Infectious Diseases Watch

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General Infectious Diseases

Faecal microbiota transplantation reduces amounts of antibiotic resistance genes in patients with multidrug-resistant organisms Antimicrob Resistance Infect Control (2022) 11:20

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Fecal microbiota transplantation (FMT) has emerged as an important strategy for decolonization. This study aimed to evaluate the genetic response of MDROs to FMT. This is a small singe center prospective study which was conducted on patients infected with VRE, CPE, or VRE/CPE who underwent FMT between May 2018 and April 2019. Genetic response was assessed as the change in the expression of the resistance genes *VanA*, *bla*KPC, *bla*NDM, and *bla*OXA on days 1, 7, 14, and 28 by PCR.

Fecal material was obtained from healthy, unrelated donors. All volunteers were screened based on their history and clinical examination for antibiotic use within 3 months, GI symptoms, and any risk of infectious disease. Donors were excluded if they had taken any antibiotics in the past 3 months. Donors were tested for hepatitis (A, B, and C), human immunodeficiency virus, syphilis, bacteria (stool culture), rotavirus/norovirus/ adenovirus (stool PCR), *C. difficile* toxin, parasites, and their eggs (rectal exam), and VRE and CPE (stool culture). Stool samples were donated, and 100 g samples were mixed with 200 mL of sterile normal saline and stored as concentrated glycerol stocks at-70 °C. FMT was performed using a preparation of the frozen fecal solution via colonoscopy, duodenoscopy, a percutaneous jejunostomy tube, or an gastric capsule. Fecal samples of subjects were obtained before FMT and 1, 7, 14, and 28 days after FMT and stored at-80 °C until used for DNA extraction

Twenty-nine patients received FMT, of which 26 (59.3%) were infected with VRE, 5 (11.1%) with CPE, and 8 (29.6%) with VRE/CPE. The mean duration of MDRO carriage before FMT was 71 days. Seventeen patients (63.0%) used antibiotics within a week of FMT. In a culture-dependent method, the expression of *VanA* and overall genes significantly decreased (p=0.011 and p=0.003 respectively). In a culture-independent method, *VanA*, *bla*NDM, and overall gene expression significantly decreased over time after FMT (p=0.047, p=0.048, p=0.002, respectively). Similar results were confirmed following comparison between each time point in both the culture-dependent and -independent methods. Regression analysis did not reveal important factors underlying the genetic response after FMT. No adverse events were observed.

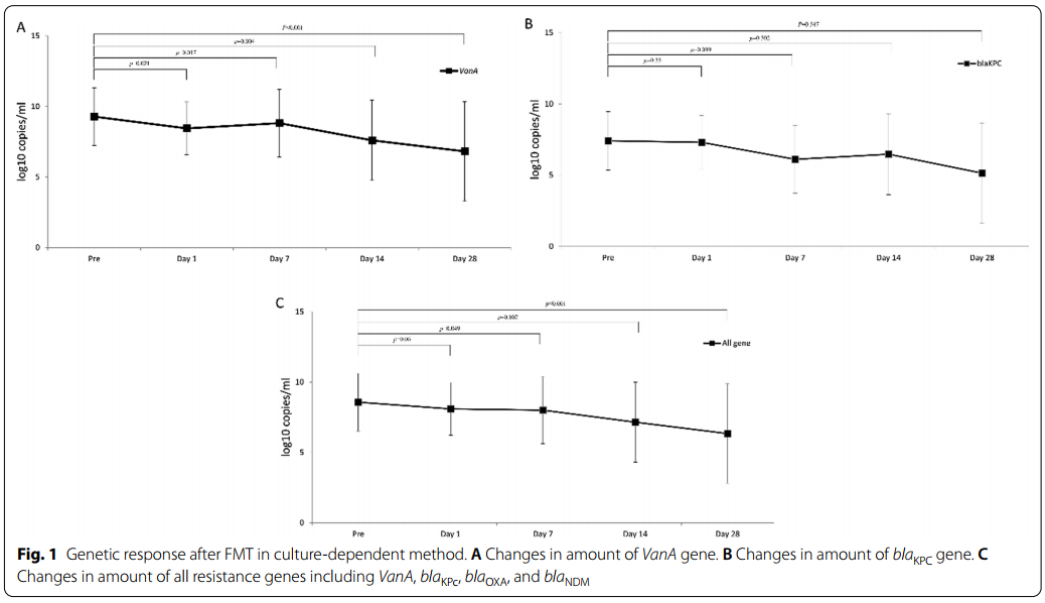


Fig. 1 Genetic response after FMT in culture-dependent method. **A** Changes in amount of *VanA* gene. **B** Changes in amount of bla_{KPC} gene. **C** Changes in amount of all resistance genes including *VanA*, bla_{KPC}, bla_{OXA}, and bla_{NDM}

Comment: The effectiveness of FMT in treating recurrent *C. difficile* infection is relatively well-established. We have good interventions to decolonize patients colonized with *S aureus,* but not other MDROs. Multiple groups have studied the decolonization of MDRO after FMT, which had a wide efficacy reported from 50–87.5% [Clin Infect Dis. 2017;65:364–70, J Hosp Infect. 2018; 99:481–6.]. The hypothesis is that FMT restores the gut microbial diversity, interacts with commensal bacteria, and increases resistance to colonization. FMT may be a potential emerging strategy facilitating MDRO decolonization. In this study, FMT in patients infected with MDROs downregulates the expression of resistance genes, especially *VanA*, and facilitates MDRO decolonization. This study gas a few weaknesses. First, the sample size was small. In addition, they did not compare the control group with patients colonized with MDROs but who were not treated with FMT. Lastly, they did not determine the clinical impact of resistance gene clearance after FMT. Further studies are warranted to determine the relationship between antibiotic resistance gene clearance and clinical outcomes.

Multicenter Cohort Study of Ceftaroline versus Daptomycin for Treatment of Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection OFID December 23, 2021

doi.org/10.1093/ofid/ofab606

While vancomycin is usually the initial treatment of choice for MRSA, reduced vancomycin susceptibility and/or adverse drug reactions can occur, and failure rates can be as high as 30%. Daptomycin, the current agent with the most clinical evidence and FDA approval for MRSA BSI, also results in treatment failures, and resistance is starting to become a concern. Ceftaroline has potent activity against MRSA, but comparative clinical data are limited, and it is not FDA-approved for MRSA BSI. Ceftaroline is often used as salvage therapy.

This study is a multicenter, retrospective, observational study on a cohort of adult patients from 2010-2017 with MRSA BSI treated with ceftaroline or daptomycin for ≥ 72 hours. Important exclusion criteria were pneumonia and clearing of cultures before study drug initiation. The

primary outcome was a composite of 30-day mortality, BSI duration ≥ 7 days on the study drug, and 60-day MRSA BSI recurrence. These components individually constituted notable secondary outcomes along with length of stay.

