Volume 1, Issue 20, 2022

Infectious Diseases Watch

Memorial Day Edition

May 30, 2022

Ed Septimus, MD

General Infectious Diseases

The Effect of Macrolides on Mortality in Bacteremic Pneumococcal Pneumonia: A Retrospective, Nationwide Cohort Study, Israel, 2009-2017 Clin Infect Dis published online April 20, 2022

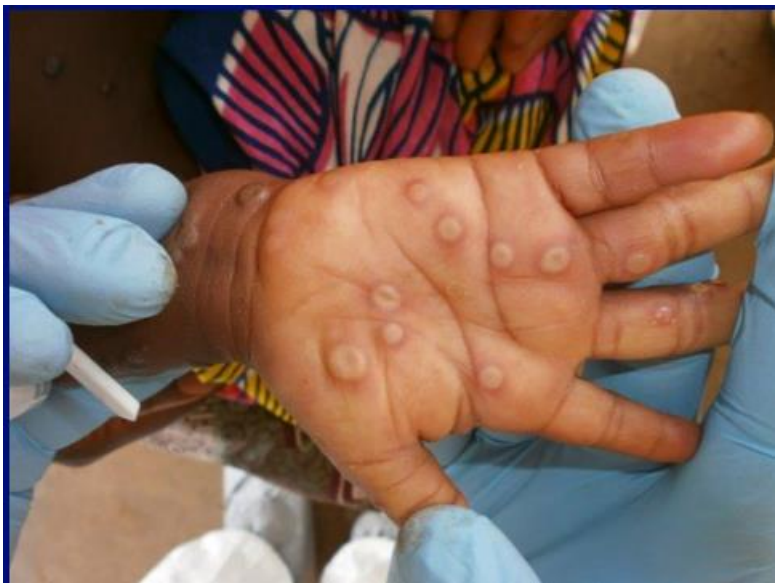
This paper reviews a historical cohort, 7/1/2009–6/30/2017, included, through active surveillance, all culture-confirmed bacteremic pneumococcal pneumonia (BPP) among adults in Israel. Logistic regression analysis was used to assess independent predictors of in-hospital mortality.

A total of 2016 patients with BPP were identified. The median age was 67.2 years (IQR 10 53.2-80.6); 55.1% were men. Lobar pneumonia was present in 1440 (71.4%), multi-lobar in 576 (28.6%). Median length of stay was 6 days (IQR 4-11). A total of 1921 cases (95.3%) received empiric antibiotics with anti-pneumococcal coverage: ceftriaxone, in 1267 (62.8%). Coverage for atypical bacteria was given to 1159 (57.5%), 64% of these, with macrolides. A total of 372 (18.5%) required mechanical ventilation and 397 (19.7%) died. Independent predictors of mortality were age (OR 1.050, 95%CI 1.039, 1.061), being at high-risk for pneumococcal disease (OR 2.090, 95%CI 1.388, 3.153), multi-lobar pneumonia (OR 2.240, 95%CI 1.659 3.024). Female sex and macrolide therapy were protective: (OR 0.708, 95%CI 0.522, 0.960; and OR 0.549, 95%CI 0.391,0.771, respectively). Either Azithromycin or roxithromycin treatment for as short as two days was protective. FQ therapy had no effect.

Comment: Empirical therapy with macrolides reduced odds for mortality by 45%. This effect was evident with azithromycin and with roxithromycin. The effect did not require a full course of therapy! FQs had no effect. The ATS/IDSA guidelines recommend a β-lactam (ampicillin plus sulbactam, cefotaxime, ceftaroline, or ceftriaxone) plus macrolide (azithromycin or clarithromycin) or monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) for the management of inpatients with nonsevere CAP. For severe CAP, they recommend that combination therapy with a β-lactam plus a macrolide or a β-lactam plus a respiratory FQ should be the treatment of choice for patients with severe CAP. (Am J Respir Crit Care Med 2019; 200: e45–e67) Several large observational studies of hospitalized patients with severe disease found decreased mortality in patients receiving β-lactam and a macrolide versus either β-lactam alone or respiratory FQ. This effect was described in patients with a defined final diagnosis of BPP, even in the setting of macrolide resistance. (Respir Med 2021; 177: 106307) Macrolide resistance is now >20% in most areas. This suggests an anti-inflammatory effect of the macrolides, rather than their antibacterial properties, an effect not shared with FQ. (Lancet Respir Med 2020; 8: 619-30)

Due to the retrospective nature of the cohort, they do not have data on the severity of patients on admission. Treatment was at the discretion of the treating physician, exposing the data to bias by indication, where treatment is given according to patient severity characteristics, which might influence outcomes.

Monkeypox



The monkeypox virus is a member of the family *Poxviridae* and the genus *Orthopoxvirus*, which includes variola (the virus that causes smallpox), vaccinia (which is used in the smallpox vaccine), and cowpox virus. Monkeypox is a zoonotic infection endemic to several Central and West African countries.

As of May 25, cases have been confirmed or are under investigation in the US (Massachusetts, New York, Florida, Utah), UK, Spain, Portugal, France, Canada, Sweden, and Italy. Not all the individuals infected traveled to West or Central Africa, where the disease is more common and is mainly transmitted to people though contact with animals. (See below) While this has given public health officials some concern, there is no proof yet that the virus has changed to become more transmissible. Much of the transmission so far has occurred among men who have sex with men, but that certainly doesn't mean it's limited to that community.

People typically catch monkeypox by coming into close contact with infected animals. That can be through an animal bite, scratch, bodily fluids, feces or by consuming meat that isn't properly cooked.

Generally, monkeypox is not easily spread between humans. According to the CDC, human-to-human transmission is thought to occur via respiratory secretions, by direct contact with body fluids or lesions, and indirect contact with lesion material through contaminated clothing or bedding. While the reservoir host of monkeypox is still unknown, it's thought that African rodents play a role in transmission.

