Infectious Diseases Watch

June 20, 2022

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General Infectious Diseases

Clinical Outcomes of Treated and Untreated C. difficile PCR-Positive/Toxin-Negative Adult Hospitalized Patients: a Quasi-Experimental Noninferiority Study

J Clin Microbiol published June 2022

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In the absence of a “gold standard” for the diagnosis of CDI, the optimal diagnostic testing algorithm for CDI remains controversial. Two main strategies are now recommended: use of a NAAT(PCR) alone for symptomatic individuals with unexplained and new-onset diarrhea (≥3 unformed stools in 24 h) or use of a two-step approach, such as NAAT followed by a toxin test. C. difficile toxins mediate disease, so individuals with both positive NAAT and direct toxin assays have been shown to have a longer duration of symptoms, increased length of stay, and increased mortality compared to individuals with only positive by NAAT. [JAMA Intern Med 2015; 175:1792-1801; Clin Infect Dis 2019; 69:1667-1674]

The role of therapy for positive PCR(PCR^+) and negative toxin($toxin^-$) remains unclear. The objective of this study was to determine whether clinical outcomes of PCR^+/cycle threshold-based toxin ($CT\text{-}toxin^-$) individuals vary by result reporting and treatment strategy. The clinical microbiology laboratory previously validated a toxin prediction algorithm based on the PCR (PCR) cycle threshold (CT) value, enabling prediction of a CT-based toxin (termed CT-toxin) result with a sensitivity of 96.0% and negative predictive value of 99.8% at a CT of 26.35 when using C. Diff Quik Chek Complete rapid membrane enzyme immunoassay (RMEIA) toxin (TechLab, Blacksburg, VA) as the reference method [J Clin Microbiol 2017;55:2651-266013]. CT-toxin was 92.0% sensitive when using either EIA or cell culture cytotoxicity neutralization assay (CCNA) as the reference standard. With this information, they performed a quasi-experimental noninferiority study comparing clinical outcomes of PCR^+/$CT\text{-}toxin^-$ individuals by reporting PCR result only (most patients treated) with reporting CT-toxin result only (most patients untreated) in a single-center, tertiary academic hospital. The primary outcome was symptomatic PCR^+/ $CT\text{-}toxin^-$ conversion at 8 weeks. Secondary outcomes included 7-day diarrhea resolution, hospital length of stay, and 30-day all-cause mortality.

A total of 663 PCR^+/$CT\text{-}toxin^-$ test results were analyzed from 632 individuals with a median age of 61 years (interquartile range [IQR], 44 to 72) and 50.4% immunocompromised. Individuals in the preintervention group were more likely to have received CDI therapy than those in the intervention group (91.5 versus 15.1%; P= 0.001). Symptomatic toxin conversion at 8 weeks and hospital length of stay failed to establish the predefined thresholds for noninferiority. However, lack of diarrhea resolution at 7 days and 30-day all-cause mortality was similar and

established noninferiority (20.0 versus 13.7%; adjusted odds ratio [aOR], 0.57; 90% confidence interval [CI], 0.32 to 1.01; P = 0.1; and 8.6 versus 6.5%; aOR, 0.46; 90% CI, 0.20 to 1.04; P = 0.12). There were no changes to the infection control guidelines for room cleaning, hand hygiene, or isolation procedures during this study.

Comment: As observed in this study, a major benefit of reporting the CT-toxin result alone is the favorable impact on reducing CDI overtreatment. The investigators showed a significant reduction in antibiotic treatment for CDI in patients with $PCR^+/CT\text{-}toxin^-$ results while demonstrating noninferiority for diarrhea resolution at 7 days and 30-day all-cause mortality compared to $PCR^+/CT\text{-}toxin^-$ patients who were treated. Indeed, a reduction in treatment rate from 91.5% to 15.1% in $PCR^+/CT\text{-}toxin^-$ cases between the two intervention periods was demonstrated. Reduction of unnecessary C. difficile therapy is an important antimicrobial stewardship program target given its association with increased prevalence of resistant organisms such as VRE. Furthermore, averting antibiotic therapy may limit host microbiota dysbiosis. This study has a few potential limitations. First, the single-center, retrospective study design which may not account for confounders the way a randomized-controlled trial can. CT toxin overcalls toxin positivity in $PCR^+/toxin^-$ individuals. In addition, only the Xpert C. difficile/Epi tcdB PCR assay was used in this study. Lastly, this study included a large proportion of immunocompromised populations. Despite the limitation these data support the safety of withholding antibiotics for selected hospitalized individuals with suspected CDI but negative toxin.

Chlorhexidine and Mupirocin for Clearance of Methicillin Resistant *Staphylococcus aureus* Colonization After Hospital Discharge: A Secondary Analysis of the CLEAR Trial

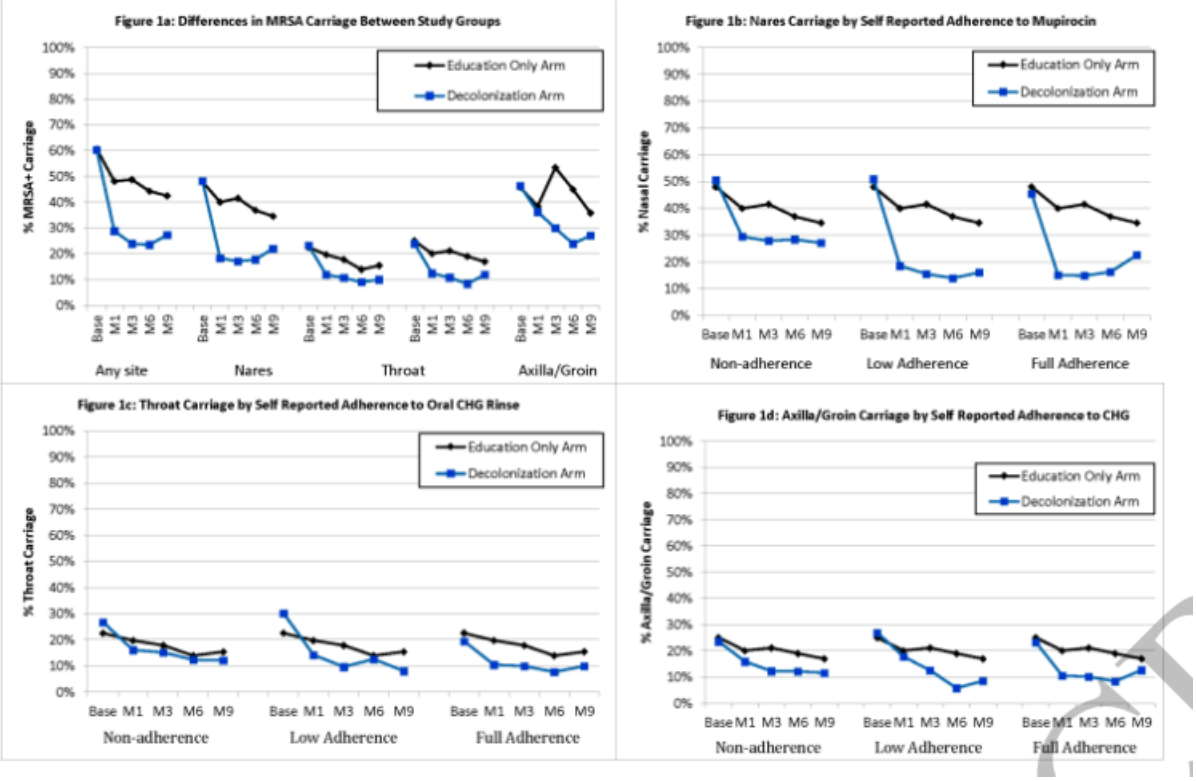
Clin Infect Dis published online May 31, 2022

doi/10.1093/cid/402/6595699

The CLEAR trial demonstrated that a multi-site body decolonization regimen reduced post-discharge infection and hospitalization in methicillin-resistant *S aureus* (MRSA) carriers. [N Engl J Med 2019; 380: 638-650] This report describes decolonization efficacy in clearing site-specific MRSA colonization during the trial up to 9 months.

