19 were performed. They conducted extensive sampling of the nervous system, including the brain, in 11 of the patients.

All of the patients died with COVID-19, and none were vaccinated. The blood plasma of 38 patients tested positive for SARS-CoV-2, 3 tested negative, and plasma was unavailable for the other 3. Twenty-seven patient (61.4%) had three or more comorbidities. The median interval from symptom onset to death was 18.5 days. Analysis showed that SARS-CoV-2, as expected, primarily infected and damaged airway and lung tissue. But the investigators also found viral RNA in 84 distinct body locations and bodily fluids, and in one case they isolated viral RNA 230 days after a patient's symptoms began. The investigators also detected SARS-CoV-2 RNA and protein in the hypothalamus and cerebellum of one patient and in the spinal cord and basal ganglia of two other patients. But they found little damage to brain tissue, "despite substantial viral burden." The investigators also isolated viable SARS-CoV-2 virus from diverse tissues in and outside the respiratory tract, including the brain, heart, lymph nodes, gastrointestinal tract, adrenal gland, and eye. They isolated virus from 25 of 55 specimens tested (45%).

**Comment:** Despite extensive distribution of SARS-CoV-2 RNA throughout the body, the investigators observed little evidence of inflammation or direct viral cytopathology outside the respiratory tract. Their data indicate that in some patients SARS-CoV-2 can cause systemic infection and persist in the body for months. Appropriate PPE should be used when performing autopsies on patients who died with known or suspected Covid-19.

## Council of State and Territorial Epidemiologists/CDC Surveillance Case Definition for Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 Infection — United States

MMWR 2022; December 16, 2022

This report summarizes the evidence and rationale supporting the components of the CSTE/CDC MIS-C surveillance case definition and describes the methods used to develop the definition. These methods included convening MIS-C clinical experts (i.e., consultants) regarding identification of MIS-C and its distinction from other pediatric conditions, a review of available literature comparing MIS-C phenotype with that of pediatric Covid-19 and other hyperinflammatory syndromes, and retrospective application of different criteria to data from MIS-C cases previously reported to CDC.

**BOX. Council of State and Territorial Epidemiologists/CDC surveillance case definition for multisystem inflammatory syndrome (MIS-C) in children associated with SARS-CoV-2 infection — United States**

**Case definition classifications**

**Confirmed:** Meets the clinical criteria and the laboratory criteria.

**Probable:** Meets the clinical criteria and the epidemiologic linkage criteria.

**Suspect:** Meets the vital records criteria.

**Clinical criteria**

An illness in a person aged <21 years characterized by all of the following, in the absence of a more likely alternative diagnosis*:

- Subjective or documented fever (temperature ≥38°C)
- Clinical severity requiring hospitalization or resulting in death
- Evidence of systemic inflammation (indicated by C-reactive protein of ≥3.0 mg/dL [30 mg/L])
- New onset manifestations in at least two of the following categories:
  - Cardiac involvement (indicated by left ventricular ejection fraction of <55%; coronary artery dilatation, aneurysm, or ectasia; or troponin elevated above laboratory normal range, or indicated as elevated in a clinical note)
  - Mucocutaneous involvement (indicated by rash, inflammation of the oral mucosa [e.g., mucosal erythema or swelling, drying or fissuring of the lips, strawberry tongue], conjunctivitis or conjunctival injection [redness of the eyes], or extremity findings such as erythema [redness] or edema [swelling] of the hands or feet)
  - Shock†
  - Gastrointestinal involvement (indicated by abdominal pain, vomiting, or diarrhea)
  - Hematologic involvement (indicated by platelet count of <150,000 cells/μL or absolute lymphocyte count of <1,000 cells/μL)

**Laboratory criteria**

- Detection of SARS-CoV-2 RNA in a clinical specimen§ up to 60 days before or during hospitalization, or in a postmortem specimen using a diagnostic molecular amplification test (e.g., polymerase chain reaction); or
- Detection of SARS-CoV-2–specific antigen in a clinical specimen§ up to 60 days before or during hospitalization, or in a postmortem specimen; or
- Detection of SARS-CoV-2–specific antibodies¶ in serum, plasma, or whole blood associated with current illness resulting in or during hospitalization

**Epidemiologic linkage criteria**

Close contact** with a confirmed or probable case of COVID-19 disease in the 60 days before hospitalization.

