Volume 1; Issue 1; 2022

Infectious Diseases Watch

January 3, 2022

Ed Septimus, MD

Welcome to the inaugural issue of the **Infectious Diseases Watch**
Given the length of this format, I am providing both a copy in the email as well as by attachment. Let me know what you would prefer moving forward.

Under General Infectious Diseases I chose two articles of general interest: one on sepsis, and one on MRSA bacteremia.

Under Covid-19 a lot to report. First a section on Covid-19 by the numbers and some public health estimates when Omicron will peak. Next is the UK Technical Briefing from December 31, 2021 demonstrating to date that Omicron appears less virulent. The next section highlights the new CDC Guidelines on Isolation and Quarantine discussed last week but updated with CDC clarification stating the guidance in fact represents a compromise. The last item is the FDA announcement they are considering recommending booster doses for 12-15-year-olds.

Under Covid-19 Journal Review I start with what I think is an important article about the sensitivity of rapid antigen testing to predict replicating-competent virus. The second article reviews the South African experience during the Omicron wave compared to previous waves. The next two articles are animal models demonstrating lower replication of Omicron in the lung. The next article reviews the T cell responses induced by either vaccination or infection against Omicron. This is followed by an article which looks at the safety of Pfizer vaccine in children aged 5-11 and the last article is on clinical outcomes in children aged <18 hospitalized with Covid-19.

I hope everyone has a great start to 2022.

Ed

General Infectious Diseases

Association Between Implementation of the Severe Sepsis and Septic Shock Early Management Bundle Performance Measure and Outcomes in Patients With Suspected Sepsis in US Hospitals

JAMA Netw Open published online December 20, 2021

doi:10.1001/jamanetworkopen.2021.38596

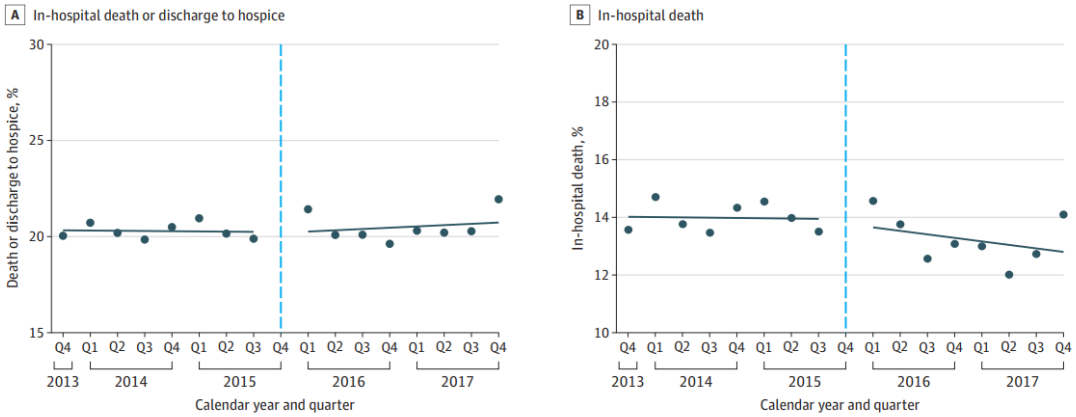
This is a retrospective study, conducted among 117,510 adults admitted to 114 hospitals with suspected sepsis from October 2013 to December 2017, aimed to analyze the impact of implementing the 2015 Centers for Medicare and Medicaid (CMS) Severe Sepsis and Septic Shock Early Management Bundle (SEP-1).

While SEP-1 has accelerated widespread sepsis quality improvement efforts, the investigators state concerns that the bundle which requires clinicians to administer broad-spectrum antibiotics to suspected sepsis patients within 3 hours, which could lead to inappropriate use of broad-spectrum antibiotics.

The primary outcome of the interrupted time series and logistic regression analysis was quarterly rates of risk-adjusted short-term mortality. Secondary outcomes included administration of anti–MRSA or antipseudomonal beta-lactam antibiotics within 24 hours of hospital arrival.

While there were increases in the use of anti-MRSA antibiotics (19.8% in Quarter 4 of 2013 to 26.3% in Q4 of 2017) and antipseudomonal antibiotics (27.7% in Q4 of 2013 to 40.5% in Q4 of 2017), these trends preceded SEP-1 and did not change with SEP-1 implementation. Unadjusted short-term mortality rates were similar in the pre–SEP-1 period (Q4 of 2013 through Q3 of 2015) versus the post–SEP-1 period (Q1 of 2016 through Q4 of 2017) (20.3% vs 20.4%), and SEP-1 implementation was not associated with changes in level (OR, 0.94; 95% confidence interval [CI], 0.68 to 1.29) or trend (OR, 1.00; 95% CI, 0.97 to 1.04) for risk-adjusted short-term mortality rates.

Figure 3. Changes in Risk-Adjusted Outcomes of Patients With Suspected Sepsis Before and After Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) Implementation



Comment: An analysis of data on sepsis patients found that adherence to a federally mandated sepsis bundle in US hospitals was not associated with a change in already increasing rates of broad-spectrum antibiotic use or with improved mortality rates. A recent study used a propensity score–matched cohort study of patient-level data reported to CMS by 3241 hospitals concluded that compliance with SEP-1 is associated with a lower 30-day mortality. This suggests that SEP-1–compliant care may, in fact, reduce preventable deaths. [Chest. Published online August 5, 2021]

