Infectious Diseases Watch

February 28,2022

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General Infectious Diseases

Blood Culture Utilization in the Hospital Setting: A Call for Diagnostic Stewardship

J Clin Microbiol published online July 14, 2021

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1. Blood cultures are the test of choice to diagnose bacteremia; however, 90% or more of blood cultures in routine clinical practice do not grow any organisms, suggesting that many are likely not indicated.
2. A large portion of blood cultures ordered in the hospital are to evaluate fever or leukocytosis, both of which have been found to correlate poorly with bacteremia.
3. Optimizing blood culture use is important both to ensure true bacteremia is identified, particularly in patients with sepsis, and to reduce harms associated with unnecessary blood cultures, such as treatment of false positive results(contaminants) with antibiotics, delays in hospital discharge and increased healthcare costs.
    a. 30-50% of blood cultures that grow organisms recover contaminants that are associated with several undesirable sequelae including unnecessary antibiotics, especially vancomycin which causes nephrotoxicity in up to 25% of exposed patients; additional testing (e.g., additional blood cultures, echocardiography or joint imaging); unnecessary removal of vascular catheters; longer hospital stay; and increased health-care costs.
    b. Improved blood culture performance (less blood culture contamination, fewer single blood cultures) has been associated with draws by phlebotomy personnel. [J Clin Microbiol 2009; 47:1021-1024] Unfortunately, many facilities are unable to cover all draws with phlebotomy personnel.
    c. In US the preferred approach is the multi- sampling strategy approach and its advantages include a better chance to discriminate between blood culture contamination and true bacteremia and a hypothetical advantage of improving bacteremia detection, and its major disadvantage being a higher rate of solitary blood cultures. [Drawing blood cultures through a line should be discouraged since drawing blood cultures through a line increases blood culture contamination. The exception may be to determine if a line is the source of the bacteremia]
    d. Pawlowicz et al [General Internal Medicine and Cl Innovations 2016; 1:20-25] Suggested criteria for drawing blood cultures using a clinical decision tool included immunocompromised status, hemodynamic instability, one major (suspected endocarditis, temperature ≥39.4C, presence of indwelling vascular catheter) or two minor (temperature 38.3-39.3C, age >64, chills/rigors, vomiting, systolic blood pressure <90mmHg, peripheral white count >18,000/mm3, bands >5%[most use >10], platelet count <150,000/μL, creatinine >2.0mg/dL), and CAP patients with severe disease (based on 2007 CAP guidelines)

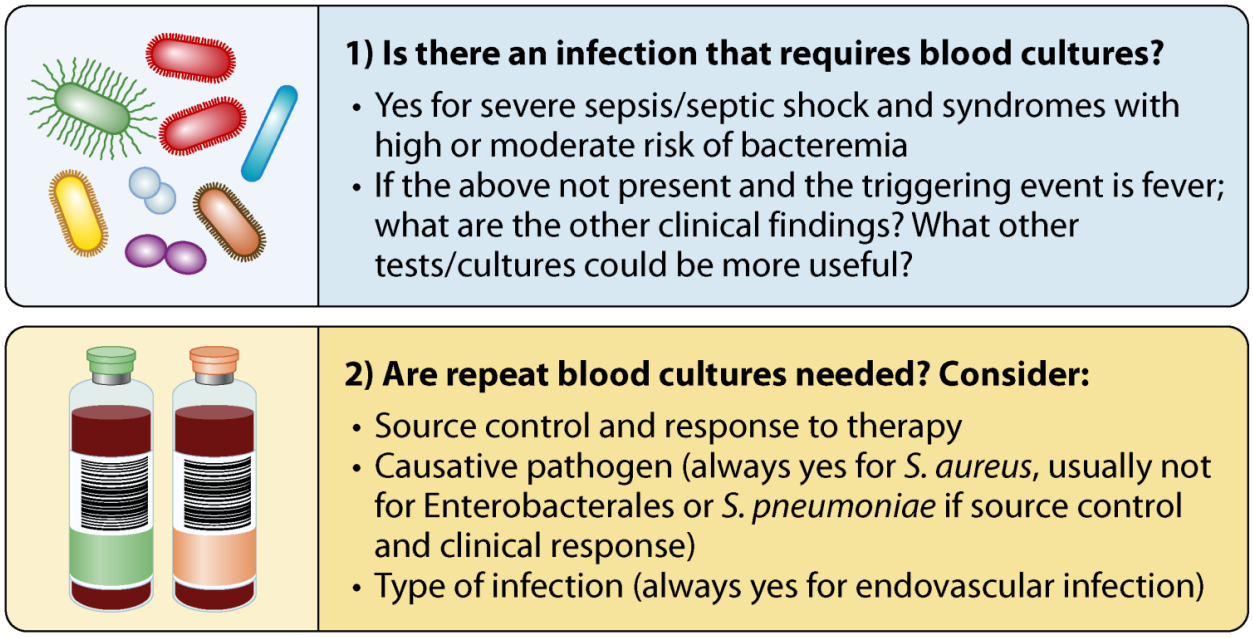
e. Hopkins[current article]: In this algorithm, consideration for initial blood cultures is based on the pre- test probability of bacteremia (high or moderate) and host characteristics (e.g., risk of endovascular infection) so that blood cultures are indicated for syndromes with high likelihood of bacteremia such as meningitis or infective endocarditis, for syndromes with moderate likelihood of bacteremia when cultures from the primary source of infection are not available or will be delayed (e.g., cholangitis), when the patient is at high risk of endovascular infection (e.g., patients with prosthetic heart valves, vascular grafts, implantable defibrillator/pacemaker, valvular heart disease, injection drug use) or when the results will impact patient management (e.g., severe non-purulent cellulitis in immunocompromised patient). Consideration for repeat blood cultures is based on the organism growing in blood (e.g., always for *S. aureus* given the frequency of persistent bacteremia and the clinical implication of this finding) [would add *Candida* spp], source of infection (e.g., always for endovascular infection) and clinical response and source control (e.g., not indicated in *Enterobacterales* bacteremia of urinary or abdominal source or in *S. pneumoniae* bacteremia in the setting of pneumonia if adequate clinical response and source control).

f. Timing of blood culture collection in 1,436 febrile adult patients admitted with bacteremia and found that bacteremia detection was not enhanced by obtaining blood cultures closer to the time of the temperature spike regardless of patient age and pathogen causing bacteremia. [J Clin Microbiol 2008; 46:1381-1385]

4. Blood volume, including both volume per blood culture bottle and overall blood volume, has been recognized as a major determinant of blood culture sensitivity.
    a. Up to 40% of blood cultures drawn in adults are single blood cultures (i.e., one set instead of the recommended two to three blood culture sets)
    b. Up to 80% of blood cultures collected from adults and children are inappropriately filled (mostly underfilled) [Clin Infect Dis 2020; 70:262-268]

