

First, I hope everyone has had time to relax and recharge. I am sure many of you feel the way I do – exhaustion, anger and frustration, and sadness/depression all at the same time. The Delta surge continues to stress our healthcare community and appears unrelenting.

Tomorrow I will be out for a religious observance, so the Covid-19 Briefing will not be published tomorrow but in its place is the Labor Day Covid-19 Briefing.

I start with an article on vaccine safety surveillance. The next article studies VE in highly vaccinated HCWs. Keeping with this theme the next article looks at breakthrough infections in vaccinated HCWs and correlation with neutralizing antibody titers. The next two articles look at impact of Covid-19 and HAIs. The last article is an update on SARS-CoV-2 seroprevalence increasing over time.

I hope everyone has a good week.

Ed

Journal Review

Safety Surveillance of COVID-19 mRNA Vaccines Through the Vaccine Safety Datalink

JAMA published online August 3, 2021

[doi:10.1001/jama.2021.14808](https://doi.org/10.1001/jama.2021.14808)

Investigators from Kaiser Permanente Vaccine Study Center led the study, which consisted of analyzing vaccine surveillance data from the Vaccine Safety Datalink (VSD) on 6.2 million vaccinated members of eight US health plans from Dec 14, 2020, to Jun 26, 2021. Participants were 12 years or older; the mean age was 49 years, 43% were White, 22% were Hispanic, 15% were Asian, and 5% were Black.

Of 6.2 million participants, 57% received the Pfizer COVID-19 vaccine, and the remainder received Moderna. Outcomes were monitored for 1 to 21 days (risk interval) after receipt of one or two vaccine doses and compared with those of a similar group of participants 22 to 42 days postvaccination with one or two doses (comparison interval).

The incidence of ischemic stroke per 1 million person-years during the risk and comparison intervals was 1,612 versus 1,781 (rate ratio [RR], 0.97), while it was 1,179 versus 1,345 (RR, 0.82) for appendicitis, 935 versus 1,030 (RR, 1.02) for heart attack, 952 versus 896 (RR, 1.16) for venous thromboembolism, and 822 versus 825 (RR, 1.00) for Bell's palsy.

From 0 to 21 days after vaccination, there were 34 cases of myocarditis or pericarditis among participants 12 to 39 years; 85% occurred in males, 82% were hospitalized (median stay, 1 day), 6% required intensive care, and all survived to hospital release. Myocarditis and pericarditis cases were significantly clustered shortly after vaccination. In the first 7 days after vaccination. Significant clustering within the first week after vaccination, especially after dose 2, provides additional evidence of an association between mRNA vaccines and myocarditis/pericarditis in younger individuals.

The incidence of anaphylaxis (severe allergic reaction) was 4.8 per million doses of the Pfizer vaccine and 5.1 per million for Moderna. Of the 55 confirmed anaphylaxis cases, 95% were in female patients, 78% had a history of allergies, 36% had a history of anaphylaxis, 98% occurred on the day of vaccination, 87% occurred within in the first 30 minutes, and 82% occurred after the first dose.

Comment: In interim analyses of surveillance of mRNA COVID-19 vaccines, incidence of selected serious outcomes was not significantly higher 1 to 21 days postvaccination compared with 22 to 42 days postvaccination. CIs, however, were wide for many outcomes. The statistical power of these early analyses was limited, especially for the less frequent outcomes. Although vaccinees were followed for several months after vaccination, possible longer-term risks of vaccination were not being monitored.

Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce

N Engl J Med published online September 1, 2021

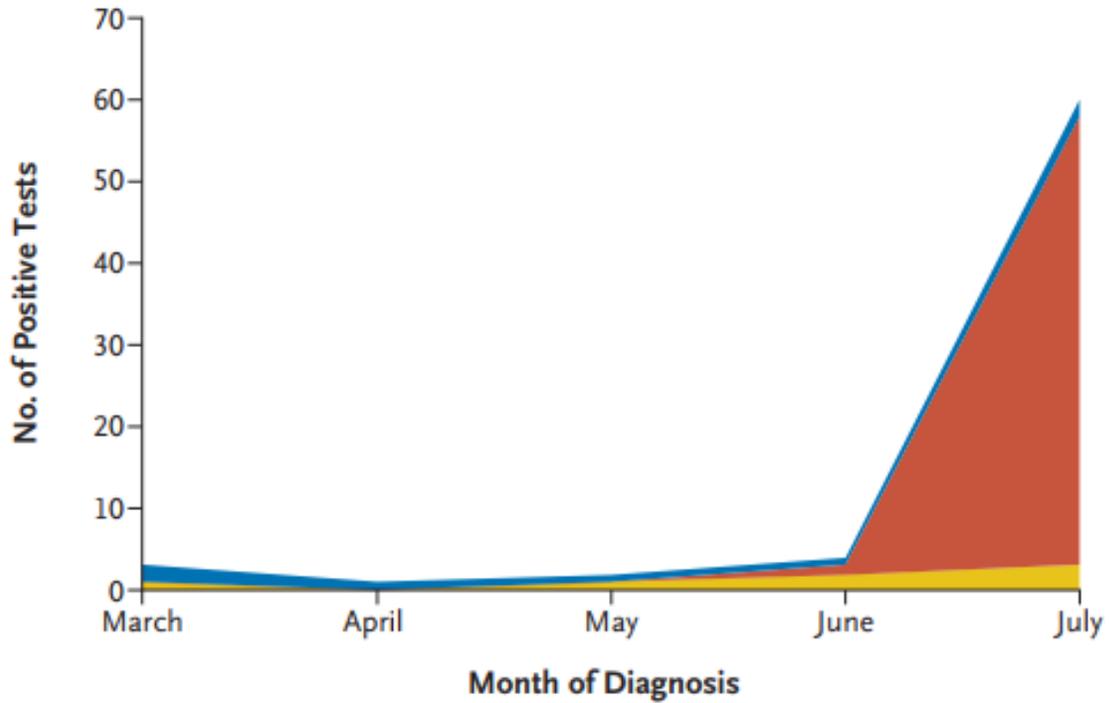
DOI: [10.1056/NEJMc2112981](https://doi.org/10.1056/NEJMc2112981)

Vaccination with mRNA vaccines began in mid-December 2020; by March, 76% of the workforce had been fully vaccinated, and by July, the percentage had risen to 83%. Infections had decreased dramatically by early February 2021. Between March and June, fewer than 30 health care workers tested positive each month. However, coincident with the end of California's mask mandate on June 15 and the rapid dominance of the delta variant that first emerged in mid-April and accounted for over 95% of UCSDH isolates by the end of July, infections increased rapidly, including cases among fully vaccinated persons. From March 1 to July 31, 2021, a total of 227 UCSDH HCWs tested positive for SARS-CoV-2 by qPCR) assay of nasal swabs; 130 of the 227 workers (57.3%) were fully vaccinated. Symptoms were present in 109 of the 130 fully vaccinated workers (83.8%) and in 80 of the 90 unvaccinated workers (88.9%). No deaths were reported in either group; one unvaccinated person was hospitalized for SARS-CoV-2-related symptoms.