CLEAR was a large, multi-center, randomized clinical trial of MRSA decolonization among adult patients after hospital discharge with MRSA infection or colonization. Participants were randomized 1:1 to either MRSA prevention education or education plus decolonization with 4% topical chlorhexidine daily[shower], 0.12% oral chlorhexidine rinse twice daily, and 2% nasal mupirocin twice daily for five consecutive days twice monthly for 6 months. Participants were swabbed in the nares, throat, axilla/groin, and wound (if applicable) at baseline, 1, 3, 6, and 9 months after randomization. The primary outcomes of this report are follow-up colonization differences between groups.

Among 2,121 participants, 1,058 were randomized to the decolonization group. By one month, MRSA colonization was lower in the decolonization group compared to the education only group (OR=0.44 [95% Confidence Interval 0.36-0.54, p<0.001). Similar magnitude of reduction was seen in the nares (OR=0.34 [0.27-0.42], p<0.001) throat (OR=0.55 [0.42-0.73], p<0.001), and axilla/groin (OR=0.57 [0.43-0.75], p<0.001). These differences persisted through month 9 except at the wound site, which had a relatively small sample size. Higher regimen adherence was associated with lower MRSA colonization (p<0.01).



Comment: The reduction in colonization reinforces the previously reported trial findings of significantly reduced MRSA infections and all-cause infections in the year following discharge and strongly suggests the benefits were driven by reduction in MRSA colonization at multiple body sites. As we have seen with other infection prevention interventions, compliance leads to better outcomes. The frequency and duration of the decolonization regimen, five days twice monthly for six months, was selected as the protocol for the CLEAR Trial. It is not known whether more frequent administration may be more effective, or alternatively, so burdensome that it would lower adherence to the regimen. This regiment was chosen by consensus by the research investigators. The investigators did not perform strain typing on MRSA isolates. Although this study focused on MRSA, and I see no reason this regiment could not be used for patients with recurrent invasive MSSA infections who are colonized with MSSA. Studies have shown that even after successful decolonization, 50-60% become recolonized after 6-9 months leading to increased risk of infection. This regiment should be considered at discharge for all patients admitted with invasive disease and colonized with MRSA or MSSA.

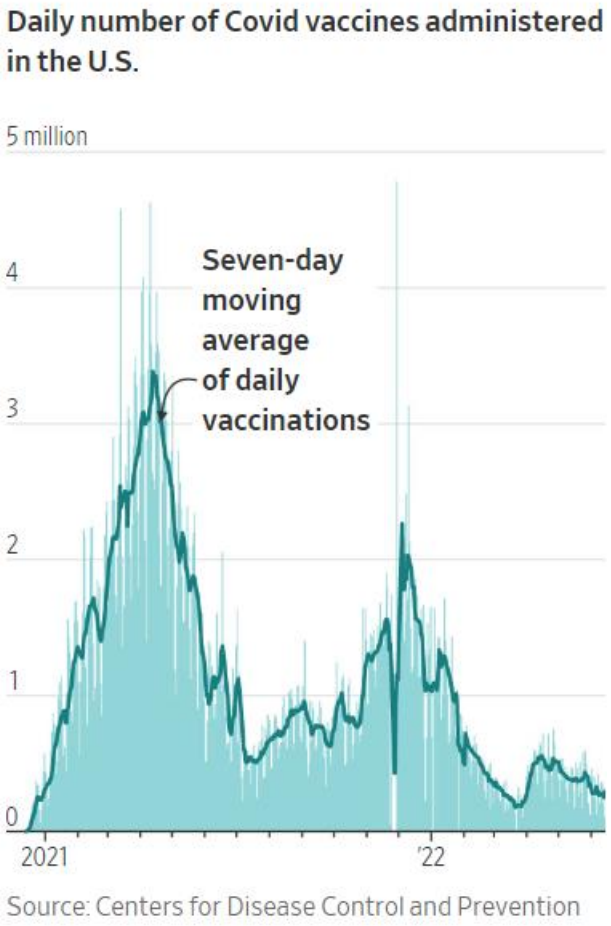
COVID-19

FDA Updates

Moderna Children 6-17

Vaccines and Related Biological Products Advisory Committee (VRBPAC) of the FDA met on Tuesday and unanimously recommended Moderna's vaccine for use in children and adolescents ages 6 to 17. The Moderna vaccine is administered 28 days apart. Children 6 through 11 receive 50 micrograms in each shot, half the adult dose. Adolescents are given the adult dose. The third, or booster, dose for both groups will be 50 micrograms, the company said. The FDA and CDC agreed with the panel's advice. The Pfizer vaccine already is available for children 5 through 17.

Comment: But having a second vaccine available might not translate into increased vaccinations at least in the 6-to-11-year-old age group, in which demand remains weak. Only 29 percent of children in that group have received the two-shot regimen of the Pfizer vaccine, according to the CDC. In general demand for vaccination has leveled off. (See graph below)



Even with the unanimous support for the vaccine, some of the advisers expressed concerns that the data on the vaccine were limited and outdated because trials were conducted before the emergence of the omicron variant. They said the vaccine would probably be beneficial in preventing serious illness but not as effective at preventing mild infections. Moderna told the advisers it is testing a booster shot for the 6-through-17 age groups and would seek FDA

authorization in coming months — perhaps as early as by July. There were no confirmed cases of myocarditis or pericarditis in the Moderna trials for infants, children and adolescents — but the trials might have been too small to pick it up.

Children 6 months through 4 years old

Outside advisers (VRBPAC) to the FDA voted unanimously on Wednesday to recommend that the agency authorize the Moderna and Pfizer vaccines for very young children, followed by approval by the FDA and CDC. Pfizer's three-dose vaccine would cover children 6 months through 4 years old, while Moderna two-dose vaccine would be for children 6 months through 5 years old. Moderna's EUA applies to children ages 6 months through 5 years, given in two 25-microgram doses, which is one fourth of the adult dose. Pfizer's EUA applies to kids ages 6 months through 4 years, given in three 3-microgram doses, one tenth of the adult dose. There were no confirmed cases of myocarditis or pericarditis among participants aged 6 months through 17 years in Moderna's studies.