**Vital records criteria**

A death of a person aged <21 years whose death certificate lists MIS-C or multisystem inflammatory syndrome as an underlying cause of death or a significant condition contributing to death.

**Criteria to distinguish a new case from an existing case**

A case should be enumerated as a new case if the person had never been enumerated as a case or if the person was most recently enumerated as a case with illness onset date (if available) or hospital admission date >90 days previous.

* If documented by the clinical treatment team, a final diagnosis of Kawasaki disease should be considered an alternative diagnosis. These cases should not be reported to national MIS-C surveillance.
† Clinician documentation of shock meets this criterion.
§ Positive molecular or antigen results from self-administered testing using over-the-counter test kits meet laboratory criteria.
¶ Includes a positive serology test regardless of COVID-19 vaccination status. Detection of anti-nucleocapsid antibody is indicative of SARS-CoV-2 infection, whereas anti-spike protein antibody might be induced either by COVID-19 vaccination or by SARS-CoV-2 infection.
** Close contact is typically defined as being within 6 feet for at least 15 minutes (cumulative over a 24-hour period). However, close contact depends on the exposure level and setting (e.g., in the setting of an aerosol-generating procedure in a health care settings without proper personal protective equipment, close contact might be defined as any duration).

**Comment:** The CSTE/CDC surveillance case definition for MIS-C includes four important changes, in comparison with the 2020 CDC MIS-C case definition. These changes are 1) no required duration of subjective or measured fever; 2) requirement of C-reactive protein ≥3.0 mg/dL to indicate systemic inflammation; 3) adjustments to criteria of organ system involvement to include addition of shock as a separate category and elimination of respiratory, neurologic, and renal criteria; and 4) new requirements on timing of positive SARS-CoV-2 laboratory testing relative to the MIS-C illness. Although MIS-C is not a nationally notifiable condition and reporting is voluntary, CSTE and CDC recommend that all states and territories report all cases meeting confirmed, probable, or suspect criteria of the CSTE/CDC MIS-C surveillance case definition beginning January 1, 2023, for cases with MIS-C illness onset on or after that date.

The CSTE/CDC MIS-C surveillance case definition does not include all manifestations of MIS-C that distinguish it from other conditions; certain clinical features are impractical for surveillance programs to review. For this reason, the case definition is not designed as a set of diagnostic criteria, and its direct application in clinical care might miss cases of MIS-C. Clinicians should use all available clinical features, laboratory results, and imaging studies in diagnosis of MIS-C and for management decisions.

**Alarming antibody evasion properties of rising SARS-CoV-2 BQ and XBB subvariants** Cell published online December 13, 2022

Highlights

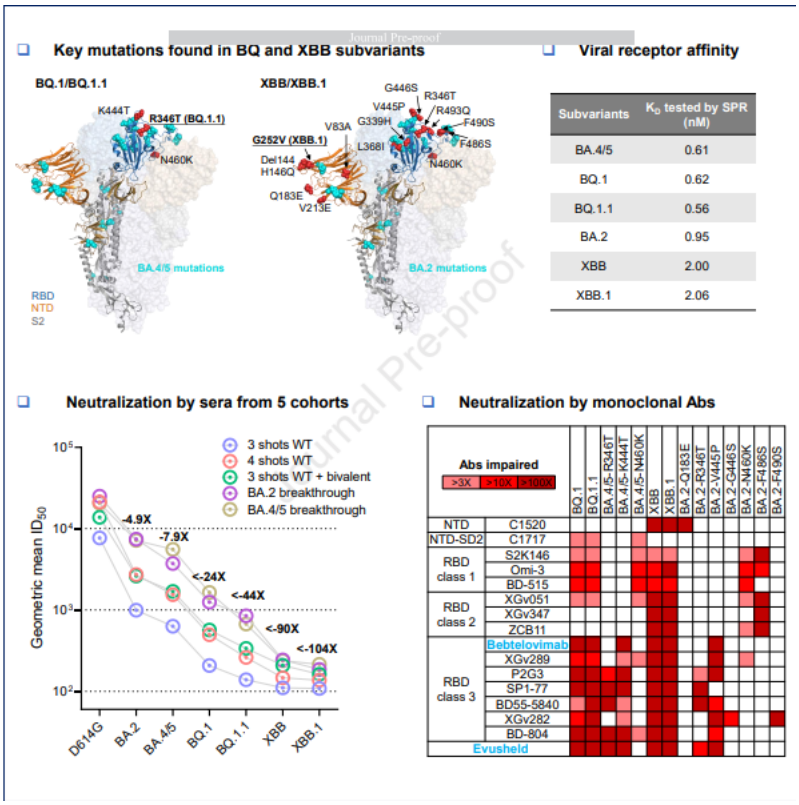
- BQ.1, BQ.1.1, XBB, and XBB.1 are the most resistant SARS-CoV-2 variants to date
- Serum neutralization was markedly reduced, including with the bivalent booster
- All clinical monoclonal antibodies were rendered inactive against these variants
- The ACE2 affinity of these variants were similar to their parental strains.

