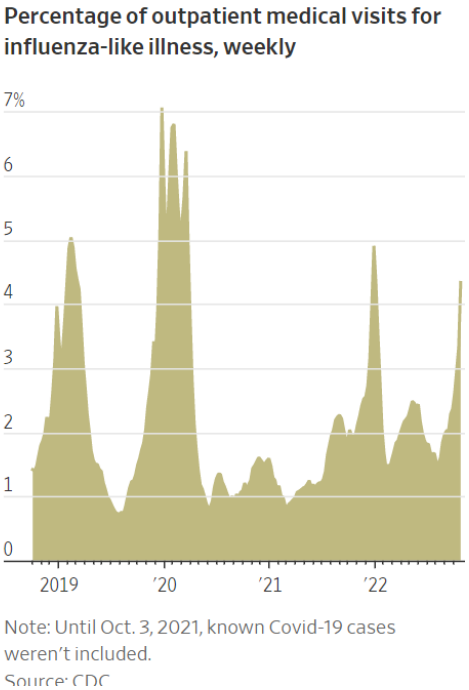
Infectious Diseases Watch

November 14, 2022

Ed Septimus, MD

VII: Warnings of a tripledemic

Over the last few weeks, I have read articles and heard news reports on the concept of a "tripledemic" which I think deserves some perspective. The term "tripledemic" has been tossed around because recently as we have seen a rise in influenza and RSV co-circulating with SARS-CoV-2. It may be a catchy term, but this may be causing unnecessary panic. Prior to the pandemic we saw respiratory pathogen increasing every year during the winter months, but I admit this year is a little different for the reasons discussed below.



This year, CDC reports that the percentage of RSV tests coming back positive climbed from below 5% in August to above 15% as of late October. [See graphs below] For the influenza, 9% of tests are coming back positive, up from just over 1% a month ago. The CDC also tracks the percentage of people who show up at the doctor for outpatient visits for influenza-like illness. [see graph above] In the final week of October, the figure was 4.3% of visits, which is high for this early in the influenza season, but not unprecedented. To be clear, what is making this year especially challenging is that it has coincided with the circulation of several other respiratory pathogens, including SARS-CoV-2, but also enterovirus D68, parainfluenza viruses, and rhinoviruses.

For clarity let me define the term pandemic. Pandemic refers to a global outbreak of a new strain, such as H1N1 in 2009 or other influenza strains in 1957 and 1968 and SARS-CoV-2 in 2020. This year, most influenza viruses detected has been a familiar strain: H3N2. Such a strain can still be serious, but not at the scale of a pandemics. And the good news is the vaccine appears to be a good match this year. What I can say is that we are seeing an early season, but it is too early to say how severe the season will be. In fact CDC officials have said last week that this is an early season, but not yet a severe one.

We are also seeing an early RSV season which appears to be larger in scope. In the last week of October, 2.6 out of 100,000 people were hospitalized with RSV and 1.2 out of 100,000 for influenza. Before the pandemic there were at least 8-12 weeks in which seasonal hospitalization rates for respiratory viruses were high, but just not this early. For those of us who remember H1N1 in 2009, we saw a peak in October/November.

What are some of the reasons we are now seeing these increases. One explanation is what some call “immunity debt.” For RSV most children are exposed to RSV during the first year of life. Subsequent infections are typically milder. Like influenza there was essentially no RSV in 2020. In addition, masking and other Covid-19 mitigation strategies have also reduced risk of transmission for both influenza and RSV in 2020 and to some extent in 2021. Currently most Covid-19 mitigation strategies have been relaxed. We are seeing larger indoor in-person gatherings, travel is increasing, and children and adults went back to school, daycare, and the offices without masks, enabling these viruses to spread through communities more rapidly with little to no immunity.

The message we should be emphasizing is that influenza and Covid-19 vaccines are effective in reducing infection and at keeping people out of the hospital. The number of people who get vaccinated could influence the severity of this season. Although there are currently no vaccines for RSV late-phase trials of a vaccine administered during pregnancy and a vaccine for older adults, who are also susceptible to severe RSV infection, look very promising. Vaccines for infants are also within reach.

For now, let us refrain on using alarming rhetoric. Given the messaging and politics around the pandemic I think we have an obligation to be more sensitive and mindful not to stoke unnecessary fear. What we need now is honest common-sense guidance based on the latest science not fear.

General Infectious Diseases

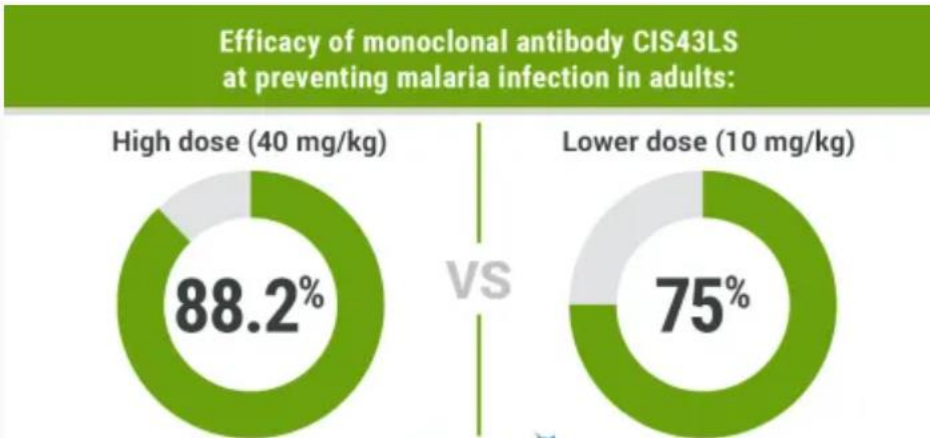
Safety and Efficacy of a Monoclonal Antibody against Malaria in Mali N Eng J Med published online October 31, 2022

DOI: 10.1056/NEJMoa2206966

The single infusion of antibodies was assessed in two parts. In Part A, safety was assessed at three escalating dose levels, the authors said. In Part B, participants were randomly assigned (in a 1:1:1 ratio) to receive 10 milligrams (mg) of CIS43LS per kilogram of body weight, 40 mg of CIS43LS per kilogram, or placebo.

A total of 330 healthy adults (ages 18 to 55) participated in Part B, with 110 assigned to each group. *P falciparum* infections were detected on blood-smear examination in 39 participants (35.5%) who received 10 mg of CIS43LS per kilogram, 20 (18.2%) who received 40 mg of CIS43LS per kilogram, and 86 (78.2%) in the placebo group. The infusions lasted 30 minutes.All the participants received a standard treatment course of artemether-lumefantrine 7 to 21 days before administration of the antibody infusion to clear possible *P falciparum* blood-stage infection.

After 24 weeks, the efficacy of 40 mg of CIS43LS per kilogram compared with placebo was 88.2% (adjusted 95% confidence interval [CI], 79.3 to 93.3; $P < 0.001$), and the efficacy of 10 mg of CIS43LS per kilogram compared with placebo was 75.0% (adjusted 95% CI, 61.0 to 84.0; $P < 0.001$). No major safety concerns were reported, but the risk of moderate headache was 3.3 times as high with 40 mg of CIS43LS per kilogram as with placebo.



Comment: There are 200 million to 400 million cases of malaria resulting in more than 500,000 deaths each year, the majority of which occur in African children. Unfortunately, progress against malaria has stalled since 2014. In 2020, 29 countries accounted for 96% of malaria cases globally, and 6 African countries accounted for approximately 55% of all cases worldwide. Despite the encouraging results, the delivery of the monoclonal antibody remains challenging since the implementation of such a large-scale of administering as a single intravenous infusion of 100 ml over a period of 30 minutes in low resource countries is problematic. Despite these challenges the data provides a proof of concept that a monoclonal antibody with an extended half-life can protect against P. falciparum infection during intense transmission for a defined time period.

Routine sterile glove and instrument change at the time of abdominal wound closure to prevent surgical site infection (ChEETAh): a pragmatic, cluster-randomised trial in seven low-income and middle-income countries Lancet published online October 31, 2022

doi.org/10.1016/ S0140-6736(22)01884-0

WHO and CDC does not make recommendations for changing gloves and instruments before wound closure owing to limited evidence. This study aimed to test whether a routine change of gloves and instruments before wound closure reduced abdominal SSI.

ChEETAh is a multicenter, cluster randomized trial in seven low-income and middle-income countries (Benin, Ghana, India, Mexico, Nigeria, Rwanda, South Africa). Any hospitals doing abdominal surgery in participating countries were eligible. Clusters were randomly assigned to current practice versus intervention (routine change of gloves and instruments before wound closure for the whole scrub team). Consecutive adults and children undergoing emergency or elective abdominal surgery (excluding caesarean section) for a clean– contaminated, contaminated, or dirty operation within each cluster were identified and included. The primary outcome was SSI within 30 days after surgery (participant-level), assessed by US CDC criteria and on the basis of the intention-to-treat principle. The trial has 90% power to detect a minimum reduction in the primary outcome from 16% to 12%, requiring 12,800 participants from at least 64 hospitals.

Between June 24, 2020, and March 31, 2022, 81 hospitals were randomly assigned, which included a total of 13,301 consecutive patients (7157 to current practice and 6144 to intervention group). Overall, 11,825 (88·9%) of 13,301 patients were adults, 6125 (46·0%) of 13,301 underwent elective surgery, and 8086 (60·8%) of 13,301 underwent surgery that was clean–contaminated or 5215 (39·2%) of 13301 underwent surgery that was contaminated–dirty. Glove and instrument change took place in 58 (0·8%) of 7157 patients in the current practice group and 6044 (98·3%) of 6144 patients in the intervention group. The SSI rate was 1280 (18·9%) of 6768 in the current practice group versus 931 (16·0%) of 5789 in the intervention group (adjusted risk ratio: 0·87, 95% CI 0·79–0·95; p=0·0032).

Comment: Colorectal surgeries present a high risk of surgical site infection (SSI), with an incidence up to 16.9%. This study was well designed pragmatic, cluster-randomized, multicenter trial evaluating the efficacy of intraoperative changing of gloves and instruments in preventing SSI after abdominal surgery. The investigators acknowledge that higher income countries typically have higher rates of minimally invasive surgery [laparoscopy and robotic] which is associated with lower infection rates. However, abdominal incisions are still commonly required, and SSI rates remain high even in well-resourced settings (15% to 20% in high quality trials) [Lancet Infect Dis 2018; 18**:** 516–25] Studies incorporating using separate closing trays in colorectal surgery have demonstrated reduced SSIs. [Am J Infect Control 2019; 47:718−719] The study was not blinded, which may make the Hawthorne effect more pronounced in the intervention sites compared with the control sites. Some of the missing outcomes necessitating a modified intention-to-treat analysis could led to additional selection bias and residual confounding. Nonetheless many facilities in the US have incorporate changing gloves and instruments to close as part of a bundle to reduce SSIs in colorectal surgery.

Comparative Safety and Attributable Health Care Expenditures Following Inappropriate versus Appropriate Outpatient Antibiotic Prescriptions among Adults with Upper Respiratory Infections Clin Infect Dis published online November 12, 2022

DOI: 10.1093/cid/ciac879

The investigators used a cohort of adults 18–64 years with an outpatient diagnosis of a bacterial (pharyngitis, sinusitis) or viral respiratory infection (influenza, viral URI, nonsuppurative otitis media (OM), bronchitis) from April 1, 2016 to September 30, 2018 using Merative™ MarketScan® Commercial Database.

They analyzed inappropriate versus appropriate prescriptions, focusing on the relationship between inappropriate antibiotics and adverse drug events and 30-day attributable expenditures. Inappropriate antibiotics were defined as non–guideline-recommended antibiotics for bacterial infections and any antibiotic for viral infections.

Among 3,294,598 eligible adults (median age, 43 years; 41% male), there were 1,656,960 bacterial respiratory infections and 1,637,638 viral respiratory infections. The proportion of adults with bacterial infections who received inappropriate antibiotics differed by infection, ranging from 43% (sinusitis) to 56% (pharyngitis), while inappropriate antibiotics for viral infections ranged from 7% (influenza) to 66% (bronchitis).

Analysis of different infections found that inappropriate antibiotics for pharyngitis were associated with an increased risk of *C difficile* infection (hazard ratio [HR], 2.90; 95% confidence interval [CI], 1.31 to 6.40) and nausea/vomiting/abdominal pain (HR, 1.10; 95% CI, 1.03 to 1.08), while an increase of vulvovaginal candidiasis was linked to inappropriate antibiotics for viral upper respiratory infections (HR, 1.24; 95% CI, 1.14 to 1.34) and non-suppurative otitis media (ear infection; HR, 1.39; 95% CI, 1.09 to 1.77). The mean 30-day total attributable expenditure for inappropriate antibiotics for bacterial infections ranged from $18 (sinusitis) to $67 (pharyngitis) and from –$53 (bronchitis) to $49 (influenza) for viral infections.

Comment: Inappropriate antibiotic prescriptions for respiratory infections were associated with increased risks of patient harm and higher health care expenditures. This report and others call for urgent action to implement outpatient antibiotic stewardship programs. The investigators did not attempt to study the long-term effects of antibiotic exposure (e.g., dysbiosis), and antibiotic-resistant infections. This problem has been identified for decades despite calls for action. ☹

Viral Shedding 1 Year Following First-Episode Genital HSV-1 Infection JAMA. 2022; 328:1730-1739.

doi:10.1001/jama.2022.1906

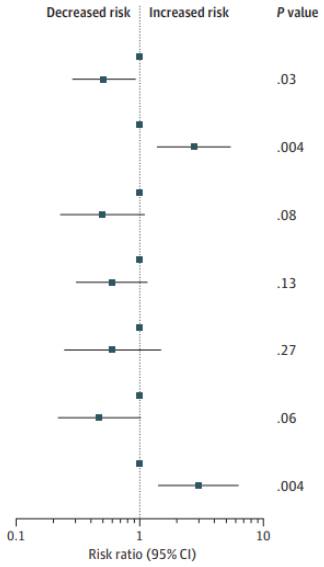
Herpes simplex virus type 1 (HSV-1) is responsible for a rising proportion of genital herpes, yet most data on virologic shedding pertain to HSV-2 infection. This study was a prospective cohort followed up for up to 2 years, with 82 participants followed up between 2013 and 2018. Participants were recruited from sexual health and primary care clinics in Seattle, Washington. Persons with laboratory-documented first-episode genital HSV-1 infection, without HIV infection

or current pregnancy, were referred for enrollment. Participants self-collected oral and genital swabs for HSV PCR testing for 30 days at 2 and 11 months and up to 2 years after diagnosis of genital HSV-1. Blood samples were collected at serial time points to assess immune responses to HSV-1. Primary HSV-1 infection was defined as absent HSV antibody at baseline or evolving antibody profile using the University of Washington HSV Western Blot. HSV-specific T-cell responses were detected using interferon γ enzyme-linked immunospot.

Any genital shedding was detected in 65% of participants during session 1 and 33% of participants during session 2. Most shedding was asymptomatic, with genital lesions reported by 15% and 4% of participants in sessions 1 and 2, respectively. HSV-1 seroconversion occurred in 86% and 95% of participants at 12 and 52 weeks after the first symptoms of genital infection, and all tested participants had HSV-1–specific CD4+ T-cells. Participants with primary infection were more likely to have genital HSV-1 shedding and genital lesions than those with nonprimary infection.