Comment: Both the vaccines appear significantly less effective against symptomatic infection than the adult vaccines when they were introduced. The FDA in part attributes the lower VE to the Omicron variants which are far more immune evasive against infection than prior strains of the virus. Moderna vaccine like the Pfizer vaccine is more effective after a third dose show an extra dose will be needed in the pediatric population. Importantly, neither vaccine has been tested against subvariants currently circulating the US. Given weak demand for children ages 5-11, it is unclear what the demand will be for ages 6 months to 4 years. I do not expect the availability of pediatric vaccines for young children to change the overall trajectory of the pandemic, however, the vaccine should provide more flexibility for families, day cares and preschools.

hase 2/3 EPIC-SR (Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients) study -Update (nirmatrelvir/ ritonavir)

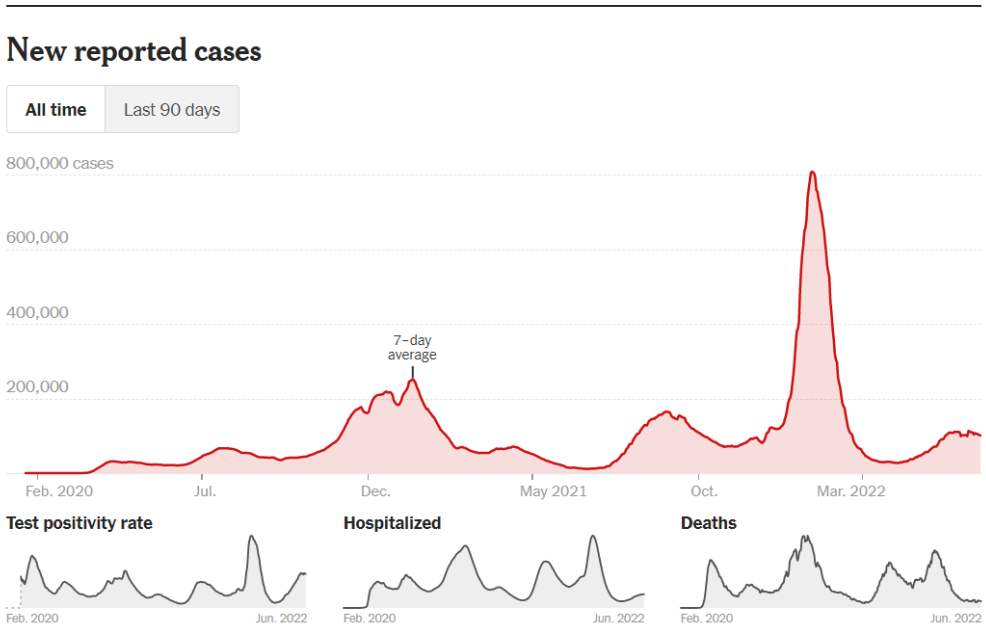
Pfizer updated the findings from a nirmatrelvir/ritonavir (Paxlovid) trial in standard-risk COVID-19 suggest the antiviral's benefits are less clear for those not at high risk of severe outcomes.

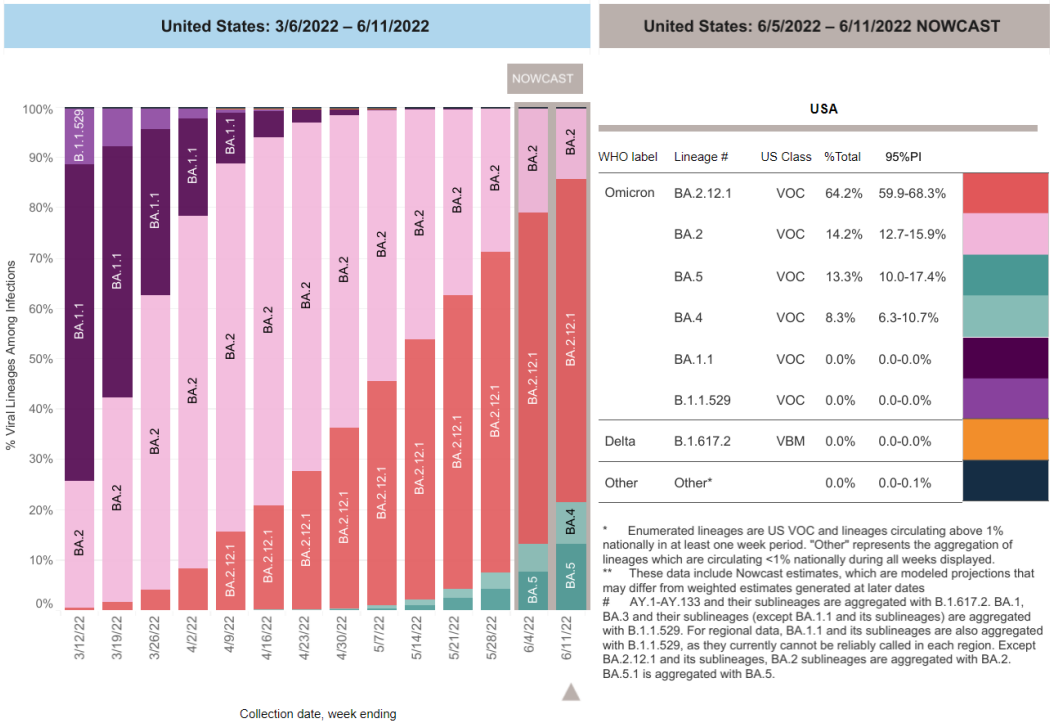
- In the EPIC-SR study of Paxlovid (nirmatrelvir- ritonavir), the novel primary endpoint of self-reported, sustained alleviation of all symptoms for four consecutive days was not met, as previously reported
- Data from standard-risk patients, both vaccinated and unvaccinated, while not all statistically significant, are supportive of efficacy data observed in EPIC-HR study and will be included in upcoming NDA submission to U.S. FDA for high-risk patients
- Pre-specified secondary endpoint resulted in a nominally significant 62% decrease in COVID-19-related medical visits per day across all patients, relative to placebo
- In a sub-group analysis, non-significant 57% reduction in hospitalizations and death observed in PAXLOVID-treated vaccinated patients with at least one risk factor for severe COVID-19
- Pfizer to cease enrollment into the EPIC-SR trial due to low rate of hospitalization or death in the standard-risk population; will continue to evaluate treatment in populations with high unmet need
- Another prespecified analysis showed a 72% reduction in the average number of days in the hospital for those who got nirmatrelvir/ritonavir. There was also a trend indicating an advantage in ICU admission with the drug, but this was not significant.

- Adverse events were comparable, at about 23% in both groups, and most were mild. Serious adverse events were also comparable, at 1.4% with the drug and 1.9% with placebo.

Comment: A reminder**,** the EPIC-**HR (high risk)** study was a randomized, double-blind, 2-arm study included 2246 patients with laboratory-confirmed SARS-CoV-2 infection and mild to moderate symptoms. Final results demonstrated that nirmatrelvir/ritonavir significantly reduced the risk of COVID-19- related hospitalization or death from any cause by 88% (within 5 days of symptom onset) compared with placebo (*P* <.0001). In the June 6th ID Watch I review and pre-publication study that demonstrated nirmatrelvir/ritonavir therapy was associated with a 67% reduction in Covid-19 hospitalizations and an 81% reduction in Covid-19 mortality in patients 65 years and above. However, no significant benefit in avoidance of severe Covid-19 outcomes was shown in younger adults (40-64). These studies suggest we should only prescribe nirmatrelvir/ritonavir therapy only in the high-risk population.