The final cohort included 270 patients, 83 on ceftaroline and 187 on daptomycin, which exceeded the size calculated to have sufficient power for the prespecified 15% noninferiority margin. No significant difference in composite treatment failure was observed between daptomycin (39%) and ceftaroline (32.5%) patients (weighted risk difference, 7.0% [95% confidence interval, -5.0% to 19.0%]). This was also true of secondary outcomes, meeting the definition of noninferiority. Creatine phosphokinase elevation and rash were more common in the daptomycin and ceftaroline groups, respectively.

Comment: This study was well done and, within the limitations of a retrospective, observational study. They addressed bias/confounding using best practices including inverse probability treatment weighting derived from a propensity score that compared well to the actual treatment assignments. This study provides good, real-world clinical evidence that ceftaroline is noninferior to daptomycin for MRSA BSI. Of note, however, 33% of the daptomycin and 19% of the ceftaroline patients had the drug started as first-line therapy. Guidelines and many hospitals still recommend vancomycin use initially, only switching to daptomycin or ceftaroline for failure to clear bacteremia or other signs of clinical progression after 4-5 days of treatment. However, these patients with vancomycin failure largely would have been excluded, so we cannot assume these results generalize to the context of salvage therapy after vancomycin failure, which deserves further study. In Issue 1 of ID Watch on January 3, 2022, I review a paper from CID [2021; 73:2353-2560] on the utility of combination antimicrobial therapy in MRSA bacteremia. Studies show starting with a failing monotherapy[vancomycin] up front then changing to combination salvage therapy may result in longer durations of salvage combination and greater total antibiotic exposure overall. Instead, the authors of that paper advocate intensive therapy with combination therapy [ceftaroline+daptomycin] up front and narrow down for the remainder of treatment based on patient response.

COVID-19

COVID-19 News

US Considers Lengthening Gap Between First 2 COVID Shots to 8 Weeks

U.S. health officials on Friday said they are considering lengthening the recommended interval between the first two doses of the most widely used COVID-19 vaccines to eight weeks to lower the risk of heart inflammation and improve their effectiveness. CDC was considering making the recommendation for Moderna and Pfizer/BioNTech shots during a meeting of the ACIP on February 4th.

Summary:

- Reported rates of myocarditis/pericarditis following mRNA COVID-19 vaccination are higher than background; rates are highest after dose 2 in adolescent and young adult males.

- In most safety monitoring systems, myocarditis/pericarditis risk appears higher after dose 2 Moderna than dose 2 Pfizer-BioNTech COVID-19 vaccination.
- Rates of myocarditis/pericarditis were lower with extended interval (≥8 weeks) between first and second dose of mRNA vaccine primary series
- In addition, extending interval increased VE
- Canadian health officials had presented data to the group earlier in the day about why they had settled on a recommended eight-week interval between shots of the two vaccines.

Comment: Benefits for both mRNA COVID-19 vaccines far outweigh risk of myocarditis, compared with no vaccine. The new recommendation of eight-week interval makes sense since the longer dosing interval is associated with a better response and lower risk for myocarditis. UK used a dosing interval of up to 3 months to vaccinate as many persons as possible with one dose given supply issues. It also turned out to provide a better response. The first dose provided a VE up to 85% against the ancestral strain which was circulating at the time.

COVID-19 vaccine for kids under 5 delayed

Pfizer announced Friday they were delaying the application process for EUA for their vaccine for children ages 6 months to 4 years old and gathering more information on two and three doses of the vaccine.

Comment: Based on the FDA's preliminary assessment, and to allow more time to evaluate additional data, the FDA believed additional information regarding the ongoing evaluation of a third dose should be considered before granting EUA and I agree.

FDA Authorizes New MCA, Bebtelovimab for Treatment of COVID-19

Friday, the FDA issued an EUA for a new MCA for the treatment of COVID-19 that retains activity against the omicron variant. The EUA for bebtelovimab is for the treatment of mild to moderate COVID-19 in adults and pediatric patients (12 years of age and older weighing at least 40 kilograms, which is about 88 pounds) with a positive COVID-19 test, and who are at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate. Bebtelovimab is not authorized for patients who are hospitalized due to COVID-19 or require oxygen therapy due to COVID-19.

The placebo-controlled portion of the trial enrolled 380 low-risk patients (i.e., patients without risk factors for progression to severe COVID-19 illness). Patients in this part of the trial were randomized to receive a single infusion of bebtelovimab alone, bebtelovimab with other monoclonal antibodies or a placebo. Treatment with bebtelovimab resulted in a reduction in time to sustained symptom resolution compared to placebo. Reduction in viral load relative to placebo was also seen on Day 5 after treatment.

In another part of the trial involving mostly high-risk individuals (i.e., patients with risk factors for progression to severe COVID-19 illness), 150 patients were randomized to receive a single infusion of bebtelovimab alone or a single infusion of bebtelovimab with other monoclonal antibodies. An additional 176 high-risk patients received bebtelovimab with other monoclonal antibodies in an open-label treatment arm. The rates of COVID-19 related hospitalization and

death through Day 29 seen in those who received bebtelovimab alone or with other monoclonal antibodies were generally lower than the placebo rate reported in prior trials of other monoclonal antibodies in high-risk patients.

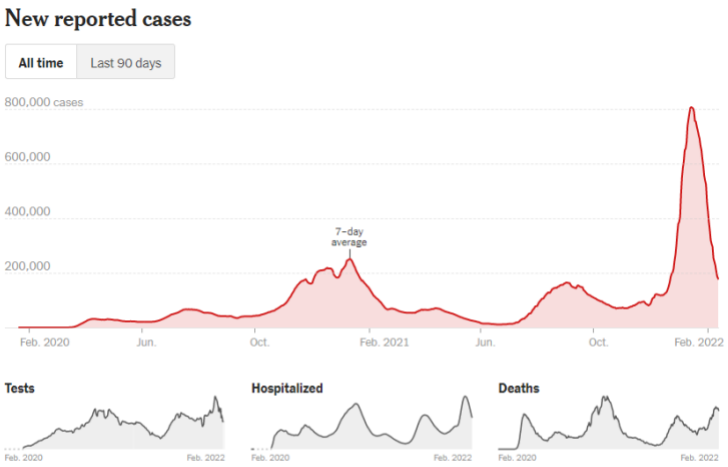
Comment: The addition of another MCA active against omicron is welcomed. However, bebtelovimab has not been tested in a study that can clearly show whether it can prevent severe disease. Therefore, FDA said it should not be a preferred product and instead should be used only when alternative treatments are not "accessible or clinically appropriate." I hope supply of active MCA and antivirals will soon be able to meet the current and future needs our patients.