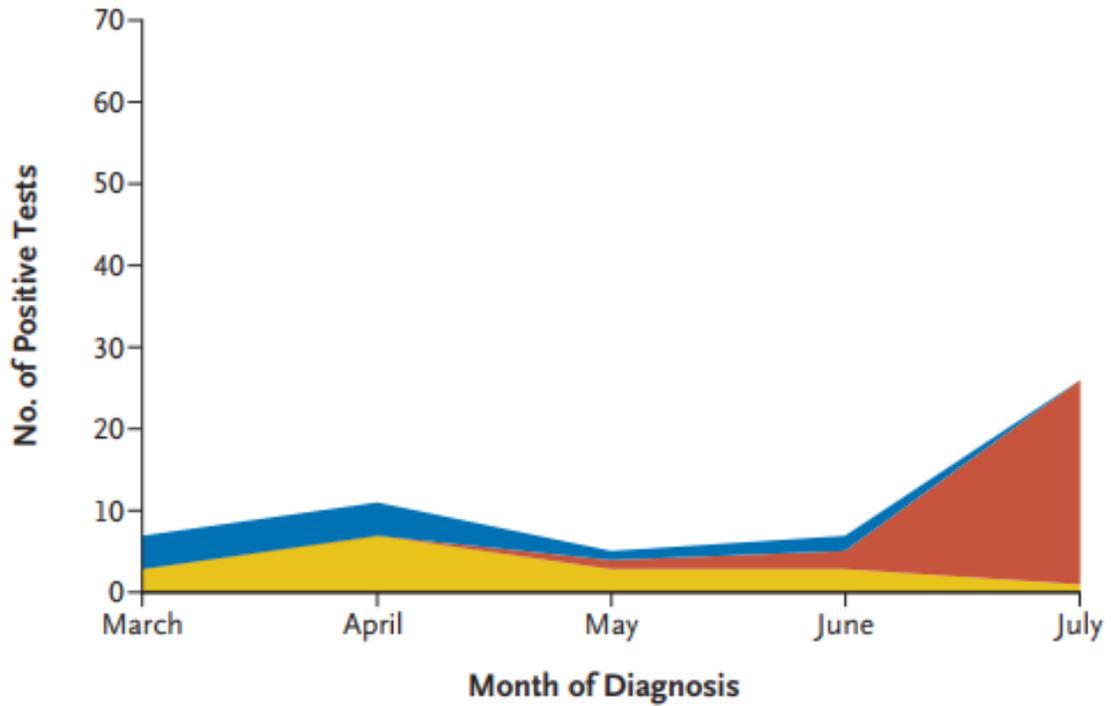
VE was calculated for each month from March through July. In HCWs completing vaccination in January or February, the attack rate was 6.7 per 1000 persons (95% CI, 5.9 to 7.8), whereas the attack rate was 3.7 per 1000 persons (95% CI, 2.5 to 5.7) among those who completed vaccination during the period from March through May. Among unvaccinated persons, the July attack rate was 16.4 per 1000 persons (95% CI, 11.8 to 22.9).

Alpha Delta Other

A Vaccinated Workers (N=70)



B Unvaccinated Workers (N=56)



Comment: The data suggest that VE against any symptomatic disease is considerably lower against the delta variant and may wane over time since vaccination. In fact, VE vaccine efficacy against symptomatic illness fell from 94% in June to 65% in July as Delta spread. The “attack rate” for fully vaccinated HCW increased 19-fold. Fully vaccinated HCW were more likely to get infected in July than unvaccinated workers were in March!

Their findings support reinstating NPI, such as indoor masking and increased testing strategies, in addition to continued efforts to increase vaccinations. Furthermore, if their findings on waning immunity support that booster doses may be indicated.