The typical incubation period for monkeypox is 7 to 14 days but can range from 5 to 21 days. Among the first symptoms to appear are flu-like symptoms, including fever, aches, and fatigue. Monkeypox infection also involves enlargement of the lymph nodes. Then, typically 1 to 3 days later -- though sometimes longer -- a rash develops. It often starts on the face before spreading

to other parts of the body. The typical monkeypox lesions involve the following: deep-seated and well-circumscribed lesions, often with central umbilication; and lesion progression through specific sequential stages—macules, papules, vesicles, pustules, and scabs Illness typically lasts about 2 to 4 weeks. (See picture above)

While the Congo Basin strain of monkeypox is thought to have a fatality rate of 10%, the West African strain -- which was confirmed in the UK outbreak -- has a fatality rate of about 1%. To date, all cases confirmed by PCR testing are infected with the West African clade of monkeypox, which historically is less virulent than the Congo Basin (Central African) clade

In 2003, there were 47 confirmed and probable cases of monkeypox in people in the Midwest. All had become ill after encountering pet prairie dogs that had been infected after being housed near animals imported from Ghana. There were also two travel-related cases in the U.S. in July and November 2021.

According to the CDC, there's no proven treatment for monkeypox specifically, but the smallpox vaccine, antivirals, and vaccinia immune globulin can be used. While there are no proven antivirals specific to monkeypox, cidofovir and tecovirimat may be used. Vaccinia immune globulin is also available. Jynneos is a live attenuated vaccine licensed by the FDA in 2019 and is indicated for prevention of monkeypox. ACAM 2000 licensed in 2007 for prevention of smallpox but has EUA for prevention of monkeypox. (See below)

	ACAM2000	JYNNEOS
Vaccine virus	Replication-competent vaccinia virus	Replication-deficient Modified vaccinia Ankara
"Take"	"Take" occurs	No "take" after vaccination
Inadvertent inoculation and autoinoculation	Risk exists	No risk
Serious adverse event	Risk exists	Fewer expected
Cardiac adverse events	Myopericarditis in 5.7 per 1,000 primary vaccinees	Risk believed to be lower than that for ACAM2000
Effectiveness	FDA assessed by comparing immunologic response and "take" rates to Dryvax*	FDA assessed by comparing immunologic response to ACAM2000 & animal studies
Administration	Percutaneously by multiple puncture technique in single dose	Subcutaneously in 2 doses, 28 days apart

Comment: The good news is that there is no evidence yet to suggest that the monkeypox virus has evolved or become more infectious. DNA viruses like monkeypox are generally much more stable and evolve extremely slowly compared to RNA viruses. Research has shown that incidences of humans contracting viruses from contact with animals —" zoonotic spillovers" — have become more common in recent decades. Increasing urbanization and deforestation means that humans and wild animals are coming into contact more often. At present there is no reason to panic.

Global report on infection prevention and control WHO May 5, 2022

A new report from the WHO shows that where good hand hygiene and other evidence-based strategies practices are followed, 70% of HAIs can be prevented. According to the report out of every 100 patients in acute-hospitals, seven patients in high-income countries and 15 patients in low- and middle-income countries will acquire at least one HAI during their hospital stay. On average, 1 in every 10 affected patients will die from their HAI. People in intensive care and newborns are particularly at risk. And the report reveals that approximately one in four hospital-treated sepsis cases and almost half of all cases of sepsis with organ dysfunction treated in adult intensive-care units are health care-associated. The report reveals that high-income countries are more likely to be progressing their IPC work and are eight times more likely to have a more advanced IPC implementation status than low-income countries.

The report notes that HAIs are among the most common adverse events experienced in healthcare, and many HAIs are caused by multidrug-resistant organisms. The report includes these details:

- It is predicted that of every 100 patients in acute-care hospitals, an average of seven patients in high-income countries and 15 in low- and middle-income countries will acquire at least one HAI while hospitalized: as many as 30% of patients in intensive care encounter HAIs.
- Of all cases of hospital-treated sepsis, 23.6% were linked to healthcare; 48.7% of all sepsis cases involving organ dysfunction treated in adult intensive care were acquired in the hospital; 24.4% of patients and 52.3% of those in intensive care who were affected by healthcare-associated sepsis died.
- The European Centre for Disease Prevention and Control calculated those 4.5 million episodes of HAIs occurred each year among patients in acute care hospitals in countries of the European Union and the European Economic Area.
- CDC estimated that on any day, 1 in 31 hospital patients and 1 in 43 nursing home residents has an HAI.
- Up to 41% of hospitalized patients with confirmed COVID-19 were infected with SARS-CoV-2 in healthcare settings.

	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%

Infect Control Hosp Epidemiol published online September 2, 2021

Comment: Hospitals across the world, including the US saw increased rates of HAIs during the COVID-19 pandemic**.** Now that we have a handle on Covid-19, we need to get back to basics. The Compendium is being updated and 2 sections have been published: CLABSI and VAP/non-VAP HAP.

Influenza Update

The number of flu patients admitted to the hospital increased slightly for the week ending May 14, the CDC's latest FluView report shows. Overall, flu positivity levels remain unseasonably high for May, with some states reporting increases. Almost all H3N2.

Eight CDC updates:

1. Of all specimens tested in a clinical lab, 7 percent were positive for the flu for the week ending May 14, down from 8.6 percent the week prior.

2. For the week ending May 14, 3,153 lab-confirmed flu cases were admitted to a hospital, up slightly from 3,071 the week before.

3. No state reported very high flu activity. New Mexico reported high flu activity, down from the very high activity it had reported for three consecutive weeks before. Florida and Puerto Rico also reported high levels of flu activity. Colorado, New York, Massachusetts, Maine, New Jersey, Rhode Island and the District of Columbia reported moderate activity. Six states — Washington, Virginia, Nevada, South Carolina, Maryland and Connecticut — and New York City reported low flu activity. Remaining states reported minimal activity. Oklahoma reported insufficient data.