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

High diagnostic value of *repeat* blood cultures	**Exceptions**
• To document clearance of *S. aureus* bacteremia • To document clearance of *S. lugdunensis* bacteremia • Any organism suspected to be causing infective endocarditis/endovascular infection • Concern for persistent bacteremia • To distinguish contamination from true bacteremia	**NA**
Low diagnostic value of *repeat* blood cultures	**Exceptions**
• *S. pneumoniae* or β-hemolytic streptococci bacteremia from pulmonary source • Gram-negative organisms from urinary/abdominal source • *Enterococcus* bacteremia from urinary or biliary source • Cases likely to represent contamination*	• Infective endocarditis/endovascular infection suspected • Inadequate clinical response • Absence of source control



Comment: This is a nice companion article to the article reviewed in ID Watch [January 17, 2022] on obtaining optimal urine cultures. Diagnostic stewardship an essential component to a robust and effective antimicrobial stewardship program.

Descriptive Epidemiology and Outcomes of Nonventilated Hospital-Acquired, Ventilated Hospital-Acquired, and Ventilator-Associated Bacterial Pneumonia in the United States, 2012–2019 Crit Care Med 2022; 50:460-468

DOI: 10.1097/CCM.0000000000005298

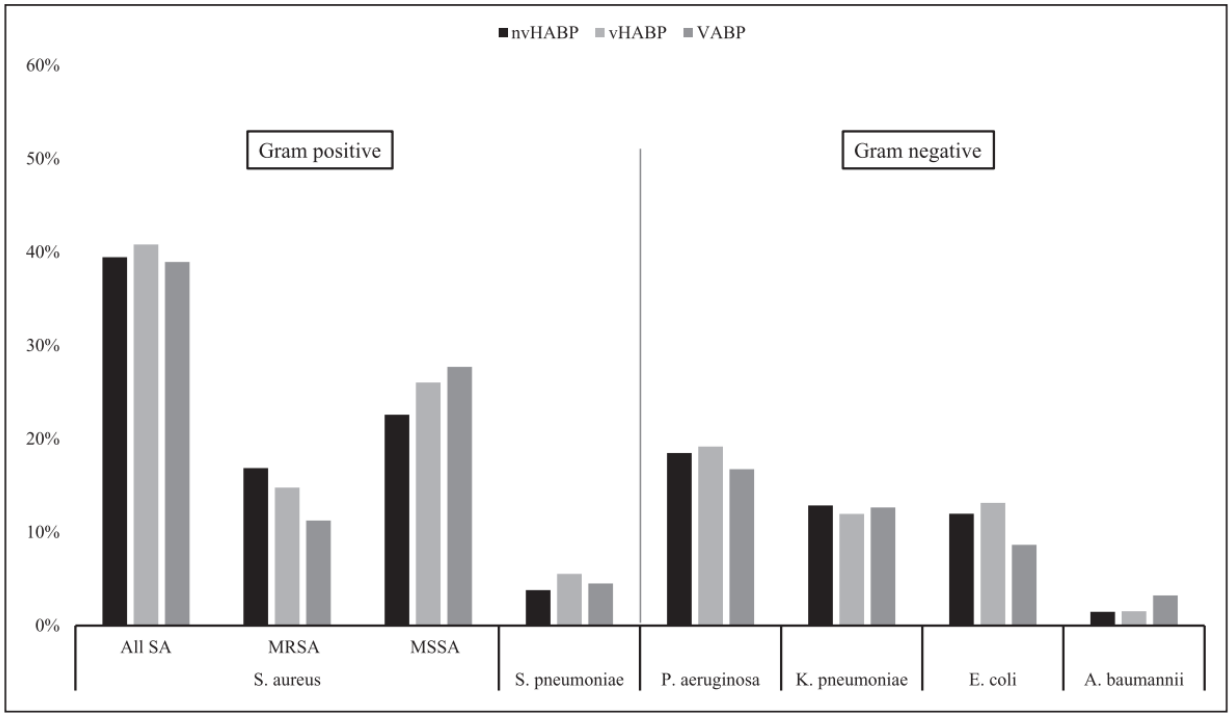
Microbiology, empiric therapy and its impact on the outcomes of non-ventilated hospital-acquired, ventilated hospital-acquired, and ventilator-associated bacterial pneumonia in the United States, 2014–2019. Infect Control Hosp Epidemiol published online February 2022

Hospital-acquired pneumonia (HAP) is one of the most common and serious healthcare-associated infection with a high mortality. [NEJM 2018; 379:1732-1744] Antibiotic prescribing for possible HAP is one of the most common reasons of broad-spectrum antimicrobial use. The diagnosis of HAP is challenging and clinically may mimic other clinical entities such as CHF, atelectasis, pulmonary emboli, COPD, ARDS etc. This leads to diagnostic uncertainty and the potential for overtreatment especially with broad spectrum antibiotics. Many of the studies on this topic were published over a decade ago. These two papers by the same authors attempt to explore the epidemiology and outcomes of patients with HAP.

First a few definitions: Pneumonia was defined as HABP if at the time of the index culture the patient was not on MV and VABP if at the time the index culture the patient had been on MV for more than 3 days. HABP was further subdivided into vHABP and nvHABP. Specifically, vHABP designation was given for patients who needed MV less than or equal to 5 days following the onset of index HABP episode and nvHABP if MV was not required.

In the paper in Crit Care Med the investigators performed a multicenter retrospective cohort study of patients with nvHABP, vHABP, or VABP. Two hundred fifty-three acute-care hospitals in US, contributed data (including microbiology) to Premier database, 2012–2019. Patients with hospital-acquired bacterial pneumonia or ventilator associated bacterial pneumonia identified based on a slightly modified previously published *International Classification of Diseases,* 9th Edition/*International Classification of Diseases,* 10th Edition-Clinical Modification algorithm.