Covid-19 Breakthrough Infections in Vaccinated Health Care Workers

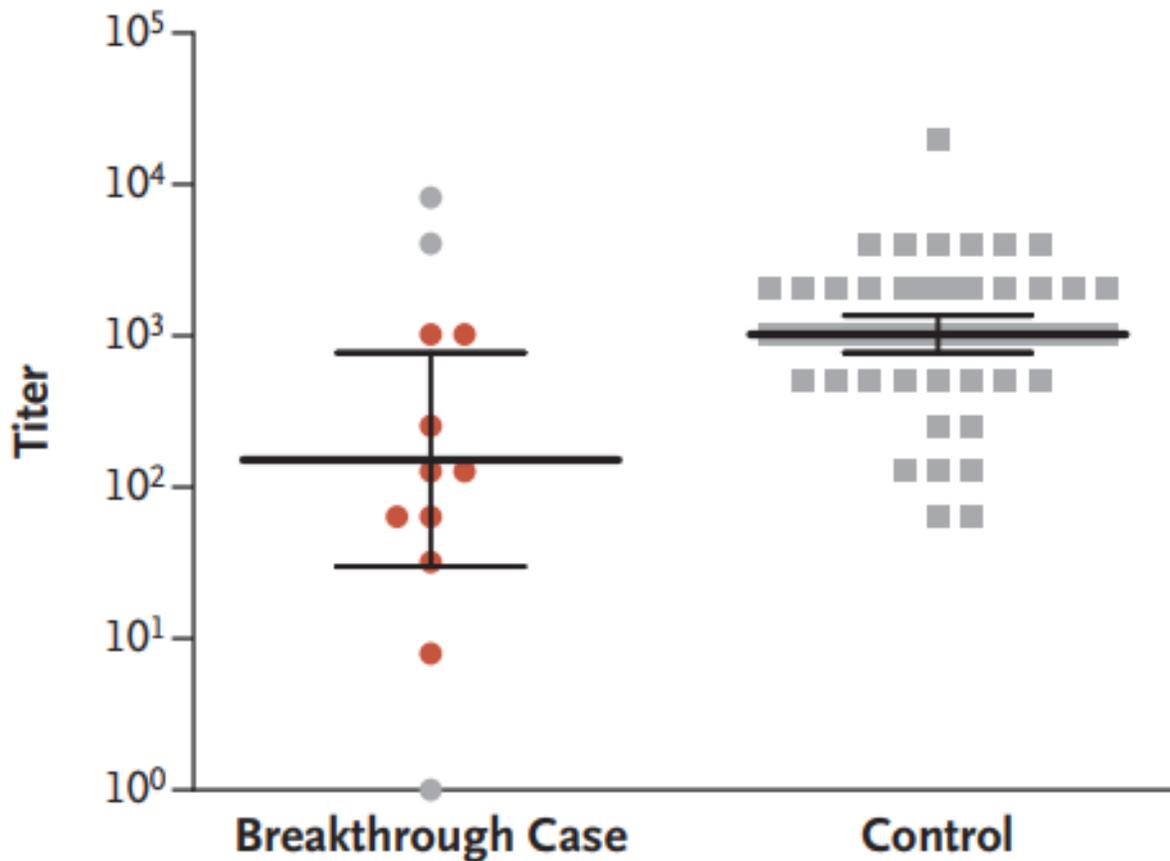
N Engl J Med published online July 23, 2021

[DOI: 10.1056/NEJMoa2109072](https://doi.org/10.1056/NEJMoa2109072)

The investigators at a large medical center in Israel identified breakthrough infections by performing extensive evaluations of HCWs who were symptomatic or had known exposure. These evaluations included epidemiologic investigations, repeat PCR, antigen-detecting rapid diagnostic testing (Ag-RDT), serologic assays, and genomic sequencing. Correlates of breakthrough infection were assessed in a case-control analysis. They matched patients with breakthrough infection who had antibody titers obtained within a week before SARS-CoV-2 detection (peri-infection period) with four to five uninfected controls and used generalized estimating equations to predict the geometric mean titers among cases and controls and the ratio between the titers in the two groups. They also assessed the correlation between neutralizing antibody titers and N gene cycle threshold (Ct) values with respect to infectivity. HCWs received the Pfizer vaccine.

Among 1497 fully vaccinated health care workers for whom PCR data were available, 39 SARS-CoV-2 breakthrough infections were documented. Neutralizing antibody titers in case patients during the peri-infection period were lower than those in matched uninfected controls (case-to-control ratio, 0.361; 95% confidence interval, 0.165 to 0.787). Higher peri-infection neutralizing antibody titers were associated with lower infectivity (higher Ct values). Most breakthrough cases were mild or asymptomatic, although 19% had persistent symptoms (>6 weeks). The alpha variant was found in 85% of samples tested. A total of 74% of case patients had a high viral load (Ct value, <30) at some point during their infection; however, of these patients, only 17 (59%) had a positive result on concurrent Ag-RDT. No secondary infections were documented.