IDSA Convalescent Plasma Guideline Update January 31, 2022

Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)

Comment: This is a weak recommendation, but given short supply of antivirals and MCA, plasma may be a back up for high-risk patients.

COVID-19 by the Numbers



	DAILY AVG. ON FEB. 12	14-DAY CHANGE	TOTAL REPORTED
Cases	178,705	-67%	77,594,205
Tests	1,309,278	-27%	—
Hospitalized	96,535	-34%	—
In I.C.U.s	18,010	-28%	—
Deaths	2,454	-5%	917,902

Comment: As has been reported, in most areas of the US, new cases and hospitalizations are significantly down. The past week we have seen a reversal in deaths which also have begun to decline. CDC is beginning to post wastewater surveillance for select communities.

Vaccinations

As of Feb. 10, about 251.7 million people — 75.8 percent of the total U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 213.4 million people, or 64.3 percent of the population, have received both doses.

About 90.9 million additional or booster doses in fully vaccinated people have been reported. The CDC said 53.2 percent of people eligible for a booster dose have not gotten one.

Journal Review

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

Researchers in South Africa evaluated the ability of vaccine-elicited T cells to react with Omicron's spike protein in vaccine recipients and in unvaccinated COVID-19 survivors.

Among the 70 participants, 70% to 80% of the CD4+ and CD8+ T-cell response to Omicron was maintained across all three study groups. The concentrations of Omicron cross-reactive T cells were similar to those against the Beta and Delta variants, even though Omicron is considerably more mutated. Among the 19 hospitalized patients infected with Omicron, T-cell responses to the variant's spike, nucleocapsid, and membrane proteins were comparable to the 49 patients hospitalized in previous pandemic waves in which the wild-type, Beta, or Delta variants were dominant.

The investigators evaluated both cellular and antibody immune response in 47 COVID-19 vaccine recipients 1 and 8 months after vaccination. Using intracellular cytokine staining assays, the authors report that, 8 months after vaccination, both types of vaccine induced comparative spike-protein-specific CD8+ and CD4+ T cell responses against the ancestral WA1/2020, Delta and Omicron variants. The data suggests that median Omicron-specific CD8+ T cell responses were 82–84% of WA1/2020-specific responses, and CD4+ T cell responses were 82–100% of WA1/2020-specific responses. By contrast, 5 unvaccinated individuals who had never been infected had negligible spike-specific CD8+ and CD4+ T cell responses.

Among COVID-19 vaccine recipients, median Omicron spike-specific CD8+ T-cell responses were durable and were 82% to 84% of those elicited by the wild-type virus. T-cell cross-reactivity against both Delta and Omicron was 80%.

Comment: Immunological context for the observation that current vaccines still provide robust protection against severe disease and hospitalization due to the Omicron variant despite substantially reduced neutralizing antibody responses and increased breakthrough infection. Breakthrough infections do not mean vaccine failure!

This is similar to researchers in South Africa who reported that among the 70 participants, 70% to 80% of the CD4+ and CD8+ T-cell response to Omicron was maintained across all three

study groups. The concentrations of Omicron cross-reactive T cells were similar to those against the Beta and Delta variants, even though Omicron is considerably more mutated. Among the 19 hospitalized patients infected with Omicron, T-cell responses to the variant's spike, nucleocapsid, and membrane proteins were comparable to the 49 patients hospitalized in previous pandemic waves in which the wild-type, Beta, or Delta variants were dominant.

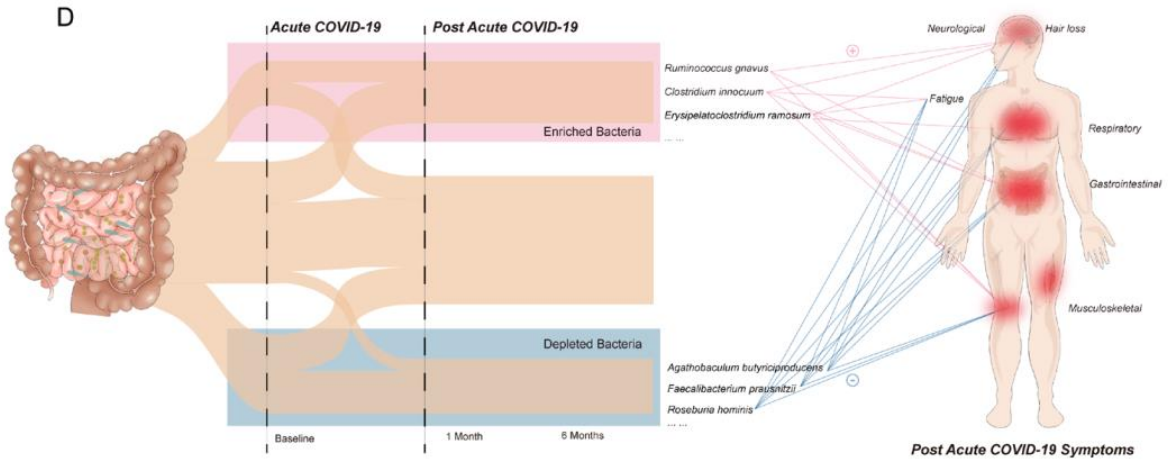
Given the role of CD8+ T cells in clearance of viral infections, it is likely that cellular immunity [T and B cell] contributes substantially to vaccine protection against severe SARS-CoV-2 disease. This appears be particularly relevant for Omicron which has been shown to be more immune evasive, but individuals who are up-to-date on vaccinations still have significant protection against severe disease, hospitalizations, and deaths.

Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome Gut published online January 25, 2022

doi:10.1136/gutjnl-2021-325989

Investigators analyzed the gut microbiome of more than 100 Covid-19 patients at the time of their initial infection, one month later, and again six months later. They compared the results to a control group of 68 healthy people. They defined post-acute COVID-19 syndrome (PACS) as at least one persistent symptom 4 weeks after clearance of the SARS-CoV-2 virus.

At 6 months, 76% of patients had PACS and the most common symptoms were fatigue, poor memory and hair loss. Gut microbiota composition at admission was associated with occurrence of PACS. Patients without PACS showed recovered gut microbiome profile at 6 months comparable to that of non-COVID-19 controls. Gut microbiome of patients with PACS were characterized by higher levels of Ruminococcus gnavus, Bacteroides vulgatus and lower levels of Faecalibacterium prausnitzii. Persistent respiratory symptoms were correlated with opportunistic gut pathogens, and neuropsychiatric symptoms and fatigue were correlated with nosocomial gut pathogens, including Clostridium innocuum and Actinomyces naeslundii (all $p<0.05$). Butyrate-producing bacteria, including Bifidobacterium pseudocatenulatum and Faecalibacterium prausnitzii showed the largest inverse correlations with PACS at 6 months.