Among 17,819 patients who met enrollment criteria, 26.5% had nonventilated hospital-acquired bacterial pneumonia, 25.6% vHAPB, and 47.9% ventilator-associated bacterial pneumonia. Patients with nonventilated hospital-acquired bacterial pneumonia were oldest (mean 66.7 ± 15.1 yr), whereas those with ventilator-associated bacterial pneumonia were youngest (59.7 ± 16.6 yr). Ventilated hospital-acquired bacterial pneumonia was associated with the highest comorbidity burden (mean Charlson score 4.1 ± 2.8) and ventilator-associated bacterial pneumonia with the lowest (3.2 ± 2.5). Similarly, hospital mortality was highest among patients with ventilated hospital-acquired bacterial pneumonia (29.2%) and lowest in nonventilated hospital-acquired bacterial pneumonia (11.7%), with ventilator-associated bacterial pneumonia in-between (21.3%). Among survivors, 24.5% of nonventilated hospital-acquired bacterial pneumonia required a rehospitalization within 30 days of discharge, compared with 22.5% among ventilated hospital-acquired bacterial pneumonia and 18.8% ventilator-associated bacterial pneumonia. Unadjusted hospital length of stay after infection onset was longest among ventilator-associated bacterial pneumonia and shortest among nonventilated hospital-acquired bacterial pneumonia patients. Median total hospital costs mirrored length of stay: ventilator-associated bacterial pneumonia $77,657, ventilated hospital-acquired bacterial pneumonia $62,464, and nonventilated hospital acquired bacterial pneumonia $39,911. The microbiology is shown below. S aureus is still the #1 with MSSA>MRSA. Pseudomonas is most common gram-negative.



The second article provides helpful new data on not just the pathogens, but also antimicrobial susceptibilities associated with HABP. The authors are the same and they use the same dataset. Approximately half the patients had VABP and half had nvHABP. Of the patients with nvHABP, about half required mechanical ventilation and half did not. The pathogens associated with VABP, nvHABP requiring mechanical ventilation, and nvHABP not requiring mechanical ventilation were relatively similar (see above from CCM): Staphylococcus aureus accounted for about 40%, Pseudomonas aeruginosa accounted for 17%–19%, Klebsiella pneumoniae accounted for 12%–13%, and Escherichia coli accounted for 9%– 13%. Antibiotic resistance rates were also fairly similar across all 3 HABP types: about 40% of Staphylococcus aureus isolates were MRSA, 13%–15% of gram-negative isolates were resistant to third generation cephalosporins, 7%–9% were resistant to carbapenems, and 15%–16% were resistant to antipseudomonal β-lactams.

Inappropriate empiric regimens were prescribed for 7% of patients with VABP, 6% of patients with nvHABP requiring mechanical ventilation, and 9% of nvHABP who did not require mechanical ventilation. Inappropriate empiric therapy was associated with longer lengths of stay (1.8 extra days for VABP, 2.3 extra days for nvHABP requiring mechanical ventilation, 8.7 extra days for nvHABP not requiring mechanical ventilation) and higher hospital costs but not with increased mortality or 30-day readmissions. The authors concluded that for HABP we should consider empiric broad spectrum antibiotics to cover ESBL and carbapenem resistant organisms.

Comment: There is much to learn from these two articles. First the pathogens associated with these 3 HAPs are similar with S aureus and Pseudomonas leading the way. I look at the susceptibility differently from the authors of these articles. There is a misperception that antimicrobial resistance is high for HAIs. In these studies, the susceptibility rates are 84%–93%. To include carbapenems for all empiric regimens for HABP means treating about 85% of patients with a broader regimen than is justified. The authors did not consider the

overdiagnosis of pneumonia. The signs and symptoms of pneumonia are not specific and overlap with common conditions including heart failure, atelectasis/mucous plugging, ARDS, thromboembolic disease, etc. The risk of overtreatment is an important consideration. Studies have emerged indicating that overtreatment can be as harmful as undertreatment. A recent study found that unnecessarily broad antibiotic regimens for patients with sepsis was associated with increased risk for hospital mortality, AKI, adverse events, and C. difficile infection. [JAMA Netw Open 2020;3:e202899**]** Rather I believe empiric antibiotics should be based on local epidemiology and susceptibilities. Finally, the best way to decrease antibiotic use is to prevent HABP in the first place. We have had decades of studies on best practice practices on preventing VAP, but very few studies on preventing nvHABP. In addition, most hospitals have focused at preventing VABP, but recent studies have shown that most HABP are in nonventilated patients. We urgently need research on best practice in preventing nvHABP.

COVID-19

COVID-19 News

FDA Eyes Second Covid-19 Booster Shot

U.S. health regulators are looking at potentially authorizing a fourth dose of a Covid-19 vaccine in the fall. The authorization would depend on ongoing studies establishing if a fourth dose will reduce their risk of symptomatic and severe disease. Among the issues that need to be resolved is whether the second booster should be authorized for all adults or particular age groups, and whether it should target the Omicron variant or be formulated differently. Whether the fourth booster could ultimately be the start of an annual Covid-19 vaccination is also under consideration.

Comment: In January, Israel's health ministry published an initial study saying a fourth shot provided threefold protection against serious illness and twofold protection against infection compared with people who were four months after their third shot, however, Israeli researchers in a separate study cast doubt on whether a fourth shot added significant protection against Omicron. The Israeli government has cleared use of four doses in certain groups of people, including those who are at least 60 years old, the immunocompromised and healthcare workers.

Sanofi, Glaxo Seek Covid-19 Vaccine Approval

Sanofi SA and GlaxoSmithKline said they are seeking EUA authorization for their Covid-19 vaccine. Sanofi and Glaxo said Wednesday that their vaccine was 100% effective at preventing severe disease and 75% effective against moderate-to-severe illness. The vaccine was 57.9% effective at preventing any symptomatic disease,

Comment: The vaccine combines a synthetic version of the virus's spike protein with an adjuvant. The approach, is like that used by Novavax.

FDA authorizes revisions to Evusheld dosing February 24, 2022

Based on the most recent information and data available, Evusheld may be less active against certain Omicron subvariants. The dosing regimen was revised because available data indicate that a higher dose of Evusheld may be more likely to prevent infection by the COVID-19 Omicron subvariants BA.1 and BA.1.1 than the originally authorized Evusheld dose.

Previously, the authorized Evusheld dosage was 150 mg of tixagevimab and 150 mg of cilgavimab administered as two separate consecutive intramuscular injections, with repeat doses every six months while SARS-CoV-2 remains in circulation. With this EUA revision, FDA has increased the initial authorized dose to 300 mg of tixagevimab and 300 mg of cilgavimab. Patients who have already received the previously authorized dose (150 mg of tixagevimab and 150 mg of cilgavimab) should receive an additional dose of 150 mg of tixagevimab and 150 mg of cilgavimab as soon as possible to raise their monoclonal antibody levels to those expected for patients receiving the higher dose.

Comment: This is an important revision to provide optimal dosing for our most vulnerable individuals.

BA.2 Update

WHO announced on February 22 that sequences of the BA.2 omicron subvariant are rising, with the strain now dominant in 18 countries. So far, the strain has been detected in 85 countries and is now dominant in 18. "This trend is most pronounced in the Southeast Asia region, followed by the Eastern Mediterranean, African, Western Pacific and European regions.