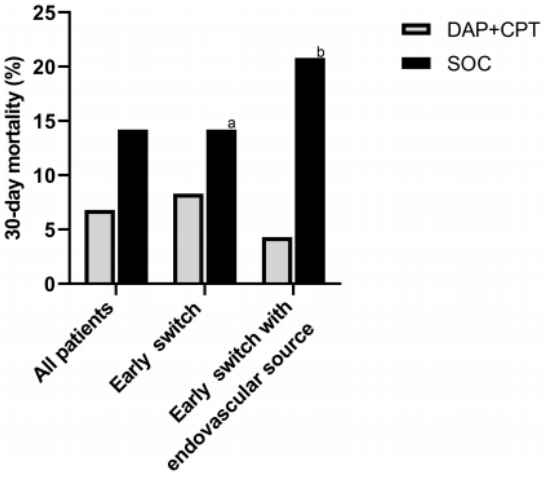
SEP-1 was introduced by CMS in October 2015, having been reviewed, passionately debated, revised, and ultimately endorsed (and recently re-endorsed) by NQF, but not without controversy. SEP-1 is a complex, composite, "all or none" quality measure that requires a high degree of manual medical record abstraction. One way forward for SEP-1 may be to deconstruct the metric and/or revisit the "all or none" nature and concentrate of septic shock and which bundle element is most impactful in terms of outcomes. Also developing an electronic measure based on the work by Rhee et al. [JAMA 2017; 318**:**1241-1249] would help with extraction and remove subjectivity. I hope this passion around sepsis can be harnessed to improve outcomes for patients with sepsis. I believe a group of respected experts and interested societies with the support of CMS, CDC, and the NIH could lead such this effort. We can do more than just SEP-1, and I believe we can do better.

Current Paradigms of Combination Therapy in Methicillin Resistant *Staphylococcus aureus* (MRSA) Bacteremia: Does it Work, Which Combination, and For Which Patients? Clin Infect Dis; 2021; 73:2353-2560

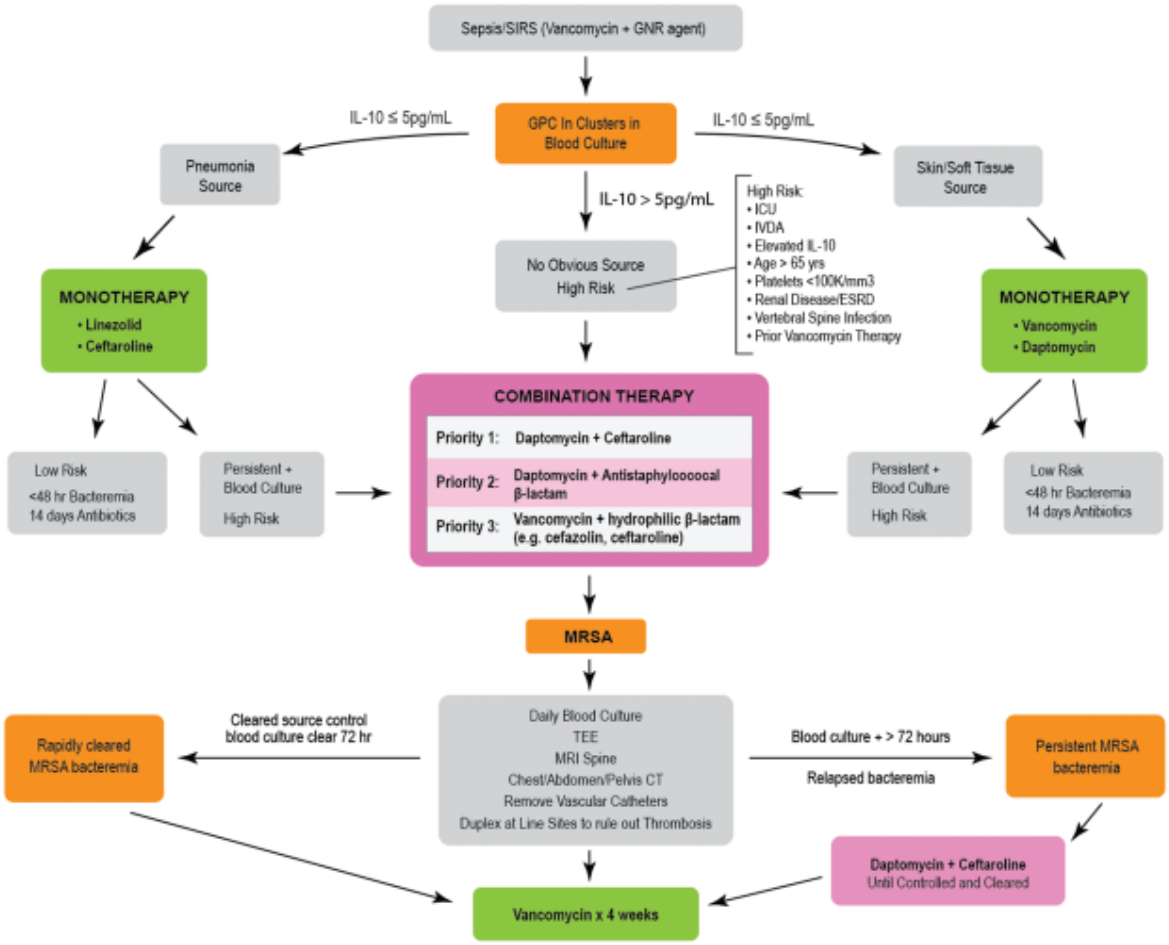
DOI: 10.1093/cid/ciab452

This article reviews current literature about the utility of combination antimicrobial therapy, particularly in the salvage of refractory MRSA bacteremia. Although daptomycin and linezolid costs have fallen dramatically, vancomycin remains the standard initial treatment of MRSA bacteremia at most institutions. *S. aureus* vancomycin resistance continues to be extremely rare; however, vancomycin treatment failure, including persistent bacteremia is quite common. Ceftaroline has attracted a lot of attention. Ceftaroline is active against MRSA by binding to PBP2A and inhibiting peptidoglycan transpeptidation. Ceftaroline enhances daptomycin cell

membrane binding which has led to several studies examining combination ceftaroline and daptomycin. A large retrospective matched cohort study among 3 institutions compared patients with MRSA bacteremia treated with SOC versus daptomycin plus ceftaroline [OFID 2020.7: ofz538]. Many of the combination patients was used in a salvage role, but despite this consideration, daptomycin-ceftaroline resulted in clearance of persistent MRSA bacteremia and a numerically lower 30-daymortality rate than SOC (8.3% vs 14.2% at 30 days). In patients switched to combination early during bacteremia with an endovascular source, there was a further trend for improved survival. (See below)