Comment: Investigators found that Covid-19 patients with healthy gut bacteria were less likely to develop long Covid and had a microbiome similar to people in the healthy control group. Patients who went on to develop long Covid had a less diverse and abundant microbiome.

Further studies should investigate whether microbiota modulation can facilitate timely recovery from post-acute COVID-19 syndrome. Studies pre-Covid-19 in general have shown that when people are sick their microbiome changes, so more data is needed to see if changing the gut microbiome might work as a treatment.

Association of SARS-CoV-2 Infection With Serious Maternal Morbidity and Mortality From Obstetric Complications JAMA published online February 7, 2022

doi:10.1001/jama.2022.1190

This is a retrospective cohort study evaluating the outcomes of 41,104 women who delivered at 17 US hospitals from March 1 to December 31, 2020, and following them up to February 11, 2021. Among the patients, 2,352 had COVID-19 and 11,752 did not.

Most women (80.1%) tested positive for COVID-19 in the third trimester, while 17.6% were in the second trimester, and 2.3% were in the third trimester. Among the 103 patients (4.4%) who first tested positive after delivery, the median timing was 18 days after delivery. COVID-19 was categorized as critical in 59 patients (2.5%), severe in 180 (7.7%), moderate in 347 (14.8%), mild in 728 (31.0%), and asymptomatic in 1,038 (44.1%).

Relative to uninfected patients, those diagnosed as having COVID-19 were significantly more likely to die or become seriously ill because of high blood pressure-related pregnancy disorders, postpartum hemorrhage, or other respiratory infection (13.4% vs 9.2%; adjusted relative risk [aRR], 1.41). All five maternal deaths occurred in COVID-positive women. Moderate to severe COVID-19, compared with asymptomatic or mild illness, was significantly tied to serious maternal illness, cesarean birth (45.4% vs 32.4%), intensive care unit (ICU) admission (12.8% vs 1.2%), and death (26.1% vs 9.2%). Patients with asymptomatic or mild infection were at significantly higher risk for superficial or deep surgical-site infection (1.8% vs 0.7%; RR, 2.55) and high blood pressure–related pregnancy disorders (7.1% vs 6.5%; aRR, 1.28).

Other adverse maternal outcomes, including the need for mechanical ventilation, vasopressor support for treating low blood pressure, cardiomyopathy, and venous thromboembolism, were significantly more common among COVID-19 patients than their uninfected counterparts. All four patients who needed extracorporeal membrane oxygenation had COVID-19.

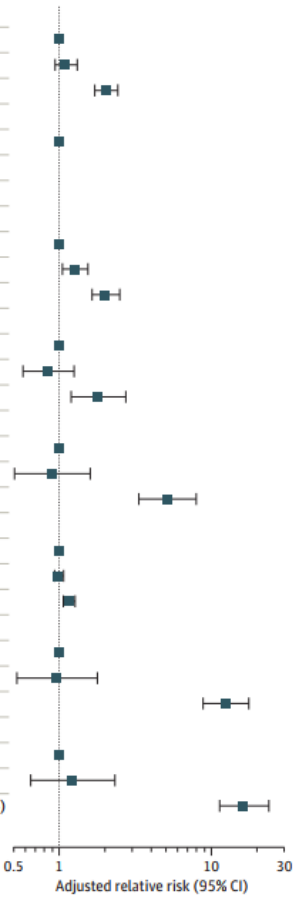
A total of 14,471 newborns were included in the analysis; 2,297 were delivered by women who had COVID-19 while pregnant, and 12,017 were born to uninfected women. SARS-CoV-2 exposure was significantly linked to preterm birth at less than 37 weeks' gestation (17.7% vs 14.1%; aRR, 1.15) and to admission to a neonatal ICU (22.0% vs 17.8%; aRR, 1.15).

Most preterm births among COVID-19 patients were medically indicated or didn't result from spontaneous preterm labor (58.8%). COVID-19 was the indication for preterm birth in 8.3% of women who had a medically indicated preterm birth. Among 1,323 live births to COVID-19 patients, 1.2% of neonates tested positive for COVID-19 before hospital release.

Overall, COVID-19 infection was not significantly linked with cesarean birth (34.7% vs 32.4%; aRR, 1.05), and 1,766 patients with asymptomatic or mild infections were not more likely to become seriously ill or die (9.2% vs 9.2%; aRR, 1.11) or to give birth via cesarean (31.2% vs 32.4%; aRR, 1.00). Patients with moderate or severe COVID-19, however, were prone to cesarean delivery (45.4% vs 32.4%; aRR, 1.17).

Figure 2. Maternal Outcomes Stratified by COVID-19 Severity

Maternal outcomes	No./total (%)	Difference (95% CI)	Relative risk (95% CI)	Adjusted relative risk (95% CI)
Primary composite outcome of death or serious morbidity from hypertensive disorders of pregnancy, postpartum hemorrhage, or non-SARS-CoV-2 infection				
Not SARS-CoV-2 positive	1076/11752 (9.2)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	163/1766 (9.2)	0.0 (-1.4 to 1.4)	1.00 (0.85 to 1.17)	1.11 (0.94 to 1.32)
Moderate, severe, or critical	153/586 (26.1)	16.9 (13.3 to 20.4)	2.83 (2.44 to 3.28)	2.06 (1.73 to 2.46)
Death (any cause)				
Not SARS-CoV-2 positive	0	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	0	NA	NA	NA
Moderate, severe, or critical	5/586 (0.9)	NA	NA	NA
Hypertensive disorders of pregnancy[a]				
Not SARS-CoV-2 positive	761/11752 (6.5)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	126/1766 (7.1)	0.6 (-0.6 to 1.8)	1.10 (0.91 to 1.32)	1.28 (1.05 to 1.56)
Moderate, severe, or critical	112/586 (19.1)	12.6 (9.4 to 15.8)	2.94 (2.45 to 3.53)	2.05 (1.66 to 2.53)
Postpartum hemorrhage[b]				
Not SARS-CoV-2 positive	282/11752 (2.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	31/1766 (1.8)	-0.7 (-1.3 to -0.1)	0.72 (0.50 to 1.04)	0.85 (0.58 to 1.26)
Moderate, severe, or critical	30/586 (5.1)	2.7 (0.9 to 4.5)	2.09 (1.45 to 3.03)	1.83 (1.20 to 2.77)
Infection other than SARS-CoV-2[c]				
Not SARS-CoV-2 positive	103/11752 (0.9)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	16/1766 (0.9)	0.0 (-0.4 to 0.5)	1.01 (0.60 to 1.71)	0.90 (0.51 to 1.61)
Moderate, severe, or critical	39/586 (6.7)	5.8 (3.7 to 7.8)	7.43 (5.16 to 10.69)	5.25 (3.39 to 8.15)
Cesarean birth				
Not SARS-CoV-2 positive	3811/11752 (32.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	551/1766 (31.2)	-1.4 (-3.6 to 0.8)	0.96 (0.89 to 1.03)	1.00 (0.93 to 1.07)
Moderate, severe, or critical	266/586 (45.4)	12.8 (8.7 to 16.8)	1.39 (1.27 to 1.53)	1.17 (1.07 to 1.28)
ACOG and SMFM–defined severe morbidity or mortality[d]				
Not SARS-CoV-2 positive	163/11752 (1.4)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	12/1766 (0.7)	-0.7 (-1.1 to -0.3)	0.49 (0.27 to 0.88)	0.97 (0.52 to 1.80)
Moderate, severe, or critical	78/586 (13.3)	11.9 (9.2 to 14.7)	9.55 (7.35 to 12.40)	12.84 (9.05 to 18.21)
ICU admission				
Not SARS-CoV-2 positive	139/11752 (1.2)	0 [Reference]	1 [Reference]	1 [Reference]
Asymptomatic or mild	11/1766 (0.6)	-0.6 (-0.9 to -0.2)	0.53 (0.29 to 0.98)	1.23 (0.65 to 2.35)
Moderate, severe, or critical	75/586 (12.8)	11.6 (8.9 to 14.3)	10.91 (8.30 to 14.35)	16.98 (11.65 to 24.74)



