Infectious Diseases Watch

June 6, 2022

Ed Septimus, MD

General Infectious Diseases

Association of Inappropriate Outpatient Pediatric Antibiotic Prescriptions With Adverse Drug Events and Health Care Expenditures

JAMA Netw Open 2022;5(5):e2214153.

doi:10.1001/jamanetworkopen.2022.14153

Investigators at Pew and the Washington University School of Medicine in St. Louis analyzed a large database containing outpatient insurance claims and outpatient pharmacy-dispensed medications for patients with commercial insurance. Their aim was to quantify the downstream consequences of children receiving inappropriate antibiotic prescriptions for common childhood infections like ear and sinus infections, beyond the well-established public health threat of antibiotic resistance.

Previous research by Pew and others suggests that ~ 30% of the outpatient antibiotic prescriptions US children receive are inappropriate—either because the infection is caused by a virus and doesn't require antibiotic therapy or because the child didn't receive the guideline-recommended antibiotic.

To look at ADE, the investigators analyzed the records of more than 2.8 million US children ages 6 months to 17 years who were diagnosed as having one of seven common bacterial and viral infections (suppurative otitis media [ear infection with discharge], pharyngitis, sinusitis, influenza, viral upper respiratory infection, bronchiolitis, and bronchitis) from April 2016 through September 2018. They then compared adverse events—such as *C difficile* infection, non–*C difficile* diarrhea, anaphylaxis (severe allergic reaction), nausea/vomiting/abdominal pain, and rash—in children who received inappropriate antibiotics with those who received appropriate antibiotics.

Antibiotics were considered inappropriate if they were prescribed for any viral infection or if the agent prescribed for a bacterial infection was not the guideline-recommended agent. The investigators used this expanded definition of inappropriate prescribing because previous studies had shown that even when children correctly receive an antibiotic for a bacterial infection, the agent selected is not always the first-line recommended antibiotic. In some cases, the non-recommended antibiotics are broader-spectrum agents that promote the development of resistance and may have an increased risk of adverse events. Their primary analysis compared outcomes among children who received guideline-discordant therapy with those who received first-line antibiotic agents (amoxicillin for otitis media; amoxicillin or penicillin for pharyngitis; and amoxicillin or amoxicillin-clavulanate for sinusitis). GI ADEs, including nausea, vomiting, abdominal pain, and diarrhea, were more common in children who received guideline-discordant therapy.

Looking at antibiotic prescriptions by diagnosis, the analysis found that 36% of children with sinusitis, 34% of children pharyngitis, and 31% of children with suppurative otitis media received an inappropriate antibiotic. For children with viral infections, the proportion who received an inappropriate antibiotic ranged from 4% for those with flu to 70% of children with bronchitis.

Analysis of adverse events found that, in the children with bacterial infections, the increased risk for an adverse event associated with an inappropriate antibiotic prescription was significant. Inappropriate antibiotic selection for pharyngitis was associated with a more than eightfold increase in the risk of *C difficile* infection (hazard ratio [HR], 8.42; 95% confidence interval [CI], 3.09 to 23.0). Children who received the non-guideline recommended antibiotic for suppurative otitis media more had a quadrupled risk of severe allergic reaction (HR, 4.14; 95% CI, 2.48 to 6.92). For children with viral infections, unnecessary antibiotics were associated with higher risk of rash or urticaria (hives). In general, severe adverse events like *C difficile* infection and anaphylaxis were rare, while rashes, nausea/vomiting/abdominal pain, and non–*C difficile* diarrhea were more common.

The increased risk of adverse events was costly as well. When the investigators looked at the excess costs attributed to those inappropriate prescriptions—including follow-up clinician visits and additional medications prescribed for the adverse event within 30 days of the initial diagnosis—they found that the additional per-patient cost for children who received inappropriate antibiotics was $21 for sinusitis, $42 for pharyngitis, and $56 for otitis media.