BQ.1 and BQ.1.1 evolved from BA.5, whereas XBB and XBB.1 resulted from a recombination between two BA.2 lineages, BJ.1 and BA.2.75. [see page 23] The spike protein of the predominant BQ.1 subvariant harbors the K444T and N460K mutations in addition to those found in BA.5, with BQ.1.1 having an additional R346T mutation. Interestingly, the spike of the predominant XBB subvariant has 14 mutations in addition to those found in BA.2, including 5 in the N-terminal domain (NTD) and 9 in the receptor-binding domain (RBD), whereas XBB.1 has an additional G252V mutation.

To better understand if BQ.1, BQ.1.1, XBB, and XBB.1 have increased resistance to serum antibodies, they set out to evaluate the neutralization of these four new subvariants by sera from five different clinical cohorts: The five clinical cohorts included individuals who received three or four doses of one of the original COVID-19 mRNA vaccines (termed “3 shots WT” or “4 shots WT”, respectively), those who received one of the recently authorized bivalent (WT and BA.5) COVID-19 mRNA vaccines as a 4th shot after three doses of one of the original COVID-19 mRNA vaccines (termed “3 shots WT + bivalent”), and patients who had BA.2 and BA.4 or BA.5 breakthrough infection after vaccination (termed “BA.2 breakthrough” and “BA.4/5 breakthrough”, respectively).

Consistent with previous reports, BA.2 and BA.4/5 showed stronger evasion to serum neutralization relative to the ancestral strain D614G across all five cohorts. Disturbingly, in the “3 shots WT” cohort, neutralization titers were far lower against BQ.1, BQ.1.1, XBB, and XBB.1, with reductions of >37-fold to >71-fold compared to D614G. In addition, while all sera had detectable titers against BA.2 and BA.4/5, a majority of samples did not neutralize the new subvariants at the lowest dilution (1:100) of serum tested. A similar trend was also noted in the other four cohorts, with the lowest titers observed against XBB.1, followed by XBB, BQ.1.1,and BQ.1.

To understand the types of serum antibodies that lost neutralizing activity against BQ.1, BQ.1.1, XBB, and XBB.1, they constructed pseudoviruses for each subvariant, as well as for each individual mutation found in the subvariants, and then evaluated their susceptibility to neutralization by a panel of 23 monoclonal antibodies (mAbs) targeting various epitopes on the spike. They showed that these new subvariants were completely or partially resistant to neutralization by most monoclonal antibodies tested.




**Comment:** Together, these findings indicate that BQ and XBB subvariants present serious threats to current Covid-19 vaccines, render inactive all authorized antibodies, and have gained dominance in the population because of their advantage in evading antibodies. BQ.1 and BQ.1.1 evolved from BA.5, whereas XBB and XBB.1 resulted from a recombination between two BA.2 lineages, BJ.1 and BA.2.75.