Comment: Among pregnant and postpartum individuals, SARS-CoV-2 infection was associated with increased risk of a composite outcome of maternal mortality or serious morbidity from obstetric complications. Data were collected in 2020 prior to wide circulation of the Delta variant of SARS-CoV-2, which may result in increased disease severity in pregnancy. [Am J Obstet Gynecol. 2021;226(1):149-151] The association between the more recent Omicron variant and morbidity from obstetrical complications similarly could not be assessed. 16 of the 17 included sites were academic centers, which may limit generalizability. Last, the study was conducted almost entirely prior to the availability of SARS-CoV-2 vaccination in December 2020.

Characteristics, Outcomes, and Severity Risk Factors Associated With SARS-CoV-2 Infection Among Children in the US National COVID Cohort Collaborative
JAMA Netw Open published online February 8, 2022

doi:10.1001/jamanetworkopen.2021.43151

This is a prospective cohort study of encounters with end dates before September 24, 2021. This was conducted at 56 National COVID Cohort Collaborative (N3C) facilities throughout the US. Participants included children younger than 19 years at initial SARS-CoV-2 testing. The question was to determine what the characteristics are, changes over time, outcomes, and severity risk factors of children with SARS-CoV-2 within the N3C.

A total of 1,068,410 children were tested for SARS-CoV-2 and 167,262 test results (15.6%) were positive (82,882 [49.6%] girls; median age, 11.9 [IQR, 6.0-16.1] years). Among the 10,245 children (6.1%) who were hospitalized, 1423 (13.9%) met the criteria for severe disease: mechanical ventilation (796 [7.8%]), vasopressor-inotropic support (868 [8.5%]), extracorporeal membrane oxygenation (42 [0.4%]), or death (131 [1.3%]).

Male sex (odds ratio [OR], 1.37; 95% CI, 1.21-1.56), Black/African American race (OR, 1.25; 95% CI, 1.06-1.47), obesity (OR, 1.19; 95% CI, 1.01-1.41), and several pediatric complex chronic condition (PCCC) subcategories were associated with higher severity disease. Vital signs and many laboratory test values from the day of admission were also predictive of peak disease severity.

Variables associated with increased odds for MIS-C vs acute COVID-19 included male sex (OR, 1.59; 95% CI, 1.33-1.90), Black/African American race (OR, 1.44; 95% CI, 1.17-1.77), younger than 12 years (OR, 1.81; 95% CI, 1.51-2.18), obesity (OR, 1.76; 95% CI, 1.40-2.22), and not having a pediatric complex chronic condition (OR, 0.72; 95% CI, 0.65-0.80). The children with MIS-C had a more inflammatory laboratory profile and severe clinical phenotype, with higher rates of invasive ventilation (117 of 707 [16.5%] vs 514 of 8241 [6.2%]; $P < .001$) and need for vasoactive-inotropic support (191 of 707 [27.0%] vs 426 of 8241 [5.2%]; $P < .001$) compared with those who had acute COVID-19.

When comparing children during the Delta vs pre-Delta eras, there was no significant change in hospitalization rate (1738 [6.0%] vs 8507 [6.2%]; $P = .18$) and lower odds for severe disease (179 [10.3%] vs 1242 [14.6%]) (decreased by a factor of 0.67; 95% CI, 0.57-0.79; $P < .001$).

Comment: This study documented clinical data elements that could assist with early identification of children at risk for severe disease due to SARS-CoV-2 infection. Male sex, African American, obesity, and higher inflammatory profiles are among some of the risk factors to consider. This study was pre-omicron. Because their data were aggregated from many health systems using 4 different common data models that vary in granularity, some sites had missing variables. Some respiratory data (oxygen flow, fraction of inspired oxygen, and specific ventilator settings) were not fully available across all sites. The exact timing of laboratory specimens is inconsistently provided by sites. As in adults, with high rates of asymptomatic to minimally symptomatic pediatric infections and increasing adoption of universal SARS-CoV-2 testing policies for pediatric hospital admissions, they could not definitively attribute reasons for hospital admissions (SARS-CoV-2 vs another unrelated cause).