Peak Neutralizing Antibody Level



Comment: Among fully vaccinated health care workers, the occurrence of breakthrough infections with SARS-CoV-2 was correlated with neutralizing antibody titers. They also found that neutralizing antibody titers correlated with the viral load and thus with the infectivity of breakthrough cases. It remains to be determined whether the decay of serum antibody levels is a good indicator for the timing of booster administration. (See article above) The degree of protection may depend more on the initial immune response than on the decay of antibody levels, since memory cells are expected to respond to future exposures although recent studies suggest declining neutralizing antibody may correlate with breakthrough cases with Delta. 39 HCWs with breakthrough infections reported symptoms six weeks later even though none were hospitalized. In the article reviewed in the Briefing September 3rd, the risk of long COVID was reduced in individuals who are fully vaccinated. This study was performed pre-Delta. The controls were not matched according to testing or exposure but only according to the timing of serologic testing in vaccinated, uninfected health care workers. Thus, they could not control for differences in the risk of exposure to Covid-19. This factor may have led to an underestimation of the difference in protection between cases and controls. In summary the investigators found that although the Pfizer vaccine is extremely effective, rare breakthrough infections carry an infectious potential and create a special challenge, since such infections are often asymptomatic.

The controversy around booster doses continues. Fauci and others point to the study from Israel finding that a Pfizer booster shot reduced the risk of both infection and severe illness for people over age 60 by more than 10-fold. Another study from Israel this week found that a third Pfizer shot reduced the risk of

infection by 70% to 84% after 14 to 20 days. [Reviewed in the Briefing August 31, 2021] Two FDA officials have resigned amid what media leaks claim is too much political pressure for Covid vaccine booster shots. One key respected member of the FDA’s advisory panel, Dr. Paul A. Offit, the director of the Vaccine Education Center at CHOP, argues boosters may be premature based on available evidence. He does not believe there is compelling reason to get a third dose now. Stay tuned.

The Impact of Coronavirus Disease 2019 (COVID-19) on Healthcare-Associated Infections in 2020: A Summary of Data Reported to the National Healthcare Safety Network

Infect Control Hosp Epidemiol published online September 2, 2021

To determine the impact of COVID-19 pandemic on HAI incidence in US hospitals, national- and state-level standardized infection ratios (SIRs) were calculated for each quarter in 2020 and compared to those from 2019.

Significant increases in the national SIRs for CLABSI, CAUTI, VAE, and MRSA bacteremia were observed in 2020. Changes in the SIR varied by quarter and state. The largest increase was observed for CLABSI, and significant increases in VAE incidence and ventilator utilization were seen across all 4 quarters of 2020.

	2020 Q1	2020 Q2	2020 Q3	2020 Q4
CLABSI	-11.8%	27.9%	46.4%	47.0%
CAUTI	-21.3%	No Change ¹	12.7%	18.8%
VAE	11.3%	33.7%	29.0%	44.8%
SSI: Colon surgery	-9.1%	No Change ¹	-6.9%	-8.3%
SSI: Abdominal hysterectomy	-16.0%	No Change ¹	No Change ¹	-13.1%
Laboratory-identified MRSA bacteremia	-7.2%	12.2%	22.5%	33.8%
Laboratory-identified CDI	-17.5%	-10.3%	-8.8%	-5.5%

Comment: Several factors probably contributed to the increase in HAIs. First our leadership had to divert resources to focus on the pandemic. Many facilities were faced with staffing challenges including staff illness or in quarantine which led to critical staff shortages. We lost experienced nurses who opted to become traveling nurses at a much higher income. In addition, staff were often asked to work in unfamiliar areas. Staff have become fatigued, stressed, and angry. In the end because we shifted our focus on prevention of SARS-CoV-2 transmission we had to reduce or suspend our usual infection prevention activities. We need to get back to basics and hard wire our practices especially when our hospitals are stressed due to emerging infectious diseases. The article concludes: “These data highlight the need to return to conventional infection prevention and control practices and build resiliency in these programs to withstand future pandemics.” This is consistent with articles from Ascension and HCA.