A Genital HSV-1 shedding

Effect	Model-predicted shedding rate (95% CI)	Regressions model	Risk ratio (95% CI)	P value
Session				
1	0.062 (0.043-0.089)	Bivariable	1 [Reference]	
2	0.032 (0.018-0.057)	Bivariable	0.52 (0.29-0.93)	.03
Infection type				
Nonprimary/unknown	0.029 (0.017-0.050)	Bivariable	1 [Reference]	
Primary	0.079 (0.054-0.117)	Bivariable	2.75 (1.40-5.44)	.004
Sex				
Women	0.062 (0.043-0.905)	Bivariable	1 [Reference]	
Men	0.031 (0.016-0.062)	Bivariable	0.50 (0.23-1.10)	.08
Age, y				
<26	0.064 (0.041-0.100)	Bivariable	1 [Reference]	
≥26	0.039 (0.024-0.064)	Bivariable	0.60 (0.31-1.16)	.13
Session among nonprimary infections				
1	0.034 (0.019-0.061)	Multivariable	1 [Reference]	
2	0.021 (0.009-0.050)	Multivariable	0.61 (0.25-1.48)	.27
Session among primary infections				
1	0.102 (0.067-0.156)	Multivariable	1 [Reference]	
2	0.049 (0.024-0.100)	Multivariable	0.48 (0.22-1.02)	.06
Infection type during session 1				
Nonprimary	0.034 (0.019-0.061)	Multivariable	1 [Reference]	
Primary	0.102 (0.067-0.156)	Multivariable	3.02 (1.45-6.29)	.004



Comment: Genital HSV-1 shedding was frequent after first-episode genital HSV-1, particularly among those with primary infection, and declined rapidly during the first year after infection. HSV-1 has surpassed HSV-2 to become the leading cause of first-episode genital herpes in some populations, and this is expected to increase over time. Although it is known that HSV-1 causes less-frequent genital recurrences than HSV-2, [Ann Intern Med. 1999;131:14-20] this is the first study to my knowledge to comprehensively assess genital and oral HSV-1 viral shedding using PCR. Genital HSV-1 still follows a pattern similar to HSV-2 meaning shedding decreases over time and mostly asymptomatic. Characterizing shedding rates is clinically important because patients with genital herpes are often concerned about transmission to sexual partners, which usually occurs in the absence of lesions. [Sex Transm Dis. 1985;12:33-39] A previous study using viral culture to assess genital HSV-1 shedding was very small. There was a 22% loss to follow-up at the end of year 1 in this study. Second, the study was conducted in a single geographic location in the US and the population comprised predominantly White individuals. Nonetheless, this study fills in a knowledge gap around the natural history of genital HSV -1.

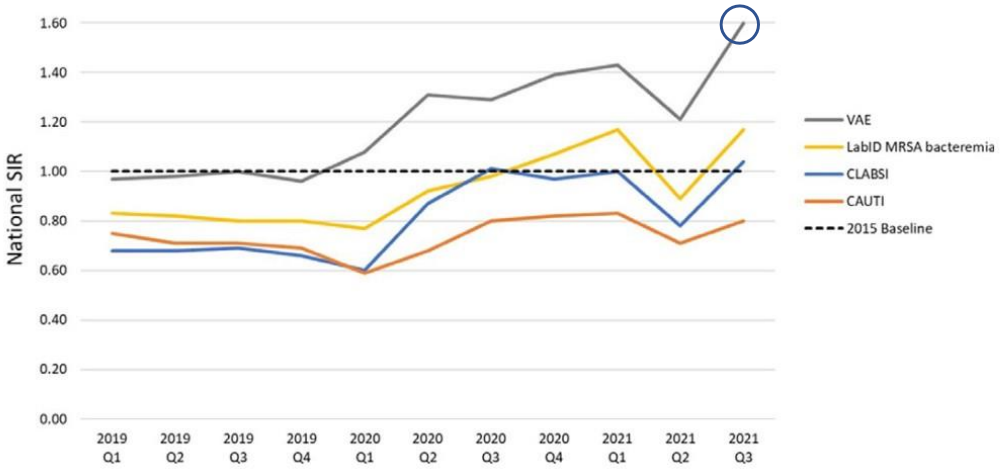
2021 National and State Healthcare-Associated Infections Progress Report

Changes in SIRs among acute care hospitals from 2020 to 2021 include:

- Overall, 7% increase in CLABSI between 2020 and 2021
  Largest increase in ICUs (10%)
- Overall, 5% increase in CAUTI between 2020 and 2021
  Largest increase in ICUs (9%)
- Overall, there was a 12% increase in VAE between 2020 and 2021
  Observed a 12% increase in ICUs
  Observed a 16% increase in non-ICUs
- Overall, there were no significant changes in SSI related to the 10 select procedures tracked in the report between 2020 and 2021
- 14% increase in methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia
- 11% increase in surgical site infections (SSIs) following abdominal hysterectomy
- No change in colon surgery SSIs
- 5% increase in catheter-associated urinary tract infections (CAUTI
- 3% decrease in *C. difficile* infection

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

Covid-19 Second Year



Infect Control Hosp Epidemiol published online May 20, 2022 [18]

Comment: In 2021, we continued to experience unprecedented challenges due to the COVID-19 pandemic, which impacted surveillance for and incidence of HAIs. [see 2020 review above] Compared to pre-pandemic years, hospitals across the nation experienced higher than usual hospitalizations and shortages and turnover of HCWs, and shortages of PPE, which may have resulted in deterioration in multiple patient safety metrics since the beginning of the pandemic. Findings from review of the quarterly 2021 NHSN data compared with 2019 showed continued increases in 2021 in the quarterly SIRs for CLABSI, CAUTI, VAE, and MRSA bacteremia. Despite a decrease in the SIR for 2021 Q2 compared to the preceding quarter [see 2021 curve-the rates were dependent on level of Covid and went back up 3rd quarter], the SIRs for CLABSI, VAE, and MRSA bacteremia remained higher than in 2019 Q2. The 2021 quarterly SIRs for CDI showed decreases and the SSI-COLO, SSI-HYST SIRs remained largely unchanged. It is time to get back to the basics. Over my decades of work in this area, it is the small things done consistently well that results in the best outcomes. With staffing shortages and turnover, it is challenging to meet this standard.

Monkeypox

WHO: Monkeypox still a public health emergency November 1, 2022
HHS renews monkeypox public health emergency

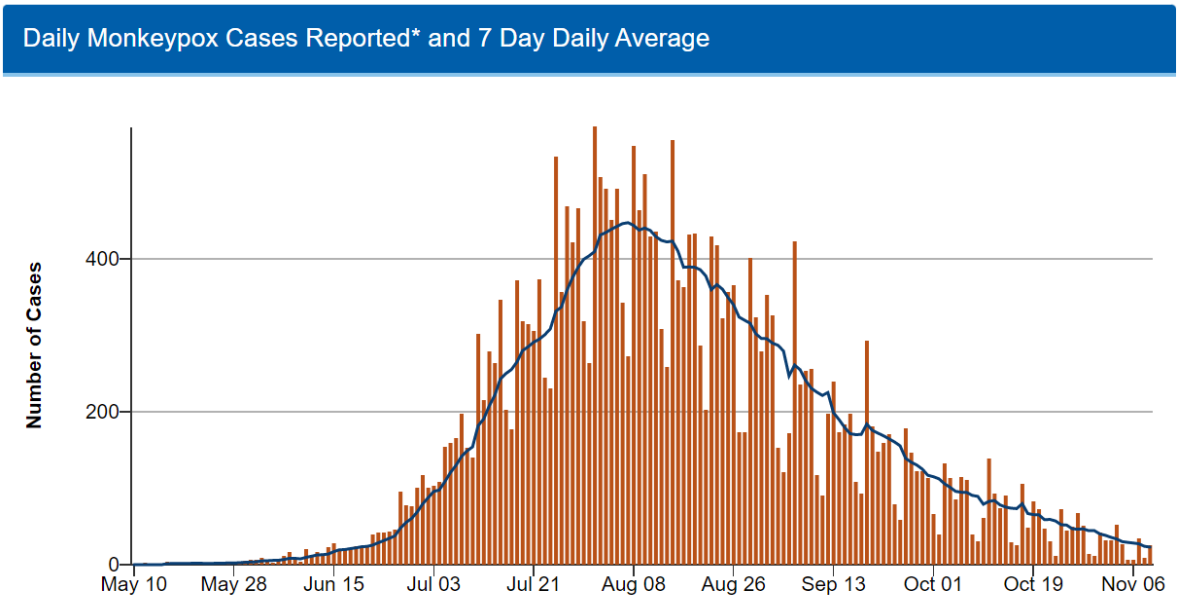
The agency's emergency committee met October 20th to discuss the state of the monkeypox outbreak, which has infected more than 79,000 people globally, CDC data shows.

In a November 1st statement on the meeting, the WHO's emergency committee cited ongoing transmission in certain regions, the ongoing risk of stigma and discrimination, potential case underreporting in some developing countries, and a lack of equitable access to vaccines and treatments as the primary reasons for ongoing international concern. The picture is mixed referring to the range in countries' progress at curbing the outbreak. While the group currently deems the public health risk moderate globally, it's considered high in the Americas. Monkeypox was first deemed a global public health emergency July 23rd. They also acknowledged progress that has been made to slow the outbreak, such as increased vaccine uptake and behavioral changes.

In the US, 28,881 cases had been confirmed as of November 11th. A recent CDC report found the majority of monkeypox patients in the US who developed illness that required hospitalization were immunocompromised, often from HIV. HHS extended the nation's monkeypox public health emergency due to "continued consequences of an outbreak of monkeypox cases across multiple states." the decision also included the need to maintain data flow across the US as well as providing ample time for vaccine effectiveness studies.

Comment: Overall there has been progress to slow the outbreak, due to education, increased vaccine uptake and behavioral changes. See below

Monkeypox by the Numbers



Comment: The cases continue to decline, however HHS for reasons discussed above has elected to continue to make monkeypox a public health emergency.

Transmission dynamics of monkeypox in the United Kingdom: contact tracing study BMJ2022;379: e073153

doi.org/10.1136/ bmj-2022-073153

To estimate both the serial interval and the incubation period of monkeypox the investigators used a large sample from the UK Health Security Agency (UKHSA) surveillance and contact tracing data. To obtain data on the incubation period they analyzed completed case questionnaires and linked infected individuals to probable exposure dates. To obtain the serial interval data they used self-reported symptom onset dates and linked case-contact pairs (linked pairs of primary and secondary cases). They then applied a Bayesian model correcting for double interval censoring (ICC)17 and a Bayesian model correcting for double interval censoring, right truncation, and epidemic phase bias (ICRTC) to these data to estimate the serial interval and incubation period distributions of monkeypox.

Data were collected on monkeypox from UKHSA health protection teams, targeted testing of infected individuals (with specimens processed by UKHSA affiliated laboratories and NHS laboratories), and questionnaires (collected by UKHSA health protection teams). They defined a confirmed case as an individual with a positive PCR test result for monkeypox virus, and a highly probable case as an individual with a positive PCR test result for orthopoxvirus. UKHSA health protection teams identified pairs of linked individuals through contact tracing.

2746 people with polymerase chain reaction confirmed monkeypox virus in the UK between 6 May and 1 August 2022 were included. The mean age of participants was 37.8 years and 95% reported being gay, bisexual, and other men who have sex with men (1160 out of 1213 reporting). The mean incubation period was estimated to be 7.6 days (95% credible interval 6.5

to 9.9) using the ICC model and 7.8 days (6.6 to 9.2) using the ICRTC model. The estimated mean serial interval was 8.0 days (95% credible interval 6.5 to 9.8) using the ICC model and 9.5 days (7.4 to 12.3) using the ICRTC model. This study found evidence of pre-symptomatic transmission of monkeypox, using contact tracing data and adjustments for interval censoring, right truncation, and epidemic phase bias. The maximum time that transmission was detected before symptoms manifested for infected individuals who could be linked through reliable personal identifiable information was four days.

Comment: The shorter median estimate for the serial interval relative to the incubation period suggests that pre-symptomatic transmission might be more substantial than was previously thought. Their analyses were specific to the dynamics of the outbreak. Incubation periods can vary with severity and personal characteristics of infected individuals, and serial intervals are highly dependent on viral transmission dynamics. Therefore, these distributions might not be the same for outbreaks in other settings. This presymptomatic transmission could also be transmission before symptoms are detected rather than before clinical symptom onset because individuals could have lesions of which they are unaware—this might be more important for perineal lesions. From the perspective of public health policy, this transmission before the detection of symptoms poses additional challenges. If a substantial proportion of secondary transmission occurs before symptom onset, the implications will be that many infections cannot be prevented by isolating individuals with symptoms. The main limitations of this analysis relate to the nature of the data, which often rely on patient reported variables. In particular, symptom onset date is defined as the date patients noticed they had an infection. Another challenge arising from the patient reported data is that they relied on contact tracing to identify case-contact pairs. Individuals report other individuals who they have been in contact with or who they think might have infected them, but this does not necessarily mean transmission occurred during that contact. Nonetheless, investigators estimated that 53% of monkeypox infections could spread pre-symptomatically. Based on this study the virus could be transmitted up to four days before symptoms start.

Epidemiologic and Clinical Features of Children and Adolescents Aged <18 Years with Monkeypox — United States, May 17–September 24, 2022 MMWR 2022; 71: 1407-1411

During May 17–September 24, 2022, children and adolescents who received a positive polymerase chain reaction (PCR) test result for MPXV, nonvariola Orthopoxvirus (NVO), or generic Orthopoxvirus (OPXV) were identified through national surveillance or during CDC clinical consultations. Demographic and exposure characteristics and clinical features of children and adolescents aged monkeypox-compatible symptoms§ who received a positive NVO, OPXV, or MPXV PCR test result were analyzed.

During May 17–September 24, 2022, MPXV infections in children and adolescents aged <18 years were rare, representing 0.3% of all U.S. cases; none resulted in critical illness or death. Younger children typically acquired MPXV infection after skin-to-skin contact with a household member with monkeypox during caregiving activities; adolescents were most frequently exposed through male-to-male sexual contact. No secondary transmission was identified during instances when children attended school or a child care facility while symptomatic, although incomplete case ascertainment and reporting might have limited detection of such events.

Comment: Additional monkeypox cases in children and adolescents might be prevented through strengthened vaccination efforts and education around preventive measures and sexual health. The absence of known secondary transmission in schools and childcare facilities despite the presence of symptomatic persons in these settings suggests that widespread child-to-child transmission might be unlikely. This report could potentially underestimate the number of MPXV infections occurring if children and adolescents aged <18 years with monkeypox did not receive testing.

Global monkeypox case hospitalisation rates: A rapid systematic review and meta-analysis eClin Med published online October 31, 2022

doi.org/10. 1016/j.eclinm.2022. 101710

The authors systematically searched PubMed, Embase, the Lancet Preprints, and MedRxiv for studies published between January 1, 1950 and August 2, 2022. They included documents which contained both the number of cases and associated hospitalizations of MPXV infections. From eligible studies they then extracted the country, the year of the study, the study design type, the clade of MPXV, the participant characteristics, transmission type, any treatments used, number of cases (including suspected, probable, or laboratory confirmed diagnosis), number of hospitalizations, hospitalized patient outcomes, and case definition. Case hospitalization rate (CHR) was defined as the proportion of cases that were admitted to hospital care while case fatality rate (CFR) was defined as the proportion of cases that died. CHR and CFR were analyzed in a fully Bayesian meta-analytic framework using random effects models, including sub-group analysis with heterogeneity assessed.