On national level, that translated to an excess cost of $7.1 million, $21.3 million, and $25.3 million for the three infections. Unnecessary antibiotics for viral upper respiratory infections and flu increased healthcare costs by an estimated $20.7 million.

Comment: While many clinicians are generally aware of these potential threats, unfortunately despite education and feedback, we have a long way to go. In this study children who received inappropriate or non-recommended antibiotics for common viral and bacterial infections had an increased risk of adverse side effects such as *C. difficile* infection, severe allergic reactions, and rashes. The additional medical care needed to address these adverse events resulted in roughly $74 million in excess healthcare costs in 2017. The current study confirms that investments, such as dedicated antibiotic stewardship personnel and initiatives, could lead to a substantial return on investment.

Exploration of Primary Care Clinician Attitudes and Cognitive Characteristics Associated With Prescribing Antibiotics for Asymptomatic Bacteriuria

JAMA Netw Open 2022;5(5):e2214268.

doi:10.1001/jamanetworkopen.2022.14268

The survey, conducted from June 2018 through November 2019, presented four clinical scenarios to primary care clinicians from 30 clinics in Texas, the Mid-Atlantic, and the Pacific Northwest. One of the scenarios was the hypothetical case of a 65-year-old man with asymptomatic bacteriuria. The respondents were asked to indicate whether they would prescribe antibiotics and to estimate the probability that the patient in the scenario had a UTI. Study authors also analyzed factors associated with reported increased willingness to prescribe an antibiotic for asymptomatic bacteriuria.

The 551 respondents who answered all the questions included 288 resident physicians, 202 attending physicians, and 61 advance-practice clinicians. Overall, 392 of 551 (71%) indicated

they would prescribe an antibiotic for the patient described in the scenario. On average, respondents who said they would prescribe antibiotics estimated a 90% probability of a UTI.

In multivariable analyses, clinicians with a background in family medicine (odds ratio [OR], 2.93; 95% confidence interval [CI], 1.53 to 5.62) or a high score on the Medical Maximizer-Minimizer Scale (indicating stronger medical maximizing orientation; OR, 2.06; 95% CI, 1.38 to 3.09) were more likely to prescribe antibiotic treatment for asymptomatic bacteriuria. Resident physicians (OR, 0.57; 95% CI, 0.38 to 0.85) and clinicians in the Pacific Northwest (OR, 0.49; 95% CI, 0.33 to 0.72) were less likely to prescribe antibiotics for asymptomatic bacteriuria.

Comment: The results of this survey study suggest that most primary care clinicians would ignore widely accepted guidelines by prescribing antibiotics for asymptomatic bacteriuria in the absence of risk factors. This and the prior paper were big disappointments given all the discussion about inappropriate treatment of URIs and UTIs. The results of these studies also suggest that the Choosing Wisely campaign recommending against antibiotic for ABU and most URIs has failed to make a significant impact in the US. ☹

The survey was conducted to assess responses to a hypothetical patient. Most important, the survey included a single clinical scenario related to asymptomatic bacteriuria and, as such, cannot reflect the many ways that asymptomatic bacteriuria may present among real patients. Respondents' reported tendencies toward antibiotic prescribing may not match their actual practice when faced with a living patient. In my experience when physicians are asked about guidelines they know the right answers, but in practice they tend to treat. In addition, although the response rate to the survey was high, the sample may not be sufficiently large to be adequately powered for multiple subgroup analyses. We need better tools to change prescribing behavior.