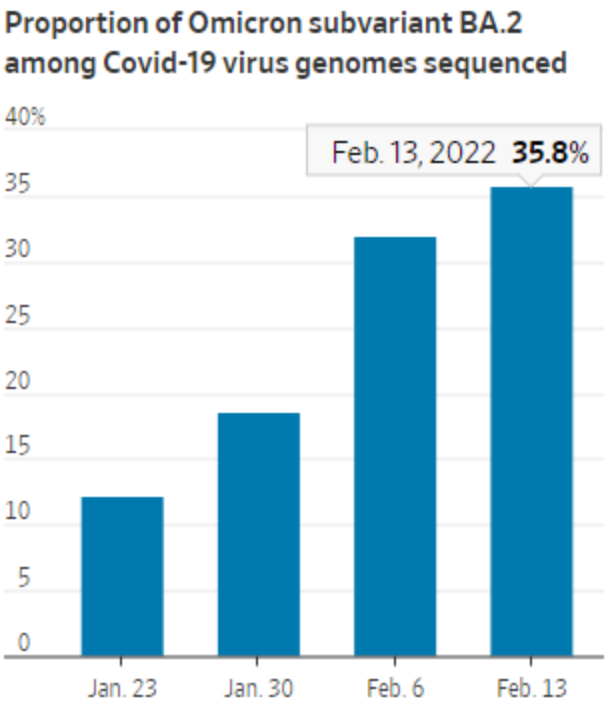
As of Feb. 21, the US has identified 1,359 COVID-19 cases involving BA.2. The strain has been identified in every state but Iowa, Maine and Oklahoma, though its overall prevalence in each state is very low, accounting for 0.38 percent or less of all samples sequenced. See below

Initial data indicates BA.2 has a growth advantage over BA.1. The WHO said in its Feb. 15 weekly update that early evidence based on growth rates in Denmark indicate the strain is 30 percent more transmissible than BA.1.

Although there have been documented cases of reinfection with BA.2 after infection with BA.1, though early data based on population-level studies suggest that infection with BA.1 provides strong protection against reinfection from the omicron subvariant. (See Journal Review [medRxiv[)

So far, real-world data from South Africa, the U.K. and Denmark have found no significant difference in disease severity between BA.2 and BA.1. Investigators are continuing to monitor whether the efficacy of current therapeutics and vaccines are affected by the subvariant.

The WHO has also said BA.2 should remain classified as an omicron sublineage rather than getting its own name, based on available data so far.



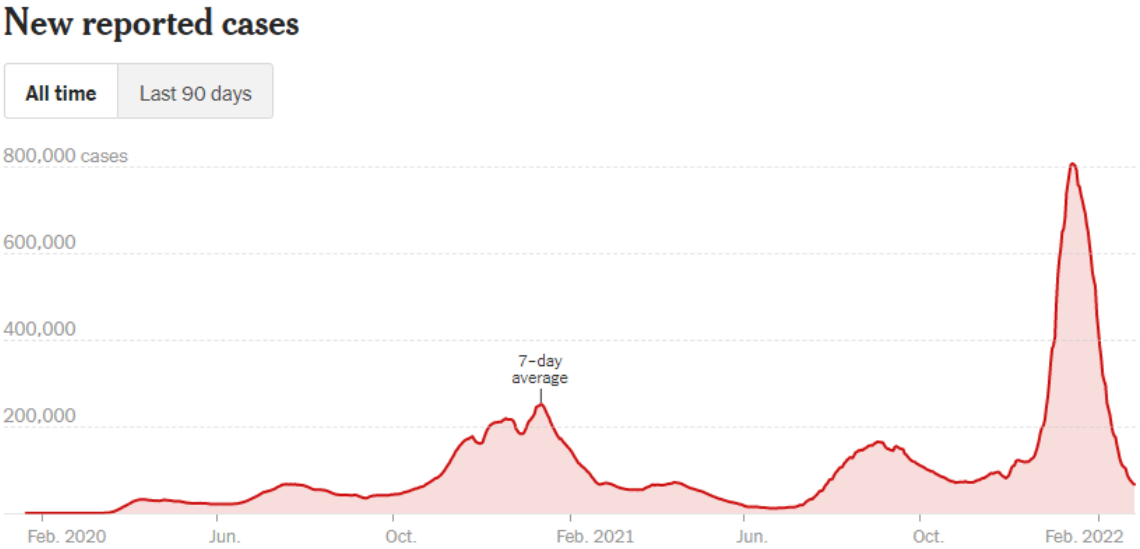
Comment: So far in US <5% of subvariants is BA.2 -see below Delta is now zero!

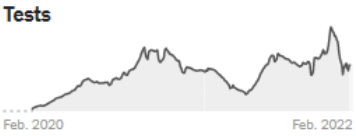
United States: 2/13/2022 – 2/19/2022 NOWCAST

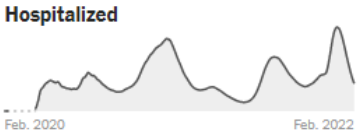
USA

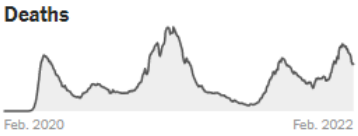
WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.1.1	VOC	75.6%	71.1-79.7%
	B.1.1.529	VOC	20.6%	16.7-25.1%
	BA.2	VOC	3.8%	3.0-4.8%
Delta	B.1.617.2	VOC	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

COVID-19 by the Numbers









	DAILY AVG. ON FEB. 26	14-DAY CHANGE	TOTAL REPORTED
Cases	66,441	-63%	78,825,844
Tests	1,381,683	+25%	—
Hospitalized	53,767	-44%	—
In I.C.U.s	10,202	-43%	—
Deaths	1,872	-24%	946,686

Comment: The numbers speak for themselves. Continued sharp decrease in new cases, hospitalizations, and deaths. I believe we now have increasing level of immunity after Omicron between vaccinated and naturally infection. In addition to vaccines, we have greater access to testing and better therapeutics. I think we are turning the corner on this chapter of the pandemic.