COVID-19 by the Numbers





Comment: Cases are declining in roughly half the states, particularly in the Northeast and Midwest. In the past two weeks, parts of New England have seen cases fall by 30 percent or more. In the South and West, however, cases and hospitalizations are increasing substantially. Reports of new deaths remain low. The spread of two new omicron subvariants, BA.4 and BA.5, is gaining in the United States and could create another rise in cases. (see above)

COVID-19 Journal Review

Accuracy of Rapid Antigen vs Reverse Transcriptase–Polymerase Chain Reaction Testing for SARS-CoV-2 Infection in College Athletes During Prevalence of the Omicron Variant JAMA Netw Open published online June 15, 2022

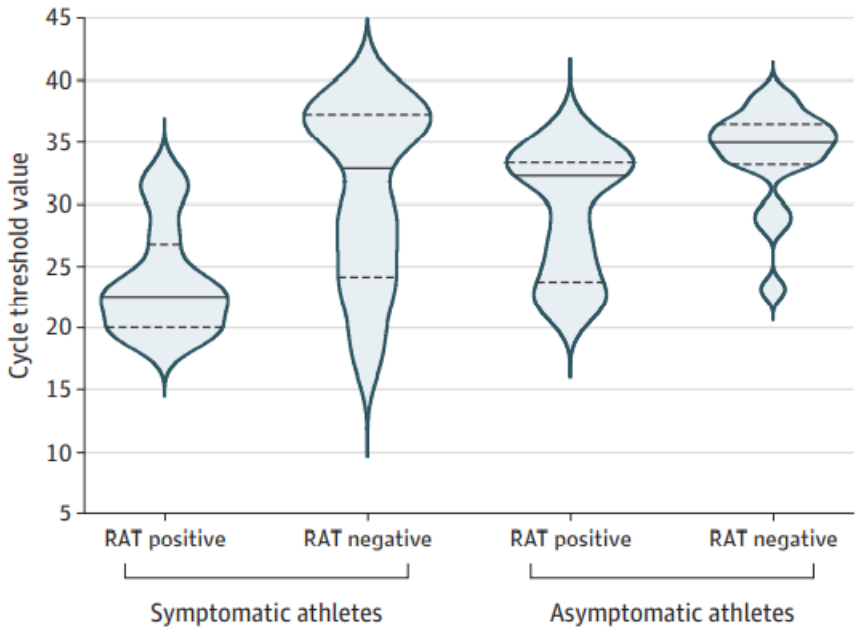
doi:10.1001/jamanetworkopen.2022.17234

All Stanford University student athletes who reported no history of SARS-CoV-2 infection in the previous 90 days and returned to campus from January 1 through January 11, 2022, self-administered an RAT (BinaxNOW) within 24 hours of campus arrival. Symptomatic students with a positive RAT result were isolated without confirmatory PCR testing; asymptomatic students with a positive RAT result underwent RT-PCR testing.

Participants included 723 students aged 17 to 23 years (376 [52.0%] female; 709 [98%] received 2-dose Pfizer or Moderna or 1-dose J&J vaccines). Forty-six participants (6.4%) had positive RAT findings, of whom 35 (76.1%) had symptomatic infections. Among these 35 participants, 12 received a positive RT-PCR result within 24 hours, whereas the remaining 23 were presumed to have positive results. Twenty-seven participants had a negative RAT result

followed by a positive RT-PCR result within 24 hours, for a total of 73 diagnosed SARS-CoV-2 infections in the included cohort (infectivity rate, 73 of 723 [10.1%]). Overall, RAT had a sensitivity of 63.0% (95% CI, 51.9%-74.1% [46 of 73]) and specificity of 99.8% (95% CI, 99.5%-100% [1 of 650]). Among symptomatic participants, RAT had a sensitivity of 77.8% (95% CI, 65.6%-89.9% [35 of 45]); among asymptomatic patients, 39.2% (95% CI, 21.2%-57.4% [11 of 28]).

Participants with RAT and RT-PCR positive findings (n = 23) had a lower median Ct value of 24.6 (IQR, 22.2-32.3) compared with those with RAT-negative and PCR–positive findings (n = 27), with a median Ct value of 35.0 (IQR, 29.8-36.6; P < .001). In the PCR–positive cohort, symptomatic individuals (n = 22) had lower Ct values compared with their asymptomatic counterparts (24.7 [IQR, 22.4-31.9] vs 33.6 [IQR, 29.3-35.7]; P = .004). In the PCR analysis, the Omicron variant represented 44 of 46 positive cases (95.7%). Four specimens could not be genotyped owing to low viral loads.



Comments: RAT performed similarly in the detection of the Omicron variant compared with previous variants, with high specificity but poor sensitivity, particularly among asymptomatic individuals. Of interest, if you were RAT negative even if symptomatic your Ct values were >30 which some would say means low risk of transmission.

Clinical outcomes associated with SARS-CoV-2 Omicron (B.1.1.529) variant and BA.1/BA.1.1 or BA.2 subvariant infection in southern California Nat Med published online June 8, 2022

doi. org/10.1038/s41591-022-01887-z (2021)

Investigators compared COVID-19 severity outcomes among individuals infected with the SARS-CoV-2 Omicron and Delta variants. They also explored differences in risks of severe COVID-19 outcomes among individuals infected with Omicron BA.1/BA.1.1 and BA.2 subvariants in South California.

Omicron infections were assessed between December 15, 2021, and January 17, 2022, and Omicron BA.2 subvariant infections were assessed between February 3 and March 17, 2022. Data of PCR-diagnosed COVID-19 cases detected in outpatient settings were obtained from electronic health records (EHRs) of the Kaiser Permanente of Southern California (KPSC) healthcare system. The causative variant was identified by SARS-CoV-2 spike (S)-gene target failure (SGTF) analysis. Variant-specific risks of five endpoints viz. any hospitalization, symptomatic hospitalization, ICU admission, mechanical ventilation requirements, and death per 1000 cases were determined, and differences in the endpoints based on vaccination were evaluated.

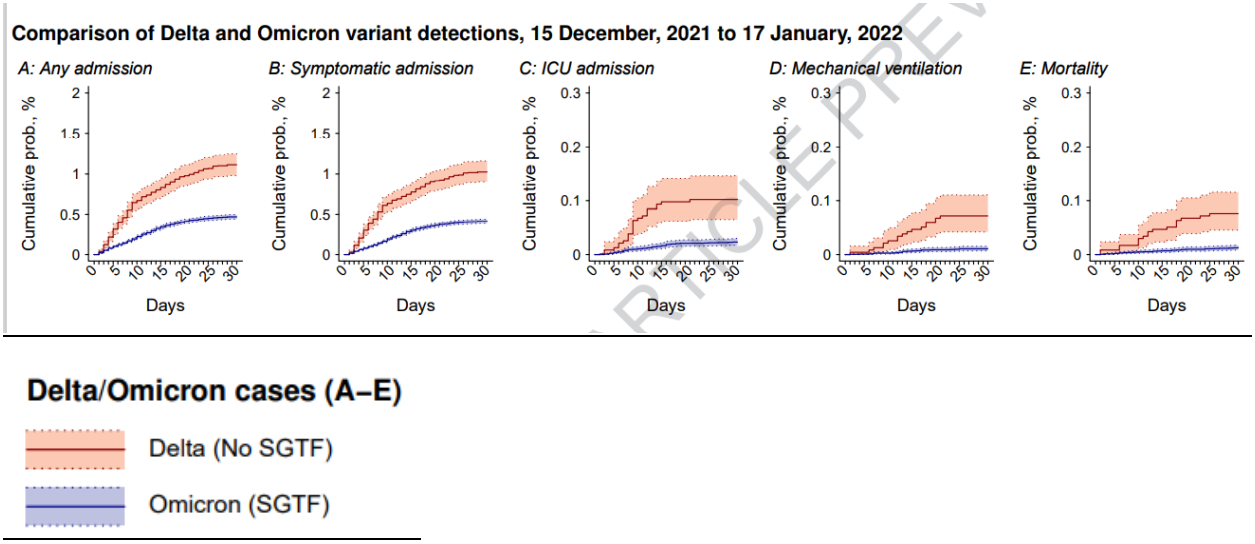
A total of 222,688 Omicron cases, 23,305 Delta cases, 12,756 BA.1 cases, and 1,905 Omicron BA.2 were detected. No significant differences were found in the immune protection against SARS-CoV-2 among BA.1 and BA.2 cases based on vaccine doses, vaccination timing, and COVID-19 history. Likewise, no differences in the severity outcomes, duration of hospital stay, or likelihood of discharge among BA.1 and BA.2 cases.