Of the 259 unique documents identified, 19 studies were eligible for inclusion. Included studies represented 7553 reported cases among which there were 555 hospitalizations. Of the 7540 cases for which outcomes were available, there were 15 recorded deaths. The median age of cases was 35 years (interquartile range 28–38, n = 2010) and primarily male (7339/7489, 98%) in studies where age or sex were available. Combined CHR was estimated to be 14.1% (95% credible interval, 7.5–25.0, I2 97.4%), but with a high degree of heterogeneity. Further analysis by outbreak period indicates CHRs of 49.8% (28.2–74.0, I2 81.4%), 21.7% (7.2–52.1, I2 57.7%), and 5.8% (3.2–9.4, I2 92.4%) during the pre-2017, 2017–2021, and 2022 outbreaks, respectively, again with high levels of heterogeneity. CFR was estimated to be 0.03% (0.0–0.44, I2 99.9%), with evidence of large heterogeneity between the studies.

Comment: There is limited data for MPXV hospitalization rates in countries where MPXV has been traditionally nonendemic until the current outbreak. Due to substantial heterogeneity, caution is needed when interpreting these findings. Rapid identification of infection and use of appropriate therapies such as antivirals and vaccination play a role reducing the CHR and associated CFR.

The meta-analysis suggests monkeypox patients have a 14.1% hospitalization rate. The results from pooled estimates suggest that there has been an attenuation of the case hospitalization rate from nearly 50% during pre-2017 outbreaks to 3.2–9.4% during the 2020 outbreak. This may be related to the clade currently circulating.

Until the global outbreak of 2022, most studies on MPXV have been small, and establishing CHRs and CFRs has been difficult. Public health officials have known the Congo Basin clade of

the virus, found mostly in Africa, is associated with a CFR of 10%, while the West African clade—the cause of the current outbreak—has a CFR of 3% to 6%. Another factor may be because most cases are occurring in upper middle- to high-income countries, among young and middle-aged men who have sex with men who are most often otherwise healthy except if they have HIV. As sustained human-to-human transmission has been observed and the number of cases grow, it will be important to quantify the morbidity and mortality of MPXV infections and the potential for CHR and CFR to evolve.

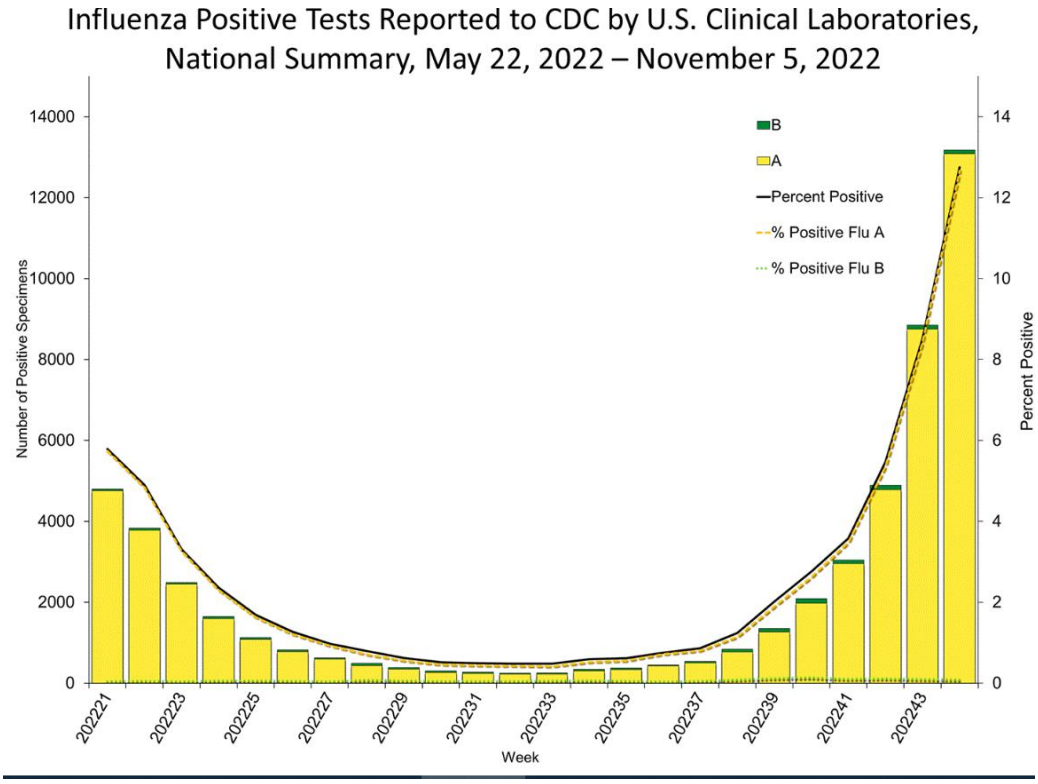
Influenza and RSV

Nine states (Texas, Mississippi, Alabama, Georgia, Tennessee, North Carolina, South Carolina, Virginia, Maryland), New York City and Washington, DC, reported very high flu activity for the week ending Oct. 29. Eight states (New Mexico, Louisiana, New Jersey, Arkansas, Kentucky, Florida, West Virginia and Connecticut) reported high activity. California, Colorado, Nebraska and Ohio reported moderate activity. The remaining states reported low or minimal activity.

Two flu-associated pediatric deaths were reported to the CDC for the week ending October 29. One death occurred during the 2021-22 flu season, bringing the total number of pediatric deaths last season to 44. There have now been three influenza-associated pediatric deaths during the 2022-23 season.

Clinical laboratories tested 83,742 specimens for influenza for the week ending October 29th. As of November 5th, 12.8 percent were positive, most of which for influenza A. The positivity rate was 9.2 % the previous week. The percentage of visits to an outpatient provider for influenza-like illness — meaning fever plus cough or sore throat, not lab-confirmed flu — was 4.3 percent for the week ending October 29. This is above the national baseline of 2.5 percent. Nationwide, 0.8 percent of 14,221 long-term care facilities reported at least one flu-positive test among residents for the week ending October 29.

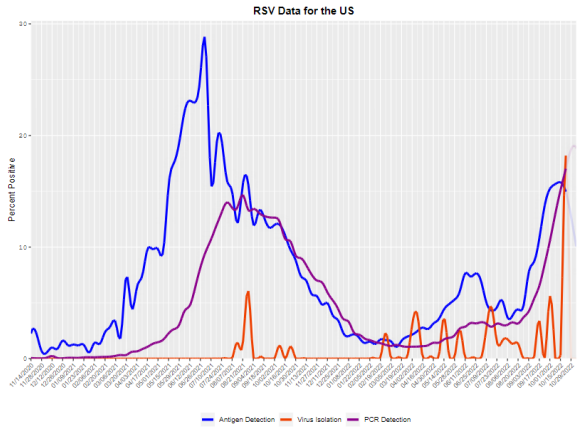
The national flu, pneumonia and/or COVID-19 mortality rate is 9.1 percent, which sits above the epidemic threshold of 6 percent for the week. Among the 2,153 deaths reported for the week, 988 had COVID-19 and 29 had the flu listed as an underlying or contributing cause of death. This indicates the current death rate for pneumonia, influenza and COVID-19 is primarily due to COVID-19.



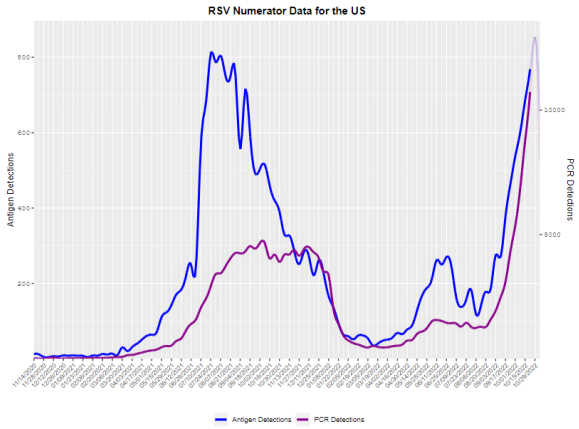
Comment: These 2 graphs tell the story. We are seeing an early flu season with N3N2 predominating so far. There is a good match with the current vaccine. If you have not gotten your influenza vaccine, it is not too late. See editorial above

Respiratory Syncytial Virus (RSV)

Percent Positive



Detections



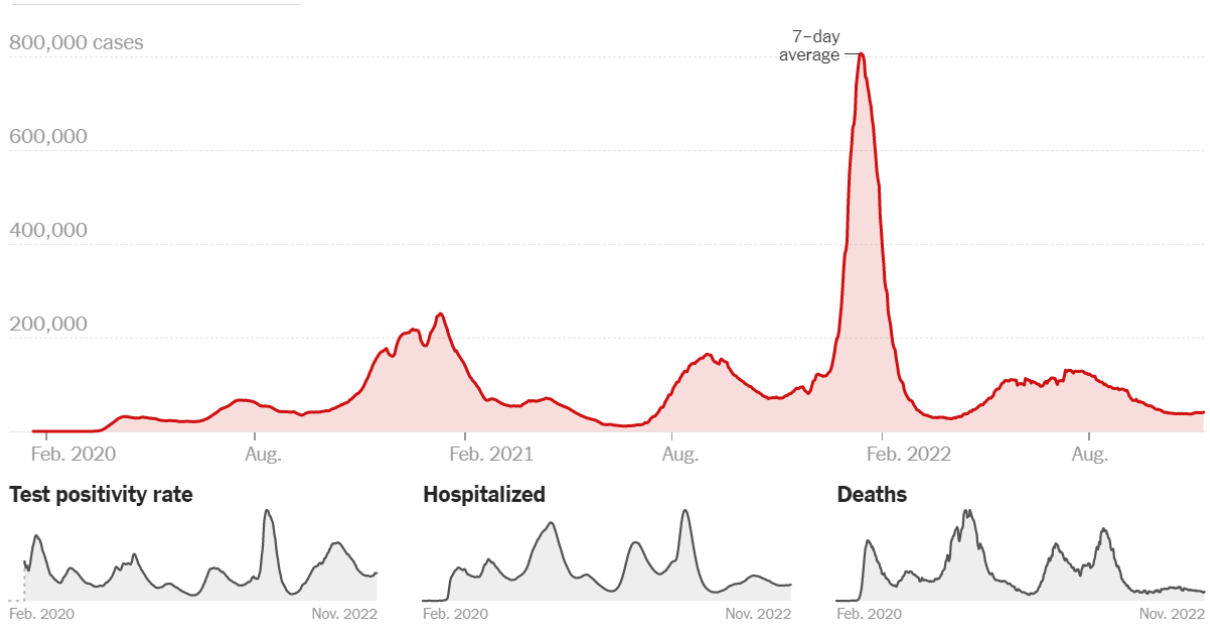
Comment: The trend graph above displays the weekly national average percent of diagnostic tests positive for RSV among all the diagnostics performed to detect RSV, as reported by

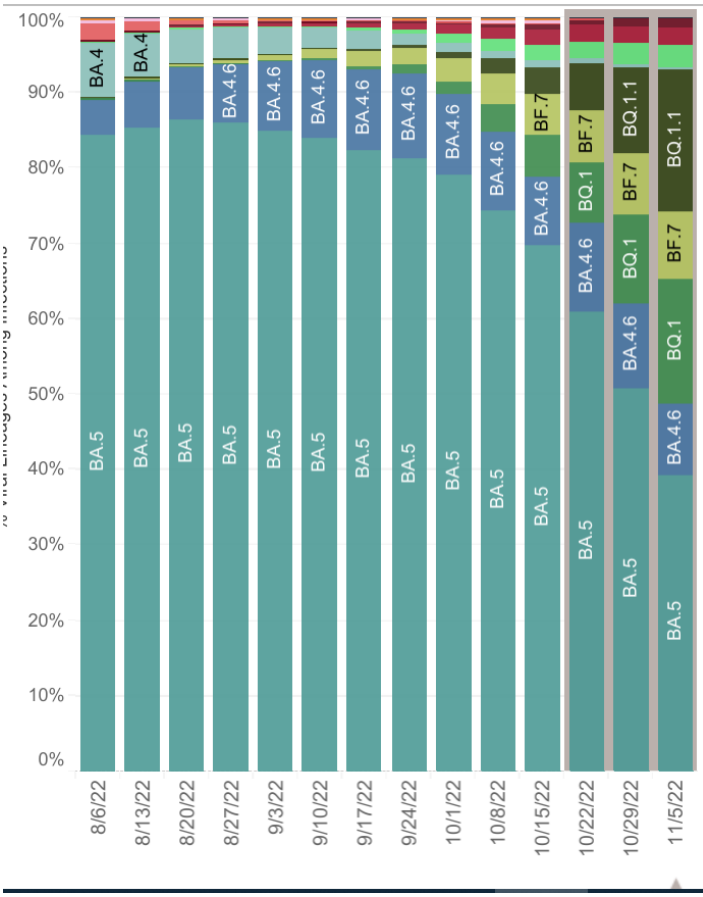
participating laboratories. Like influenza we are seeing an early surge of RSV resulting in increased hospitalizations in pediatric hospitals. See editorial above

COVID-19

COVID-19 News

The Rise of BQ Strains and COVID-19 by the Numbers





USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	39.2%	36.2-42.3%
	BQ.1.1	VOC	18.8%	15.7-22.4%
	BQ.1	VOC	16.5%	13.6-20.0%
	BA.4.6	VOC	9.5%	8.6-10.5%
	BF.7	VOC	9.0%	7.9-10.1%
	BA.5.2.6	VOC	3.1%	2.5-3.7%
	BA.2.75	VOC	2.3%	1.9-2.8%
	BA.2.75.2	VOC	1.3%	0.9-1.7%
	BA.4	VOC	0.2%	0.2-0.3%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.1%	0.0-0.1%

* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.

** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates

BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2 and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BA.5.2.6, BQ.1 and BQ.1.1,

Comments As of November 2nd, the nation's seven-day case average was 39,016, a 4.7 percent increase from the previous week's average. This marks the first week of increase seen in more than three months, CDC data shows. The seven-day hospitalization average for October 26th to November 1st was 3,272, a 1 percent decrease from the previous week's average. As of November 3rd, 2 percent of counties, districts or territories had high COVID-19 community levels, 20.1 percent had medium community levels and 77.5 percent had low community levels. The current seven-day death average is 358, down 3 percent from the previous week's average. BAQ strains now make up over 35% of variants identified. BA.5 is now down to 39%. As of November 2nd, about 266.4 million people — 80.2 percent of the U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 227.4 million people, or 68.5 percent of the population, have received both doses. About 112.5 million people have received a booster dose, and more than 26.4 million people have received an updated omicron booster. However, 49.1 percent of people eligible for a booster dose have not yet gotten one, the CDC said. About 38 percent of the US is reporting moderate to high virus levels in wastewater. Of these surveillance sites, 12 percent are seeing some of the highest levels since December 1, 2021. About 58 percent of sites are reporting an increase in virus levels, and 33 percent of sites are seeing a decrease.

HHS to extend COVID-19 public health emergency (PHE)

The US will extend the COVID-19 public health emergency through at least April 11, 2023. This is the 12th extension of the PHE since the first in January 2020. The PHE allows the country to continue operating under pandemic-era policies, which led to a complete overhaul of telehealth and who can use it, fast-tracked approvals of COVID-19 vaccines and treatments etc.

Comment: It is unclear from a purely public health perspective that we need to continue Covid-19 as a PHE. However, we need to have an exit plan to consider how we unwind some of the flexibilities we implemented, and which ones should be retired, and which ones perhaps should be permanent or extended.

Pfizer Bivalent Vaccine Study

Pfizer researchers drew sera from 114 study participants before and after the receipt of a 30-microgram mRNA Omicron BA.4/BA.5-adapted booster dose or a booster dose of the original monovalent (one-strain) vaccine, according to a company news release on updated data from its phase 2/3 multicenter clinical trial.