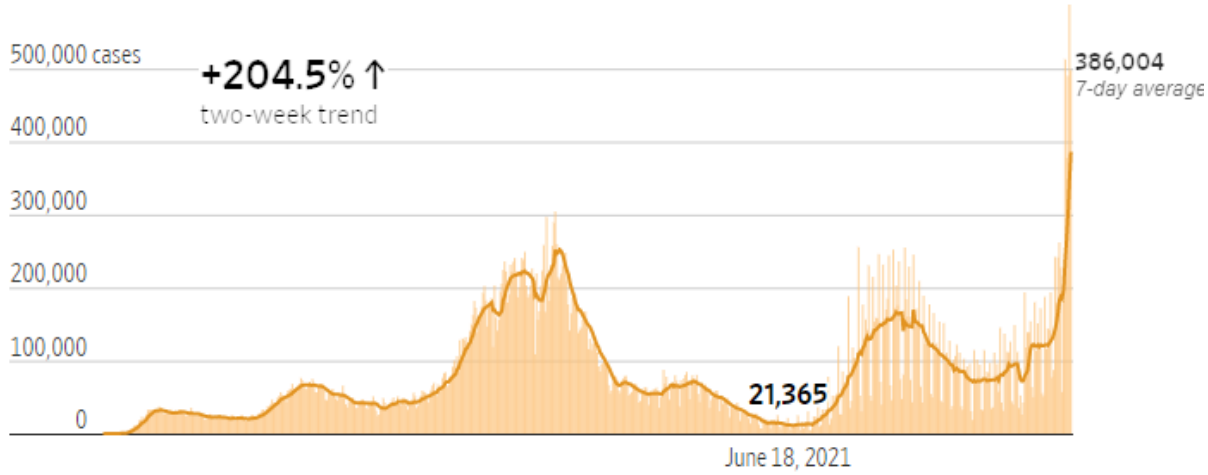
Clinical trials in *S. aureus* bacteremia (SAB) tend to follow a “one size fits all” approach where all patients are treated in the same manner regardless of outcome risk. SAB trials enroll patients with bacteremia from skin and soft tissue infection and catheter sources as well as endovascular sources. Retrospective analyses of combination therapy are significantly biased because clinicians frequently deploy combination antibiotic therapy for MRSA bacteremia in the highest risk patients outside of clinical trial settings, usually in a salvage approach. Along with clinical judgement of infection severity, source of infection (e.g., endovascular vs nonendovascular), SAB clearance, and comorbidities, some novel applications of biomarkers show promise. In the randomized pilot study by Geriak et al, no patients randomized to daptomycin plus ceftaroline died, but 6 patients receiving SOC died. Among these 6 patients, 5 had interleukin (IL)-10 concentrations upon admission of >5 pg/mL (threshold for elevated IL-10), whereas no patients died in the combination group with elevated IL-10. The anti-inflammatory cytokine IL-10, driven by endovascular bacterial burden, is a recently identified but consistent host biomarker for increased SAB mortality risk. [Clin Infect Dis 2020; 70:2634-2640]



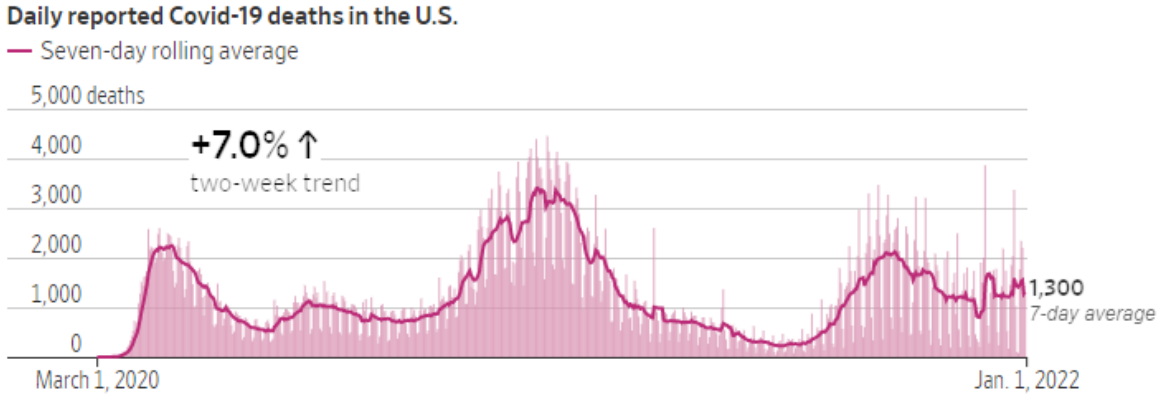
Comment: Traditional guidelines recommend 4-6 weeks of therapy for complicated SAB. Since guidelines tend to be for the average patient, they may not account for inoculum size and certain host comorbidities. Of course, most of us do not have IL-10 levels routinely available, but the authors suggest combination antimicrobial therapy is important to initiate early, within the first 72 hours of onset, and ideally within the first 24 hours to prevent complications of persistent bacteremia. However, combination therapy may not be needed for the entire 4–6 weeks in SAB. In fact, studies show starting with a failing monotherapy up front that results in combination salvage therapy may result in longer durations of salvage combination and greater total antibiotic exposure overall. Instead, they advocate intensive therapy up front and narrow down for the remainder of treatment based on patient response. (See above) Most of us have access to molecular diagnostics for +blood cultures. Therefore, a + blood culture for gram-positive cocci in clusters can be identified as MRSA within hours. This discussion also reminds of the argument of nafcillin versus cefazolin for MSSA bacteremia where a subset with patients with high inoculum infection may respond better to nafcillin compared to cefazolin. Some have suggested starting with nafcillin and when blood cultures have cleared reducing the inoculum size then switching to cefazolin. Early combination therapy offers advantages over monotherapy in high-risk endovascular infection in patients with MRSA bacteremia. Using daptomycin plus ceftaroline appeared very promising initially. More studies will be needed to examine relative differences on efficacy, safety, and pharmacoeconomic advantages of different combinations.