The cumulative risks of symptomatic hospitalization, any hospitalization, mechanical ventilation requirements, ICU admission, and mortality among Delta cases were 9.7, 10, 0.7, 1.1, and 0.7, respectively. For Omicron cases, the corresponding risks were 3.9, 4.5, 0.1, 0.2, and 0.1, respectively. The aHR estimates for COVID for any hospitalization and symptomatic hospitalization comparing cases with Omicron and Delta infections were 0.6 and 0.6, respectively.

For ICU admissions, mechanical ventilation requirements, and deaths, the aHRs comparing Omicron and Delta cases over 60 days after detection in outpatient settings were 0.5, 0.36, and 0.2, respectively. The estimates were similar after the inclusion of cases diagnosed at or following the hospitalization date and after limiting the analyses to cases that were asymptomatic when testing was performed in outpatient settings, among which Omicron infections were associated with a lesser risk of symptom development than Delta infections (aHR=0.9).

Among unvaccinated cases, the aHRs for Omicron versus Delta infections for any hospitalization, symptomatic hospitalization, ICU admission, mechanical ventilation requirements, and deaths were 0.4, 0.4, 0.3, 0.2, and 0.1, respectively. Variant-specific risks of any hospitalization or symptomatic hospitalization were not detected among individuals with ≥3 mRNA vaccinations and were attenuated among doubly vaccinated individuals.

No differences were observed in the risk of mechanical ventilation requirements and ICU admissions among vaccinated individuals infected with Delta or Omicron. However, among them, Omicron cases had a lesser mortality risk than Delta infections (aHR=0.3). Among hospitalized Delta cases, the proportions of cases with hospital stay ≤5 days, ≤10 days, and ≤15 days were 66%, 85%, and 89%, respectively, compared to 85%, 91%, and 92% among hospitalized Omicron cases. About 74% and 86% of hospitalized Delta and Omicron cases, respectively, were discharged within ≤30 days. The 30-day likelihood of mortality or discharge to a hospice following hospitalization was 1% and 0.4% for Omicron infections, respectively.



Comment: Overall, the study findings showed that Omicron infections were associated with lower COVID-19 severity than Delta infections in South California, and the differences were most prominent among unvaccinated individuals. In contrast, Omicron BA.1- and BA.2-infected individuals were equally prone to severe COVID-19. Previous studies have estimated reductions in risk of hospital admission associated with Omicron variant infection. The investigators state: "While statistical adjustment for differences in demographic, clinical, and immunological aspects of cases supported efforts to define associations of each variant with risk of severe outcomes, given acquisition of infection, unobserved attributes of cases which predict both their infecting variant and risk of severe clinical outcomes remain of concern, as in all observational epidemiologic research." Lower risk of severe clinical outcomes among cases with Omicron variant infection should influence public health response amid establishment of the Omicron variant as the dominant SARS-CoV-2 lineage globally. These finding underscore the value of monitoring variant-specific infection severity alongside ongoing surveillance efforts aimed at tracking epidemiologic dynamics of novel variants to inform intervention deployment and healthcare capacity planning. The current situation in US indicate the number of patients hospitalized with the virus is still growing, but doing so slowly, with the average hovering for most of this week around 29,000. There is very little increased in ICU admission and deaths have stayed below 400 a day for several weeks. These facts support the results of this study, that although the Omicron variants are more transmissible, they result milder disease and lower severity compared to prior variants such as delta. This study was done before BA.2.12.1, BA.4, and BA.5.

Association of Omicron vs Wild-type SARS-CoV-2 Variants With Hospital-Onset SARS-CoV-2 Infections in a US Regional Hospital System JAMA published online June 15, 2022

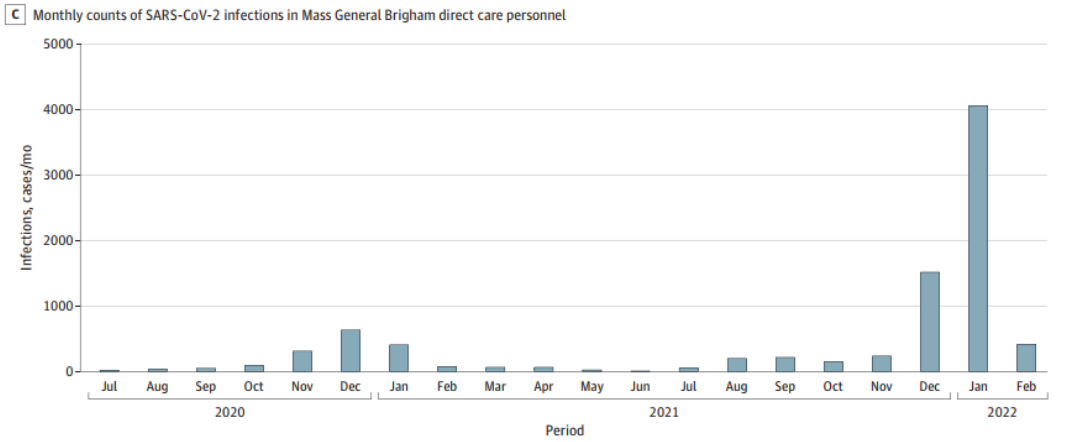
doi:10.1001/jama.2022.9609

The authors retrospectively identified all SARS-CoV-2 cases diagnosed in 12 hospitals within the Mass General Brigham health care system between July 1, 2020, and February 28, 2022. All patients were tested on admission with polymerase chain reaction (PCR) assays, and, starting November 2020, were retested 72 hours after admission to identify cases with virus incubating on admission. Retesting was also required for new

symptoms, after possible exposures, before aerosol-generating procedures, and before discharge if requested by destination facilities.

They calculated monthly incidence rates for SARS-CoV-2 infections first identified on hospital days 5 or later, 8 or later, and 15 or later per 1000 non–COVID-19 patient-days. They selected these periods as increasingly likely to identify hospital acquired infections, given the incubation period of SARS-CoV-2 (wild-type median 5 days, Delta 4 days, and Omicron 3 days) They then compared the incidence of hospital-onset(HO) cases during December 15, 2021, to February 28, 2022, when the Omicron variant predominated, vs December 15, 2020, to February 28, 2021, when wild-type virus predominated. Infection control policies were similar across periods and included universal masking, daily employee health attestations, testing on admission and 72 hours after admission, visitor restrictions, contact tracing, and free on-demand testing for employees.

The incidence of HO infections was significantly higher during the winter 2021-2022 Omicron surge vs the prior winter surge: 0.87 vs 0.56 cases per 1000 patient-days for diagnoses on hospital day 5 or later (relative risk [RR], 1.54; 95% CI, 1.22-1.95), 0.57 vs 0.35 for diagnoses on hospital day 8 or later (RR, 1.62; 95% CI, 1.21-2.18), and 0.37 vs 0.16 for diagnoses on hospital day 15 or later (RR, 2.31; 95% CI, 1.53-3.49). The increase in HO infections during the Omicron wave vs the prior winter wave mirrored similar increases in community and health care worker case numbers during these same periods.



Comment: The Omicron surge was associated with a significant increase in hospital-onset SARS-CoV-2 infections compared with the prior winter surge. I think the reasons include the Omicron surge's very high community and health care worker infections plus Omicron's greater transmissibility. Sources of nosocomial infections include health care workers, visitors, and other patients. Findings may not be generalizable to hospitals with fewer baseline infection control measures (e.g., vaccination requirements, testing all patients on admission and 72 hours after admission). This article underscores the risk of nosocomial transmission despite robust enhanced infection control strategies, especially when community incidence rates are high. This same group of investigators also published an article on controlling a cluster of HO infections with the universal use of N-95 masks and daily testing. [Clin Infect Dis. Published online February 7, 2022] In a separate article Klompas et al recommended 3 additional measures to reduce nosocomial transmission during Omicron: (1) mandate booster dose; (2) test more frequently; (3) universal use of N-95 masks. [JAMA. 2022;327(7):619-620.] This article also underscores my concern when the CDC shortened the length of isolation without testing for HCWs.