A subset of participants, evenly stratified by those with and without a previous infection, consisted of 38 adults 18 to 55 years old and 36 of those 56 and older. The team compared their results with those of 40 participants older than 55 years who had received an equivalent dose of the monovalent booster in an earlier study. Bivalent vaccine recipients had received their third monovalent dose roughly 10 or 11 months earlier, and monovalent booster recipients had received their most recent dose about 7 months earlier. Prebooster SARS-CoV-2 antibody concentrations were similar.

One month after receipt of the bivalent booster, neutralizing antibody levels rose 13.2-fold (95% confidence interval [CI], 8.0 to 21.6) in adults older than 55 (geometric mean titer [GMT], 896) and 9.5-fold (95% CI, 6.7 to 13.6) higher (GMT, 606) in those aged 18 to 55. In comparison, the monovalent (single-strain) vaccine generated a 2.9-fold (95% CI, 2.1 to 3.9) increase in neutralizing antibody levels.

Comment: The Omicron BA.4/BA.5 neutralizing antibody titers were approximately 4-fold higher for the bivalent vaccine compared to the companies' original Covid-19 vaccine in individuals over 55 years of age. Levels of antibodies against BA.4/BA.5 also rose significantly in all participants and to a greater extent in the previously infected recipients. Reports of adverse events were similar to those noted after receipt of the monovalent vaccine. The number of participants in the study was small, with 36 people over 55 receiving the new booster and 40 people in that age group receiving the old one. And because the study measured antibody levels only a month after trial participants were boosted, it did not provide any indication about the potential durability of the protection in the longer term. This study had better results than the 2 studies reported in Issue 11 of ID Watch. The Pfizer release did not specify the neutralization assay used. All 3 studies were small. BQ is rising and is related to BA.5, but it too early to know the extent of protection from the bivalent vaccine, but the study below suggests the bivalent vaccine broadens humoral immunity against the Omicron subvariants. The duration of protection is unknown.

FDA issues emergency use authorization for Anakinra to treat COVID-19

According to a statement from the FDA this past week, the EUA is specifically for adult patients hospitalized with pneumonia requiring supplemental oxygen who are at risk for progressing to severe respiratory failure and likely to have an elevated plasma soluble urokinase plasminogen activator receptor. Anakinra is an IL-1 receptor antagonist.

The decision was largely based on data from the clinical trial SAVE-MORE, a randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of anakinra (Kineret, SOBI) in adult patients with COVID-19 pneumonia who were at risk of developing severe respiratory failure. [Rheumatology 2021; doi:10.1093/rheumatology/keab447.] Anakinra is currently approved by the FDA for rheumatoid arthritis, cryopyrin-associated periodic syndromes and deficiency of interleukin-1 receptor antagonist.

Comment: This drug will be added to tocilizumab and baricitinib which already have EUA for treatment of severe Covid-19 usually in combination with dexamethasone.

COVID-19 AAP Report November 3, 2022

COVID-19 cases among children have been rising nationwide for two consecutive weeks, according to a November 3rd report from the American Academy of Pediatrics(AAP). Nearly 30,000 children in the U.S. tested positive for COVID-19 in the week ending November 3rd , up about 30 percent from the 23,000 cases reported the week prior. This figure likely represents a substantial undercount, AAP said.

Comment: The increase comes as children's hospitals face significant capacity issues amid a surge in patients with respiratory illnesses [RSV and influenza], and as pediatric COVID-19 vaccination rates lag nationwide. Data from Kaiser Family Foundation shows pediatric vaccination rates have stalled across all age groups. As of Nov. 3, 3.2 percent of children under 5, 31.8 percent of kids ages 5-11 and 61.1 percent of those 12-17 had completed their primary vaccination series. See below

COVID-19 Journal Review

COVID-19–Associated Hospitalizations Among U.S. Infants Aged < 6 months

MMWR 71;1442–1448

CDC analyzed data from Covid-19-Associated Hospitalization Surveillance Network on infant COVID-19 hospitalizations in 13 states from June 20, 2021, to August 31, 2022. The study spanned the Delta-predominant (June 20 to December 18, 2021) and the Omicron (December 19, 2021, to August 31, 2022) waves.

The investigators noted that hospitalizations of children younger than 5 years increased faster than those in other age-groups. On June 22, 2022, the CDC began recommending COVID-19 vaccination of children 6 months and older. Infants remain ineligible. Weekly COVID-19 hospitalizations of infants younger than 6 months rose 11-fold from a low point of 2.2 the week of Apr 9, 2022, to a peak of 26.0 the week of July 23 and then declined.

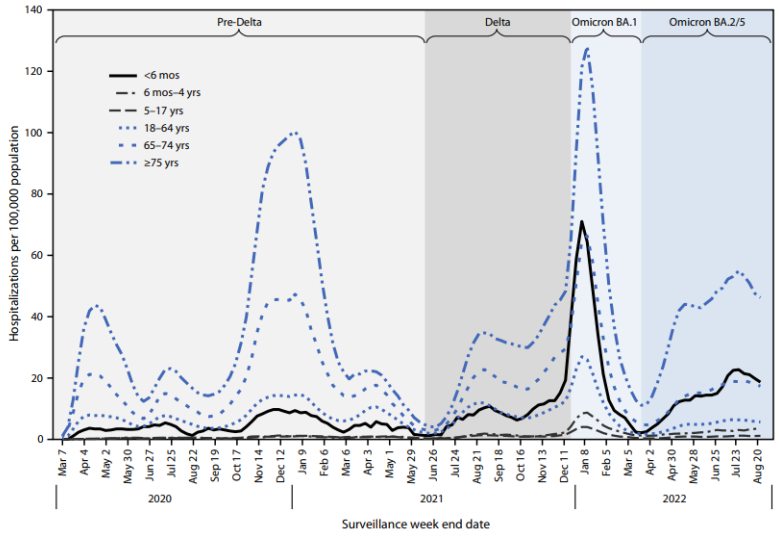
The average weekly hospitalization rate in infants was higher during the Omicron BA.2/BA.5 subvariant period (13.7) than during Delta (8.3) (rate ratio [RR], 1.6). Relative to the Delta period, rates were also higher during BA.2/BA.5 among children 6 months to 4 years old (RR, 1.9) and adults 75 and older (RR, 1.4) but lower among children 5 to 17 (RR, 0.9), adults 18 to 64 (RR, 0.5), and adults 65 to 74 (RR, 0.8).

The average weekly hospitalization rate among infants during the Omicron BA.2/BA.5 wave (13.7) was less than that of adults 75 and older (39.4), similar to that of those 65 to 74 (13.8) and higher than that in other preschoolers (2.3 and 0.8 for children aged 6 to 23 months and 2 to 4 years, respectively) and in adults younger than 65.

Indicators of severe disease among 1,116 hospitalized infants younger than 6 months with clinical data were generally lower during Omicron than Delta, and in-hospital deaths were rare, at less than 1%. Such indicators included length of hospital stay, the proportion of intensive care unit admissions, the use of supplemental oxygenation via high-flow nasal cannula or bilevel positive airway pressure/continuous positive airway pressure, and mechanical ventilation.

Among 473 infants hospitalized during Omicron, 84% had COVID-19 symptoms, and 38% were younger than 1 month; 39% were birth hospitalizations. Fully 87% of infants who tested positive during their birth hospitalization showed no symptoms. Similar proportions of infants with non-birth hospitalizations had symptoms, including 94% of those younger than 1 month, 97% of those aged 1 to 2 months, and 96% of those aged 3 to 5 months.

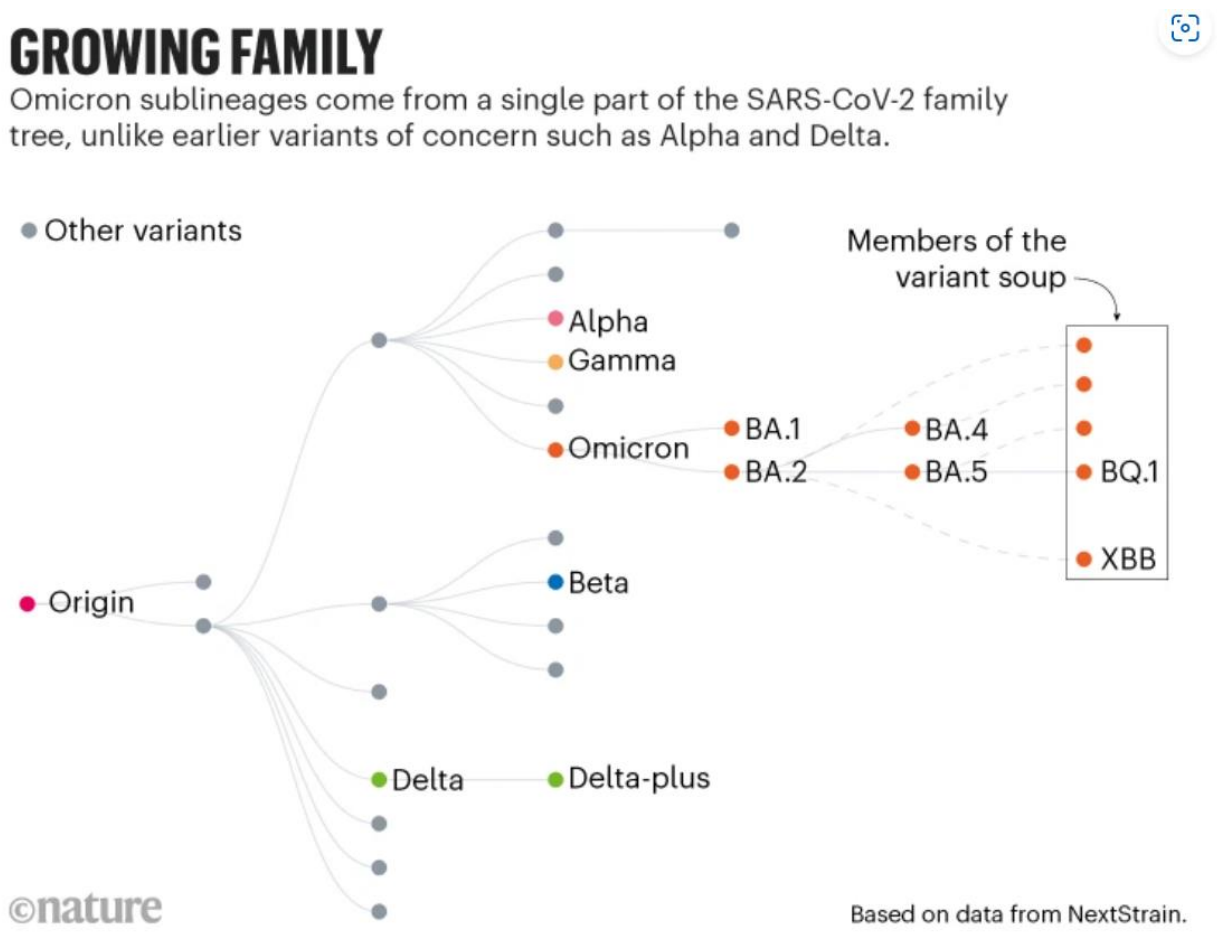
Twenty-six percent of hospitalized infants 1 to 2 months old and 36% of those aged 3 to 5 months had at least one underlying medical condition. The most common underlying condition was prematurity, at 20% of those aged 1 to 2 months and 25% of those 3 to 5 months. Most infants had a fever at hospitalization (74% of those 1 to 2 months and 68% of those 3 to 5 months old.

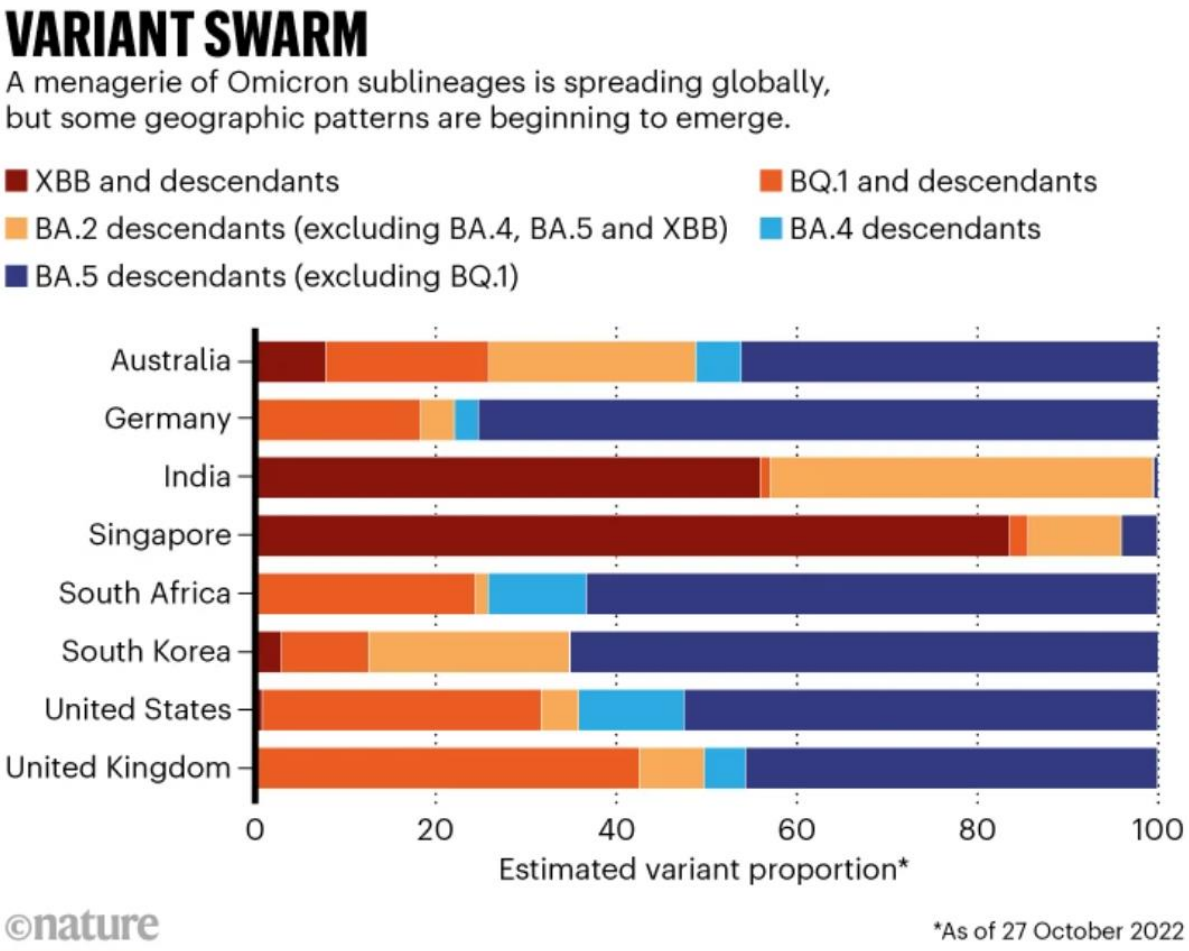


Comment: Although population-based COVID-19–associated hospitalization rates among infants aged < 6 months increased in the Omicron variant periods compared with the Delta variant period, indicators of the most severe disease among hospitalized infants aged < 6 months did not. This is similar to what has been reported in adults. It was not possible to account for changes in public health policies and testing and treatment practices over time. In addition, maternal vaccination, or previous infection, which might confer some immunity to infants, was not assessed. The investigators noted that maternal COVID-19 vaccination has been proven to protect infants younger than 6 months, and both the CDC and the American College of Obstetricians and Gynecologists recommend the vaccine for women who are pregnant, breastfeeding, or planning a pregnancy.