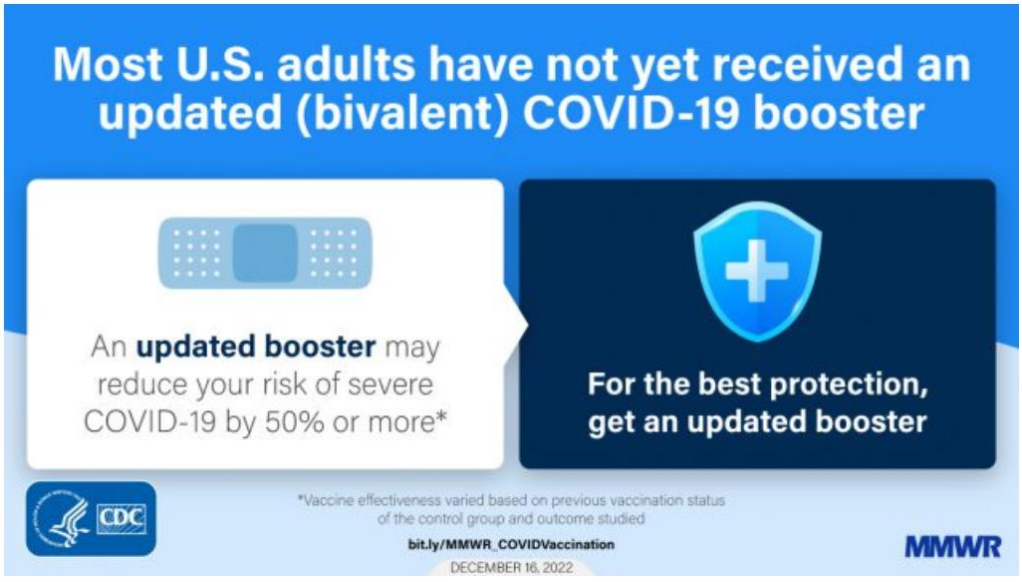
**Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Emergency Department or Urgent Care Encounters and Hospitalizations Among Immunocompetent Adults — VISION Network, Nine States, September–November 2022** MMWR early release December 16, 2022

**Early Estimates of Bivalent mRNA Vaccine Effectiveness in Preventing COVID-19–Associated Hospitalization Among Immunocompetent Adults Aged ≥65 Years — IVY Network, 18 States, September 8–November 30, 2022** MMWR early release December 16, 2022

In the first study, investigators calculated vaccine effectiveness (VE) from September 13 to November 18, 2022 using data from the VISION Network. The investigators compared VE of a bivalent mRNA booster dose (after 2, 3, or 4 monovalent doses) compared with no previous vaccination, and previous receipt of 2, 3, or 4 monovalent-only mRNA vaccine doses, among adults ages 18 years or older with an emergency department/urgent care (ED/UC) visit or hospitalization for a Covid-19–like illness.

In total, 78,303 ED/UC encounters with Covid-19–like illness were included in the study, and 9,009 (12%) case-patients and 69,294 (89%) control patients were identified. Overall, 31% were unvaccinated, and only 5% adults had received a bivalent booster dose, 216 (6%) had received 2 monovalent doses, 1,679 (43%) had received 3 monovalent doses, and 2,010 (51%) had received 4 monovalent vaccine doses.

VE of a bivalent booster dose (after 2, 3, or 4 monovalent doses) against Covid-19–associated hospitalizations were 57% compared with no vaccination, 38% compared with monovalent vaccination only with last dose 5–7 months earlier, and 45% compared with monovalent vaccination only with last dose ≥11 months earlier. Among 15,527 patient hospitalizations with Covid-19–like illness included in the study, 1,453 (9%) case-patients and 14,074 (91%) control patients were identified, of which 26% were unvaccinated. Again, 5% of adults had received a bivalent booster dose, 49 (6%) had received 2 monovalent doses, 32% had received 3 monovalent doses, and 62% had received 4 monovalent doses.