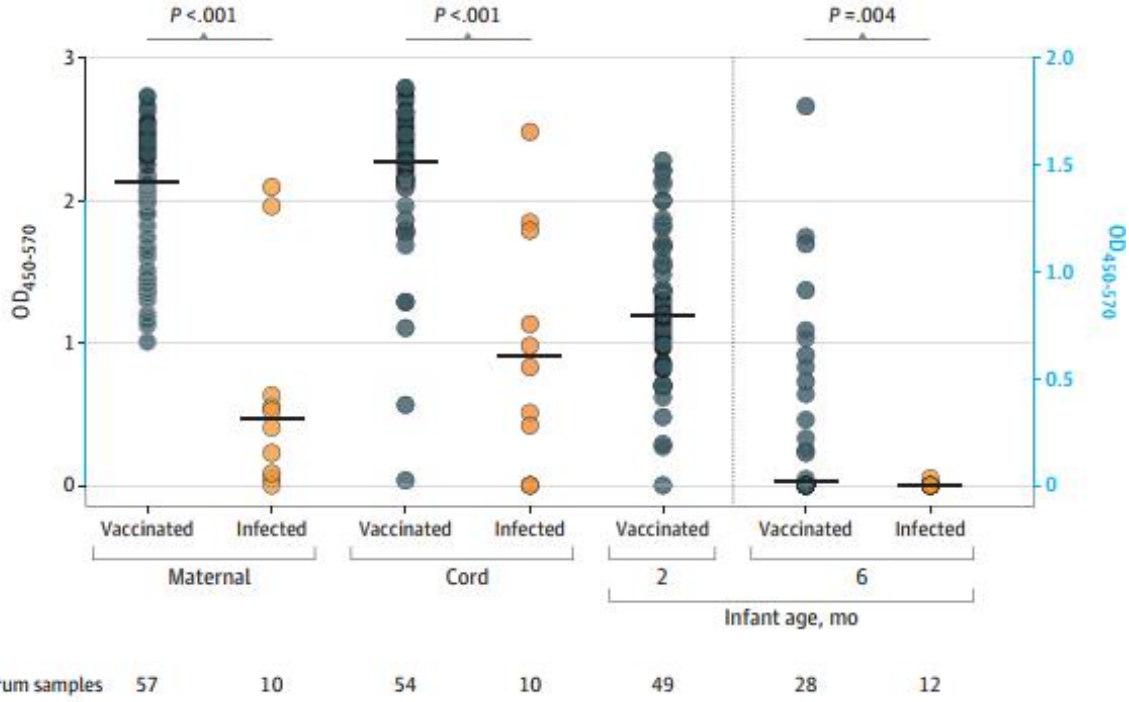
Durability of Anti-Spike Antibodies in Infants After Maternal COVID-19 Vaccination or Natural Infection JAMA published online February 7, 2022

doi:10.1001/jama.2022.120

The study included individuals who had received an mRNA COVID-19 vaccine in pregnancy or were infected with SARS-CoV-2 at 20 to 32 weeks' gestation, had enrolled in a prospective study at 2 academic medical centers in Boston, and had enrolled their infants in this follow-up study conducted from July 21, 2021, to October 22, 2021. Individuals vaccinated or infected at 20 to 32 weeks' gestation were enrolled because previous studies have demonstrated superior transplacental transfer of antibodies during this window compared with vaccination closer to delivery. Those infected before vaccination were excluded. Matched maternal and umbilical cord serum samples were collected at birth. Infant serum samples were collected at 2 months after birth for infants of vaccinated mothers and at 6 months for infants of mothers who were vaccinated and mothers who had been infected with SARS-CoV-2. Antibody titers against the SARS-CoV-2 spike protein were quantified using an enzyme-linked immunosorbent assay.

Vaccinated mothers had significantly higher titers at delivery compared with mothers after infection ($P < .001$). Similarly, the respective mean (SD) cord titers were higher after vaccination vs natural infection ($P < .001$). Among infants of vaccinated mothers at 2 months, 98% (48 of 49) had detectable anti-S IgG. Vaccination resulted in significantly greater antibody persistence in infants than infection. At 6 months, 57% (16 of 28) of infants born to vaccinated mothers had detectable antibodies compared with 8% (1 of 12) of infants born to infected mothers ($P = .005$)

Figure. Persistence of Antibody in Infants After Maternal COVID-19 Vaccination or Infection



Comment: Understanding the persistence of maternal antibody levels in infants is important because COVID-19 infections in this age group account for a disproportionate burden of

pediatric SARS-CoV-2–associated morbidity and because COVID-19 vaccines are not currently available to infants < 6 months of age. The study was limited in part because of the small numbers and the longer follow-up in the infected group. Lastly, this article looked only at titers and not clinical outcomes.

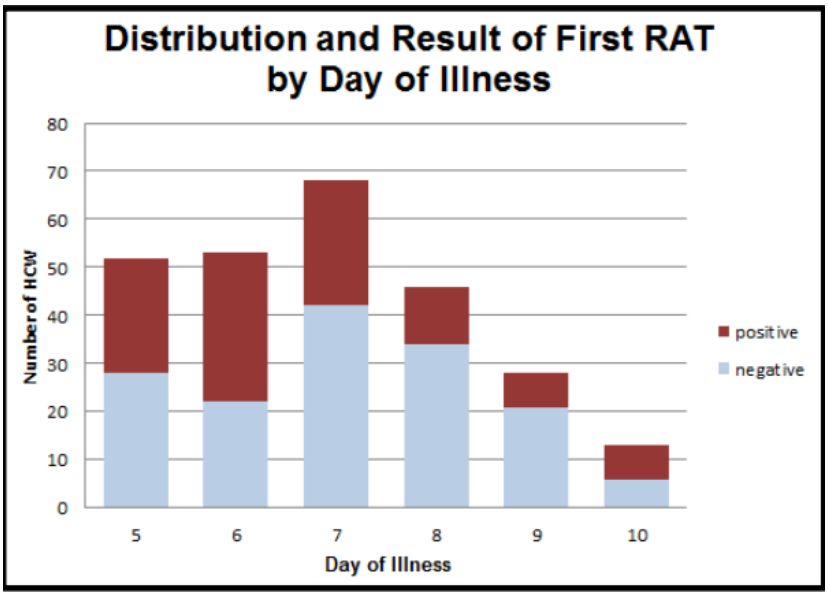
High Rates of Rapid Antigen Test Positivity After 5 days of Isolation for COVID-19

medRxiv posted February 2, 2022

doi.org/10.1101/2022.02.01.22269931

Fully vaccinated and non-immunocompromised HCW at a large, urban, academic medical center who tested positive for COVID-19 starting in late December 2021 (when omicron was the predominant circulating strain) were allowed to return to work early if all symptoms had resolved excepting mild, intermittent cough and/or lingering loss of taste/smell, provided a rapid antigen test was negative upon return. Those with negative tests were allowed to return to work with the stipulations that they always wear an N95 and take breaks and eat meals apart from others. Those with positive tests on first attempt could return 24-48 hours later to test again for as many days as needed to achieve a negative result or until they completed 10 days of restriction from work.

There were 309 total rapid antigen tests (RAT) done on 260 separate HCW on day 5-10 of illness. Overall, 43% (134 of 309) of all RAT were positive between days 5-10. The greatest percent positive RAT was noted among HCW returning for their first test on day 6 (58%). The rate of positivity was greatest (58%) among HCW returning for their first test on day 6. HCW returning on day 8 and 9 were less likely to have a positive test (26%, 19/74). In RAT positive HCW returning for their first test on days 5 or 6 (and for which line intensity was recorded) 49% (25/51) were recorded as having the darkest intensity on their RAT. HCW who test positive on their first test most often remained positive on their second test, with 56% of second tests, aggregated across all days 6-10, remaining positive. Over all first tests performed on days 5-10, boosted HCW were nearly twice as likely to test RAT positive: 53% (75 out of 141) of boosted HCW tested positive.