COVID variants to watch, and more — this week's best science graphics Nature November 1, 2022

doi.org/10.1038/d41586-022-03533-7





Comment: Since the Omicron variant emerged in late 2021, it has spawned a series of subvariants that have generated global surges of infection. In the past few months, scientists have identified more than a dozen extra subvariants to watch. How this plays out as we approach winter in the Northern Hemisphere is unclear, but increased infections are likely. Based on level of immunity and this past summer's experience, hopefully this increase in infections will not result in significant hospitalizations and deaths. For example, the BQ.1.1 variant's marked immune evasion in the lab is not playing out clinically to date. It is dominant (>50% of cases) in France and all signs are pointing in the opposite direction, towards actual improvement. To remind our readers, we will likely see multiple respiratory viruses circulating this winter including influenza and RSV which has already impacted several cities in the US. We are still seeing on average 2600 deaths per week due to Covid-19 which is still too high.

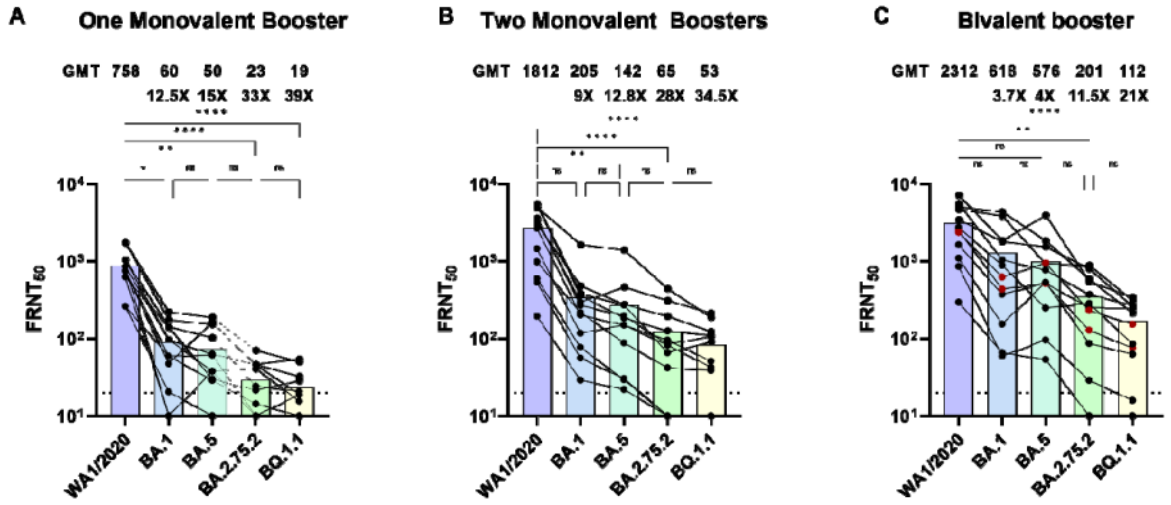
Remember BQ.1 and BQ.1.1 are likely resistant to tixagevimab/cilgavimab (Evusheld) and bebtelovimab.

mRNA bivalent booster enhances neutralization against BA.2.75.2 and BQ.1.1
posted bioRxiv online November 1,2022

doi.org/10.1101/2022.10.31.514636

The bivalent COVID-19 mRNA booster 23 vaccine within the United States is comprised of the ancestral and the Omicron BA.5 spike. Since its approval and distribution, additional Omicron subvariants have been identified with key mutations within the spike protein receptor binding domain that are predicted to escape vaccine sera. Of particular concern is the R346T mutation which has arisen in multiple subvariants, including BA.2.75.2 and BQ.1.1. Using a live virus neutralization assay, we evaluated serum samples from individuals who had received either one or two monovalent boosters or the bivalent booster to determine neutralizing activity against wild-type (WA1/2020) virus and Omicron subvariants BA.1, BA.5, BA.2.75.2, and BQ.1.1. In the one monovalent booster cohort, relative to WA1/2020, we observed a reduction in neutralization titers of 9-15-fold against BA.1 and BA.5 and 28-39-fold against BA.2.75.2 and BQ.1.1. In the BA.5-containing bivalent booster cohort, the neutralizing activity improved against all the Omicron subvariants. Relative to WA1/2020, they observed a reduction in neutralization titers of 3.7- and 4-fold against BA.1 and BA.5, respectively, and 11.5- and 21-fold against BA.2.75.2 and BQ.1.1, respectively.

Neutralizing responses against WA1/2020, BA.1, BA.5, BA.2.75.2, and BQ.1.1.



Comment: This study suggest that the bivalent mRNA booster vaccine broadens humoral immunity against the Omicron subvariants. This report is encouraging, but still unclear the clinical significance based on real world experience and duration. T cell response by other studies remains intact providing protection against severe disease. It is hope the BA.5 containing vaccine will also provide better protection against the BQ strains since the BQ strain is an offshoot of BA.5, but there are no studies at present.

Safety Monitoring of Bivalent COVID-19 mRNA Vaccine Booster Doses Among Persons Aged ≥12 Years — United States, August 31–October 23, 2022 MMWR 2022; 71:1401-1406

To characterize the safety of bivalent mRNA booster doses, CDC reviewed adverse events and health impacts reported after receipt of bivalent Pfizer-BioNTech and Moderna booster doses during August 31–October 23, 2022, to v-safe, a voluntary smartphone-based U.S. safety surveillance system established by CDC to monitor adverse events after COVID-19 vaccination, and the Vaccine Adverse Event Reporting System (VAERS), a US passive vaccine safety surveillance system managed by CDC and FDA.

During August 31–October 23, 2022, approximately 14.4 million persons aged ≥12 years received a bivalent Pfizer-BioNTech booster dose, and 8.2 million adults aged ≥18 years received a bivalent Moderna booster dose. Of the recipients, 0.7% were aged 12 to 17 years, 32.4% were 18 to 49, 27.9% were 50 to 64, and 39.0% were 65 years and older. A total of 211,959 people aged 12 years and older reported receiving a bivalent booster dose (58.0% Pfizer and 42.0% Moderna) to v-safe. The vast majority said that the booster dose was their fourth or fifth COVID-19 vaccine dose (45.4% and 50.2%, respectively). Injection-site and systemic reactions were common in the week after receipt (60.8% and 54.8%, respectively) and decreased with age. The most common reactions were injection-site pain (range, 45.0% to 70.5%), fatigue (30.0% to 53.1%), headache (19.7% to 42.8%), muscle pain (20.3% to 41.3%), and fever (10.2% to 26.3%). From 10.6% to 19.8% of adults reported an inability to complete daily activities.

VAERS received 5,542 reports of adverse events after a bivalent booster dose; 95.5% of them were not serious. Among 251 reports of serious events, 5 involved myocarditis, 4 were pericarditis, and 20 were COVID-19. Rates of myocarditis and pericarditis were similar to those observed after receipt of the primary series doses. Those reporting myocarditis or pericarditis were 12 to 78 and 46 to 78 years old, respectively, but the conditions were most common among adolescent and young men. Thirty-six people died (median age, 71 years). In the four reports of death with sufficient information for review, the cause was listed as cardiac arrest, dementia, metastatic prostate cancer, and heart attack.

The most common nonserious reactions were headache (11.9%), fatigue (10.9%), fever (10.6%), pain (9.9%), and chills (8.7%). Adverse events related to administration errors (e.g., incorrect vaccine formulation or dose, wrong product) were common, at 34.5%. Of the 877 reports of Pfizer vaccination errors and 1,037 of Moderna errors, 11.8% described an adverse event.

Comment: Overall adverse events reported after a bivalent booster dose appear consistent with those reported after a monovalent booster and are less common and less serious than health impacts associated with COVID-19 illness. V-safe is a voluntary program; therefore, data might not be representative of the vaccinated population. Second, as a passive surveillance system, VAERS is subject to reporting biases and underreporting, especially of nonserious events. Finally, conclusions drawn from these data are limited by the 7-week surveillance period; safety monitoring will continue during the bivalent booster vaccination program.

Gut microbiome dysbiosis in antibiotic treated COVID-19 patients is associated with microbial translocation and bacteremia Nat Comm published online November 1, 2022

doi.org/10.1038/s41467-022-33395-6

Although microbial populations in the gut microbiome are associated with COVID-19 severity, a causal impact on patient health has not been established. Here the investigators provide evidence that gut microbiome dysbiosis is associated with translocation of bacteria into the blood during COVID-19, causing life threatening secondary infections. They first demonstrate SARS-CoV-2 infection induces gut microbiome dysbiosis in mice, which correlated with alterations to Paneth cells and goblet cells, and markers of barrier permeability. Samples collected from 96 COVID-19 patients at two different clinical sites also revealed substantial gut microbiome dysbiosis, including blooms of opportunistic pathogenic bacterial genera known to include antimicrobial-resistant species. Analysis of blood culture results testing for secondary microbial bloodstream infections with paired microbiome data indicates that bacteria may translocate from the gut into the systemic circulation of COVID-19 patients. These results are consistent with a direct role for gut microbiome dysbiosis in enabling dangerous secondary infections during COVID-19.

On average members of the phyla Firmicutes and Bacteroidetes represented the most abundant bacteria, followed by Proteobacteria. In samples microbiome dominations, defined as a community where a single genus reached more than 50% of the population, were observed frequently, representing states of severe microbiome injury in patients with COVID-19. In addition, of the 96 patients, 25 had BSIs, with most receiving antibiotics prior to their BSI, and only 6 receiving antibiotics only after the detection of BSI.

Comment: Results from this study and others showed that most patients had low gut microbiome diversity, with a full quarter dominated by a single type of bacteria. At the same time, populations of several microbes known to include antibiotic-resistant species increased, in part due to widespread antibiotic use in the pandemic. These antibiotic-resistant bacteria found in the gut were also observed to have migrated into the bloodstream in 20% of patients.

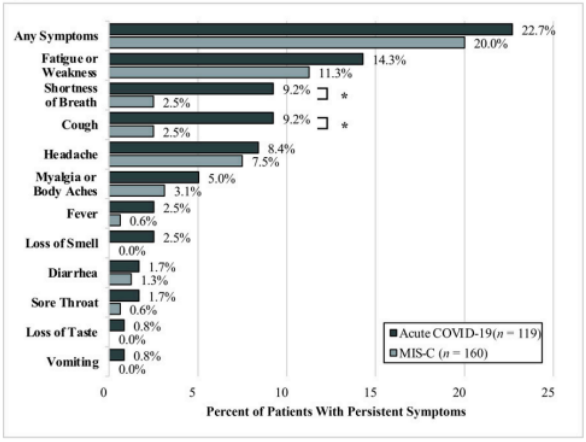
The investigators cautioned that since the patients received different kinds of treatments for their illness, the investigation could not entirely account for all factors that may have contributed to the disruption of their microbiome and worsen their disease.

Health Impairments in Children and Adolescents After Hospitalization for Acute COVID-19 or MIS-C Pediatrics (2022) 150 (3): e2022057798

doi.org/10.1542/peds.2022-057798

Multicenter prospective cohort study conducted in 25 United States pediatric hospitals. Patients <21-years-old, hospitalized May 2020 to May 2021 for acute COVID-19 or MIS-C with follow-up 2 to 4 months after admission. We assessed readmissions, persistent symptoms or activity impairment, and new morbidities. Multivariable regression was used to calculate adjusted risk ratios (aRR) and 95% confidence intervals (CI).

Of 358 eligible patients, 2-to-4-month survey data were available for 119 of 155 (76.8%) with acute COVID-19 and 160 of 203 (78.8%) with MIS-C. Thirteen (11%) patients with acute COVID-19 and 12 (8%) with MIS-C had a readmission. Thirty-two (26.9%) patients with acute COVID-19 had persistent symptoms (22.7%) or activity impairment (14.3%) and 48 (30.0%) with MIS-C had persistent symptoms (20.0%) or activity impairment (21.3%). For patients with acute COVID-19, persistent symptoms (aRR, 1.29 [95% CI, 1.04–1.59]) and activity impairment (aRR, 1.37 [95% CI, 1.06–1.78]) were associated with more organ systems involved. Patients with MIS-C and pre-existing respiratory conditions more frequently had persistent symptoms (aRR, 3.09 [95% CI, 1.55–6.14]) and those with obesity more frequently had activity impairment (aRR, 2.52 [95% CI, 1.35–4.69]). New morbidities were infrequent (9% COVID-19, 1% MIS-C).



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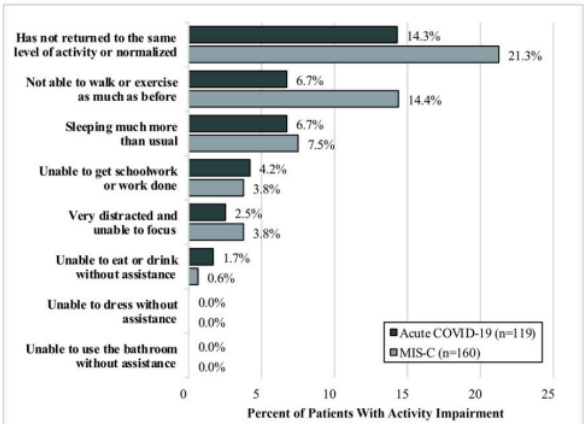


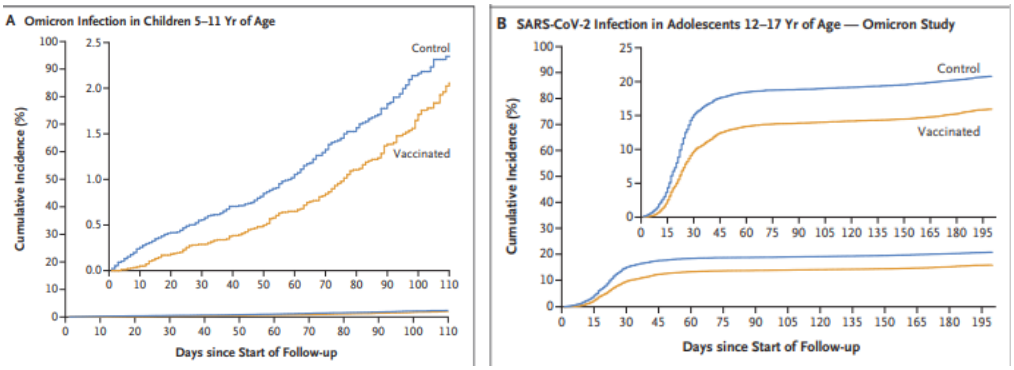
Comment: Over 1 in 4 children hospitalized with acute COVID-19 or MIS-C experienced persistent symptoms or activity impairment for at least 2 months. Patients with MIS-C and respiratory conditions or obesity are at higher risk of prolonged recovery. This article highlights even though children are at low risk, that does not mean no risk.

Covid-19 Vaccine Protection among Children and Adolescents in Qatar N Engl J Med published online November 2, 2022

DOI: 10.1056/NEJMoa2210058

We assessed the real-world effectiveness of the BNT162b2 vaccine against infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) among children and adolescents in Qatar. To compare the incidence of SARS-CoV-2 infection in the national cohort of vaccinated participants with the incidence in the national cohort of unvaccinated participants, we conducted three matched, retrospective, targettrial, cohort studies — one assessing data obtained from children 5 to 11 years of age after the B.1.1.529 (omicron) variant became prevalent and two assessing data from adolescents 12 to 17 years of age before the emergence of the omicron variant (pre-omicron study) and after the omicron variant became prevalent. Associations were estimated with the use of Cox proportional-hazards regression models.