In this early study of immunocompetent adults, significant protection from a booster dose of bivalent mRNA COVID-19 vaccine (after receipt of 2, 3, or 4 monovalent doses) compared with no vaccination was found, as well as significant relative benefits of a bivalent booster dose when compared with previous receipt of monovalent doses only. Previous SARS-CoV-2 infection was not accounted for in this analysis. A large proportion of the population has now experienced SARS-CoV-2 infection which decreases the risk of severe Covid-19 illness and might affect observed VE due to background immunity. Their models adjusted for relevant confounders; however, residual confounding is possible, including by behavioral differences and use of Covid-19 treatments such as nirmatrelvir/ritonavir. This study was done before the rise of BQ variants.

The second study, based on data from 22 hospitals in 18 states participating in the IVY Network, shows the bivalent booster offers even more protection to adults ages 65 and older whose immune systems are not compromised.

VE against Covid-19–associated hospitalization was estimated by comparing the odds of bivalent booster dose receipt with no Covid-19 vaccination between case-patients and control patients in the test-negative study.

From September 8 and November 30, 2022, the investigators included 798 adults in the analysis (381 case-patients and 417 control patients), with a median age of 76 years. Seventy-four percent of participants had underlying health conditions.

Among the 381 case-patients, 81 (21%) were unvaccinated, 280 (73%) had received 2 or more monovalent-only mRNA vaccine doses, and 20 (5%) had received a bivalent booster dose. Among controls, 14% had been boosted with a bivalent vaccine.

When compared with unvaccinated patients, VE of a bivalent booster dose in preventing Covid-19–associated hospitalization was 84%. When compared with patients who had received ≥2 monovalent-only mRNA vaccine doses ≥2 months before illness onset, relative VE of a bivalent booster dose was 73%.

**TABLE 2. Effectiveness of a bivalent COVID-19 mRNA booster dose against COVID-19–associated hospitalization among immunocompetent adults aged ≥65 years — IVY Network, 22 hospitals,* 18 states, September 8, 2022–November 30, 2022**

| Characteristic | Received BV vaccine dose, by case status, n/N (%) | | Median interval† from last vaccine dose to illness onset (IQR), days | Adjusted VE, % (95% CI)§ |
|---|---|---|---|---|
| | Case-patients | Control patients | | |
| **Absolute VE (BV booster dose versus no vaccine)** | | | | |
| Unvaccinated (Ref) | — | — | NA | — |
| BV booster dose¶ ≥7 days before illness onset | 20/101 (20) | 59/121 (49) | 29 (15–45) | 84 (64–93) |
| **Relative VE (BV booster dose versus MV-only, by interval since last dose)** | | | | |
| ≥2 MV-only mRNA doses, last dose ≥2 mos before illness onset (Ref) | — | — | 305 (168–377) | — |
| BV booster dose ≥7 days before illness onset | 20/300 (7) | 59/355 (17) | 29 (15–45) | 73 (52–85) |
| ≥2 MV-only mRNA doses, last dose 2–5 mos before illness onset (Ref) | | | 137 (111–155) | — |
| BV booster dose ≥7 days before illness onset | 20/82 (24) | 59/155 (38) | 29 (15–45) | —** |
| ≥2 MV-only mRNA doses, last dose 6–11 mos before illness onset (Ref) | — | — | 304 (258–333) | — |
| BV booster dose ≥7 days before illness onset | 20/155 (13) | 59/176 (34) | 29 (15–45) | 78 (57–89) |
| ≥2 MV-only mRNA doses, last dose ≥12 mos before illness onset (Ref) | — | — | 528 (386–575) | — |
| BV booster dose ≥7 days before illness onset | 20/103 (19) | 59/142 (42) | 29 (15–45) | 83 (63–92) |

**Abbreviations:** BV = bivalent; MV = monovalent; NA = not applicable; Ref = referent group; VE = vaccine effectiveness.

**Comment:** The authors said their findings should reinforce the importance of bivalent boosters for older adults, who are most at risk for severe outcomes of Covid-19 infections. Currently bivalent booster dose coverage in the US remains low among adults, with only 16% of those aged 18 to 64 boosted, and 36% of those 65 and older.