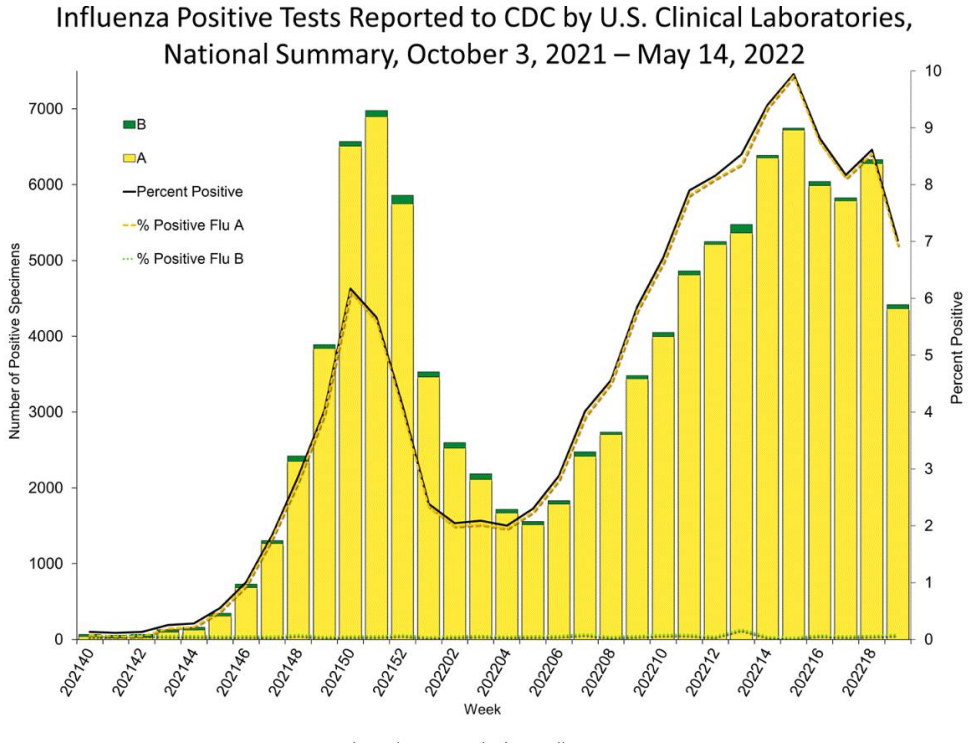
4. No pediatric flu deaths were reported for the week ending May 14. There have been 24 pediatric flu deaths so far this season.

5. The percentage of visits to an outpatient provider for respiratory illness was 2.4 percent for the week ending May 14, about the same as the week before. This is below the national baseline of 2.5 percent.

6. Nationwide, 0.7 percent of long-term care facilities reported more than one flu-positive test among residents, about the same as the week prior.

7. The national flu, pneumonia and/or COVID-19 mortality rate is 7.5 percent, which exceeds the epidemic threshold of 6.5 percent for the week ending May 14. Among 1,409 deaths reported for the week, 592 had COVID-19 listed as an underlying or contributing case of death, and 27 listed the flu. This indicates the current death rate for pneumonia, influenza and COVID-19 is primarily due to COVID-19, the CDC said.

8. The CDC estimates there have been at least 6.7 million flu illnesses, 69,000 hospitalizations and 4,200 flu-related deaths so far this season.



Comment: This report highlights that SARS-CoV-2 is not the only circulating respiratory virus. The usual pattern of respiratory viruses has been upset by Covid-19. If you remember last year, RSV surged during the summer! Bottom line when you see increased respiratory infections, think more broadly than just Covid-19 and if testing for Covid-19 is negative consider doing a viral respiratory panel to define the epidemiology in your community.

COVID-19

VII: A status report on the pandemic

We are now seeing increasing cases due to BA.2.12.1. It has a mutation in the spike protein which makes it better able to reinfect individuals who have recovered from previous infections — including BA.1 — and which is also shared by BA.4 and BA.5, which are surging in South Africa. We are also seeing more transmission and more cases in schools now than we were with BA.1. This is in large part why we are seeing increased cases, but nowhere near what we saw in January, even accounting for the fact that we know we are undercounting cases in part due to home rapid tests which are not being reported. There is no indication yet that BA.2.12.1, causes more severe disease than earlier forms. The subvariant now account for almost 60% of all new US cases, according to estimates by the CDC for the week ending May 21.

Are we in the post-pandemic phase?

Many have said we are done with the virus, but unfortunately the virus is not done with us. I think we are going through a transition, and we are heading in right direction, but I am not sure we are there yet. For the moment I think the country is in a relatively good place in terms of severe disease and deaths. We will continue to see increase cases at least for the next several weeks. I think the level of community immunity will hopefully blunt the current wave. What will happen this fall and winter is unclear and will depend on immunity/vaccination, human behavior, and emergence of new variants. Regardless I think we will continue to see "waves" due to complacency, diminishing immunity, and new variants, but hopefully severe disease and deaths will be kept in check.

Masks

How do you promote the use of masks without mandates? First, we need to take the politics out of the equation. We have learned that politicizing such an initiative will not work. I think we can increase mask use without mandates by making high quality masks widely available in any public setting in which people spend time together indoors (e.g., concerts, sporting events, religious services etc.), especially during surges or in settings with poor ventilation. Currently I recommend at minimum wearing a high-quality mask indoors in public indoor setting including travel, if around high-risk individuals, if you are in a high-risk category, if indoors where the ventilation is poor and during surges.

Testing

Rapid test kits should be distributed anywhere people work or congregate indoors or at home. These kits require no medical personnel to administer. For example, if you are going to events where high-risk people are present, traveling in an airplane, or going to a large gathering, consider doing a rapid test beforehand. If you have symptoms stay home.

Vaccination

Vaccine mandates appear to have become increasingly unpopular, but deaths from Covid among high-risk groups like the elderly can be prevented now that vaccines are available. Cities should consider bringing back vaccine requirements for certain businesses and indoor events. It is true that infections can occur even if vaccinated but infections tend to be mild and in most studies' infection clear faster. As a policy, this does not require anyone to be vaccinated, but

they place limits on where unvaccinated people can attend especially in indoor settings. I realize the logistics can be challenging, but this is a public safety issue. I also accept this recommendation may not be popular. We should continue to encourage everyone to be “up to date” on their Covid-19 vaccination. In the next month, I predict the FDA will approve vaccination for children 6 month-4 years of age. About 19 million children are under the age of 5 and the only Americans not yet eligible for vaccination against Covid-19. (See below)

Air Quality

In public health, the most effective interventions are those that do not require individuals to change their behavior. We need a global effort to improve indoor air quality and reduce Covid-19 transmission (and other respiratory pathogens) through ventilation, filtration, and air disinfection. Businesses should be encouraged to improve their HVAC systems to increase the number of air exchanges and upgrade to a medical grade filter. To accomplish this, we should consider comprehensive legislation that requires facilities to adhere to stricter indoor air quality standards.