Among children, the overall effectiveness of the 10-μg primary vaccine series against infection with the omicron variant was 25.7% (95% confidence interval [CI], 10.0 to 38.6). Effectiveness was highest (49.6%; 95% CI, 28.5 to 64.5) right after receipt of the second dose but waned rapidly thereafter and was negligible after 3 months. Effectiveness was 46.3% (95% CI, 21.5 to 63.3) among children 5 to 7 years of age and 16.6% (95% CI, −4.2 to 33.2) among those 8 to 11 years of age. Among adolescents, the overall effectiveness of the 30-μg primary vaccine series against infection with the omicron variant was 30.6% (95% CI, 26.9 to 34.1), but many adolescents had been vaccinated months earlier. Effectiveness waned over time since receipt of the second dose. Effectiveness was 35.6% (95% CI, 31.2 to 39.6) among adolescents 12 to 14 years of age and 20.9% (95% CI, 13.8 to 27.4) among those 15 to 17 years of age. In the pre-omicron study, the overall effectiveness of the 30-μg primary vaccine series against SARS-CoV-2 infection among adolescents was 87.6% (95% CI, 84.0 to 90.4) and waned relatively slowly after receipt of the second dose.



Comments: Vaccination in children was associated with modest, rapidly waning protection against omicron infection. Vaccination in adolescents was associated with stronger, more durable protection, perhaps because of the larger antigen dose. See article below on myocarditis/pericarditis.

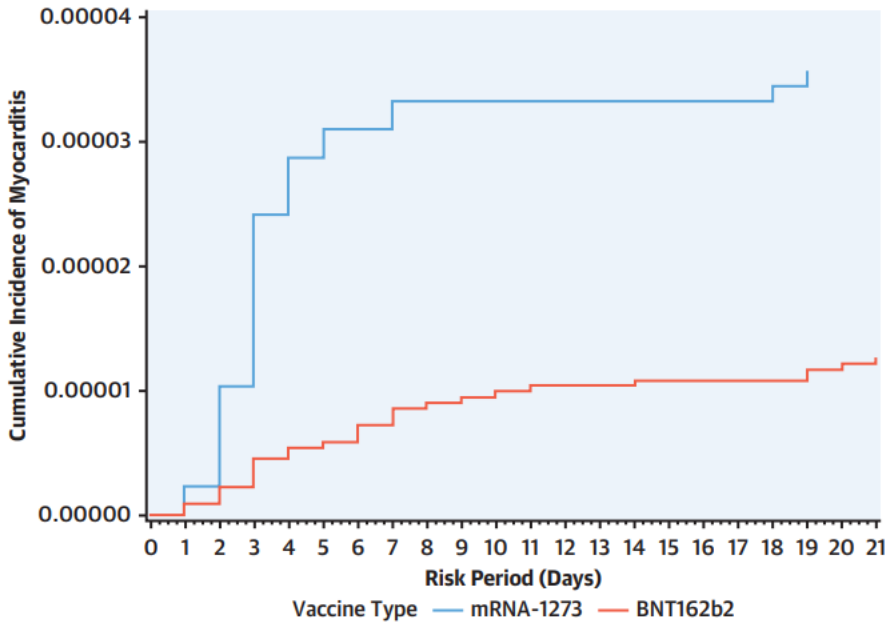
Comparative Risk of Myocarditis/ Pericarditis Following Second Doses of BNT162b2 and mRNA-1273 Coronavirus Vaccines

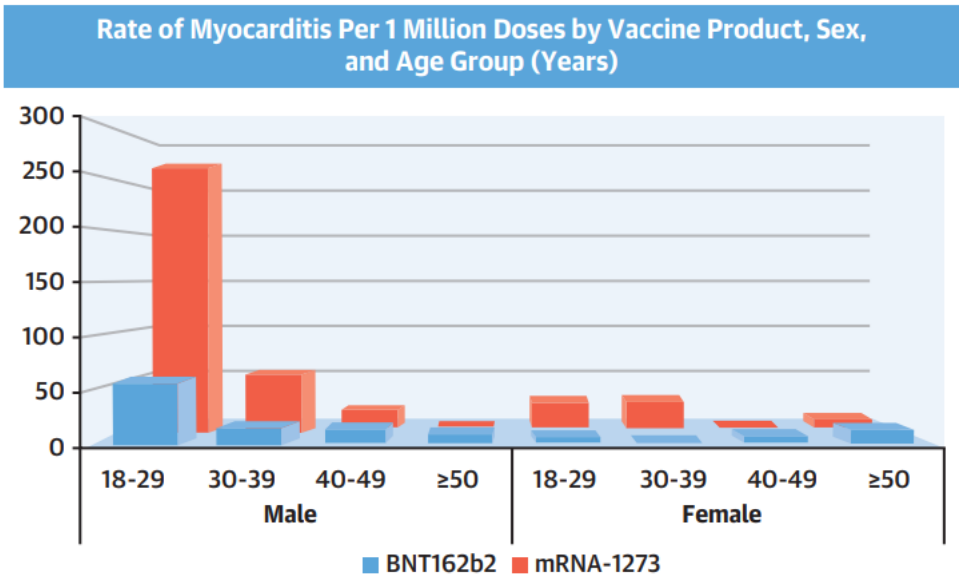
J Am Coll Cardiol 2022; 80:1900-1908

doi.org/10.1016/j.jacc.2022.08.799

The investigators used data from the British Columbia COVID-19 Cohort (BCC19C), a population-based cohort study. The exposure was the second dose of an mRNA vaccine. The outcome was diagnosis of myocarditis, pericarditis, or myopericarditis during a hospitalization or an emergency department visit within 21 days of the second vaccination dose. They performed multivariable logistic regression to assess the association between vaccine product and the outcomes of interest.

The rates of myocarditis and pericarditis per million second doses were higher for mRNA-1273[Moderna] (n = 31, rate 35.6; 95% CI: 24.1-50.5; and n = 20, rate 22.9; 95% CI: 14.0-35.4, respectively) than BNT162b2[Pfizer] (n = 28, rate 12.6; 95% CI: 8.4-18.2 and n = 21, rate 9.4; 95% CI: 5.8-14.4, respectively). mRNA-1273 vs BNT162b2 had significantly higher odds of myocarditis (adjusted OR [aOR]: 2.78; 95% CI: 1.67-4.62), pericarditis (aOR: 2.42; 95% CI: 1.31-4.46) and myopericarditis (aOR: 2.63; 95% CI: 1.76-3.93). The association between mRNA-1273 and myocarditis was stronger for men (aOR: 3.21; 95% CI: 1.77-5.83) and younger age group (18-39 years; aOR: 5.09; 95% CI: 2.68-9.66).





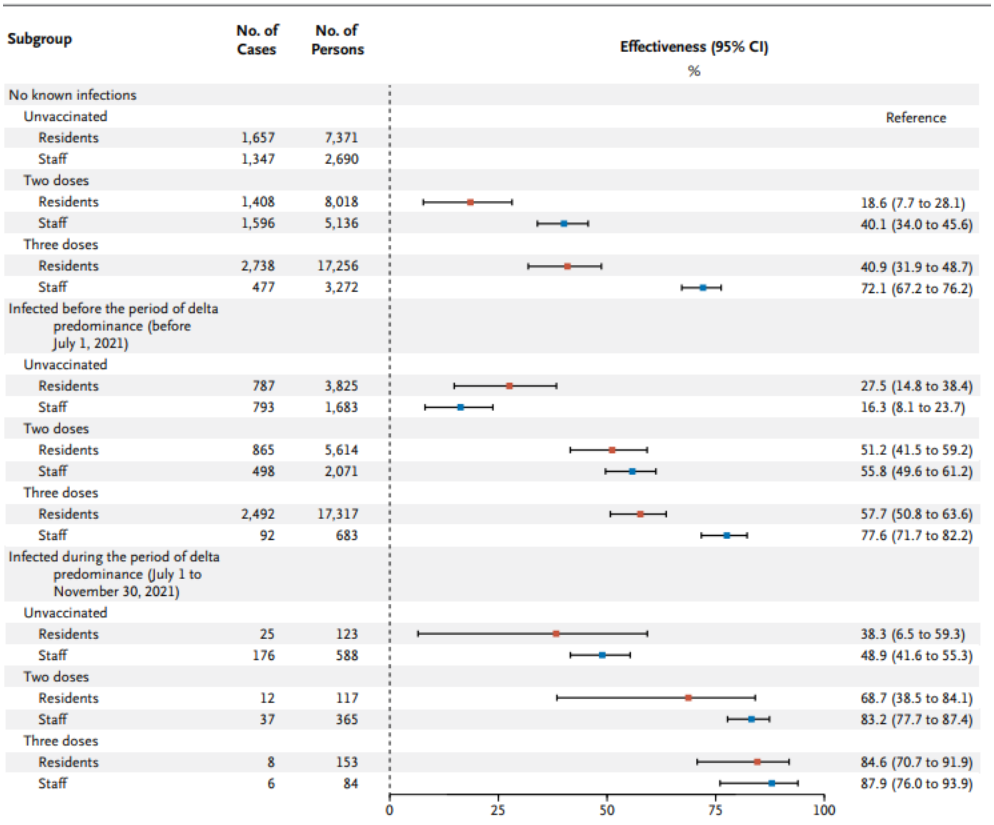
Comment: The investigators observed 2- to 3-fold higher odds of myocarditis and pericarditis among individuals who received mRNA-1273 compared with BNT162b2. Compared with the background rates of myocarditis calculated for 2018 from BCC19C (overall = 2.01 per million, aged 18-39 years = 1.79 per million, and aged $40 years = 2.20 per million), both Moderna and Pfizer had higher overall as well as age-specific rates. However, overall rates of outcomes per million second doses were still very low for both vaccine products (myocarditis: 35.6 for mRNA-1273 and 12.6 for BNT162b2; pericarditis: 22.9 and 9.4), highlighting their favorable safety profile. The postvaccination rates were higher for men and in younger age groups for both vaccine products—with the highest rate observed in men aged 18 to 29 years following a second dose of mRNA-1273 (269.6 events per million doses). This has also been observed in other studies of mRNA vaccines. [N Engl J Med. 2021;385(23):2140–2149]. In addition, the increased odds of myocarditis with mRNA-1273 (vs BNT162b2) were not present at older ages (>40 years), although odds of pericarditis were higher with mRNA-1273 for both younger and older individuals. Since this was an observational study, this limits the ability to infer causality. Despite adjustment for potential confounders, residual confounding may contribute to the differences in the rate of outcomes across vaccine products. Furthermore, because of the rarity of events, they were unable to control for additional potential confounders. Moving forward given the very low risk of Covid-19 in young persons, do I give additional boosters with mRNA vaccines if they have received the primary series and at least one booster? If another booster is appropriate, do I use Pfizer over Moderna?

Protection against Omicron from Vaccination and Previous Infection in a Prison System N Engl J Med published online October 26, 2022

DOI: 10.1056/NEJMoa2207082

The investigators evaluated the protection conferred by mRNA vaccines and previous infection against infection with the omicron variant in two high-risk populations: residents and staff in the California state prison system. We used a retrospective cohort design to analyze the risk of infection during the omicron wave using data collected from December 24, 2021, through April 14, 2022. Weighted Cox models were used to compare the effectiveness of vaccination and previous infection across combinations of vaccination history (stratified according to the number of mRNA doses received) and infection history (none or infection before or during the period of B.1.617.2 [delta]–variant predominance). A secondary analysis used a rolling matched-cohort design to evaluate the effectiveness of three vaccine doses as compared with two doses.

Among 59,794 residents and 16,572 staff, the estimated VE of previous infection against omicron infection among unvaccinated persons who had been infected before or during the period of delta predominance ranged from 16.3% (95% confidence interval [CI], 8.1 to 23.7) to 48.9% (95% CI, 41.6 to 55.3). Depending on previous infection status, the estimated VE of vaccination (relative to being unvaccinated and without previous documented infection) ranged from 18.6% (95% CI, 7.7 to 28.1) to 83.2% (95% CI, 77.7 to 87.4) with two vaccine doses and from 40.9% (95% CI, 31.9 to 48.7) to 87.9% (95% CI, 76.0 to 93.9) with three vaccine doses. Incremental VE estimates of a third (booster) dose (relative to two doses) ranged from 25.0% (95% CI, 16.6 to 32.5) to 57.9% (95% CI, 48.4 to 65.7) among persons who either had not had previous documented infection or had been infected before the period of delta predominance.



Comment: This study in a high-risk population suggest that mRNA vaccination and previous infection were effective against omicron infection, with lower estimates among those infected before the period of delta predominance. Perhaps the most important take way is that three vaccine doses offered significantly more protection than two doses, including among previously infected persons. This study was performed before BA.4 and BA.5 became predominant. Although a variety of covariates — including those related to vaccine acceptance and the risk of previous infection — were used to balance baseline characteristics, residual confounding may remain. Vaccine uptake and the occurrence of previous infections varied between residents and staff. Differences in infection risks between the two populations may in part reflect complex interactions of vaccine and previous infection levels and timing. Distinct testing programs and exposures for residents and staff during the study period may also have introduced confounding. Nearly all staff were tested at least once weekly, which provided nearly complete case detection. Second, testing for residents was not routine, random, or compulsory, but testing was relatively consistent across vaccination and previous infection statuses (range of means, 0.5 to 0.7 tests per week). Estimates of VE focused on confirmed infections and not on other important outcomes such as symptomatic infections or severe disease. The incidence of hospitalization and death in our sample was too low to support rigorous analysis of those outcomes according to the combinations of vaccine and previous infection histories analyzed, and symptom reporting was unreliable during the study period. Finally, the generalizability of our results to jails, other prisons, other high-risk populations (e.g., residents of nursing homes and health care workers), and lower-risk populations is unknown. Lastly the findings from this study suggest that, although mRNA vaccines and previous infection provide less protection against infection with the omicron variant than they did against earlier variants [more immune evasive and more transmissible], boosters continue to provide additional effectiveness, including among previously infected persons.