Comparison of the global prevalence and trend of human intestinal carriage of ESBL-producing Escherichia coli between healthcare and community settings: a systematic review and meta-analysis

JAC Antimicrob Resist published online June 2, 2022

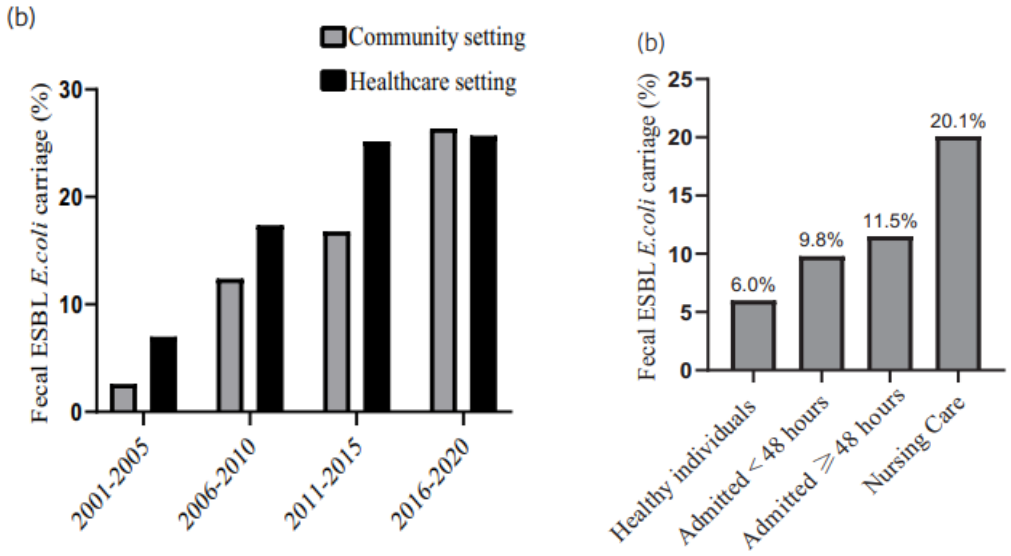
doi.org/10.1093/jacamr/dlac048

This is a systematic review including 133 articles published between 1 January 2000 and 22 April 2021 and indexed in PubMed, EMBASE or Google Scholar. A random-effects meta-analysis was performed to obtain the global pooled prevalence (community and healthcare settings). Subgroup meta-analyses were performed by grouping studies using the WHO regions and 5-year intervals of the study period.

They found that 21.1% (95% CI, 19.1%–23.2%) of inpatients in healthcare settings and 17.6% (95% CI, 15.3%–19.8%) of healthy individuals worldwide carried ESBL E. coli in their GI track. The global carriage rate in healthcare settings increased 3-fold from 7% (95% CI, 3.7%–10.3%) in 2001–05 to 25.7% (95% CI, 19.5%– 32.0%) in 2016–20, whereas in community settings it increased 10-fold from 2.6% (95% CI, 1.2%–4.0%) to 26.4% (95% CI, 17.0%–35.9%) over the same period. While Europe and the Americas had the lowest colonization rate, all the other WHO regions had a carriage rate of above 20% in both community and healthcare settings. Over the past 20 years (2000–21), the global human intestinal ESBL E. coli carriage rate increased steadily in both healthcare and community settings. The upward trend was observed in each of the six WHO regions. The rate of increase appeared to be higher in the community

than in healthcare settings, and colonization rates in the community were approaching values in the healthcare areas.

In healthcare settings, the highest carriage rate by World Health Organization region was found in the Eastern Mediterranean (45.6%), followed by Southeast Asia (32.9%), Africa (32.4%), and the Western Pacific (24.1%). In community settings, the highest carriage rates were observed in Southeast Asia (35.1%), the Western Pacific (25.3%), Africa (21.4%), and Eastern Mediterranean (20.6%). The investigators also found, based on data from Europe, that fecal ESBL E coli colonization increased with duration of contact/stay in healthcare settings and NHs.