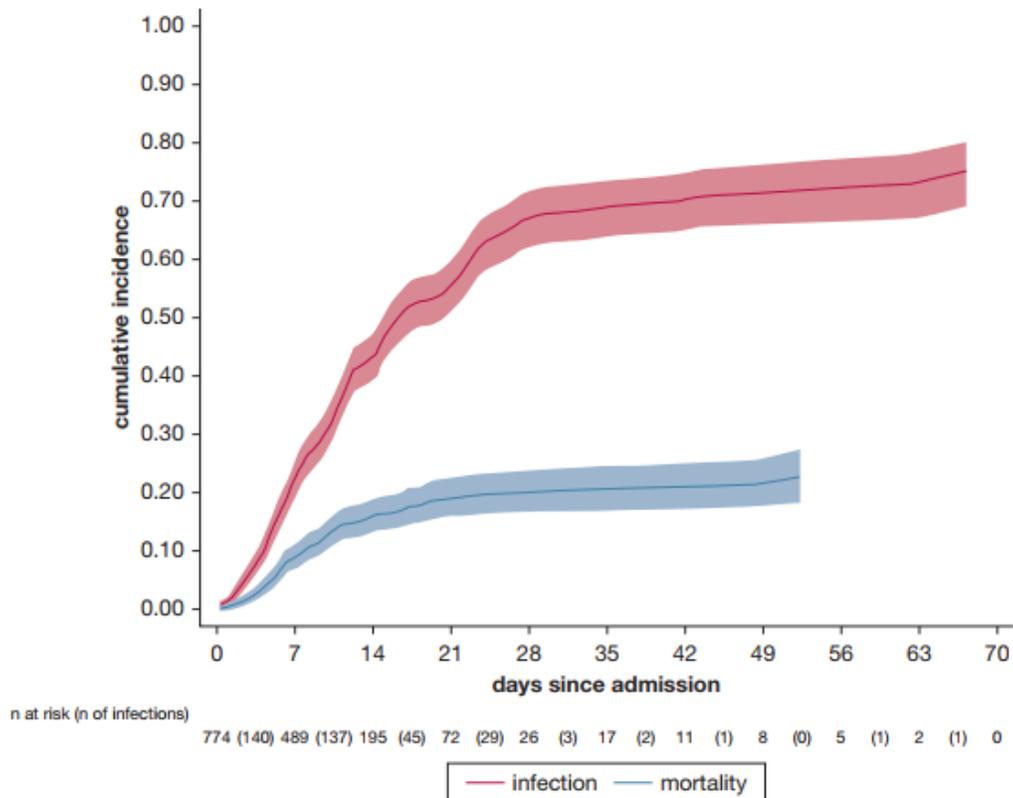
Hospital-Acquired Infections in Critically Ill Patients With COVID-19

Chest 2021; 160:454-465

doi.org/10.1016/j.chest.2021.04.002

The investigators looked at characteristics in critically ill patients with COVID-19 associated with HAIs and how HAIs are associated with outcomes in these patients. This was a multicenter retrospective analysis of prospectively collected data including adult patients with severe COVID-19 admitted to eight hub hospitals in Italy from February 20, 2020, through May 20, 2020.