Conclusion

Overall, we are in a much better place than a year ago. We have high community immunity due to vaccinations and/or natural infection and have effective antivirals such as Paxlovid. I do believe the worse is behind us, but this is not yet the time to be complacent. The commonsense recommendations I have outlined above should go a long way in helping us get back to our “new normal” if we are all willing to do our part.

COVID-19 News

Fluvoxamine

The FDA rejected an emergency use authorization (EUA) application for the use of the selective serotonin reuptake inhibitor fluvoxamine to treat COVID-19 on Monday.

In a brief summary of their decision, attached to their detailed analysis of the evidence for the rejection, the agency noted that "the data are insufficient to conclude that fluvoxamine may be effective in the treatment of nonhospitalized patients with COVID-19 to prevent progression to severe disease and/or hospitalization."

According to the FDA, the fluvoxamine trials included in the EUA application had shortcomings. The double-blind randomized controlled TOGETHER trial measured a composite endpoint of more than 6 hours of observation in a COVID emergency setting or transfer to a tertiary hospital due to COVID by day 28, which they deemed less "clinically meaningful" than other outcomes, such as a reduction in deaths.

STOP COVID 2 and COVID-OUT were both "terminated early for futility."(see comments below) The FDA also noted that the trials included in the application were conducted at different times during the pandemic and among different populations. The agency further stated that the mechanism by which fluvoxamine works "has not yet been well characterized" and the optimal dosing regimen is unclear.

Comment: I understand the FDA’s action, but I am still disappointed. The FDA seems to be using an inconsistent definition of "hospitalization" to evaluate brand-name versus generic drugs. For example, while the FDA used COVID-hospitalizations and deaths by day 28 as the "regulatory endpoint" for EUAs, hospitalization was defined as more than 24 hours of acute care

for molnupiravir and ritonavir/nirmatrelvir (Paxlovid). Molnupiravir had an equally modest effect as fluvoxamine and was still authorized for emergency use.

Moreover, because so many more people are now vaccinated and boosted, using hospitalizations and deaths as a primary endpoint may be unrealistic. A medication is beneficial for many reasons, including shortening duration of illness or preventing progression to severe COVID-19. In addition, the STOP COVID 2 trial wasn't stopped because fluvoxamine wasn't effective, but because investigators were having trouble recruiting enough participants with the funding available. Lastly, the need for fluvoxamine is now not as critical due to wider availability of antivirals, but for patients who cannot take Paxlovid, there still needs to be other options.

CDC Update Covid-19 guidance for domestic travel

The CDC has updated its coronavirus guidance for domestic travel, urging travelers to take a test close to departure regardless of vaccination status. The agency said on its website that anyone traveling within the US should think about “getting tested as close to the time of departure as possible,” no more than three days ahead of a trip. The agency previously only recommended testing before domestic travel for those not up to date on their COVID-19 vaccinations. The CDC considers someone up to date if they have received all doses in their primary series and one booster shot once they are eligible.

Comment: The CDC also has a preflight testing rule in place for international travel to the US, requiring that air travelers 2 years and older show a negative coronavirus test result from no more than one day before boarding a flight, or proof of recovery from the disease in the previous 90 days. Foreign citizens must also show proof of vaccination.

Pfizer Vaccine for Young Children

In a news release, Pfizer said the three-dose regimen had been 80 percent effective in preventing symptomatic infection in a subset of the 1,678 trial participants, who were 6 months through 4 years old. About 19 million children are under the age of 5 and the only Americans not yet eligible for vaccination against SARS-CoV-2. In this study, children 6 months to 5 years old received a 3-microgram dose of vaccine. The third dose was given two months after the primary series. The number of children who became ill was too small to make a definitive statement on efficacy. Only 10 participants became ill with Covid after those in the vaccination group were given the third dose. The clinical trial’s protocol specified that analysis of vaccine efficacy required at least 21 Covid cases. There were no safety concerns.

By comparison, individuals 12 years and older receive a primary series of two 30-microgram doses. Children ages 5 to 11 receive two 10-microgram doses and are eligible for a booster of the same dose.

Comment: The FDA has scheduled meetings of their outside advisors for June 14th and 15th to discuss data from both Pfizer and Moderna in young children. Moderna is proposing a two-dose regimen for children younger than 6, using a dose one- quarter the strength of its adult dose. Moderna said its vaccine appeared to be 51 percent effective against symptomatic infection among children younger than 2, and 37 percent effective among those 2 to 5 The company has said it anticipates that a third dose will be necessary as a booster shot.