**Predictors of Severe Acute Respiratory Syndrome Coronavirus 2 Infection Following High-Risk Exposure** Clin Infect Dis 2022;75: e276–88

doi.org/10.1093/cid/ciab1040

The investigators conducted a test-negative design case-control study enrolling cases (testing positive for SARS-CoV-2) and controls (testing negative) with molecular SARS-CoV-2 diagnostic test results reported to California Department of Public Health between 24 February–12 November 2021. They used conditional logistic regression to estimate adjusted odds ratios (aORs) of case status among participants who reported contact with an individual known or suspected to have been infected with SARS-CoV-2 ("high-risk exposure") ≤14 days before testing.

751 of 1448 cases (52%) and 255 of 1443 controls (18%) reported high-risk exposures ≤14 days before testing. Adjusted odds of case status were 3.02-fold (95% confidence interval: 1.75–5.22) higher when high-risk exposures occurred with household members (vs. other contacts), 2.10-fold (1.05–4.21) higher when exposures occurred indoors (vs. outdoors only), and 2.15-fold (1.27–3.67) higher when exposures lasted ≥3 hours (vs. shorter durations) among unvaccinated and partially-vaccinated individuals; excess risk associated with such exposures was reduced among fully-vaccinated individuals. Cases were less likely than controls to report mask usage during high-risk exposures (aOR = 0.50 [0.29–0.85]). The adjusted odds of case status were lower for fully-vaccinated (aOR = 0.25 [0.15–0.43]) participants compared to unvaccinated participants. Benefits of mask usage were greatest among unvaccinated and partially vaccinated participants, and in interactions involving non-household contacts or interactions occurring without physical contact.

**Comment:** This study confirmed what many of us have been saying: The risk of transmission is highest in household exposure, indoors, and exposures lasting > 3 hours. Vaccinations lower risk and masks may have a role especially among unvaccinated.

**Impact of SARS-CoV-2 variants on inpatient clinical outcome** Clin Infect Dis published online December 19, 2022

doi.org/10.1093/cid/ciac957

Inpatients with COVID-19 at five hospitals in the eastern United States were included if they had hypoxia, tachypnea, tachycardia, or fever, and SARS-CoV-2 variant data, determined from whole genome sequencing or local surveillance inference. Analyses were stratified by history of SARS-CoV-2 vaccination or infection. The average effect of SARS-CoV-2 variant on 28-day risk of severe disease, defined by advanced respiratory support needs, or death was evaluated using models weighted on propensity scores derived from baseline clinical features.

Severe disease or death within 28 days occurred for 977 (29%) of 3,369 unvaccinated patients and 269 (22%) of 1,230 patients with history of vaccination or prior SARS-CoV-2 infection.

Among unvaccinated patients, the relative risk of severe disease or death for Delta variant compared to ancestral lineages was 1.30 (95% confidence interval [CI] 1.11-1.49) Compared to Delta, this risk for Omicron patients was 0.72 (95% CI 0.59-0.88) and compared to ancestral lineages was 0.94 (95% CI 0.78-1.1). Among Omicron and Delta infections, patients with history of vaccination or prior SARS-CoV-2 infection had half the risk of severe disease or death (adjusted hazard ratio 0.40, 95% CI 0.30-0.54).

**Comment:** Although risk of severe disease or death for unvaccinated inpatients with Omicron was lower than Delta, it was similar to ancestral lineages. Severe outcomes were less common in vaccinated or patients with prior SARS-CoV-2.

## Outcomes and Adverse Effects of Baricitinib Versus Tocilizumab in the Management of Severe COVID-19 Crit Care Med published online December 19, 2022

*DOI:* 10.1097/CCM.0000000000005756

This is a retrospective observational cohort trial of 11 acute care hospitals in Georgia. Adult patients with severe COVID-19 who received at least one dose of either baricitinib or tocilizumab between June 2021 and October 2021 were included. The primary outcome was in-hospital mortality. The key secondary outcome was occurrence rate of adverse effects.