COVID-19

COVID-19 by The Numbers January 1, 2022



Note: For all 50 states and D.C., U.S. territories and cruises. Last updated Jan. 1, at 6:00 a.m.
Source: Johns Hopkins Center for Systems Science and Engineering



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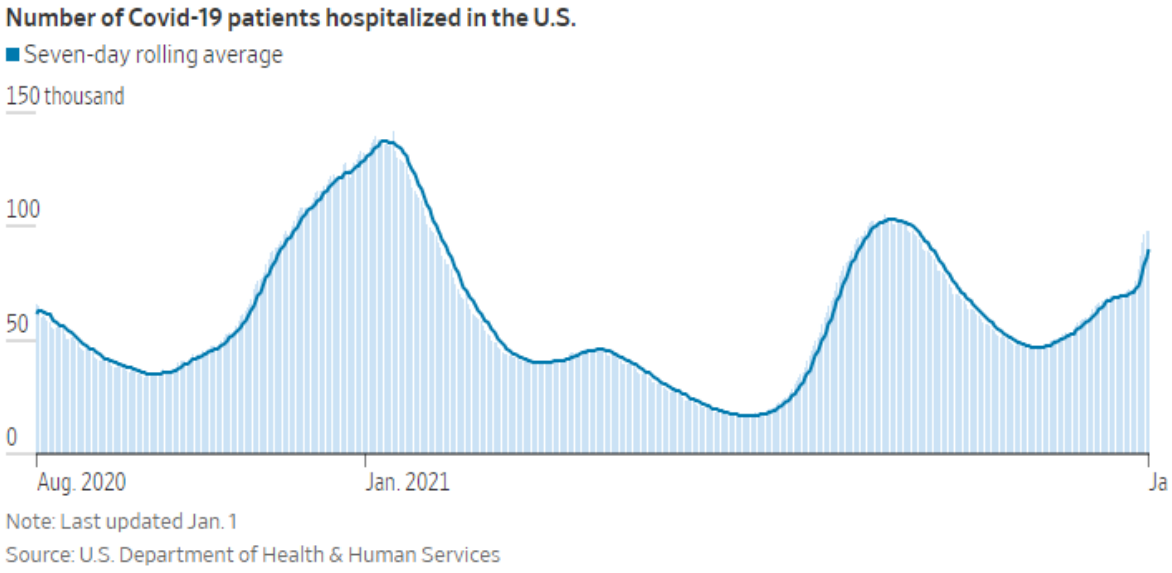
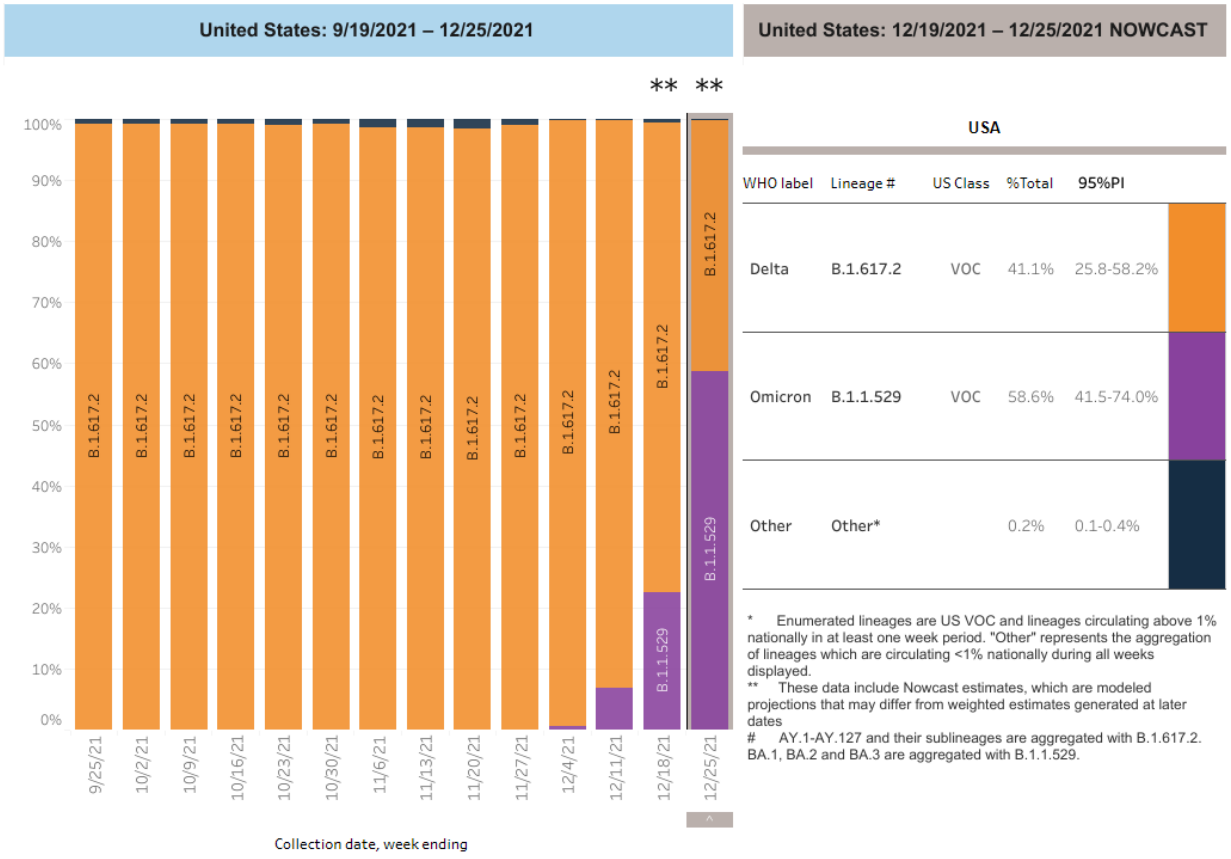




Comment: Last Tuesday, CDC said new cases of omicron accounted for just 22.5% of new cases for the week ending Dec. 18, not 73% as originally estimated. But Omicron still appears to have surpassed delta as the dominant strain in new cases over the last week. For the week ending Dec. 25, Omicron accounted for 58.6% of new coronavirus cases compared to 41.1% of

Delta. Other variants accounted for only 0.2%. According to a study from South African published Thursday, patient deaths from Omicron was lower as well as need for supplemental oxygen and mechanical ventilations. The average length of stay for Omicron patients was 3 days — less than half the average for other strains. (See review below) In US deaths are up ~7% while hospitalizations are up 26% and new cases up 200%. In the end I believe Omicron may be nature's vaccine.