COVID-19 Rebound After Paxlovid Treatment CDC HAN

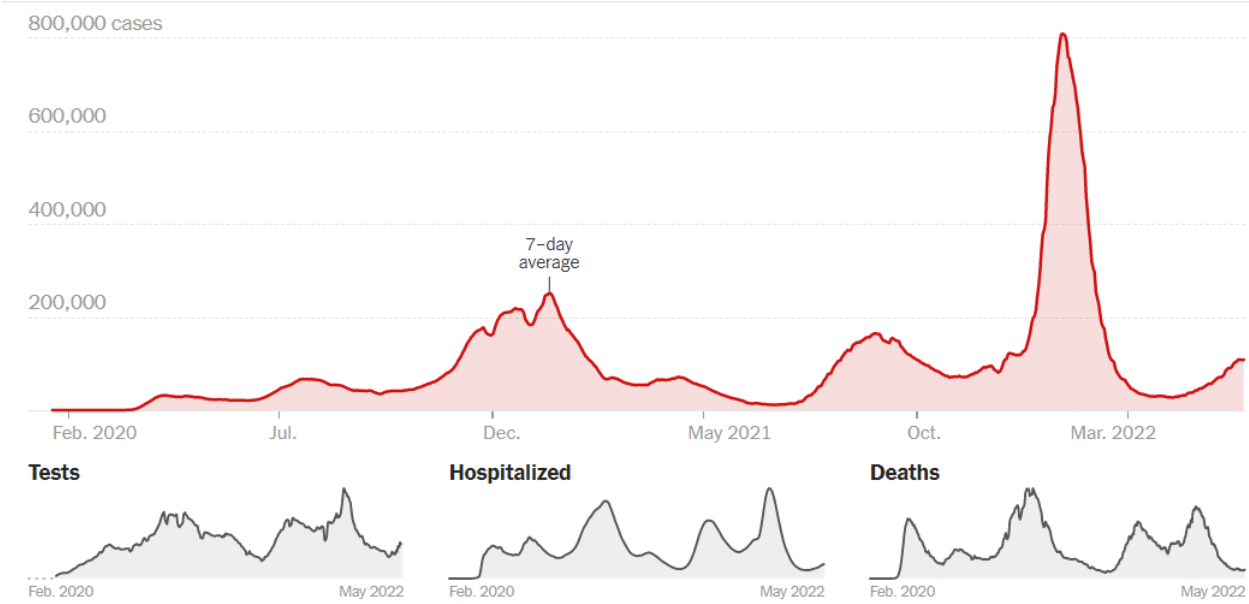
CDC issued a Health Alert Network (HAN) Health Advisory to update healthcare providers, public health departments, and the public on the potential for recurrence of COVID-19 or "COVID-19 rebound**."** Paxlovid continues to be recommended for early-stage treatment of mild to moderate COVID-19 among persons at high risk for progression to severe disease**.** Paxlovid treatment helps prevent hospitalization and death due to COVID-19. COVID-19 rebound has been reported to occur between 2 and 8 days after initial recovery and is characterized by a recurrence of COVID-19 symptoms or a new positive viral test after having tested negative. A brief return of symptoms may be part of the natural history of SARS-CoV-2 **in**fection in some persons, independent of treatment with Paxlovid and regardless of vaccination status**.** Limited information currently available from case reports suggests that persons treated with Paxlovid who experience COVID-19 rebound have had mild illness; there are no reports of severe disease. There is currently no evidence that additional treatment is needed with Paxlovid or other anti-SARS-CoV-2 therapies in cases where COVID-19 rebound is suspected. Regardless of whether the patient has been treated with an antiviral agent, risk of transmission during COVID-19 rebound can be managed by following CDC's guidance on isolation, including taking other precautions such as masking.

Recommendations for Healthcare Providers**:** For patients with COVID-19 rebound

- There is currently no evidence that additional treatment for COVID-19 is needed for COVID-19 rebound. Based on data available at this time, patient monitoring continues to be the most appropriate management for patients with recurrence of symptoms after completion of a treatment course of Paxlovid.
- Advise people with COVID-19 rebound to follow CDC's guidance on isolation and take precautions to prevent further transmission. Patients should re-isolate for at least 5 days. Per CDC guidance, they can end their re-isolation period after 5 full days if fever has resolved for 24 hours (without the use of fever-reducing medication) and symptoms are improving. The patient should wear a mask for a total of 10 days after rebound symptoms started.
- Consider clinical evaluation of patients who have COVID-19 rebound and symptoms that persist or worsen.
- Healthcare providers are encouraged to report cases of COVID-19 rebound to Pfizer after Paxlovid treatment using the following online tool: Pfizer Safety Reportingexternal icon and to FDA MedWatch. Complete and submit a MedWatch formexternal icon, or complete and submit FDA Form 3500 (health professional) by fax (1-800-FDA-0178). Call 1-800-FDA-1088 for questions.

Comment: This was reported in ID Watch several weeks back. The HAN guidance is welcomed as more and more patients will receive Paxlovid as supply has improved and cases have risen in many areas of the country.

COVID-19 by the Numbers



	DAILY AVG. ON MAY 24	14-DAY CHANGE	TOTAL REPORTED
Cases	108,082	+40%	83,457,379
Tests	984,857	+39%	—
Hospitalized	25,383	+30%	—
In I.C.U.s	2,704	+25%	—
Deaths	331	-10%	1,001,375

Comment: Cases are rising in most states. Hospitalizations are also increasing, though they remain well below the peak levels seen during the winter. About 25,000 people with the coronavirus are hospitalized in the United States, compared to nearly 160,000 in late January, when the initial Omicron surge was at its worst. It is still unclear what percentage of admissions are for Covid-19 versus with Covid-19. Deaths continue to decrease.

COVID-19 Journal Review

Imprinted antibody responses against SARS-CoV-2 Omicron sublineages posted May 10, 2022 bioRxiv

doi.org/10.1101/2022.05.08.491108

Omicron breakthrough infection drives cross-variant neutralization and memory B cell formation posted April 1, 2022 bioRxiv

doi.org/10.1101/2022.04.01.486695

In the first article, the University of Washington, working with Vir Biotechnology of San Francisco, looked at blood samples of vaccinated people who had breakthrough cases of Delta or Omicron and compared the samples with three other groups: people who caught COVID and were later vaccinated, vaccinated people who were never infected, and people who were infected and never vaccinated.

The vaccinated people who had a breakthrough case of Omicron produced antibodies that helped protect against coronavirus variants, whereas unvaccinated people who caught Omicron didn't produce as many antibodies.

In the second study BioNTech SE, found that people who'd been double and triple vaccinated and then became infected with Omicron had a better B-cell response than people who'd gotten a booster shot but had not been naturally infected.

Comment: The University of Washington investigators also came up with similar findings about B-cells. These studies support what I have been advocating, that we should think about breakthrough infections as essentially equivalent to another dose of vaccine. I wish the CDC would change their guidance to include natural infection.

Trajectory of long covid symptoms after covid-19 vaccination: community based cohort study BMJ 2022;377: e069676

doi.org/10.1136/ bmj-2021-069676

Investigators examined data on 28,356 adults ages 18 to 69 who participated in the COVID-19 Infection Survey and who received at least one dose of adenovirus vector or mRNA vaccine after testing positive for SARS-CoV-2.

Participants' mean age was 46, 56% were women, and 89% were white. Median follow-up was 141 days from the first vaccine dose and 67 days from the second dose. About a quarter of participants reported long COVID symptoms at least once during the follow-up period, the authors said. They noted that 84% of participants were "double vaccinated" by September 2021.