Neutralization of the SARS-CoV-2 Omicron BA.4/5 and BA.2.12.1 Subvariants N Engl J Med published online June 15, 2022

DOI: 10.1056/NEJMc2206725

In the study, investigators examined neutralizing-antibody titers in serum samples obtained from vaccinated individuals who had received a single booster dose of the same vaccine used in the two-dose series and who had been previously infected with SARS-CoV-2.

The researchers examined the neutralizing-antibody resistance to these subvariants in health care workers (HCWs) who had received 2 doses of Moderna; n = 4 or Pfizer; n = 11 vaccines. Sera were collected 3-4 weeks post-second vaccine dose for these 15 HCWs (median age 37 years). The researchers observed that the BA.4/5 and BA.2.12.1 subvariants (geometric mean 50% neutralization titers [NT_{50}] 37 and 46, respectively) had neutralization resistance that was similar to that of the BA.1 and BA.2 subvariants (geometric mean NT_{50} titers 52 and 39, respectively).

Boosted HCW samples were additionally collected 1-11 weeks post-homologous booster vaccine dose. Both HCWs who had received three doses of the Moderna vaccine and those who received three doses of the Pfizer vaccine had significant increased neutralizing-antibody titers overall (geometric mean NT_{50} titers ranged from 706 to 976). Nonetheless, compared with the response against the ancestral SARS-CoV-2 strain(D614G), neutralizing-antibody titers were 4.1 times as low against the BA.4/5 variant and 3.2 times as low against the BA.2.12.1 variant ($P < 0.001$ for both comparisons), and the titers were approximately 2.8 times as low against the BA.1 and BA.2 variants. Meanwhile, the neutralizing-antibody resistance of BA.2_L452Q was stronger than that of BA.2_S704L, which had neutralizing-antibody titers that were approximately 3.7 times and 2.9 times as low, respectively, as those against the D614G strain ($P < 0.001$ for both comparisons).

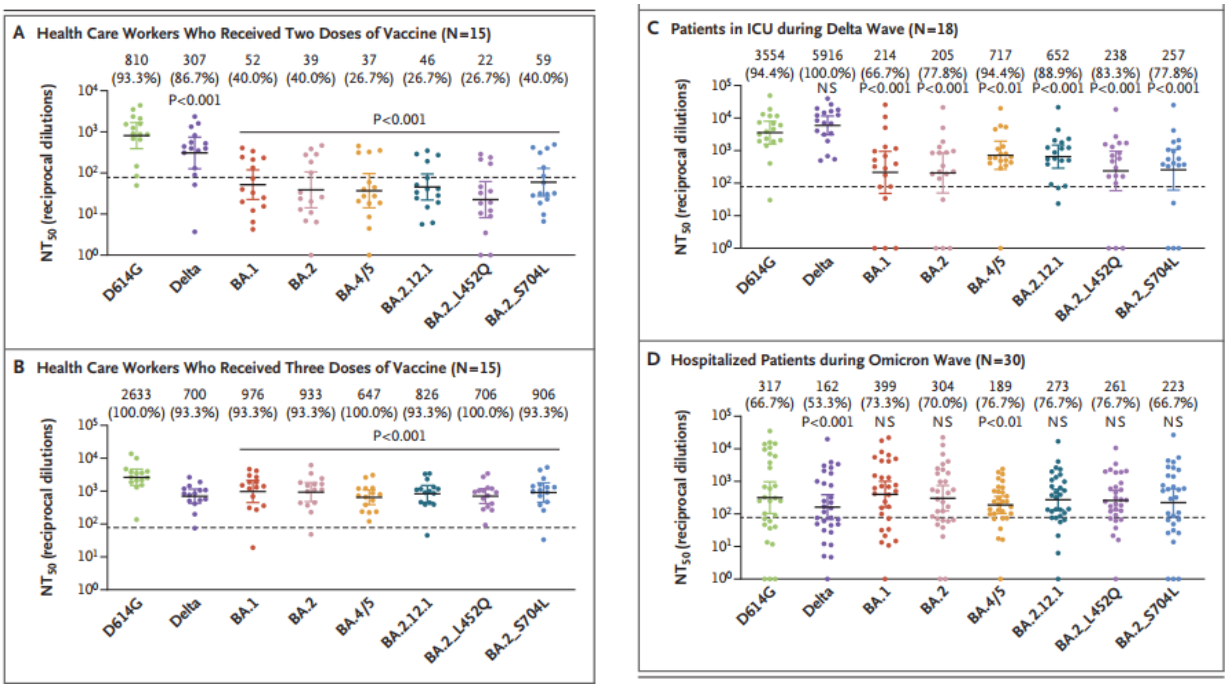
On the other hand, samples were also collected from 18 patients (median age, 60 years) who were hospitalized in the intensive care unit (ICU) during the delta wave of the pandemic 3 days after ICU admission. These delta-wave patients included 1 patient vaccinated with 1 dose of the J&J vaccine, 4 patients vaccinated with 2 doses of the Pfizer vaccine, and 1 patient vaccinated with 3 doses of the Moderna vaccine.

Study data showed that BA.4/5 and BA.2.12.1 had less escape from neutralization in serum samples obtained during the delta wave (geometric mean NT_{50} titers 717 and 652, respectively). Geometric mean values for neutralization titers were 5.0 times as low against the BA.4/5 variant as against the D614G variant ($P < 0.01$), and the values were 5.5 times as low against the BA.2.12.1 variant as against the D614G variant ($P < 0.001$). However, the neutralizing-antibody titers were 14.9 times as low against the BA.2 L452Q variant as against the D614G variant ($P < 0.001$), and the titers were 13.8 times as low against the BA.2_S704L variant as against the D614G variant ($P < 0.001$).

In addition, 30 patients (median age, 62 years) who were infected with the omicron variant and hospitalized but not admitted to the ICU had their serum samples collected 1-8 days after hospitalization. Of these patients, 8 were vaccinated with 2 doses of the Pfizer vaccine (n = 4) or Moderna vaccine (n = 4), with sample collection occurring at a median of 9 months after the second-dose vaccination, while 7 patients were vaccinated with 3 doses of the Pfizer vaccine

and sample collection occurred at a median of 5 months after booster vaccine administration. The remaining 15 patients were unvaccinated.

The researchers observed that neutralizing-antibody titers against BA.4/5 and BA.2.12.1 were 37.8% and 10.2% lower, respectively, than those against BA.2 ($P > 0.05$ for both comparisons). The BA.2 single mutants (i.e., BA.2_L452Q and BA.2_S704L) had neutralizing-antibody escape that was similar to that of the BA.4/5 and BA.2.12.1 subvariants, with neutralizing-antibody titers that were 14.1% and 26.6% lower, respectively, than those against BA.2 ($P > 0.05$ for both comparisons). Notably, 2 of 30 BA.1-infected but unvaccinated patients had high neutralizing-antibody titers against all the variants except BA.4/5, whereas patients who had received a booster dose had broader neutralization against all the variants examined.