COVID-19 News

Public Health experts believe Omicron's surge in the U.S. may will be shorter.

- The surge in infections could peak in mid-January and last weeks, rather than months, infectious-disease experts said.
- That would mirror the rise and fall in South Africa, where the coronavirus variant was first identified.(see prior Briefing December 27, 2021)
- As infections soar**,** hospitals face staff shortages and the CDC warned that even vaccinated travelers should avoid cruises.

Technical briefing: Update on hospitalisation and vaccine effectiveness for Omicron VOC-21NOV-01 (B.1.1.529) December 31, 2021

A new analysis of over a million COVID-19 cases in the UK found that the risk of hospitalization for those with the Omicron variant of coronavirus is about one-third of that from the Delta. In this analysis, the risk of hospitalization is lower for Omicron cases with symptomatic or asymptomatic infection after two and three doses of vaccine, with an 81% reduction in the risk of hospitalization after three doses compared to unvaccinated Omicron cases. Vaccines provided significantly lower protection against symptomatic infection from Omicron than Delta. However, protection against hospitalization is much greater than that against symptomatic disease, in particular after a booster dose.

Comment: The report concludes that although the numbers are going up and going up increasingly rapidly, the absence of large numbers of seriously ill older people is providing reassurance. This report and the South African experience and the emerging data that Omicron does not infect lungs as well as other variants (see reviews below) give rise to the emerging reports that in fact Omicron may be milder than prior variants. It is difficult to determine what degree of lessened severity is due to preexisting immunity or the intrinsically lower virulence of Omicron, as suggested by the animal studies, or a combination of both.

New CDC Guidelines on Isolation and Quarantine

Comment: I think one picture is worth a thousand's words. Many of you know my reservations shared last week. CDC finally came clean mid-week. They admitted it was a compromise between reducing transmission and maintaining our socioeconomic infrastructure. In fact, it was designed to reduce economic and social disruption and at the same time reduce public health risk, though they admit it will not completely eliminate the risk of transmission by people who follow them. In a perfect world, it we had adequate rapid testing, we could add a recommendation for a negative antigen test if available before returning to work. (See article below on the sensitivity of antigen to predict replicating-competent virus) Having said this, I believe shorting isolation is a step in the right direction.

Unfortunately, this is another example about lack of transparency and mixed messaging. What we have experienced throughout this pandemic is what I call disorganized chaos. [not just from CDC] CDC has been under enormous pressure and despite my misgivings about some of the messaging and guidance, I am grateful to the dedicated men and women at CDC who have worked tirelessly throughout the pandemic.

FDA Considering Booster for 12-15 year old

The FDA may announce this week extending boosters to children aged 12-15. To my knowledge the FDA is not convening their vaccine advisory panel. This may be a lost opportunity since I think parents need to hear a robust discussion of the pros and cons so they can decide to boost their children. New data concludes the Pfizer vaccine is safe in this age group and myocarditis is rare. (See MMWR article below)

COVID-19 Journal Review

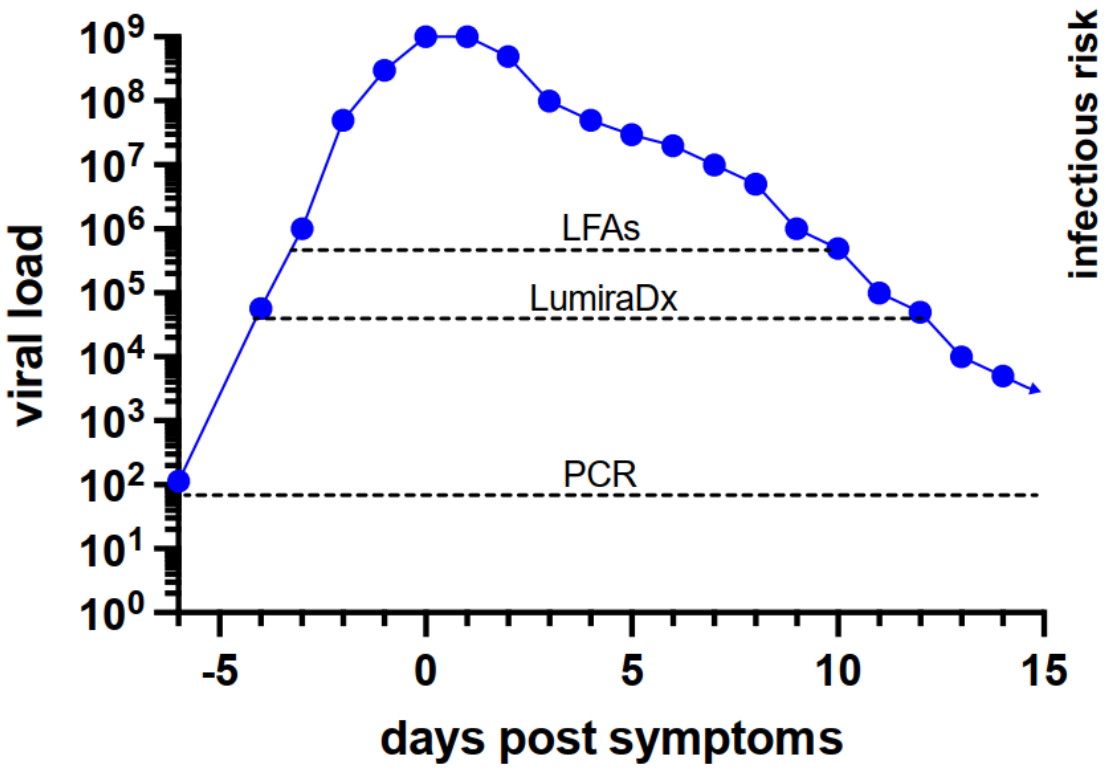
SARS-CoV-2 Antigen Tests Predict Infectivity Based on Viral Culture: Comparison of Antigen, PCR Viral Load, and Viral Culture Testing on a Large Sample Cohort

medRxiv published online December 23, 2021

doi.org/10.1101/2021.12.22.21268274

The investigators set out to determine the relationship of antigen testing results from three lateral flow and one microfluidics assay to viral culture performed in parallel in 181 nasopharyngeal swab samples positive for SARS-CoV-2. Sample viral loads, determined by RT-qPCR, were distributed across the range of viral load values observed in our testing population.