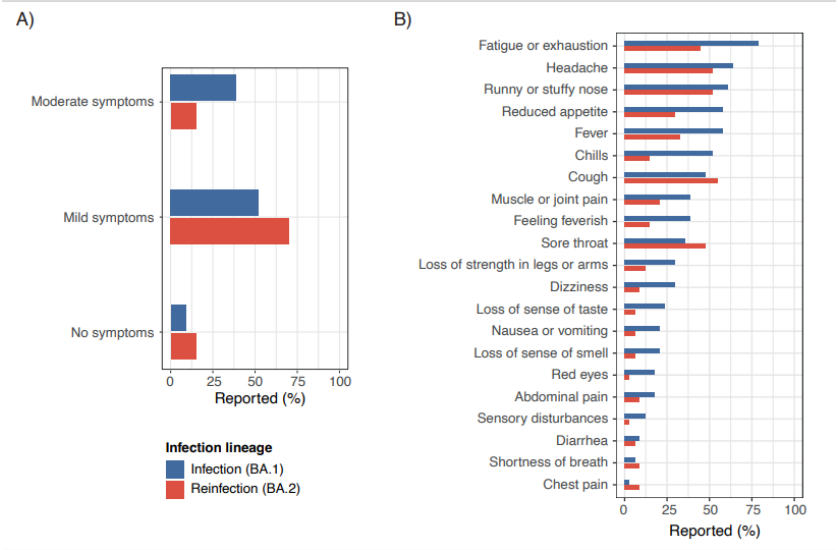
Journal Review

Occurrence and significance of Omicron BA.1 infection followed by BA.2 reinfection medRxiv posted online February 22, 2022

doi.org/10.1101/2022.02.19.22271112

With the surge of Omicron subvariants BA.1 and BA.2 in Denmark, a large number of reinfections from earlier cases had been observed, raising the question of whether BA.2 specifically can escape the natural immunity acquired shortly after a BA.1 infection.

To investigate this, they selected a subset of samples from more than 1,8 million cases of infections in the period from November 22, 2021, until February 11, 2022. Here, individuals with two positive samples, more than 20 and less than 60 days apart, were selected. From a total of 187 reinfection cases, they identified 47 instances of BA.2 reinfections shortly after a BA.1 infection, mostly in young unvaccinated individuals with mild disease not resulting in hospitalization or death. To evaluate if cases of Omicron BA.2 reinfections are caused by a specific subset of BA.2 variants circulating with intrinsically different properties than BA.2 in general, they compared the paired samples with randomly sampled Danish BA.1 and BA.2 genomes. They found no sign of clustering among BA.2 or BA.1 variants involved in reinfection compared with the randomly selected BA.1 and BA.2 sequences. They also observed significantly reduced overall viral load in secondary BA.2 infection samples compared to initial infection together with a lower ratio of subgenomic to genomic RNA. Taken together, this may suggest a more superficial and transient secondary infection that could be explained by T cell-mediated immunity obtained during the first infection.



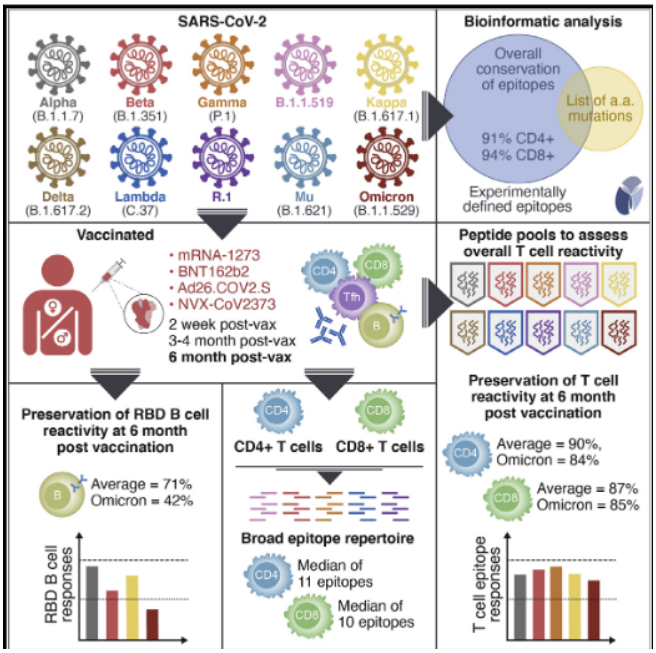
Comment: This study provided evidence that Omicron BA.2 reinfections can occur shortly after BA.1 infections but are uncommon and mild. The role of T-cell immunity appears important. (See articles that follow)

SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from Alpha to Omicron Cell published January 24, 2022

doi.org/10.1016/j.cell.2022.01.015

The La Jolla Institute for Immunology recruited healthy adults who had received the first and, when applicable, second dose of a COVID-19 vaccination including Moderna, Pfizer, J&J, and Novavax. The goal was to determine whether T cell responses induced by different vaccine platforms cross-recognize early SARS-CoV-2 variants. Blood was collected blood draws when possible two weeks after each vaccine dose administered (timepoint 1 and timepoint 2), 3.5 months after the last dose received (timepoint 3) and/or 5-6 months after the last dose (timepoint 4). All donors had their SARS-CoV-2 antibody titers measured by ELISA. Additional information on gender, ethnicity, age and timepoint of collection of the vaccinee cohorts were recorded.

T cell responses to early variants were preserved across vaccine platforms. By contrast, significant overall decreases were observed for memory B cells and neutralizing antibodies. In subjects 6 months post-vaccination, 90% (CD4+) and 87% (CD8+) of memory T cell responses were preserved against variants on average, and 84% (CD4+) and 85% (CD8+) preserved against Omicron. However, Omicron RBD memory B cell recognition was substantially reduced to 42% compared with other variants. T cell epitope repertoire analysis revealed a median of 11 and 10 spike epitopes recognized by CD4+ and CD8+ T cells, with average preservation > 80% for Omicron.



Human memory T cells induced by SARS-CoV-2 vaccines maintain the ability to recognize viral variants, including the Omicron variant.

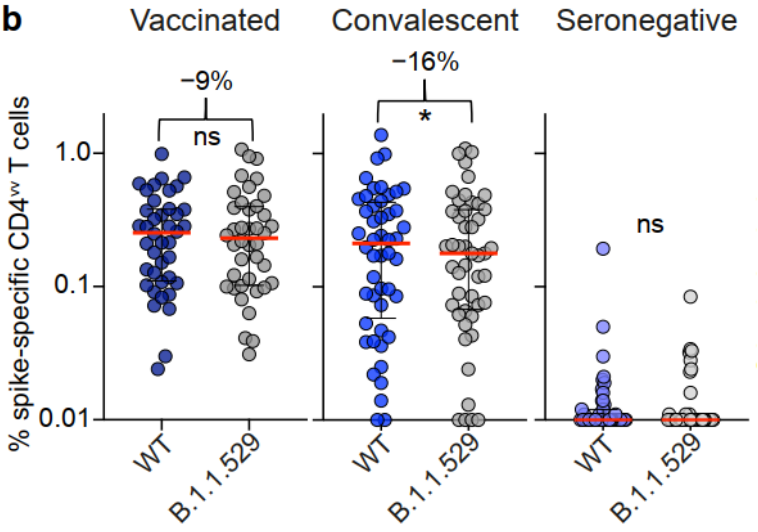
Comment: In summary T cells of vaccinees recognize SARS-CoV-2 variants, including Omicron, however, RBD memory B cells' recognition of Omicron was reduced. There was an average preservation > 80% for Omicron at the epitope level. This article confirms functional preservation of most T cell responses which continues to play an important role as a second-level defense against diverse variants and severe disease.