Fostamatinib for the Treatment of Hospitalized Adults With Coronavirus Disease 2019: A Randomized Trial

Clin Infect Dis published online August 28, 2022 article provided by Jeff Strich

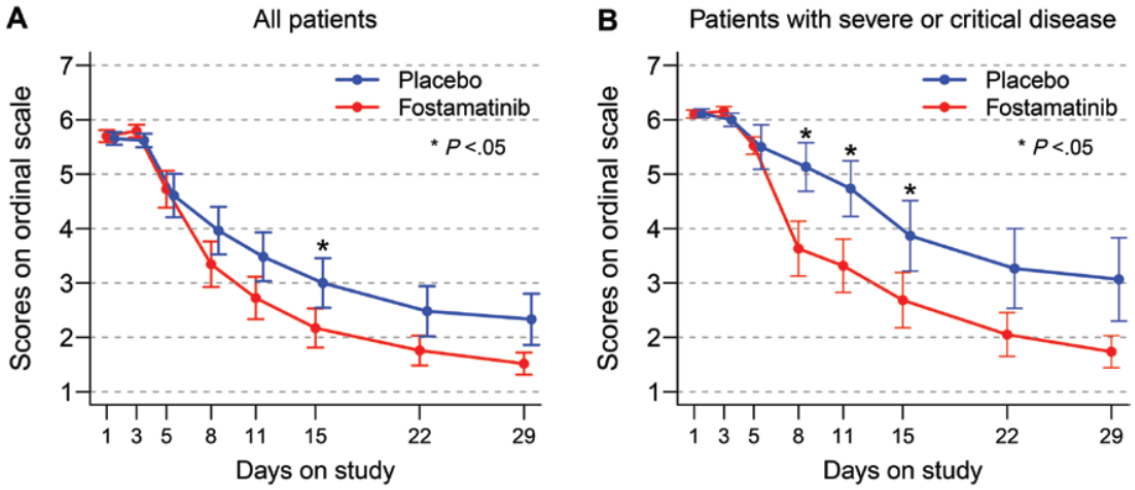
doi.org/10.1093/cid/ciab732

The underlying pathogenesis of COVID-19 is thought to be a dysregulated immune response resulting in endothelial dysfunction, a hypercoagulable state, and immunothrombosis. It is hypothesized that exuberant plasmablast and antibody responses result in more severe COVID-19, and transcriptomics have revealed that Fc receptor activation is increased in patients with COVID-19-induced acute respiratory distress syndrome (ARDS) [Res Sq 2021. doi:10.21203/rs.3.rs-141578/v1]. Spleen tyrosine kinase (SYK) is a cytoplasmic tyrosine kinase that associates primarily with immunoreceptor tyrosine-based activation motifs on Fc receptors and B-cell receptors as well as immunoreceptor tyrosine-based activation motif-like sequences on C-type lectin receptors. Fostamatinib is an oral SYK inhibitor that is FDA approved for the treatment of chronic idiopathic thrombocytopenic purpura. R406, the active metabolite of fostamatinib, inhibits both the release of proinflammatory cytokines (IL-1β, IL-6, IL-8, tumor necrosis factor, and IL-10) from macrophages and platelet-mediated thrombus formation provoked by anti-spike immune complexes (antigen/antibody complexes) predominately in an FcγRIIA-dependent manner. Further, R406 has been shown to abrogate the release of neutrophil extracellular traps (NETs) when healthy neutrophils were stimulated with plasma from

patients with COVID-19. NETs are web-like structures of citrullinated DNA, embedded with antimicrobial proteins such as neutrophil elastase and myeloperoxidase, which promote immunothrombosis and have been found in the lungs of patients who died from COVID-19 [. Blood 2020; 136:1169-79]. NETs levels have been associated with disease severity in COVID-19, and therefore agents that target NETosis are of interest as potential therapeutics to mitigate the disease. [JCI Insight 2020; 5:e138999]. In addition to decreasing inflammation and immunothrombosis, R406 has also been shown to inhibit Mucin-1, a pulmonary epithelial transmembrane protein associated with ARDS severity. Preclinical studies and awareness of the upstream role that SYK plays in disease pathogenesis provide another therapeutic approach to COVID-19 and led us to hypothesize that SYK inhibition would be therapeutically beneficial by decreasing Fc-mediated immune dysregulation and thrombosis.

To evaluate the investigators conducted a randomized, double-blind, placebo controlled, investigator-initiated trial across 2 centers: Inova Fairfax Hospital (Falls Church, VA) and the NIH Clinical Center (Bethesda, MD). The study enrolled hospitalized patients age ≥ 18 years with a laboratory confirmed SARS-CoV-2 infection within 7 days and oxygen saturation ≤ 94% on room air requiring supplemental oxygen via nasal canula, noninvasive mechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygen (5–7 on the 8-point ordinal scale). Patients treated with immunomodulators including tocilizumab within 30 days before enrollment were excluded. Eligible patients were randomized 1:1 to receive fostamatinib or placebo on day 1 in addition to standard of care (SOC). SOC was defined by each participating center and consisted primarily of remdesivir and corticosteroids. Fostamatinib or placebo was administered at a dose of 150 mg orally or via gastric tube twice daily for a total of 14 days and continued outpatient if the patient was discharged before day 14. The primary outcome was the cumulative incidence of serious adverse events (SAEs) through day 29. Additional safety endpoints included grade 3 and 4 adverse events (AEs), and proportions of the patients who developed acute renal failure, or deep vein thrombosis and pulmonary embolism. SAE and AE. Secondary efficacy endpoints, evaluated up to day 29, included 14-day and 28-day mortality; ordinal scale score at day 15 and day 29; number of days on supplemental oxygen and days hospitalized in the ICU after randomization; time to an ordinal scale score of 3 or less (defined as time to recovery [either discharge from the hospital or hospitalization for infection control reasons only], with the recovery status sustained through day 29); progression to mechanical ventilation among patients not receiving mechanical ventilation at enrollment; and changes in correlative biomarkers.

A total of 59 patients underwent randomization (30 to fostamatinib and 29 to placebo). Serious adverse events occurred in 10.5% of patients in the fostamatinib group compared with 22% in placebo (P = .2). Three deaths occurred by day 29, all receiving placebo. The mean change in ordinal score at day 15 was greater in the fostamatinib group (-3.6 ± 0.3 vs -2.6 ± 0.4, P = .035) and the median length in the intensive care unit was 3 days in the fostamatinib group vs 7 days in placebo (P = .07). Differences in clinical improvement were most evident in patients with severe or critical disease (median days on oxygen, 10 vs 28, P = .027). There were trends toward more rapid reductions in C-reactive protein, D-dimer, fibrinogen, and ferritin levels in the fostamatinib group.



Comment: For COVID-19 requiring hospitalization, the addition of fostamatinib to standard of care was safe and patients were observed to have improved clinical outcomes compared with placebo. This trial was limited by the small sample size. Because of sample size the trial was underpowered for efficacy outcomes and subgroup analysis. Although there were favorable trends in multiple secondary clinical outcomes in the fostamatinib group, these findings should be viewed with caution and need to be further assessed in a well-powered, larger randomized clinical trial.

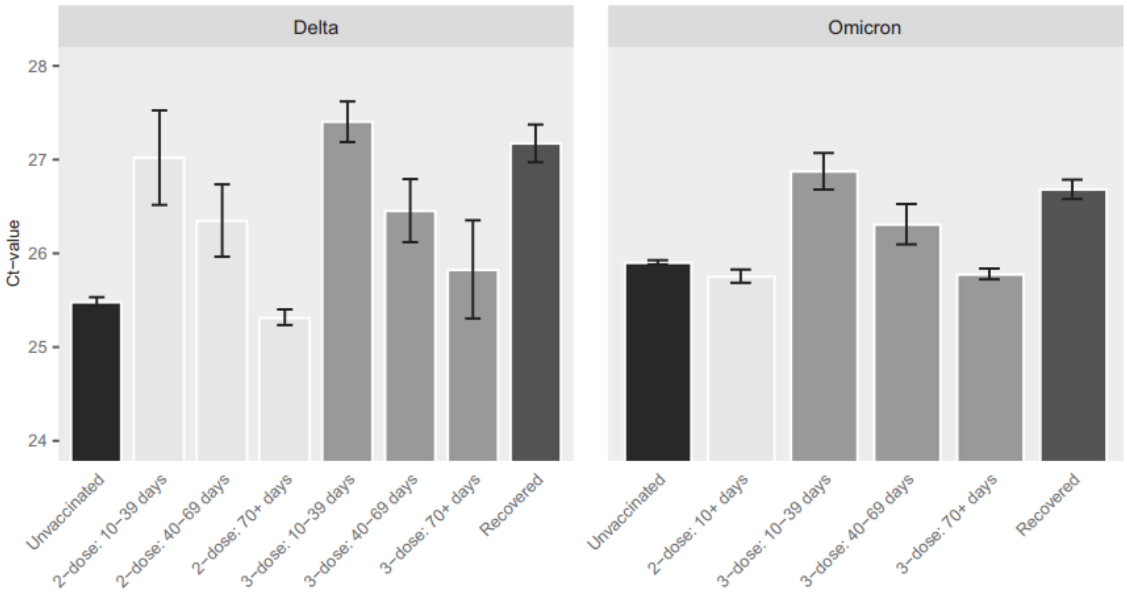
Viral load dynamics of SARS-CoV-2 Delta and Omicron variants following multiple vaccine doses and previous infection Nat Comm published online November 7, 2022

doi.org/10.1038/s41467-022-33096-0

In this retrospective study, the investigators combined the comprehensive Israeli national vaccination data with Ct data of four laboratories performing SARS-CoV-2 PCR tests. Studies on the Delta variant had shown that vaccinated individuals have higher Ct, thus considered less infective, and this effect wanes as time elapses [Nat. Med. 27, 790–792 (2021). Nat. Med. 27, 2108–2110 (2021)] They augmented these studies by examining Omicron Ct in relation to vaccination and recovery statuses, and how Ct changes with time since vaccination/infection using nationwide PCR data. Notably, the waning effect of infection-induced protection has not been thoroughly analyzed before in terms of Ct and infectivity. They then further compare Ct levels of individuals vaccinated with 2,3, or 4 doses vs. COVID-19 recovered individuals.

They analyzed Ct values dating June 15, 2021–January 29, 2022, divided into two periods of Delta and Omicron dominance. Separate analyses were conducted for the viral nucleocapsid gene (N, 315,111) and envelope gene (E, 228,125 measurements). The patterns observed for E were similar to those of N. They then performed multivariate linear regression analysis on Ct values of each variant with vaccination status, laboratory, age, sex and calendar time (7-days bins) as covariates. Vaccination status was defined as unvaccinated, 2-dose (divided to 3 bins, 10–39 days, 40–69, >70 days post-vaccination), 3-dose (divided to 3 bins, 10–39, 40–69, >70

days), 4-dose, or recovered who have not received any vaccination between the two infection events.



Comments: Viral load has been used as a surrogate for infectivity, however, infectivity is a complex process comprised of numerous pathogen- and host-related factors, which are difficult to model in both humans and animals. Nonetheless, qRT-PCR cycle threshold (Ct), has been used to investigate the infectivity-related component of vaccine effectiveness. While vaccine waning has previously been observed for viral load during the Delta wave, less is known regarding how Omicron viral load is affected by vaccination status, and whether vaccine-derived and natural infection protection are sustained. By analyzing results of more than 460,000 individuals, the investigators showed that while recent vaccination reduces Omicron viral load, its effect wanes rapidly. In contrast, a significantly slower waning rate is demonstrated for recovered COVID-19 individuals (natural infection). Thus, while the vaccine is effective in decreasing morbidity and mortality, it may have a relatively small effect on transmissibility of Omicron (as measured here by Ct) and its rapid waning call for reassessment of future booster campaigns. The combination of vaccine waning and vaccine evasion may be important drivers for potential for surges this winter.

Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19 bioRxiv posted online November 5, 2022

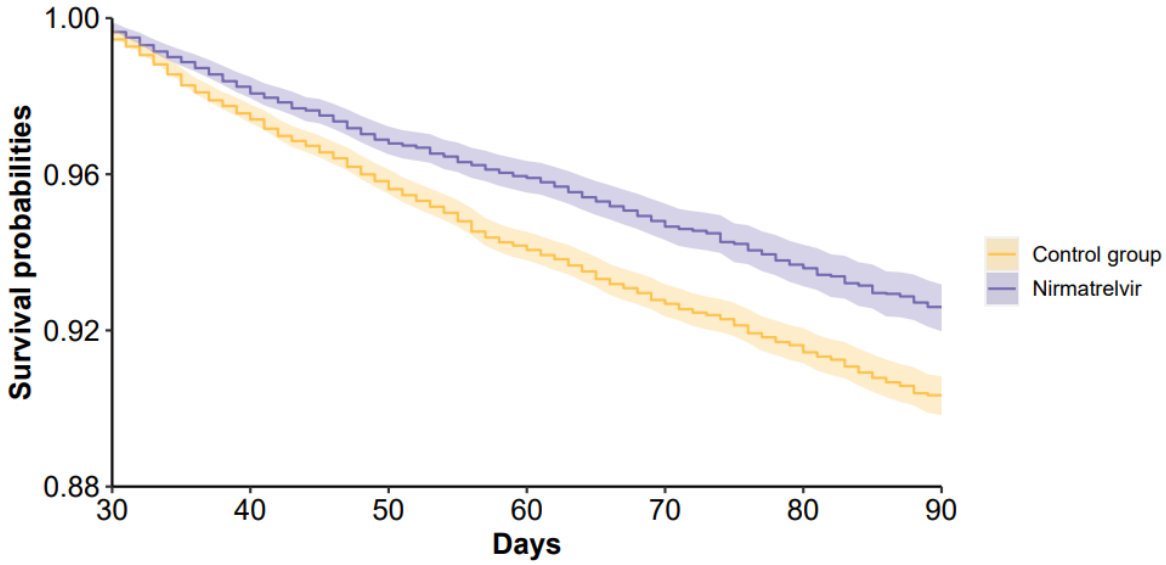
doi.org/10.1101/2022.11.03.22281783

Thea investigators set out to examine whether treatment with nirmatrelvir (Paxlovid) in the acute phase of COVID-19 is associated with reduced risk of post-acute sequelae (PASC). They used the healthcare databases of the US Department of Veterans Affairs to identify users of the

health system who were SARS-CoV-2 positive between March 1, 2022, and June 30, 2022, were not hospitalized on the day of the positive test, had at least 1 risk factor for progression to severe COVID-19 illness and survived the first 30 days after SARS-CoV-2 diagnosis. They identify those who were treated with oral nirmatrelvir within 5 days after the positive test (n=9217) and those who received no COVID-19 antiviral or antibody treatment during the acute phase of SARS-CoV-2 infection (control group, n= 47,123). Inverse probability weighted survival models were used to estimate the effect of nirmatrelvir (versus control) on a prespecified panel of 12 post-acute COVID-19 outcomes and reported as hazard ratio (HR) and absolute risk reduction (ARR) in percentage at 90 days.

Compared to the control group, treatment with nirmatrelvir was associated with reduced risk of PASC (HR 0.74 95% CI (0.69, 0.81), ARR 2.32 (1.73, 2.91)) including reduced risk of 10 of 12 post-acute sequelae in the cardiovascular system (dysrhythmia and ischemic heart disease), coagulation and hematologic disorders (deep vein thrombosis, and pulmonary embolism), fatigue, liver disease, acute kidney disease, muscle pain, neurocognitive impairment, and shortness of breath. Nirmatrelvir was also associated with reduced risk of post-acute death (HR 0.52 (0.35, 0.77), ARR 0.28 (0.14, 0.41)), and post-acute hospitalization (HR 0.70 (0.61, 0.80), ARR 1.09 (0.72, 1.46)). Nirmatrelvir was also associated with reduced risk of PASC in people who were unvaccinated, vaccinated, and boosted, and in people with primary SARS-CoV-2 infection and reinfection.

Figure 2a. Post-acute sequelae of COVID-19



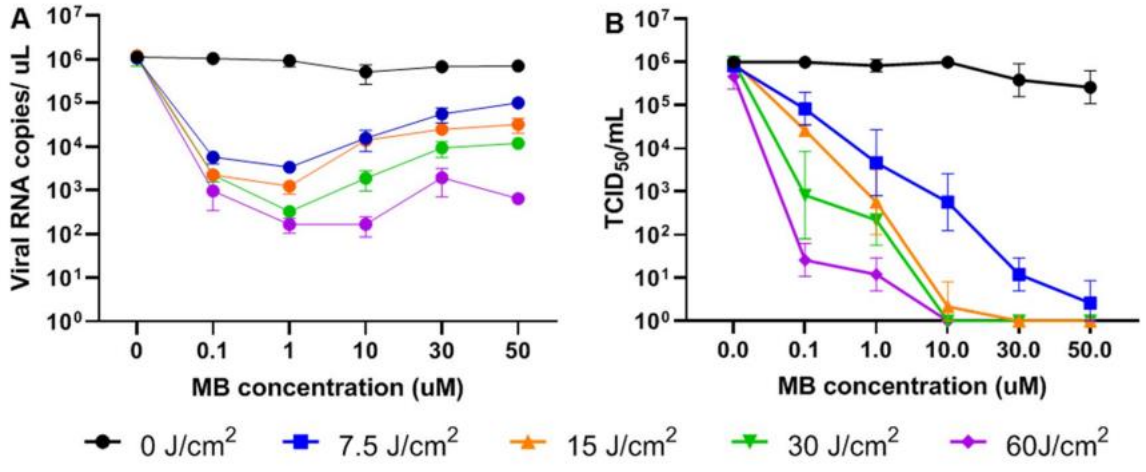
Comment: In sum, the results show that in people with SARS-CoV-2 infection who had at least 1 risk factor for progression to severe COVID-19 illness, treatment with nirmatrelvir within 5 days of a positive SARS-CoV-2 test was associated with reduced risk of PASC regardless of vaccination status and history of prior infection.