Among 774 included patients, 359 patients (46%) demonstrated 759 HAIs, 35% of them caused by MDR bacteria. VAP (50%), BSIs (34%), and catheter-related BSIs (10%) were the most frequent HAIs. Variables independently associated with infection were age, positive end expiratory pressure, and treatment with broad-spectrum antibiotics at admission. Mortality during ICU stay was 30%. Patients with HAIs complicated by septic shock showed almost doubled mortality (52% vs 29%), whereas noncomplicated infections did not affect mortality. Infections resulting from gram-negative bacteria occurred later than infections resulting from gram-positive and fungi (median, 15 days (IQR, 9-26 days) vs 10 days (IQR, 6-18 days) and 9 days (IQR, 5-20 days) from ICU admission; $P < .001$ and $P = .014$, respectively) [See below]. Onset times did not differ among VAP, urinary tract infection, BSI, and catheter-related BSI and between MDR and non-MDR infections.



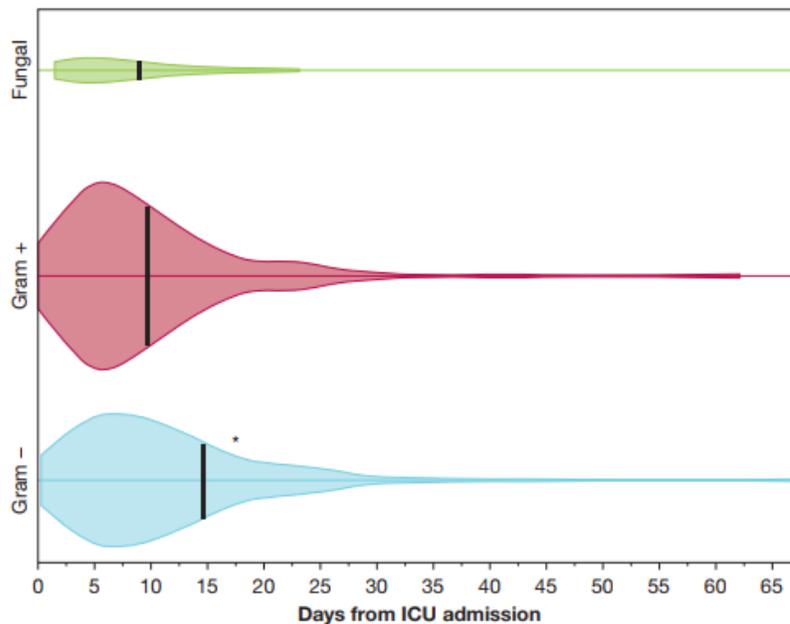


Figure 2 – Kernel density plot (violin plot) showing infection onset time. Black tick marks represent median onset time. *P < .05 vs gram-positive and fungal infections.

Comment: Critically ill patients with COVID-19 are at high risk of HAIs, in particular VAPs and BSIs resulting from MDR organisms. [See NHSN article above] HAIs prolong mechanical ventilation and hospitalization, and HAIs complicated by septic shock almost double mortality. This study was a retrospective analysis of data collected primarily for clinical reasons in one of the regions most severely hit by the pandemic, and not all data were available for all patients. In addition, no standard management approach was undertaken during the study period across different centers. Nonetheless, multiple articles in both Europe and US all agree: the stress of Covid-19 has led to an increase in HAIs and MDROs and impacts outcomes.