Researchers performed rapid antigen tests on swab samples from 181 individuals with PCR-confirmed SARS-CoV-2 infections and then tried to culture the virus on the swabs. They found that antigen tests were predictive of viral culture positivity, with the LumiraDx method showing enhanced sensitivity (90%; 95% confidence interval (95% CI) 83-94%) compared with the BD Veritor (74%, 95% *C*I 65-81%), CareStart (74%, 95% CI 65-81%) and Oscar Corona (74%, 95% CI 65-82%) lateral flow antigen tests When viral loads were below the antigen tests' level of detection, the virus particles were often incapable of growing. Antigen and viral culture positivity were also highly correlated with sample viral load, with areas under the receiver-operator characteristic curves (ROCs) of 0.94-0.97 and 0.92, respectively. A viral load threshold of 100,000 copies/mL was 95% sensitive (95% CI, 90-98%) and 72% specific (95% CI, 60-81%) for predicting viral culture positivity.



Comment: Taken together, the detection of SARS-CoV-2 antigen identified highly infectious individuals, some of whom may harbor 10,000-fold more virus in their samples than those with any detectable infectious virus. Their data support use of antigen testing in defining infectivity status at the time of sampling. This may be very useful in determining when it is safe to stop isolation in a patient with known Covid infection. (See CDC new recommendations for isolation above) To be accurate, the swabs must be collected for testing carefully, following the instructions provided with the testing kits. Antigen tests are less sensitive during the incubation period and in asymptomatic persons, but much better in detecting Covid if symptomatic. It is still recommended that if Covid is still suspected and has a negative antigen test, a PCR should be performed. FDA stated last week that rapid antigen tests may have reduced sensitivity in detecting Omicron in laboratory tests. In addition, this study was performed before Delta and Omicron.

I had asked Mary Hayden about her take on this study and with her permission this is her take: I had a preview of this study last week. It is very well done and provides useful information about the sensitivity of antigen to predict replicating-competent virus. The slight limitation is that they didn't use the WHO SARS-CoV-2 standard and I couldn't find that the genomic material that they used had been calibrated against that standard. (We've also struggled with this limitation in some of our work.)

Characteristics and Outcomes of Hospitalized Patients in South Africa During the COVID-19 Omicron Wave Compared With Previous Waves JAMA published online December 30, 2022

doi:10.1001/jama.2021.24868

On November 24, 2021, Omicron, was identified in South Africa which resulted in a fourth wave of COVID-19. The high number of spike mutations has raised concerns about its ability to evade vaccine and spread. They assessed hospitalized patients with a positive SARS-CoV-2 test result during the fourth wave compared with previous waves. Netcare is a private health care group consisting of 49 acute care hospitals (>10 000 beds) across South Africa was used to compared prior waves with Omicron.

The number of patients treated in the hospitals during the same early period of each wave differed (2351 in wave 4 vs maximum 6342 in wave 3); however, 68% to 69% of patients presenting to the emergency department with a positive COVID-19 result were admitted to the hospital in the first 3 waves vs 41.3% in wave 4. Patients hospitalized during wave 4 were younger (median age, 36 years vs maximum 59 years in wave 3; $P < .001$) with a higher proportion of females. Significantly fewer patients with comorbidities were admitted in wave 4, and the proportion presenting with an acute respiratory condition was lower (31.6% in wave 4 vs maximum 91.2% in wave 3, $P < .001$). Of 971 patients admitted in wave4, 24.2% were vaccinated,66.4% were unvaccinated, and vaccination status was unknown for 9.4%.
The proportion of patients requiring oxygen therapy significantly decreased (17.6% in wave 4 vs 74% in wave 3, $P < .001$) as did the percentage receiving mechanical ventilation. Admission to intensive care was 18.5% in wave 4 vs 29.9% in wave 3 ($P < .001$). The median LOS (between 7 and 8 days in previous waves) decreased to 3 days in wave 4. The death rate was between 19.7% in wave 1 and 29.1% in wave 3 and decreased to 2.7% in wave 4.

Table 2. Outcomes of Patients Admitted With a Positive COVID-19 Result in the 4 Waves[a]

	No. (%) of patients				
	Wave 1 (n = 2628)	Wave 2 (n = 3198)	Wave 3 (n = 4400)	Wave 4[b] (n = 971)	*P* value
Receiving oxygen therapy	2119 (80.3)	2624 (82.0)	3260 (74.0)	171 (17.6)	<.001
Receiving mechanical ventilation	431 (16.4)	259 (8.0)	548 (12.4)	16 (1.6)	<.001
Admission to intensive care	1104 (42)	1172 (36.6)	1318 (29.9)	180 (18.5)	<.001
Length of stay, median (IQR), d	8.0 (9)	7.8 (8)	7 (9)	3 (3)	<.001
Deaths	520 (19.7)	790 (25.5)	1284 (29.1)	27 (2.7)	<.001

[a] Wave 1: June 14-July 6, 2020; wave 2: December 1-23, 2020; wave 3: June 1-23, 2021; wave 4: November 15-December 7, 2021.

[b] Seventy-two patients (7%) still admitted.

Comment: The study has several limitations. First, individual virus genotyping was not available. However, the Omicron variant was estimated to be 81% of the variants isolated by November and 95% isolated by December 2021. Second, patients admitted for COVID-19 could not be differentiated from asymptomatic patients admitted for other diagnoses with an incidental positive test result, and this likely differed between waves, suggested by the lower proportion admitted with respiratory diagnoses in wave 4. This last point is very important. Many of us feel we need to move to hospitalizations as the key measure, but most systems cannot differentiate an incidental positive test from an admission due to Covid-19. Colleague Brad Spellberg said on Twitter: “I can tell you that at the two public hospitals in LA for which he reviews all Covid + tests, at this point only 1/3 of Covid+ admissions are admitted because of Covid. And only 20-25% +tests in ED are admitted.” I believe reliance upon administrative data can be misleading especially in the Omicron era. Overall, the data to date seems to support the

notion that Omicron indeed may be less virulent. (See next two articles) As I stated above, Omicron may be nature's vaccine.