Translational feasibility and efficacy of nasal photodynamic disinfection of SARS-CoV-2 Scientific Reports 2022; 12:14438

doi.org/10.1038/s41598-022-18513-0

aPDT of the nares with methylene blue (MB) and non-thermal light has been successfully utilized to inactivate both bacterial and viral pathogens in the perioperative setting. Here, the investigators evaluated the effect of MB-aPDT to inactivate human betacoronavirus OC43 and SARS-CoV-2 in vitro and in a proof-of-principle COVID-19 clinical trial to test, in a variety of settings, the practicality, technical feasibility, and short-term efficacy of the method. Due to initial limited availability of patient-derived samples containing SARS-CoV-2 virus and limited access to biosafety-level-3 laboratory facilities, dose-ranging studies with controlled light irradiation and photosensitizer delivery were carried out using the human betacoronavirus (HCoV-OC43), a clinically relevant biosafety-level-2 coronavirus. In the human trial 42 patients enrolled in the study with a positive Covid-19 diagnosis (age 14–94 y, 20 male, 18 female, 4 no sex stated) 18 were symptomatic. The study was conducted within 6 different settings: ICU (N=1), in-patient ward (N=6), out-patient Covid clinic (N=5), in subject's car (N=17), in-patient rehabilitation hospital (N=10) or on patient's home front porch (N=3). The procedures were performed by a surgeon (N=11), a surgical resident (N=18), a ward nurse (N=4) and an ER nurse (N=7). All had received training in the aPDT procedure, including pre- and post-treatment nasal swabbing and application of the MB and light. The treatment was simple to administer in all environments and well tolerated by all patients, with no discomfort, complications or side effects reported.

aPDT yielded inactivation of up to 6-Logs in vitro, as measured by RT-qPCR and infectivity assay. From a photophysics perspective, the in vitro results suggest that the response is not dependent on the virus itself, motivating potential use of aPDT for local destruction of SARS-CoV-2 and its variants. In the clinical trial they observed variable effects on viral RNA in nasal-swab samples as assessed by RT-qPCR attributed to aPDT-induced RNA fragmentation causing falsely elevated counts. However, the viral infectivity in clinical nares swabs was reduced in 90% of samples and undetectable in 70% of samples.



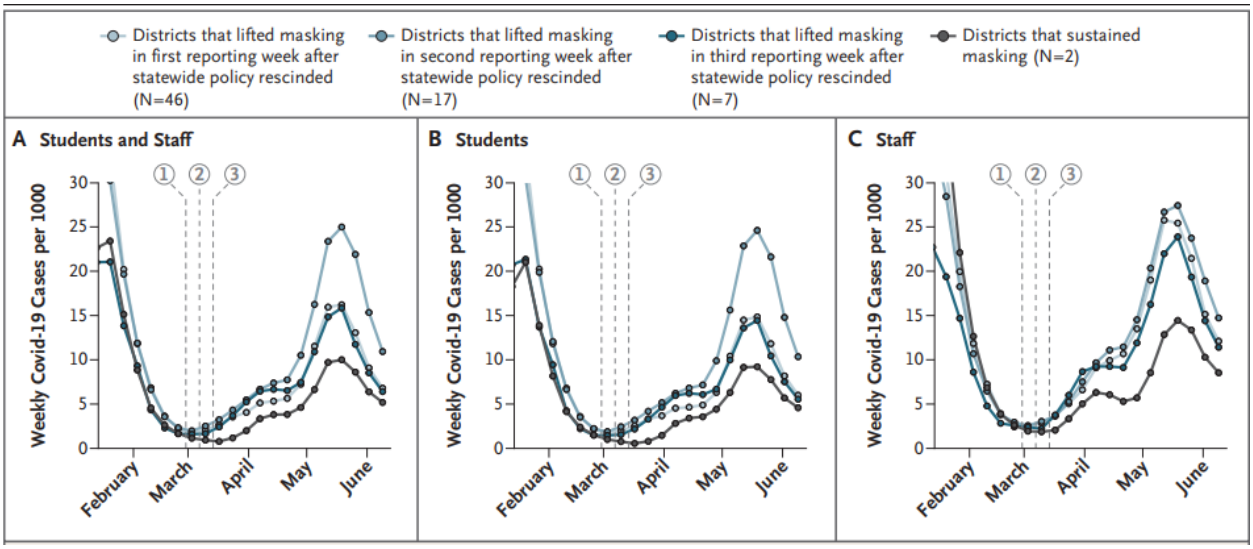
Comment: This is the first demonstration based on quantitative clinical viral infectivity measurements that MB-aPDT is a safe, easily delivered, and effective front-line technique that can reduce local SARS-CoV-2 viral load. The sample size was small. A further potential use of aPDT could be to protect acutely exposed healthcare workers. Research presented last week at the PDT-PDD Conference in France showed that a large food processing plant in Manitoba, Canada, was able to reduce the rate of COVID-19 amongst its employees following the use of aPDT. The rate of COVID-19 positive tests in the workforce fell from 6.4% to 0.5%, a reduction of over 10 times ($p<0.0001$) compared to rates in the community. The reduction in COVID-19 cases at the plant meant that food production was able to continue without disruption at a crucial time during the COVID-19 pandemic. More studies are still needed to evaluate the use of aPDT in humans.

Lifting Universal Masking in Schools — Covid-19 Incidence among Students and Staff N Engl J Med published online November 9, 2022

DOI: 10.1056/NEJMoa2211029

In February 2022, Massachusetts rescinded a statewide universal masking policy in public schools, and many Massachusetts school districts lifted masking requirements during the subsequent weeks. In the greater Boston area, only two school districts — the Boston and neighboring Chelsea districts — sustained masking requirements through June 2022. The investigators used a difference-in-differences analysis for staggered policy implementation to compare the incidence of Covid-19 among students and staff in school districts in the greater Boston area that lifted masking requirements with the incidence in districts that sustained masking requirements during the 2021–2022 school year. Characteristics of the school districts were also compared.

During the 15 weeks after the statewide masking policy was rescinded, the lifting of masking requirements was associated with an additional 44.9 cases per 1000 students and staff (95% confidence interval, 32.6 to 57.1), which corresponded to an estimated 11,901 cases and to 29.4% of the cases in all districts during that time. Districts that chose to sustain masking requirements longer tended to have school buildings that were older and in worse condition and to have more students per classroom than districts that chose to lift masking requirements earlier. In addition, these districts had higher percentages of low-income students, students with disabilities, and students who were English-language learners, as well as higher percentages of Black and Latino students and staff. The results were shown to be robust in a range of sensitivity analyses, including analyses that assessed potential differences in testing programs and analyses that adjusted for Covid-19 indicators at the community level and vaccination coverage according to age. Like much of the US, the greater Boston area has low Covid-19 vaccination coverage among children (only 53% of children 5 to 11 years of age had been fully vaccinated in Boston and Chelsea through October 2022.



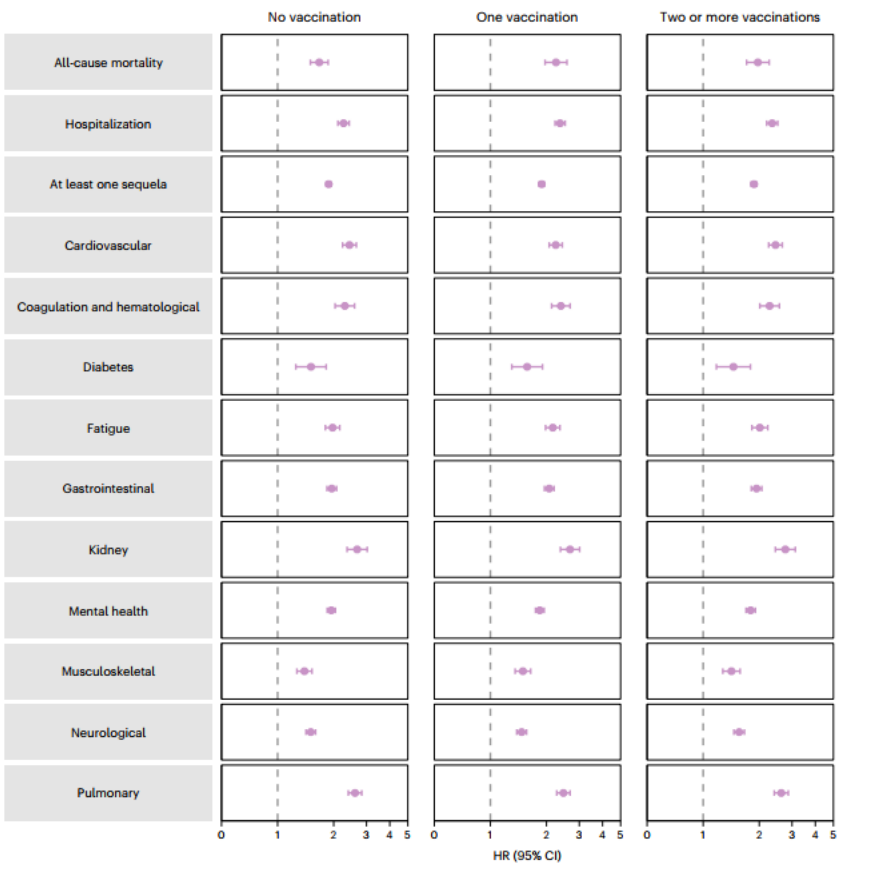
Comment: The investigators demonstrated the effect of school masking policies was greatest during the weeks when the background incidences of Covid-19 in surrounding cities and towns were highest, a finding that suggests that universal masking policies may be most effective when they are implemented just before and throughout periods of high SARS CoV-2 transmission. The study did not specify the types of masks worn by the children. This study shows that if people are wearing masks as a group, that it can reduce transmission for everyone in the population. Universal masking lowers the amount of virus exhaled into shared air, reducing the total number of cases of Covid-19 and making indoor spaces safer for populations that are vulnerable to its complications. This is in contrast to individual masking which lowers the amount of virus that a masked person inhales from shared air when others may be unmasked. Furthermore, individual masking has little effect on population-level transmission. This study was observational and not a randomized, controlled clinical trial. As such it may not be able to prove a causal relationship between mandatory masking and a lower incidence of Covid. Another limitation of this study is that they did not have data regarding Covid-19 testing in individual school districts. They went on to say: “our findings should be interpreted as the effect of universal masking policies and not as the effect of masking per se, since masks were still encouraged in most school settings. Despite this consideration, the effect of lifting masking requirements was substantial.” Returning to universal masking must be weighed against communication problems and delay in speech development especially for children with learning difficulties. Regardless, the results suggest that universal masking [prefer with high-quality masks] during periods of high transmission is an important strategy for reducing SARS-CoV-2 spread [and other respiratory viruses] and loss of in-person school days. So where do we go from here. May I suggest that universal masking should be considered if an outbreak occurs at the school or early in surges of new Covid-19 variants and throughout the year in select classrooms to protect higher-risk children and staff. [could be Covid-19, influenza etc.]. Can we leverage information from wastewater surveillance if results begin to show a significant increase in amount of virus?

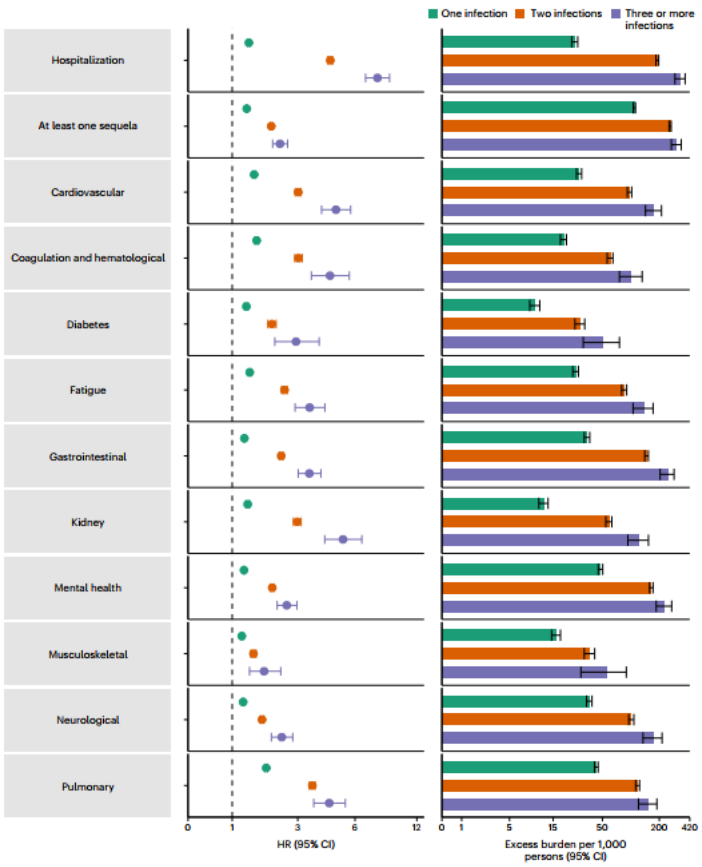
Acute and postacute sequelae associated with SARS-CoV-2 reinfection Nat Med published online November 10, 2022

doi.org/10.1038/s41591-022-02051-3

The investigators used the US Department of Veterans Affairs'(VHA) national healthcare database to build a cohort of individuals with one SARS-CoV-2 infection (*n* = 443,588), reinfection (two
or more infections, *n* = 40,947) and a noninfected control (*n* = 5,334,729). Users of the VHA with at least one positive SARS-CoV-2 test between 1 March 2020 and 6 April 2022. They used inverse probability-weighted survival models to estimate risks and 6-month burdens of death, hospitalization and incident sequelae.

Compared to no reinfection, reinfection contributed additional risks of death (hazard ratio (HR) = 2.17, 95% confidence intervals (CI) 1.93–2.45), hospitalization (HR = 3.32, 95% CI 3.13–3.51) and sequelae including pulmonary, cardiovascular, hematological, diabetes, gastrointestinal, kidney, mental health, musculoskeletal and neurological disorders. The risks were evident regardless of vaccination status. The risks were most pronounced in the acute phase but persisted in the post-acute phase at 6 months. Compared to noninfected controls, cumulative risks and burdens of repeat infection increased according to the number of infections.





Comment: As most VA studies one of the limitations included a cohort of mostly white males. The evidence shows that reinfection further increases risks of death, hospitalization and sequelae in multiple organ systems in the acute and post-acute phase. Research using EHRs may not reliably predict a casual relationship. In fact, there are studies showing that infection, reinfection, and vaccination results in boosting and diversifying the immune response that result in individuals better able to respond to newer variants. [see above] Subgroup analyses were not conducted by age, sex and race. Despite some of the limitations, reducing overall burden of death and disease due to SARS-CoV-2 will require strategies to prevent reinfection.