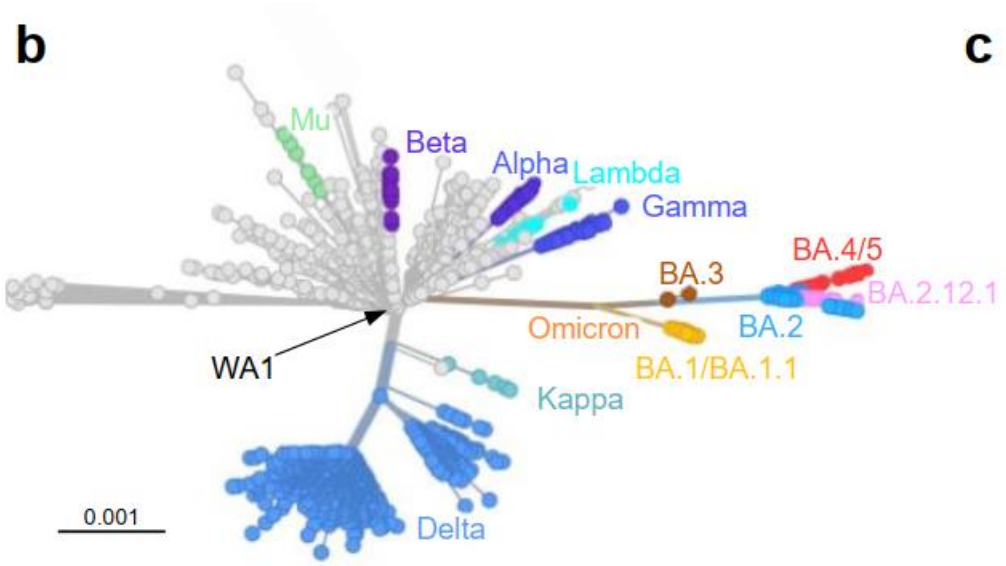
Comment: Overall, these results showed that infection during the BA.1 wave did not appear to offer effective protection against the newly emerged sub lineages like BA.5. In this study, they also characterized infection-induced immunity and vaccine-induced immunity against newly emerged omicron subvariants. Booster vaccination provided sufficient neutralizing-antibody titers against the BA.4/5 and BA.2.12.1 subvariants, albeit to a lower extent than against BA.1 and BA.2. These findings underscore the importance of booster vaccination for protection against emerging variants. See next article

SARS-CoV-2 Omicron BA.2.12.1, BA.4, and BA.5 subvariants evolved to extend antibody evasion bioRxiv posted online May 26, 2022

doi.org/10.1101/2022.05.26.493517

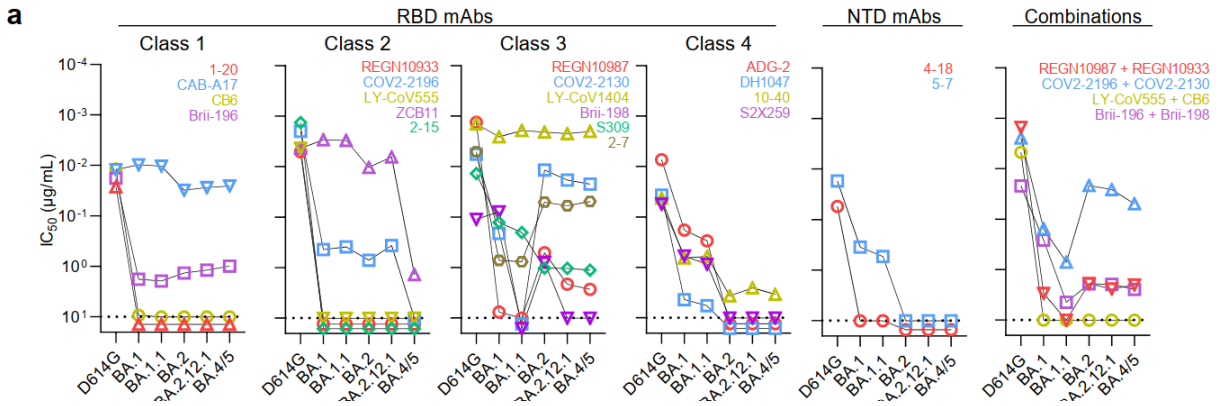
The Omicron subvariant BA.2.12.1 and BA.4/5 have surged dramatically to become dominant in the United States and elsewhere. These novel Omicron subvariants carry additional mutations

in their spike proteins that may further evade neutralizing antibodies, thereby compromising the efficacy of our COVID-19 vaccines and MCA.

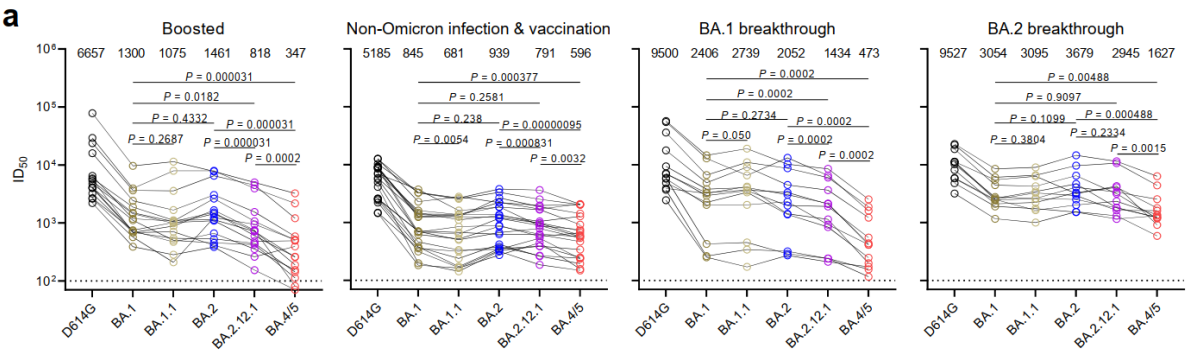


The investigators report their findings from a systematic antigenic analysis of these Omicron subvariants. Sera from individuals who received three doses of the Moderna, or Pfizer vaccine were collected at Columbia University Irving Medical Center. Sera from individuals who were infected by non-Omicron variants of SARS-CoV-2 in addition to vaccination were collected from January 2021 to September 2021. Sera from individuals who were infected by Omicron (BA.1 or BA.2) following vaccinations were collected from December 2021 to May 2022. All samples were confirmed for prior SARS-CoV-2 infection status by anti-nucleoprotein (NP) ELISA.

To study antigenic differences of BA.2.12.1 and BA.4/5 from previous Omicron subvariants (BA.1, BA.1.1, and BA.2) and the wild-type SARS-CoV-2 (D614G), they produced each pseudovirus and then assessed the sensitivity of each pseudovirus to neutralization by a panel of 21 monoclonal antibodies (mAbs) directed to known neutralizing epitopes on the viral spike. Among these, 19 target the four epitope classes in RBD4, including REGN10987 (imdevimab)5, REGN10933 (casirivimab)5, COV2-2196 (tixagevimab)6, COV2-2130 (cilgavimab)6, LY-CoV555 (bamlanivimab)7, CB6 (etesevimab)8, Brii-196 (amubarvimab)9, Brii-198 (romlusevimab)9, S309 (sotrovimab)10, LY-CoV1404 (bebtelovimab)11, ADG-212, DH104713, S2X25914, CAB-A1715 and ZCB1116, as well as 1-20, 2-15, 2-717 and 10-4018 from our group. Overall, 18 and 19 mAbs lost neutralizing activity completely or partially against BA.2.12.1 and BA.4/5, respectively. Neutralization profiles were similar for BA.2 and BA.2.12.1. Only four mAbs (CAB-A17, COV2- 2130, 2-7, and LY-COV1404) retained good in vitro potency against both BA.2.12.1 and BA.4/5 with IC50 below 0.1 μg/mL Importantly, among these four mAbs, only LY-COV1404 or bebtelovimab is authorized for therapeutic use. For antibody combinations previously authorized or approved for clinical use, all showed a substantial loss of activity in vitro against BA.2.12.1 and BA.4/5.