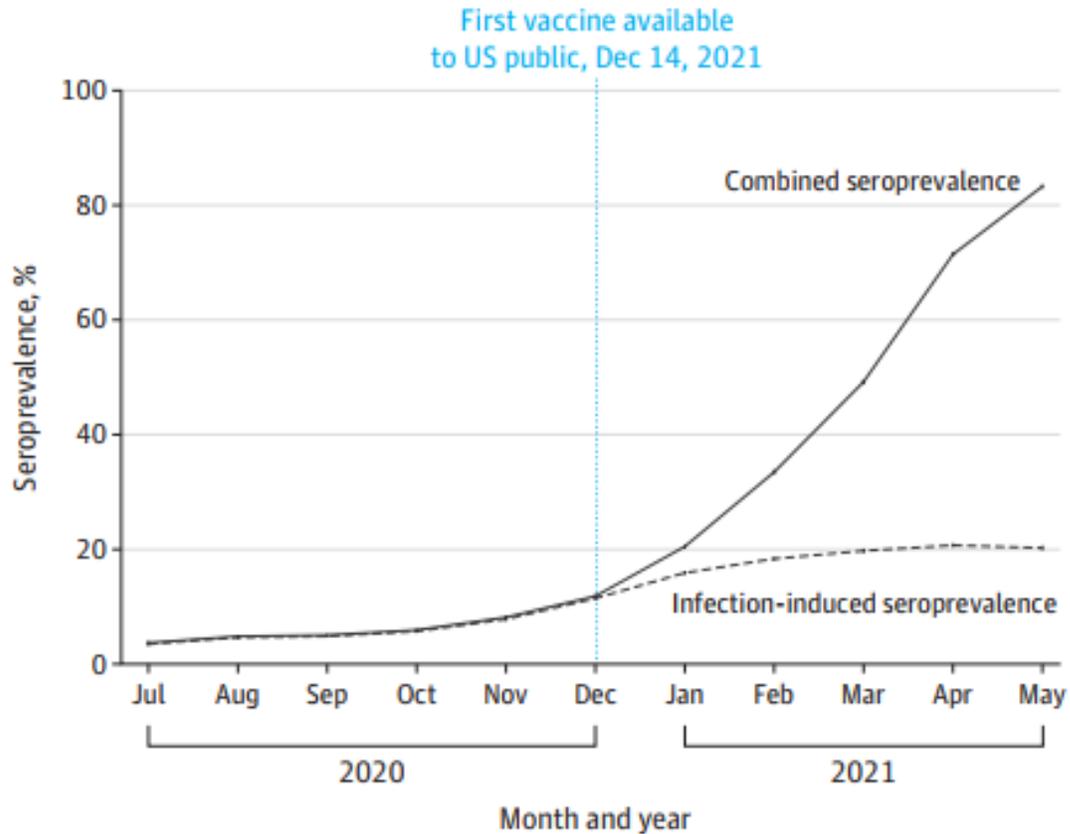
Estimated US Infection- and Vaccine-Induced SARS-CoV-2 Seroprevalence Based on Blood Donations, July 2020-May 2021

JAMA published online September 2, 2021

[doi:10.1001/jama.2021.1516](https://doi.org/10.1001/jama.2021.1516)

This is a repeated cross-sectional study conducted each month during July 2020 through May 2021, at 17 blood collection organizations with blood donations from all 50 US states. Main outcome is the proportion of persons with detectable SARS-CoV-2 spike and nucleocapsid antibodies.

In this repeated cross-sectional study that included 1,443,519 blood donation specimens from a catchment area representing 74% of the US population, estimated SARS-CoV-2 seroprevalence weighted for differences between the study sample and general population increased from 3.5% in July 2020 to 20.2% for infection-induced antibodies and 83.3% for combined infection- and vaccine-induced antibodies in May 2021. Seroprevalence differed by age, race and ethnicity, and geographic region of residence, but these differences changed over the course of the study.



Comment: Based on a sample of blood donations in the US from July 2020 through May 2021, vaccine- and infection-induced SARS-CoV-2 seroprevalence increased over time and varied by age, race and ethnicity, and geographic region. Serology assays used appear to have high sensitivity for 6 months after infection, however, estimates were not adjusted to account for a sensitivity less than 100% or potential waning of sensitivity after 6 months. Vaccine-induced seroprevalence might be higher in blood donors than in the general population. In addition, infection-induced seroprevalence estimates might be underestimated because persons with acute or long-term COVID-19 symptoms have been excluded from donating. With Delta natural immunity will increase especially given how contagious the variant is and now vaccinations have gone back up as well. Immunity is the only way to get through this pandemic but will not eradicate Covid-19. Getting natural infection in non-vaccinated persons is a terrible way to achieve herd immunity. Just get vaccinated!