Comment: The findings call into question the CDC's recent change in isolation guidelines for the public, which suggest that individuals with COVID-19 can end isolation after just 5 days if they're asymptomatic or have resolving symptoms without a negative test.

Interestingly, in the study, rapid tests were three times more likely to be positive among boosted healthcare workers versus vaccinated non-boosted healthcare workers on day 5 (61% vs 21%, respectively). Overall, tests from boosted healthcare workers were more than twice as likely to be positive on days 5-10 versus non-boosted workers (53% vs 27%). I am not sure how to explain this finding.

Unfortunately, relatively less is known about the relationship between symptom onset and viral dynamics, particularly in vaccinated individuals, infected with the newer [Omicron] variant. [see next article].

Limitations to the data include that worker participation was voluntary and limited to work areas with critical staffing needs. The authors did not collect data about when workers' symptoms resolved, and thus did not consider non-medical factors that influenced the timing of testing.

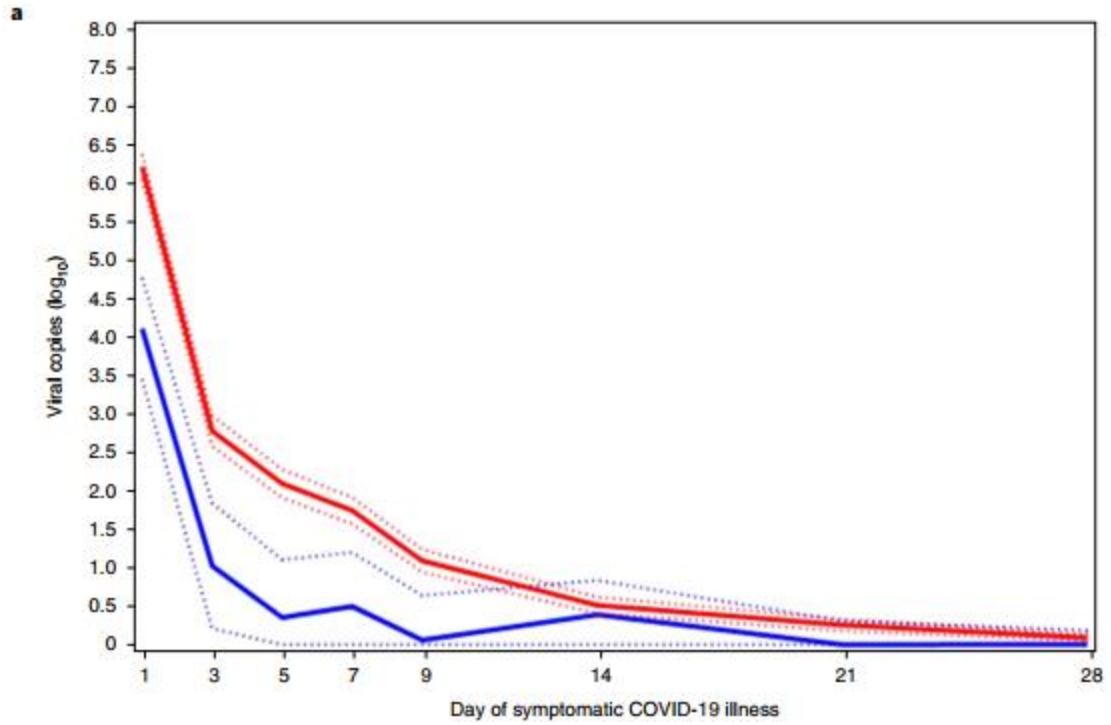
The data presented here and in other articles strongly suggests that safely ending isolation as early as day 5 since symptom onset should include a negative rapid antigen test prior to exit, regardless of vaccination or booster status since individuals may increase the risk of COVID-19 spread to others which, in turn, may undermine the intended benefits to staffing by resulting in more transmission. This article and the medRxiv article reviewed in the first issue of ID Watch on January 3, 2022 both suggest the value of using the antigen test is useful in determining when it is safe to stop isolation.

Initial analysis of viral dynamics and circulating viral variants during the mRNA-1273 Phase 3 COVE trial Nat Med published online February 10, 2022

doi.org/10.1038/s41591-022-01679-5

While Moderna vaccine has demonstrated high efficacy in prevention of COVID-19, including severe disease, its effect on the viral dynamics of SARS-CoV-2 infections is not fully understood. The investigators assessed the impact of Moderna vaccination in the ongoing COVE trial (number NCT04470427) on SARS-CoV-2 copy number and shedding, burden of disease and infection, and viral variants. Viral variants were sequenced in all COVID-19 and adjudicated COVID- 19 cases ($n = 832$), from July 2020 in the blinded part A of the study to May 2021 of the open-label part B of the study, in which participants in the placebo arm started to receive the Moderna vaccine after FDA gave EUA in December 2020. Viral copy number was assessed by SARS-CoV-2 RT–qPCR and conversion of cycle-threshold (Ct) values to viral genome copy number.

Moderna vaccination significantly reduced SARS-CoV-2 viral copy number (95% confidence interval) by 100-fold on the day of diagnosis compared with placebo (4.1 (3.4–4.8) versus 6.2 (6.0–6.4) log10 copies per ml). Median times to undetectable viral copies were 4 days for vaccination and 7 days for placebo. Vaccination also substantially reduced the burden of disease and infection scores. Vaccine efficacies (95% confidence interval) against SARS-CoV-2 variants circulating in the US during the trial assessed in this post hoc analysis were 82.4% (40.4–94.8%) for variants Epsilon and Gamma and 81.2% (36.1–94.5%) for Epsilon.



Solid lines represent placebo (red) and Moderna (blue) and dotted lines correspondingly denote 95% CIs

Comment: These data show that in SARS-CoV-2-infected individuals, vaccination reduced both the viral copy number and duration of detectable viral RNA, which may be markers for the risk of virus transmission. Studies have shown that higher viral copy number, evaluated by RT–PCR and quantitated by Ct values (lower Ct values) and/or converted to copies per ml (as assessed in this study), is related to severe COVID-19 and mortality [Lancet Respir. Med. 8, e70 (2020), Open Forum Infect. Dis. 8, ofab003 (2021], and at thresholds shown to be associated with cell culture infectivity. [Science 373, eabi5273(2021)] This study was conducted before Delta and Omicron variants in the US and an assessment of the full impact of Moderna vaccine efficacy on Delta and Omicron requires additional studies, however, the Moderna vaccine has shown effectiveness against both variants The study has small sample size of variants detected in this analysis which limits the assessment and interpretation of VE against emerging variants. However, this study and others suggests vaccinated persons clear virus faster compared to unvaccinated.