BA.2.12.1 is only modestly (1.8-fold) more resistant to sera from vaccinated and boosted individuals than BA.2. On the other hand, BA.4/5 is substantially (4.2-fold) more resistant and thus more likely to lead to vaccine breakthrough infections. Mutation at spike residue L452 found in both BA.2.12.1 and BA.4/5 facilitates escape from some antibodies directed to the so-called Class 2 and Class 3 regions of the receptor-binding domain (RBD)4. The F486V mutation found in BA.4/5 facilitates escape from certain Class 1 and Class 2 antibodies to the RBD but compromises the spike affinity for the cellular receptor ACE2. The R493Q reversion mutation, however, restores receptor affinity and consequently the fitness of BA.4/5.



Comment: The Omicron lineage of SARS-CoV-2 continues to evolve, successively yielding subvariants that are not only more transmissible but also more evasive to antibodies. Among therapeutic antibodies (MCA) authorized for clinical use, only bebtelovimab (LY-COV1404) retains full potency against both BA.2.12.1 and BA.4/5.

Ivermectin for Treatment of Mild-to-Moderate COVID-19 in the Outpatient Setting: A Decentralized, Placebo-controlled, Randomized, Platform Clinical Trial medRxiv posted June 12, 2022 article suggested by Luis Ostrosky

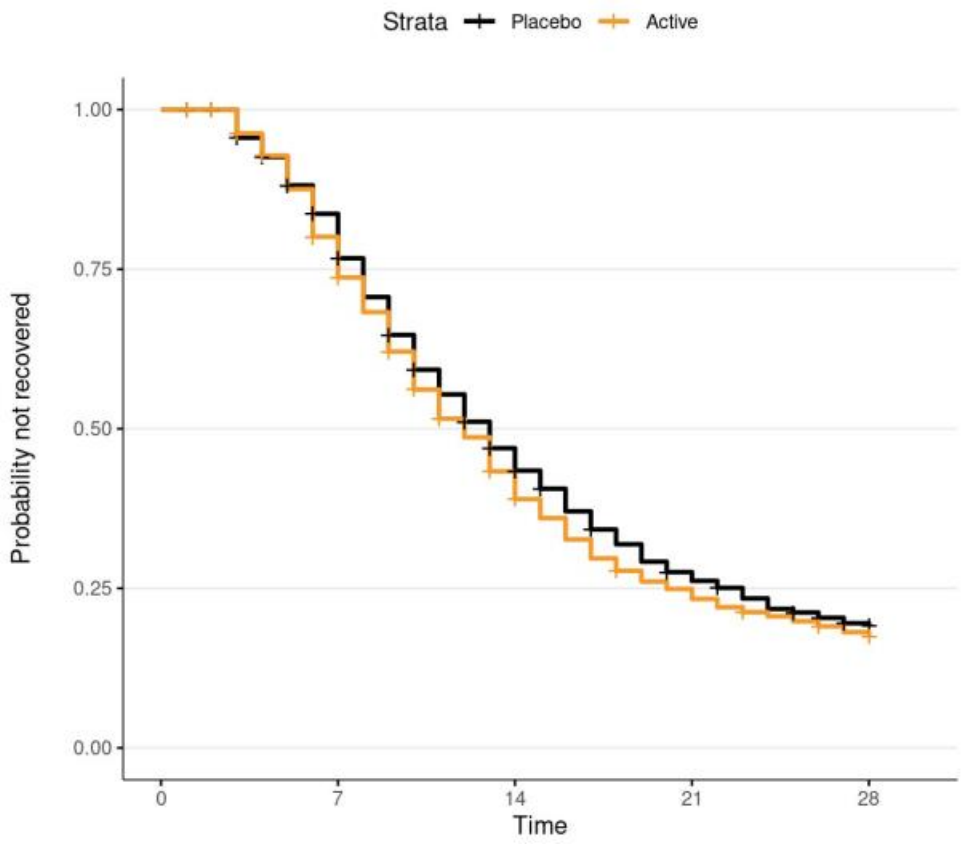
doi.org/10.1101/2022.06.10.22276252

ACTIV-6 is an ongoing, decentralized, double-blind, randomized, placebo-controlled platform trial to evaluate repurposed therapies in outpatients with mild-to-moderate COVID-19. Non-hospitalized adults age ≥30 years with confirmed COVID-19, experiencing ≥2 symptoms of acute infection for ≤7 days were randomized to receive ivermectin 400 µg/kg daily for 3 days or placebo. The main outcome measure was time to sustained recovery, defined as achieving at least 3 consecutive days without symptoms. Secondary outcomes included a composite of hospitalization or death by day 28. Participants were enrolled into the ivermectin arm or identical matched-placebo or contributing-placebo from June 23, 2021 through February 4, 2022 at 93 sites in the US.

Of the 3457 participants who consented to be evaluated for inclusion in the ivermectin arm, 1591 were eligible for this study arm, randomized to receive ivermectin 400 µg/kg (n=817) or placebo (n=774), and received study drug. Of those enrolled, 47% reported receiving at least 2 doses of SARS-CoV-2 vaccination. The posterior probability for any improvement in time to recovery was 0.91 (hazard ratio 1.07, 95% credible interval 0.96–1.17). The posterior probability of this benefit exceeding 24 hours was less than 0.01, as measured by the difference in mean time unwell. Hospitalizations or deaths were uncommon (ivermectin [n=10]; placebo [n=9]). Ivermectin at 400 µg/kg was safe and without serious adverse events as compared with placebo (ivermectin [n=10]; placebo [n=9])

Specifically, hospitalization or death were uncommon, occurring in 1.22% (10/817) with ivermectin and 1.16% (9/774) with placebo; there was one death in the ivermectin arm. Similarly, the composite secondary outcome of urgent or emergency care visits, hospitalizations, or death were similar with ivermectin (3.9% [32/817]) compared with placebo (3.6% [28/774]). The posterior probability for treatment benefit did not meet prespecified thresholds for clinical events or on the COVID Clinical Progression Scale at days 7, 14, and 28. There was no evidence of a different treatment effect with ivermectin compared with placebo for timing of symptom onset, body mass index, calendar time, or vaccination status.

Figure 1. Time to recovery from COVID-19 with ivermectin versus placebo.



Comment: Ivermectin dosed at 400 µg/kg daily for 3 days resulted in less than one day of shortening of symptoms and did not lower incidence of hospitalization or death among outpatients with COVID-19 in the United States during the delta and omicron variant time periods. The largest randomized trial until now was the TOGETHER trial, which enrolled 1358 patients in Brazil with symptomatic mild-to-moderate COVID-19 and at least 1 risk factor for disease progression. Patients received ivermectin 400 µg/kg for 3 days or placebo in an outpatient setting. No statistically significant clinical benefit of ivermectin was observed for preventing disease progression resulting in hospitalization or prolonged emergency department observation. [review in ID Watch; N Engl J Med. 2022;386(18):1721-1731] One subgroup in this study reporting severe symptoms possibly experienced benefit of faster symptom resolution with ivermectin (HR 1.79; 95% CrI, 1.06 to 3.04), however, the overall effect of symptom severity was not significant (p=0.123) and the small sample size in the severe group (51 ivermectin vs. 39 placebo) suggests this results should be considered exploratory requiring further validation in a future trial. We are awaiting the results for fluvoxamine.