Approximately 17% of participants reported "limitation of activities" at least once during the follow-up period. One dose of vaccine was associated with an initial 12.3% decrease (95% CI -19.5 to -4.5, *P*=0.003) in the odds of activity limiting long COVID, and a second dose was associated with an initial 9.1% decrease (95% CI -15.6 to -2.1, *P*=0.01), followed by a 0.5% decrease per week until the end of follow-up. There was no significant difference in long COVID

trajectories between those who received the mRNA vaccine and those who received the adenovirus vector vaccine.

Comment: The results suggest that vaccination of people previously infected may be associated with a reduction in the burden of long Covid on population health. Limitations to the study included its observational design, potential unmeasured confounders, and the fact that a change in symptoms following vaccination may simply have been due to the relapsing and remitting symptoms of long Covid-19 versus a causal effect of the vaccine..

The authors recommended further research to understand this in the context of the Omicron variant, as well as "the biological mechanisms underpinning any improvements in symptoms after vaccination, which may contribute to the development of therapeutics for long COVID."

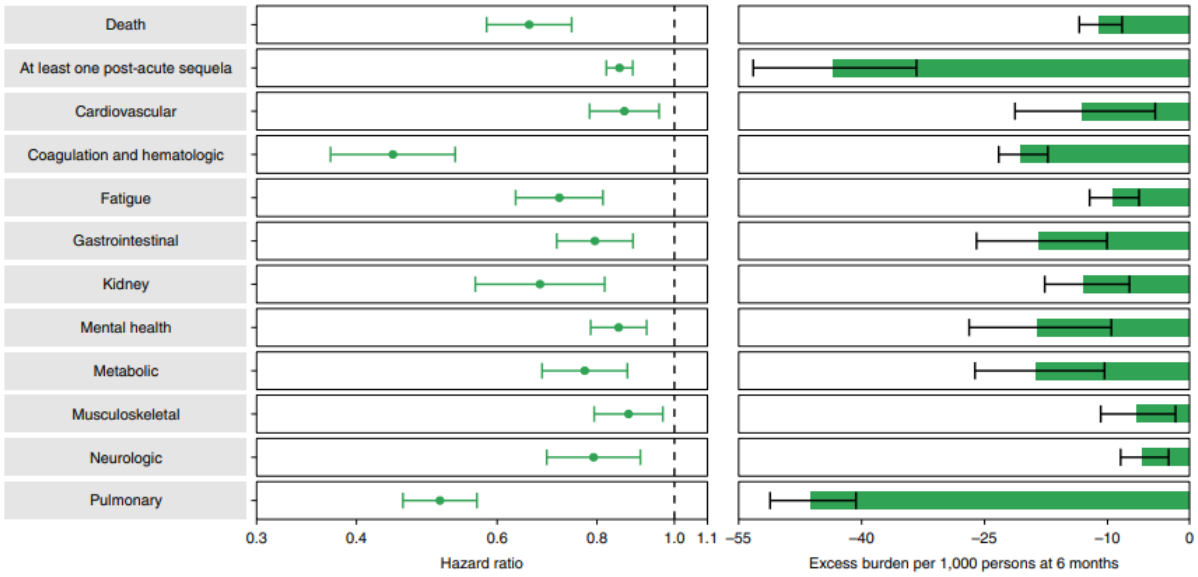
Long COVID after breakthrough SARS-CoV-2 infection Nat Med published online May 25, 2022

doi.org/10.1038/ s41591-022-01840-0.

This is part of a series of studies by the Department of Veterans Affairs on the impact of SARS-CoV-2 and was based on 33,940 people who experienced breakthrough infections (BTI) after vaccination. In this study, they used the US Department of Veterans Affairs national healthcare databases to build a cohort of 33,940 individuals with BTI and several controls of people without evidence of SARS-CoV-2 infection, including contemporary (n= 4,983,491), historical (n= 5,785,273) and vaccinated (n= 2,566,369) controls.

At 6 months after infection, they show that, beyond the first 30 days of illness, compared to contemporary controls, people with BTI exhibited a higher risk of death (hazard ratio (HR) = 1.75, 95% confidence interval (CI): 1.59, 1.93) and incident post-acute sequelae (HR = 1.50, 95% CI: 1.46, 1.54), including cardiovascular, coagulation and hematologic, gastrointestinal, kidney, mental health, metabolic, musculoskeletal and neurologic disorders.

Compared to people with SARS-CoV-2 infection who were not previously vaccinated (n= 113,474), people with BTI exhibited lower risks of death (HR = 0.66, 95% CI: 0.58, 0.74) and incident post-acute sequelae (HR = 0.85, 95% CI: 0.82, 0.89).



Risk and 6-month excess burden of post-acute sequelae in people with BTI compared to those with SARS-CoV-2 infection without prior vaccination

Comment: Six months after their initial diagnosis of Covid-19, people in the study who were vaccinated had only a slightly reduced risk of getting long Covid — 15 percent overall. The greatest benefit appeared to be in reducing blood clotting and lung complications. But there was no difference between the vaccinated and unvaccinated when it came to longer-term risks of neurological issues, gastrointestinal symptoms, kidney failure and other conditions.

The VA study also had no way to tell how different variants may change the risk of long Covid. These breakthrough infections, for example, took place at a time when alpha, delta and prior variants were at high levels in the United States. It does not cover the period when the omicron variant and its subvariants began circulating in late 2021.

Severity and Incidence of Multisystem Inflammatory Syndrome in Children During 3 SARS-CoV-2 Pandemic Waves in Israel JAMA published online May 19, 2022

doi:10.1001/jama.2022.8025

Investigators conducted a prospective study of all pediatric MIS-C patients at 12 Israeli hospitals during the same 16-week period in the Alpha (Dec 20, 2020, to Apr 10, 2021), Delta (Jul 18 to Nov 13, 2021), and Omicron (Nov 21, 2021, to Mar 12, 2022) pandemic waves. Participating hospitals account for roughly 70% of pediatric intensive care unit (ICU) admissions in Israel.

Of the 171 MIS-C patients, 59 (34.5%) were diagnosed during the Alpha wave, while 79 (46.2%) were identified during Delta, and 33 (19.3%) amid Omicron. Median patient age was 8 years, and 55% were boys.