The SARS-CoV-2 B.1.1.529 Omicron virus causes attenuated infection and disease in mice and hamsters Res Square published online December 29, 2021

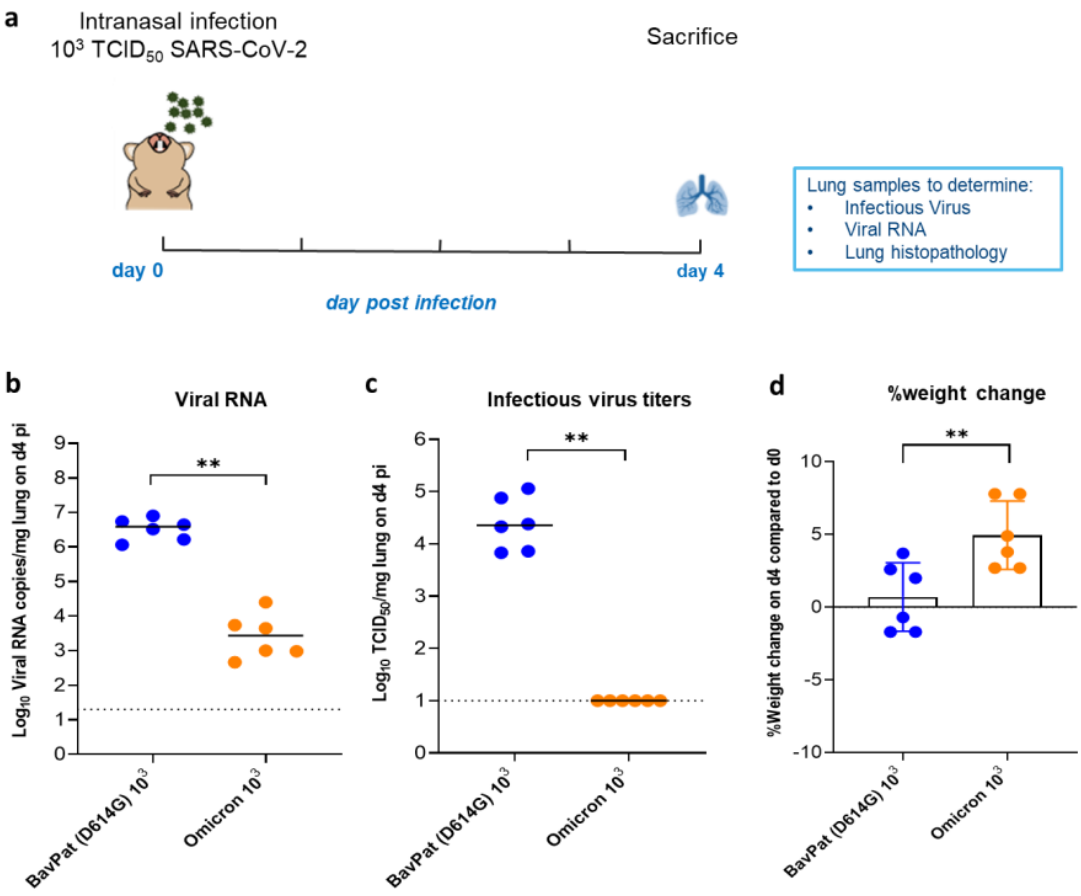
doi.org/10.21203/rs.3.rs-1211792/v1

The omicron (B.1.1.529) SARS-CoV-2 variant of concern does not readily infect Syrian hamsters published online December 26, 2021

doi.org/10.1101/2021.12.24.47408

The first article involved a large consortium of Japanese and American scientists who published on hamsters and mice that had been infected with either Omicron or one of several earlier variants. Those infected with Omicron had less lung damage, lost less weight and were less likely to die. Although the animals infected with Omicron on average experienced much milder symptoms, the scientists were particularly impressed by the results in Syrian hamsters, a species known to get severely ill with all previous versions of the virus.

In the second article they reported in hamsters that had been infected with the omicron variant, a 3 log10 lower viral RNA load was detected in the lungs as compared to animals infected with D614G [ancestral strain] and no infectious virus was detectable in this organ. Moreover, histopathological examination of the lungs from omicron-infected hamsters revealed no signs of peri-bronchial inflammation or bronchopneumonia.



Comment: A similar finding came from researchers at the University of Hong Kong who studied bits of tissue taken from human airways during surgery. In 12 lung samples, the researchers found that Omicron grew more slowly than Delta and other variants [reviewed in the Briefing December 16, 2021, and posted in Res Squire December 22, 2021 doi.org/10.21203/rs.3.rs-1189219/v1] The lower replication competence of Omicron in human lung may be compatible with reduced severity but the determinants of severe disease may be multifactorial. These studies together may help explain the observation that Omicron appears less virulent than other variants.

SARS-CoV-2 spike T cell responses induced upon vaccination or infection remain robust against Omicron medRxiv published online December 28, 2021

The investigators assessed the ability of T cells to react with Omicron spike in participants who were vaccinated with J&J or Pfizer, and in unvaccinated convalescent COVID-19 patients (n = 70).

They found that 70-80% of the CD4 and CD8 T cell response to spike was maintained across study groups. In addition, the magnitude of Omicron cross-reactive T cells was similar to that of the Beta and Delta variants, despite Omicron has considerably more mutations.