Ancestral SARS-CoV-2-specific T cells cross-recognize the Omicron variant Nat Med published online January 14, 2022

The investigators collected peripheral blood mononuclear cells from vaccinated individuals 6 months after a second dose of the Pfizer vaccine and individuals in the convalescent phase 9 months after mild or severe COVID-19, and seronegative individuals. Activation-induced marker assays were used to quantify spike-specific $CD4_+$ T cell responses via the upregulation of
CD69 and CD40L (CD154) and spike-specific $CD8_+$ T cell responses via the upregulation of CD69 and 4-1BB (CD137).

The median relative frequencies of SARS-CoV-2 spike-specific $CD4_+$ T cells that cross-recognized B.1.1.529 in previously infected or Pfizer-vaccinated individuals were 84% and 91%, respectively and the corresponding median relative frequencies for SARS-CoV-2 spike-specific $CD8_+$ T cells were 70% and 92%, respectively. Pairwise comparisons across groups further

revealed that SARS-CoV-2 spike-reactive CD4+ and CD8+ T cells were functionally and phenotypically similar in response to the ancestral strain or Omicron.



Comment: Collectively, the data indicate that established SARS-CoV-2 spike-specific CD4+ and CD8+ T cell responses, especially after Pfizer vaccination remains mostly intact against Omicron. See next article.

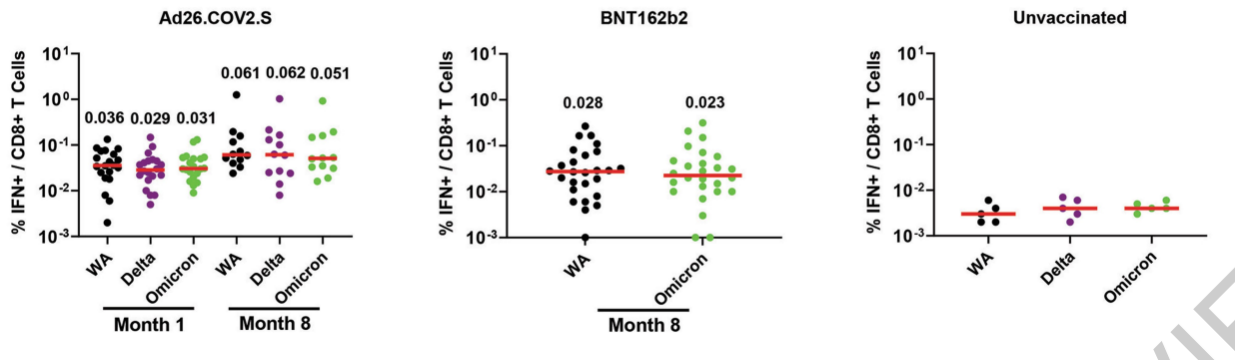
Vaccines Elicit Highly Conserved Cellular Immunity to SARS-CoV-2 Omicron

Nature published online January 31, 2022

doi.org/10.1038/s41586-022-04465-y

The Omicron variant has been shown to evade neutralizing antibody responses elicited by current vaccines that encode the ancestral Spike. In this study, all individuals were SARS-CoV-2 naïve by history and also had negative antibody responses to nucleocapsid were included. Following Pfizer vaccination, the investigators observed high WA1/2020(ancestral strain)-specific pseudovirus NAb responses at month 1, followed by a sharp decline by month 8 ($P<0.0001$) as expected. Following J&J vaccination, there were substantially initial lower WA1/2020-specific pseudovirus NAb responses at month 1, but these responses were more durable and persisted at month 8. However, minimal cross-reactive Omicron-specific NAbs were observed for both vaccines ($P<0.0001$ for both), consistent with recent data in the absence of additional boosting.

On the other hand, cellular immunity stimulated by current SARS-CoV-2 vaccines is highly conserved to the SARS-CoV-2 Omicron Spike. Individuals who received J&J or Pfizer vaccines demonstrated durable Spike-specific CD8+ and CD4+ T cell responses, which showed extensive cross-reactivity against both the Delta and Omicron variants, including in central and effector memory cellular subpopulations. Median Omicron Spike-specific CD8+ T cell responses were 82-84% of WA1/2020 Spike-specific CD8+ T cell responses.



Comment: These data provide immunologic context for the observation that current vaccines still show robust protection against severe disease with the SARS-CoV-2 Omicron variant despite the substantially reduced neutralizing antibody responses. Cellular immune responses, especially CD8+ T cell responses, likely contribute to protection against severe SARS-CoV-2 disease and death. This is a consistent theme of multiple papers including the articles reviewed in this issue of ID Watch.