Five of 79 patients (6.3%) in the Delta wave and 5 of 33 (15.1%) during Omicron had received a second COVID-19 vaccine dose at least 2 weeks before hospitalization. (Vaccination wasn't widely available in the Alpha wave.) No vaccinated patients required ICU care or treatment with vasopressors to raise their blood pressure.

Cardiac outcomes were better during the Omicron wave, and there were fewer ICU admissions (7 [21.2%]) than during Delta (39 [49.4%]) and Alpha (34 [57.6%]). Median hospital stay was also 2 days shorter amid Omicron than in previous waves.

Fewer patients required vasopressors during the Omicron surge (6.0%) than in Alpha (22%) and Delta (17.7%). Likewise, no patients needed mechanical ventilation amid Omicron, versus 8.5% in the Alpha period and 8.9% in Delta. One patient died in the Delta era. Nationwide, 188,800 pediatric patients were diagnosed as having COVID-19, and 103 had MIS-C during the Alpha wave, while 233,585 had COVID-19 and 115 had MIS-C amid Delta, and 945,779 and 36 had COVID-19 and MIS-C, respectively, during Omicron. The incidence of MIS-C per 100,000 children was 54.5 during the Alpha wave, 49.2 amid Delta, and only 3.8 in the Omicron era. Compared with the Omicron period, the incidence of MIS-C was 14.3 times higher amid Alpha and 12.9 times higher during Delta.

Pandemic wave data[a]	Alpha	Delta	Omicron	Total
MIS-C cases, No. (%)[b]	103 (40.5)	115 (45.3)	36 (14.2)	254
SARS-CoV-2 infections in persons younger than 18 y, No.[c]	188 800	233 585	946 779	1 369 164
MIS-C incidence rate[d]	54.5	49.2	3.8	
MIS-C incidence rate ratio (95% CI)[e]	14.34 (9.81-20.96)	12.94 (8.90-18.81)	1 [Reference]	

Comment: A 2022 study from South Africa on the Omicron wave reported no cases of MIS-C, a finding that corroborates these results. This study had a small sample size and single-country data. Nonetheless the incidence rate of MIS-C during the Omicron wave was lower than during the Delta and Alpha waves.

A Longitudinal Study of COVID-19 Sequelae and Immunity: Baseline Findings Ann Intern Med published online May 19, 2022

doi:10.7326/M21-4905

Self-referred adults with laboratory-documented SARS-CoV-2 infection who were at least 6 weeks from symptom onset were enrolled regardless of presence of PASC (post-acute sequelae of SARS-CoV-2 infection). A control group comprised persons with no history of COVID-19 or serologic evidence of SARS-CoV-2 infection, recruited regardless of their current health status. Both groups were enrolled over the same period and from the same geographic area. All participants had the same evaluations regardless of presence of symptoms, including physical examination, laboratory tests and questionnaires, cognitive function testing, and cardiopulmonary evaluation. A subset also underwent exploratory immunologic and virologic evaluations.

189 persons with laboratory-documented COVID-19 (12% of whom were hospitalized during acute illness) and 120 antibody-negative control participants were enrolled. At enrollment, symptoms consistent with PASC were reported by 55% of the COVID-19 cohort and 13% of control participants. Increased risk for PASC was noted in women and those with a history of anxiety disorder. Participants with findings meeting the definition of PASC reported lower quality of life on standardized testing. Abnormal findings on physical examination and diagnostic testing were uncommon. Neutralizing antibody levels to spike protein were negative in 27% of the unvaccinated COVID-19 cohort and none of the vaccinated COVID-19 cohort. Exploratory studies found no evidence of persistent viral infection, autoimmunity, or abnormal immune activation in participants with PASC. Fatigue, labored breathing, chest discomfort, parosmia,

headache, insomnia, memory impairment, anxiety, and impaired concentration were the most common persistent symptoms.

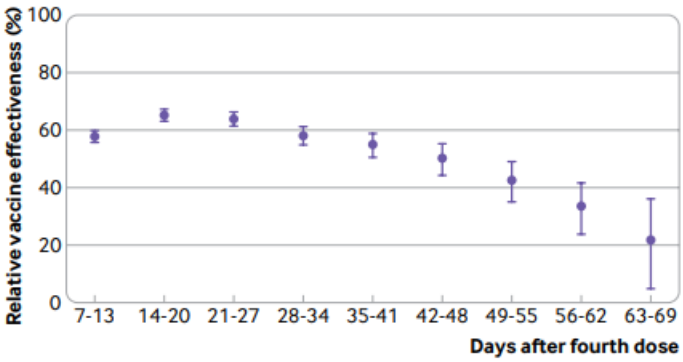
Comment: Over 50% of patients had persistent symptom after Covid-19. Extensive diagnostic evaluation revealed no specific cause of reported symptoms in most cases. Antibody levels were highly variable after COVID-19. Most participants with Covid-19 had mild to moderate acute illness that did not require hospitalization. The prevalence of reported PASC was likely overestimated in this cohort because persons with PASC may have been more motivated to enroll. Therefore, the findings in this study may not represent the full spectrum and severity of PASC experienced by persons with severe disease requiring hospitalization. Control participants were not matched to age- or gender-matched to participants with Covid-19. The study did not show evidence of abnormal systemic immune activation or persistent viral infection in participants with PASC. PASC resembles what has been described with some other illnesses, including chronic fatigue syndrome, post infection syndromes and described after resolution of certain viral and bacterial infections. The pathogenesis of PASC remains unclear and requires further study.

Short term, relative effectiveness of four doses versus three doses of BNT162b2 vaccine in people aged 60 years and older in Israel: retrospective, test negative, case-control study BMJ 2022;377:e071113

doi.org/10.1136/ bmj-2022-071113

This study looks at the VE of a fourth dose of Pfizer COVID vaccine. The study took place over 10 weeks beginning in January 2022 and compared outcomes of 69,623 adults with three doses of Pfizer with 27,876 adults who received four doses. The study was conducted when Omicron was the dominant strain in Israel.

During the 10-week follow-up period, 106 participants died, including 77 who had a third dose and 23 with a fourth dose. To gauge breakthrough infections, the investigators performed a matched analysis that compared positive cases to controls by week since vaccination. The added relative vaccine effectiveness of a fourth dose against infection quickly decreased over time, peaking during the third week at 65.1% (95% confidence interval [CI], 63.0% to 67.1%) and falling to 22.0% (95% CI, 4.9% to 36.1%) by the end of the 10-week follow-up period.