A total of 956 patients were identified. The median age was 57 years, and 53% were of male sex. The median body mass index was 33.5, and more than 94% of the population was unvaccinated. Propensity score matching by baseline characteristics resulted in a total of 582 patients, 291 in each group. There was no difference in mortality between the two groups; however, the occurrence rate of adverse effects was significantly higher in the tocilizumab group compared with baricitinib: secondary infections (32% vs 22%; $p < 0.01$); thrombotic events (24% vs 16%; $p < 0.01$); and acute liver injury (8% vs 3%; $p < 0.01$).

**Outcomes for Propensity Score-Matched Groups**

| Outcome | Baricitinib, *N* = 291 | Tocilizumab, *N* = 291 | Adjusted OR (95% CI) | *p* |
|---|---|---|---|---|
| Primary outcome | | | | |
| In-hospital mortality, *n* (%) | 90 (30.9) | 93 (32.0) | 0.95 (0.7–1.4) | 0.79 |
| Secondary outcomes | | | | |
| Adverse effects, *n* (%) | 102 (35.1) | 143 (49.1) | 0.6 (0.4–0.8) | < 0.01 |
| Infection | 64 (22.0) | 92 (31.6) | 0.6 (0.4–0.9) | < 0.01 |
| Thrombotic events | 47 (16.2) | 71 (24.4) | 0.6 (0.4–0.9) | < 0.01 |
| Acute kidney injury | 19 (6.5) | 22 (7.6) | 0.9 (0.5–1.6) | 0.63 |
| Acute liver injury | 9 (3.1) | 24 (8.3) | 0.4 (0.2–0.8) | < 0.01 |
| Time to OS < 5 or discharge (d), median (IQR)[a] | 5.0 (0.0–13.0) | 5.0 (0.0–15.0) | NA | 0.63 |
| Change in OS from day 1 to day 14, median (IQR) | −1.0 (−6.0 to 1.0) | 0.0 (−6.0 to 1.0) | NA | 0.98 |
| Hospital LOS (d), median (IQR) | 14.0 (9.0–23.0) | 13.0 (8.0–22.0) | NA | 0.26 |
| ICU LOS (d), median (IQR) | 5.0 (0.0–13.0) | 5.0 (0.0–15.0) | NA | 0.76 |
| Progression to MV or extracorporeal membrane oxygenation, *n* (%) | 69 (23.7) | 71 (24.4) | 1.0 (0.7–1.4) | 0.85 |

**Comment:** In this study of a large retrospective cohort of 582 propensity score-matched adult patients, there was no significant difference in the in-hospital mortality when baricitinib or tocilizumab was used for the management of severe COVID-19. However, there was a higher rate of adverse effects with tocilizumab. The NIH and IDSA guidelines recommend tocilizumab or baricitinib in the management of severe COVID-19. The high percentage of unvaccinated patients experiencing severe disease noted in this study is consistent with CDC incidence reports during the same time frame in which 98% of severe Covid-19 cases and 98% of Covid-19–associated deaths occurred in unvaccinated patients. Although vaccination may impact the likelihood of developing severe COVID-19, it is unlikely to significantly impact response to therapies like baricitinib and tocilizumab once severe COVID-19 has developed. Some characteristics, such as pre-existing conditions and vaccination status, were incomplete in the medical records. Significant percentages of baseline laboratory values were also missing, precluding multiple imputation, and making comparisons difficult. As a result, they were excluded from PSM (propensity scored match). Accurate estimation of race could not be done via EMRs and was not included in the study. As all patients who met criteria were included, they did not perform power and sample size calculations. Although they matched patients for potential confounding variables that are known to influence Covid-19 outcomes, there may be others that have yet to be determined and were not included in our data collection or PSM scheme.

A recently published single-center, retrospective, observational study found no difference in clinical outcomes or adverse effects with baricitinib or tocilizumab. The study considered several similar patient factors including age, sex, BMI, comorbid conditions, vaccination status, concurrent steroid or remdesivir use, and severity of Covid-19 illness at baseline. However, this study differed from current study in that the only adverse effect assessed was development of secondary infections. In addition, the study was much smaller, including only 98 total patients, and was likely underpowered. Although lacking statistical significance, the rates of death and secondary infections were numerically lower in the baricitinib group. [Medicina (Kaunas) 2022; 58:513]