Population Immunity and Covid-19 Severity with Omicron Variant in South Africa

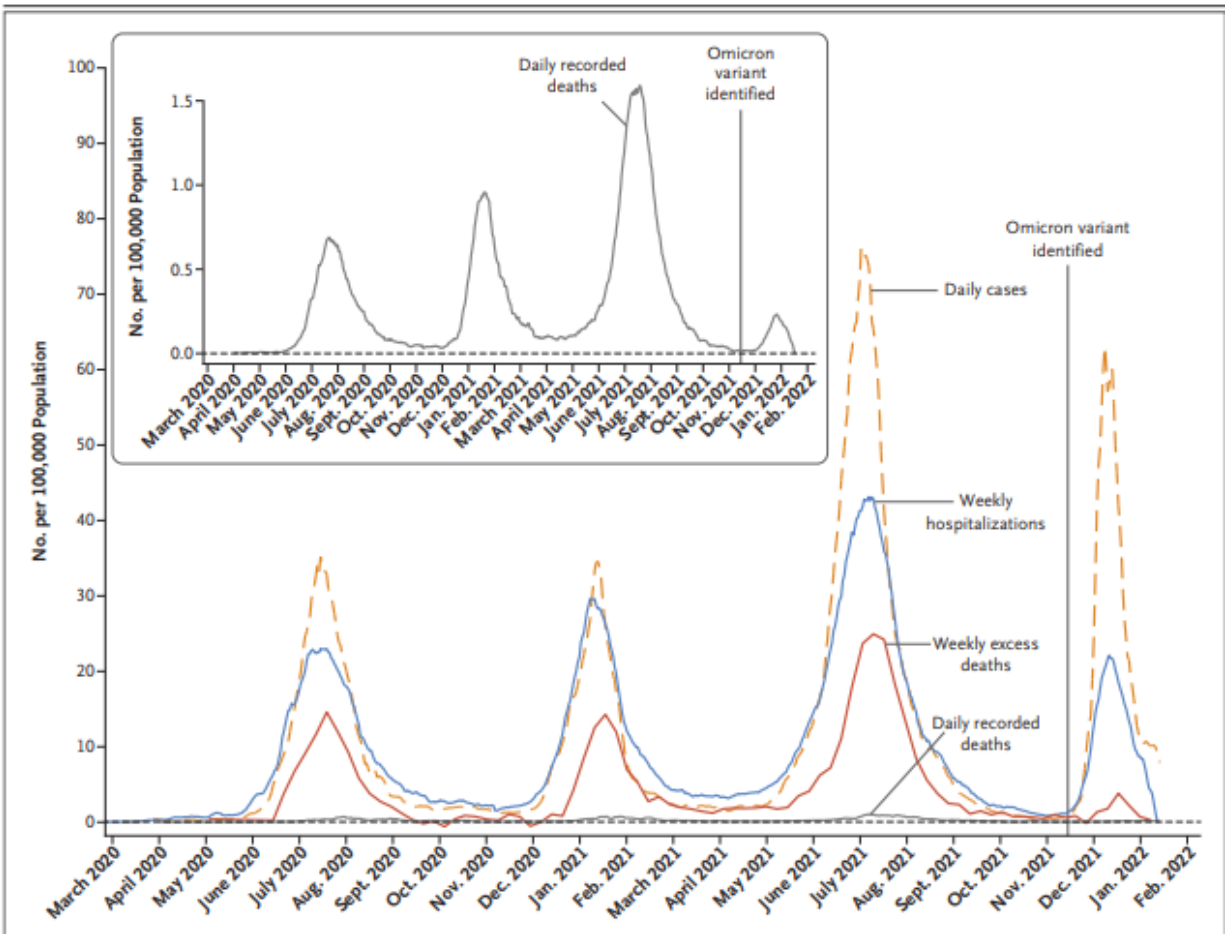
N Engl J Med published online February 23, 2022

DOI: 10.1056/NEJMoa2119658

South African investigators analyzed dried-blood samples from participants from 3,047 households from October 22 to December 9, 2021. They looked for anti–SARS-CoV-2 immunoglobulin G (IgG) antibodies and assessed COVID-19 cases, hospitalizations, and deaths and excess deaths through Jan 12, 2022. Omicron was first identified in the region on November 25, 2021 but didn't become dominant until December.

Of the 7,010 participants, 18.8% had been vaccinated against COVID-19. IgG seroprevalence ranged from 56.2% (95% confidence interval [CI], 52.6% to 59.7%) among children younger than 12 years to 79.7% (95% CI, 77.6% to 81.5%) in adults older than 50. Vaccinated participants had higher rates of IgG seropositivity than their unvaccinated peers (93.1% vs 68.4%).

A study of many of the same participants in January 2021 had found that 19.1% of the population had anti–SARS-CoV-2 IgG. According to epidemiologic data, COVID-19 cases rose and then declined faster during the study period than in previous surges, and cases were milder as well, with lower rates of hospitalization, death, and excess death.

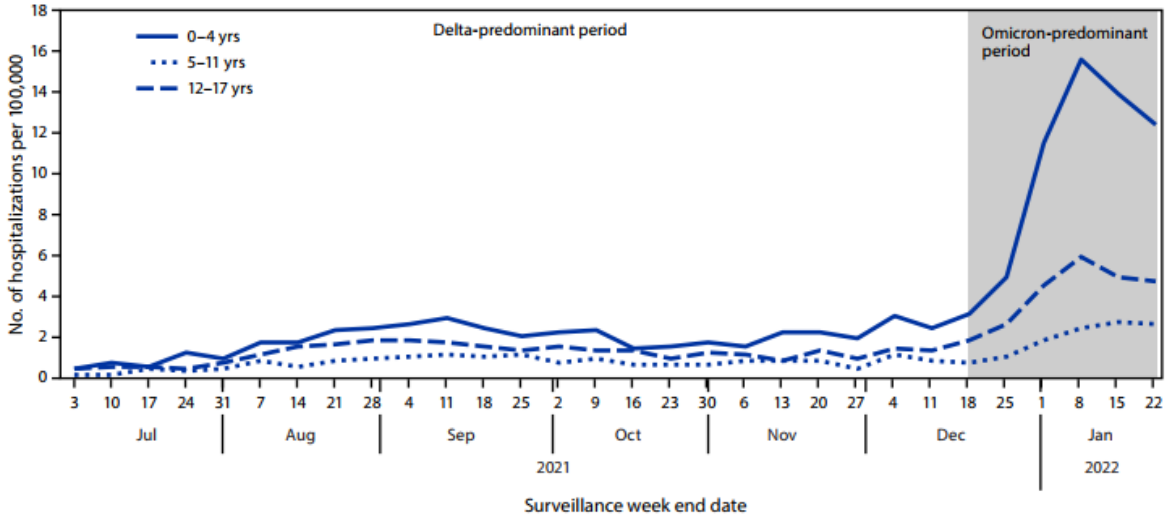


Comment: Epidemiologic data showed a decoupling of hospitalizations and deaths from infections while omicron was circulating. In this part of South Africa, immunity levels were very high, even though vaccination rates were low, suggesting that there had been a considerable amount of infection during earlier outbreaks. The authors think that the evolution of cell-mediated immunity from previous natural infection and vaccination has resulted in the decoupling of the high case incidence seen with the omicron variant from the incidence of severe disease (hospitalizations and deaths). This decoupling has occurred despite evidence that the omicron variant is immune evasive. Their hypothesis is supported by two recent publications, [see above] which indicated that most of the T-cell response induced by vaccination and/or natural infection cross-recognizes the omicron variant, thereby probably contributing to protection against severe disease. Similar to the US, their database does not distinguish between patients hospitalized for SARS-CoV-2 infection and patients hospitalized for other illnesses who incidentally had a positive test for SARS-CoV-2 on routine screening.

Hospitalizations of Children and Adolescents with Laboratory-Confirmed COVID-19 — COVID-NET, 14 States, July 2021–January 2022 MMWR 2022 / 71(7);271–278

This report analyzes data from the Coronavirus Disease 19–Associated Hospitalization Surveillance Network (COVID-NET) to describe COVID-19–associated hospitalizations among U.S. children (aged 0–11 years) and adolescents (aged 12–17 years) during periods of Delta (July 1–December 18, 2021) and Omicron (December 19, 2021–January 22, 2022) predominance. COVID-NET conducts population-based surveillance for laboratory-confirmed COVID-19–associated hospitalizations in 99 counties across 14 states. Trained surveillance staff members conducted medical chart abstractions for all pediatric COVID-NET patients using a standardized case report form through November 2021. Because of the large number of cases during December 2021, some sites examined clinical outcome data on a representative sample of hospitalized children. Data on indicators of severe disease were collected (i.e., hospital length of stay, ICU admission, use of invasive mechanical ventilation [IMV], and in-hospital death), as were data on primary reason for admission and symptoms that were present when the patient was admitted.