Protection against the Omicron Variant from Previous SARS-CoV-2 Infection N Engl J Med published online February 9, 2022

DOI: 10.1056/NEJMc2200133

The investigators estimated the effectiveness of previous infection in preventing symptomatic new cases caused by omicron and other SARS-CoV-2 variants in Qatar. In this study, they extracted data regarding Covid-19 laboratory testing, vaccination, clinical infection data, and related demographic details from the national SARS-CoV-2 databases, which include all results of PCR testing, vaccinations, and hospitalizations and deaths for Covid-19 in Qatar since the start of the pandemic.

The effectiveness of previous SARS-CoV-2 infection in preventing reinfection was defined as the proportional reduction in susceptibility to infection among persons who had recovered from infection as compared with those who had not been infected. Previous SARS-CoV-2 infection was defined as a positive result on PCR assay at least 90 days before a new positive PCR finding. They used a test-negative, case–control study design to assess the effectiveness of previous infection in preventing reinfection. In addition, they performed sensitivity analyses that included adjustment for vaccination status and that excluded vaccinated persons from the analysis. Furthermore, to ensure that epidemiologically relevant reinfections were considered in the analysis, only documented infections with a PCR cycle threshold (Ct) value of 30 or less were included as cases in this study.

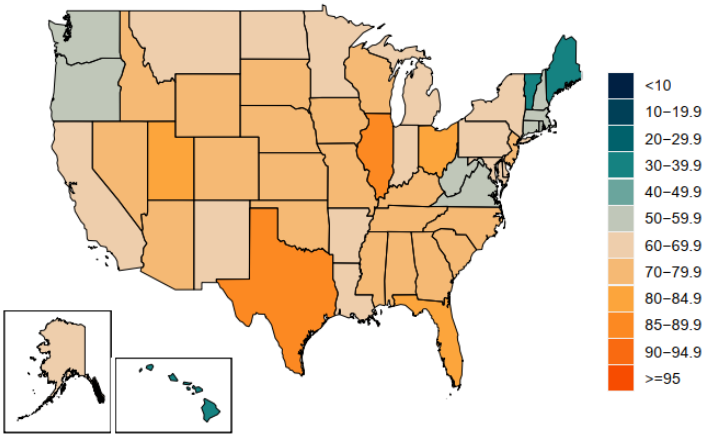
The effectiveness of previous infection in preventing reinfection was estimated to be 90.2% (95% confidence interval [CI], 60.2 to 97.6) against the alpha variant, 85.7% (95% CI, 75.8 to 91.7) against the beta variant, 92.0% (95% CI, 87.9 to 94.7) against the delta variant, and 56.0% (95% CI, 50.6 to 60.9) against the omicron variant. Sensitivity analyses confirmed the study results, as expected for this study design, which is robust regardless of the approach that is used to control for vaccine-induced immunity. An additional analysis that was adjusted for the interval since previous infection also confirmed the study results.

The effectiveness with respect to severe, critical, or fatal Covid-19 was estimated to be 69.4% (95% CI, -143.6 to 96.2) against the alpha variant, 88.0% (95% CI, 50.7 to 97.1) against the beta variant, 100% (95% CI, 43.3 to 100) against the delta variant, and 87.8% (95% CI, 47.5 to 97.1) against the omicron variant. None of the reinfections progressed to critical or fatal Covid-19.

Comment: This paper is further evidence of protection against infection and especially severe disease from prior infection. As other papers have suggested due to Omicron's immune evasive properties, protection from prior infection and/or vaccination was lower against the Omicron variant, but still highly protected against critical fatal disease. In addition, the protection of previous infection against hospitalization or death caused by reinfection appeared to be robust, regardless of variant.

The last IHME report estimates percent of population infected with Covid-19. See below

Figure 6.1. Estimated percent of the population infected with COVID-19 on January 31, 2022



Some public health officials still recommend persons with prior infection still get vaccinated to achieve a high level of immunity through what scientists' call "hybrid immunity." In US we still await guidance on this topic. To me the science suggest you do not need 3 shots if you have had documented infection. I have said many times in the Briefing and ID Watch that if we modified vaccine requirements to include natural immunity and reduced number of shots, we would probably nudge many of the vaccine hesitant to at least receive one dose of vaccine after natural infection. Based on the IHME update, many states have >80% of the population already infected with COVID-19.

Waning 2-Dose and 3-Dose Effectiveness of mRNA Vaccines Against COVID-19–Associated Emergency Department and Urgent Care Encounters and Hospitalizations Among Adults During Periods of Delta and Omicron Variant Predominance — VISION Network, 10 States, August 2021–January 2022 MMWR February 11, 2022

Waning of vaccine protection after 2 doses of mRNA vaccine has been demonstrated during the period of the Delta variant predominance, but less is known about durability of protection after 3 doses during periods of both Delta or Omicron variant predominance. A test-negative case-control study design using data from eight VISION Network sites examined VE against COVID-19 emergency department/ urgent care (ED/UC) visits and hospitalizations among US adults aged ≥18 years at various time points after receipt of a second or third vaccine dose during two periods.

The VISION Network analyzed 241,204 ED/UC encounters and 93,408 hospitalizations across 10 states during August 26, 2021–January 22, 2022. VE after receipt of both 2 and 3 doses was lower during the Omicron predominant than during the Delta-predominant period at all time points evaluated. During both periods, VE after receipt of a third dose was higher than that after a second dose; however, VE waned with increasing time since vaccination. During the omicron period, VE against ED/UC visits was 87% during the first 2 months after a third dose and decreased to 66% among those vaccinated 4–5 months earlier; VE against hospitalizations was 91% during the first 2 months following a third dose and decreased to 78% ≥4 months after a third dose. For both Delta- and Omicron-predominant periods, VE was higher for protection against hospitalizations than against ED/UC visits.

Comment: Because this study was designed to estimate VE against COVID-19–associated ED/UC visits or hospitalizations, VE estimates from this study do not include COVID-19 infections that were not medically attended [mild]. In addition, we do not know especially for omicron whether hospitalization is because of Covid-19 or an incidental positive test. Second, the median interval from receipt of a third dose to medical encounters was 49 days; thus, the observed performance of a third dose is limited to a relatively short period after vaccination. In addition, variations in waning of VE by age group, immunocompromised status, other indicators of underlying health status, or vaccine product were not examined. Further research is needed to evaluate waning VE of a third primary dose among immunocompromised adults compared with waning of VE after a booster dose among immunocompetent adults. VE was higher for protection against hospitalizations than against ED/UC visits, suggesting that vaccines still have VE against more severe disease, although there is no mention of ICU admissions or deaths. This study mirrors preliminary studies from Israel and UK.