Comment: This study showed additional protection of the fourth dose against both SARS-CoV-2 infection and severe Covid-19 relative to three doses. However, the relative VE against infection varied over time and waned sooner than that of the third dose. By the fifth week after vaccination, relative VE of the fourth dose against SARS-CoV-2 infection dropped back to levels

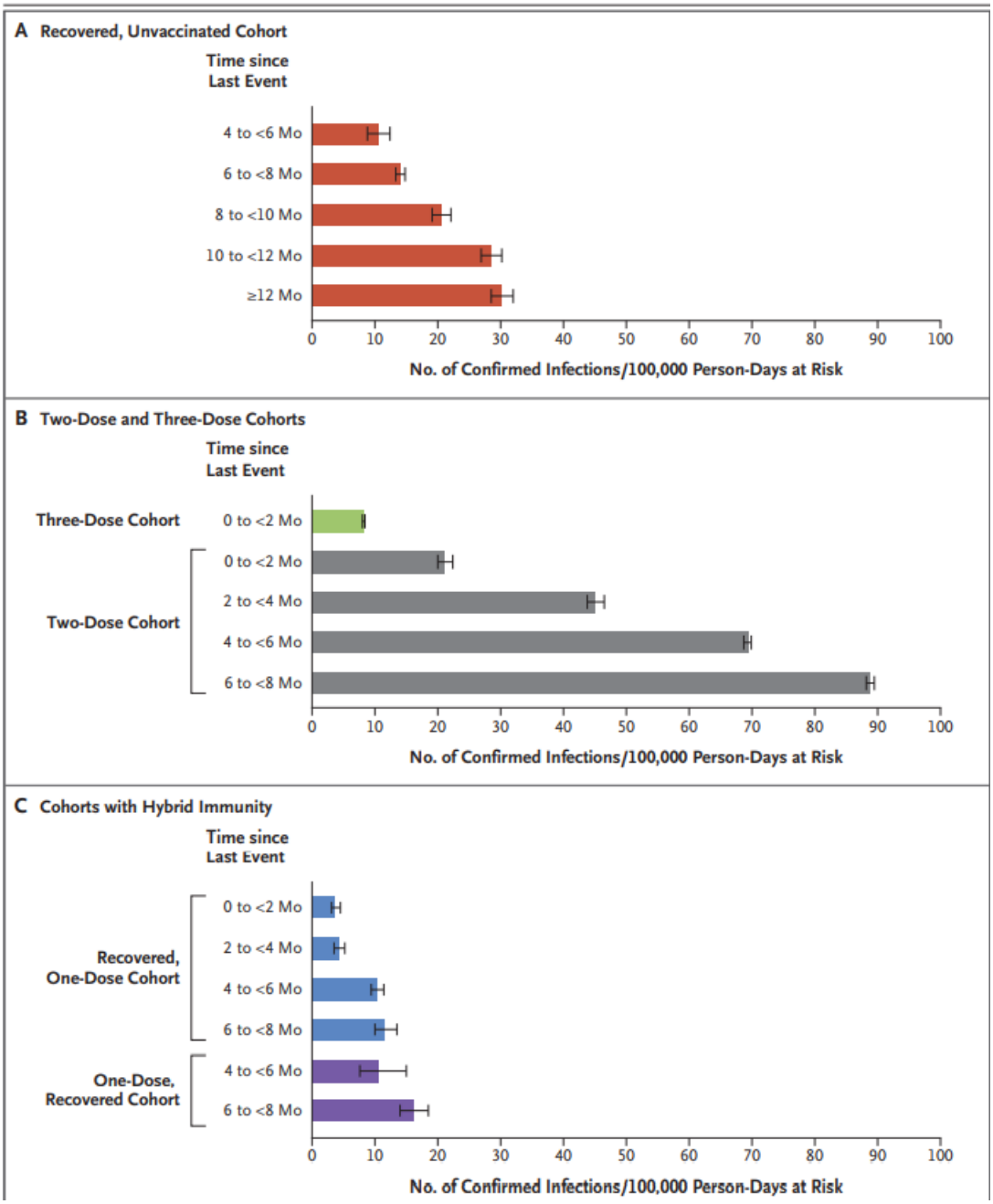
similar to those observed during the first week. As important, VE waned faster than a third dose in adults ages 60 and older. This and other studies should help us reevaluate vaccine strategies for boosters moving forward. Getting boosters even every 3-4 months is not sustainable. VE against severe disease remained high even after three doses.

Protection and Waning of Natural and Hybrid Immunity to SARS-CoV-2 N Engl J Med published online May 25, 2022

DOI: 10.1056/NEJMoa2118946

Using the Israeli Ministry of Health database, the investigators extracted data for August and September 2021, when the delta variant was predominant, on all persons who had been previously infected with SARS-CoV-2 or who had received Pfizer vaccine. They used Poisson regression with adjustment for confounding factors to compare the rates of infection as a function of time since the last immunity-conferring event.

The number of cases of SARS-CoV-2 infection per 100,000 person-days at risk (adjusted rate) increased with the time that had elapsed since vaccination or since previous infection. Among unvaccinated persons who had recovered from infection, this rate increased from 10.5 among those who had been infected 4 to less than 6 months previously to 30.2 among those who had been infected 1 year or more previously. Among persons who had received a single dose of vaccine after previous infection, the adjusted rate was low (3.7) among those who had been vaccinated less than 2 months previously but increased to 11.6 among those who had been vaccinated at least 6 months previously. Among previously uninfected persons who had received two doses of vaccine, the adjusted rate increased from 21.1 among those who had been vaccinated less than 2 months previously to 88.9 among those who had been vaccinated at least 6 months previously.



Comment: Among persons who had been previously infected with SARS-CoV-2 (regardless of whether they had received any dose of vaccine or whether they had received one dose before or after infection), protection against reinfection decreased as the time increased since the last immunity-conferring event; however, this protection was higher than that conferred after the same time had elapsed since receipt of a second dose of vaccine among previously uninfected persons. A single dose of vaccine after infection reinforced protection against reinfection.