During the Delta- and Omicron-predominant periods, rates of weekly COVID-19–associated hospitalizations per 100,000 children and adolescents peaked during the weeks ending September 11, 2021, and January 8, 2022, respectively. The Omicron variant peak (7.1 per 100,000) was four times that of the Delta variant peak (1.8), with the largest increase observed among children aged 0–4 years. During December 2021, the monthly hospitalization rate among unvaccinated adolescents aged 12–17 years (23.5) was six times that among fully vaccinated adolescents (3.8). A higher proportion of unvaccinated adolescents (70.3%) than fully vaccinated adolescents (40.8%) had COVID-19 as a primary reason for admission. A significantly higher proportion of unvaccinated adolescents were admitted to the ICU (30.3%) than were those who were vaccinated (15.5%). In hospitalized children, there were only 11 deaths (.6%) during Delta and zero deaths during Omicron .



Comment: Once the Omicron variant became predominant, peak population-based COVID-19–associated hospitalization rates among children and adolescents were four times as high as rates during the peak of the Delta period. Children aged 0–4 years, who were ineligible for vaccination during this time, experienced the largest increase in hospitalization rates. The number of hospitalized children eligible for vaccination remained low at the time of reporting, and hospitalization rates stratified by vaccination status are subject to error if misclassification of vaccination status occurred. Because children aged 5–11 years could not meet the definition for being fully vaccinated until December 7, 2021, vaccination among this age group was not

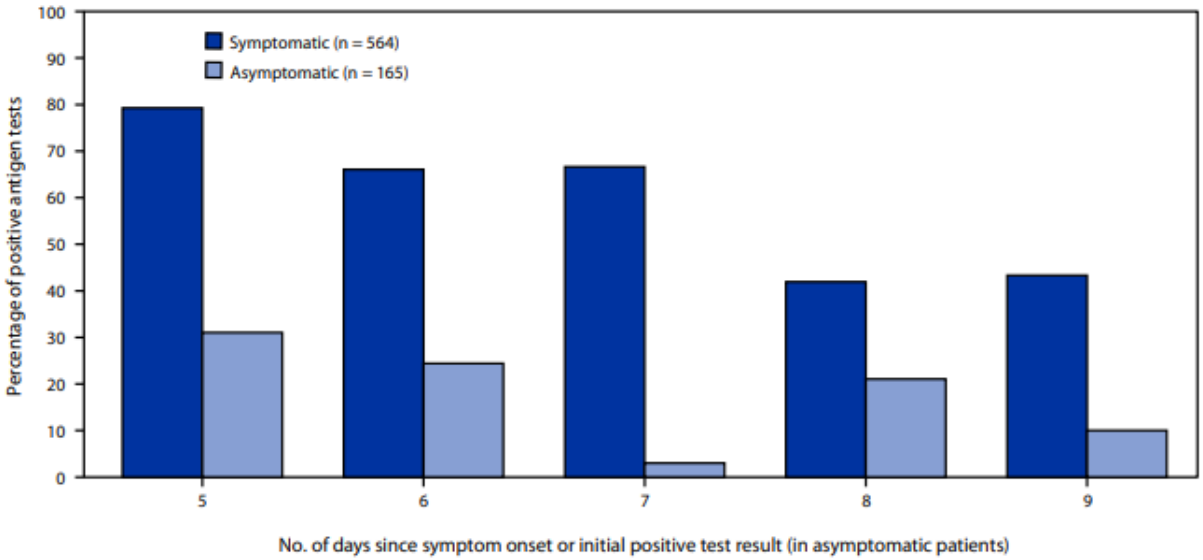
considered in this study. Only 8.3% were fully vaccinated during Delta and 22% during the Omicron wave. Further, boosters among adolescents aged 12–17 years could not be examined because the recommendation was so recent. Vaccination of eligible persons, in addition to other prevention strategies such as masking, are critical to reducing the incidence of severe COVID-19 among children and adolescents. Children remain the lowest risk of death.

Antigen Test Positivity After COVID-19 Isolation — Yukon-Kuskokwim Delta Region, Alaska, January–February 2022 MMWR 2022; 71:293-298

Isolation is recommended during acute infection with SARS-CoV-2, but the duration of infectiousness varies among individual persons. Rapid antigen test results have been correlated with detection of viable virus [J Clin Microbiol 2022;60:e0174221; J Infect Dis 2022;225:190–8] and might inform duration of isolation, but data are limited for the recently emerged Omicron variant.

On January 5, 2022, the Yukon-Kuskokwim Health Corporation (YKHC) recommended that persons with SARS-CoV-2 infection isolate for 10 days after symptom onset (or, for asymptomatic persons, 10 days after a positive nucleic acid amplification or antigen test result). However, isolation could end after 5–9 days if symptoms were resolving or absent, fever was absent for ≥24 hours without fever-reducing medications, and an Abbott BinaxNOW COVID-19 Ag (BinaxNOW) rapid antigen test result was negative.

Antigen test results and individual characteristics were analyzed among 3,502 infections reported to YKHC during January 1–February 9, 2022. After 5–9 days, 396 of 729 persons evaluated (54.3%) had a positive antigen test result, with a declining percentage positive over time. In a multivariable model, a positive antigen test result was more likely after 5 days compared with 9 days (adjusted odds ratio [aOR] = 6.39) after symptomatic infection (aOR = 9.63), and less likely after previous infection (aOR = 0.30), receipt of a primary COVID-19 vaccination series (aOR = 0.60), or after both previous infection and receipt of a primary COVID-19 vaccination series (aOR = 0.17).



Comment: Between 5 and 9 days after symptom onset or after initial diagnosis with SARS-CoV-2 infection, just over half of persons still had a positive SARS-CoV-2 antigen test meaning potential viable replicating virus capable of transmission. The proportion of positive results declined over time. Negative follow-up antigen test results were associated with asymptomatic infection, previous infection, and being vaccinated and/or prior infection. In reflecting back to the CDC revised guidance on isolation [see ID Watch January 3, 2022] and several recent publications I believe a rapid antigen test should be performed at day 5 to guide when it is safe for people to come out of isolation. The study also confirms that vaccination and/or prior infection increases viral clearance and symptomatic disease is associated with longer viral shedding.