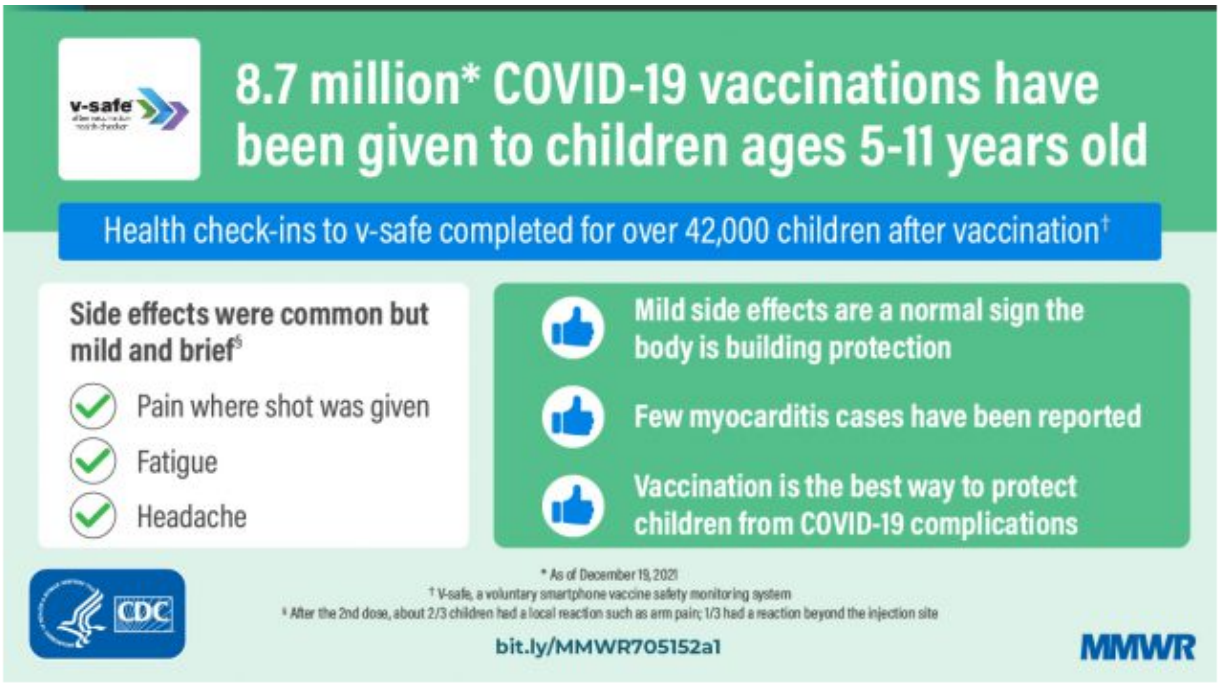
Additionally, in Omicron-infected hospitalized patients (n = 19), there were comparable T cell responses to ancestral spike, nucleocapsid and membrane proteins to those found in patients hospitalized in previous waves dominated by the ancestral, Beta or Delta variants (n = 49).

Comments: These results demonstrate that despite Omicron's extensive mutations and reduced susceptibility to neutralizing antibodies, the majority of T cell response, induced by vaccination or natural infection, cross recognizes the variant. Well-preserved T cell immunity to Omicron is likely to contribute to protection from severe COVID-19, supporting early clinical observations from South Africa. This study confirms an earlier study from the Netherlands and US. The numbers in this study are small need to be confirmed in larger studies. However, these studies found that while antibody responses fade against Omicron, the T cell response remains robust and cross reacts width other variants.

COVID-19 Vaccine Safety in Children Aged 5–11 Years — United States, November 3–December 19, 2021 MMWR December 3, 2021

In preauthorization clinical trials, Pfizer vaccine was administered to 3,109 children aged 5–11 years; most adverse events were mild to moderate, and no serious adverse events related to vaccination were reported. To further characterize safety of the vaccine in children aged 5–11 years, CDC reviewed adverse events after receipt of Pfizer vaccine reported to the Vaccine Adverse Event Reporting System (VAERS) and adverse events and health impact assessments reported to v-safe, a voluntary smartphone-based safety surveillance system for adverse events after COVID-19 vaccination, during November 3–December 19, 2021.

Approximately 8.7 million doses of Pfizer vaccine were administered to children aged 5–11 years. VAERS received 4,249 reports of adverse events after vaccination with Pfizer vaccine in this age group, 4,149 (97.6%) of which were not serious. Approximately 42,504 children aged 5–11 years were enrolled in v-safe after vaccination with Pfizer vaccine; after dose 2, a total of 17,180 (57.5%) local and 12,223 systemic (40.9%) reactions (including injection-site pain, fatigue, or headache) were reported.



Comment: Myocarditis is a rare and serious adverse event that has been associated with mRNA-based COVID-19 vaccines; reporting rates for vaccine-associated myocarditis appears highest among males aged 12–29 years. To date, myocarditis among children aged 5–11 years appears rare. ACIP recommends the Pfizer vaccine for children aged 5–11 years for the prevention of COVID-19. Preliminary safety findings reported here are similar to those described in the clinical trials. Unfortunately, <15% of children aged 5-11 have been fully vaccinated.

Characteristics and Clinical Outcomes of Children and Adolescents Aged <18 Years Hospitalized with COVID-19 — Six Hospitals, United States, July–August 2021 MMWR December 31, 2021

Among children and adolescents with SARS-CoV-2 infection admitted to six hospitals during July–August 2021, 77.9% were hospitalized for acute COVID-19. Among these patients, approximately one third aged <5 years had a viral coinfection (approximately two thirds of which were respiratory syncytial virus) and approximately two thirds of those aged 12–17 years had obesity; only 0.4% of age-eligible patients were fully vaccinated! Overall, nearly one-third of the children had to be treated in the ICU, and almost 15 percent needed mechanical ventilation. Adolescents were more likely to require ICU admission and oxygen support compared with other age groups and required the longest median duration of mechanical ventilation.

Comment: COVID-19 vaccination and other prevention strategies are important to protect children from COVID-19, particularly children with obesity and other underlying health conditions. The data reported here came from only six hospitals, five of which are in the southern US. The proportion of adolescents with obesity in the southern US is higher than in other regions which might explain the high rates of obesity described in this report. Lastly, at the time of hospitalization, persons aged 12–15 years had only been vaccine-eligible

for 2–3 months, possibly contributing to the low vaccination rates observed. FDA is considering recommending a booster in this age group. (See above)