Comment: Overestimation or underestimation of the global and regional pooled prevalence could result from what the investigators called the spatial 'maldistribution'. An example, certain WHO regions might consist of countries with low and high colonization rates, and hence regional carriage rates in the community might appear higher than in healthcare settings. Laboratory methods of ESBL identification improved over the years and this might have an influence on the rising trend in ESBL E. coli carriage. In addition, the techniques and sensitivity of the tests used might also differ in different regions of the world, leading to differences in ESBL E. coli prevalence. The other limitation of this study is that the analysis was limited to the predominant ESBL-producing species—E. coli only. The comparative prevalence of other Enterobacteriaceae needs to be addressed in future studies. Nonetheless, I think we have all seen a rise in ESBL producing organisms in the last decade. Local epidemiology and surveillance are critical in guiding empiric treatment of infections such as UTI or IAI. Travel overseas to certain regions where ESBL is high should also be considered. In addition, multiple studies have indicated an increase in AR during the pandemic. As the articles above and below highlight as well, the role of ASP across the continuum of care is even more crucial than ever.

Increased carbapenemase testing following implementation of national VA guidelines for carbapenem-resistant Enterobacterales (CRE) Antimicrob Stewardship and Healthcare Epidemiol 2022; 2:e88

doi.org/10.1017/ash.2021.220

In late 2016, the VA released guidelines that prioritized the identification of carbapenenemase-producing carbapenem-resistant Enterobacterales (CP-CRE). The new guidelines simplified antimicrobial susceptibility testing and recommended polymerase chain reaction (PCR) to identify carbapenemase production in CRE cultures. Knowing whether and what type of carbapenemase enzyme or gene is being produced can provide critical information for clinical care and optimal antimicrobial treatment, help guide real-time infection control response, and inform epidemiologic surveillance.

Overall, the investigators identified 5,778 standard cultures from 3,096 patients at 132 VAMCs that grew CRE. Of these, 1,905 (33.0%) had evidence of molecular or phenotypic carbapenemase testing, and 1,603 (84.1%) of these had carbapenemases detected.

Among the cultures confirmed as CP-CRE, 1,053 (65.7%) had molecular testing for one or more mechanism of carbapenemase production. Almost all testing included the KPC enzyme (1,047; 99.4%), with KPC detected in 914 (87.3%) of 1,047 cultures. The NDM enzyme was found in 585 cultures (55.6%), and OXA-48 was found in 507 (48.1%).

Carbapenemase testing increased over the study period, from 23.5% of CRE cultures in 2013 to 58.9% in 2018, with significant increases in testing observed after the release of the new guidelines. The study authors admit that despite the encouraging increase in testing, as of 2018, more than 40% of cultures that grew CRE in all VAMCs and more than 75% of cultures in low-complexity or rural facilities did not have evidence of carbapenemase testing.

Comment: I think this article reminds us of the value-added molecular technology has added to our toolkit. We are all seeing more resistance (see ESBL above-most due to CTX-M enzymes). Tracking if a CR-CRE is also a carbapenemase producer can guide antimicrobial therapy. The percentage of CP-CRE in this study is higher than other studies. Carbapenemase-producing isolates account for approximately 35%-59% of CRE cases in the US. (Antimicrob Agents Chemother 2021; 65(e0110521) For Carbapenem Resistant Acinetobacter (CRAB) production of carbapenemases such as OXA-24/40-like carbapenemases and OXA-23-like carbapenemases mediates resistance to carbapenems which are not commonly tested. Multidrug-resistant PA has evolved because of an interplay of multiple complex resistance mechanisms, including decreased expression of outer membrane porins (OprD), hyperproduction of AmpC enzymes, upregulation of efflux pumps, and mutations in penicillin-binding protein targets [Clin Microbiol Rev 2009; 22: 582-610]. Carbapenemase production is a minor cause of carbapenem resistance in PA in the US to date. For the latest updates on treatment use the links below.

https://www.idsociety.org/practice-guideline/amr-guidance/

https://www.idsociety.org/practice-guideline/amr-guidance-2.0/

Monkeypox Update

The CDC has identified 21 monkeypox cases in 11 states, and the numbers are expected to rise. Genetic analysis has revealed that while most of the cases appear to be closely related to the outbreak in Europe, two patients have versions of the virus that seems to have evolved from a monkeypox case identified in Texas last year. Of 17 patients for whom the CDC has detailed information, all but one were among men who had sex with men; 14 had traveled to other countries in the three weeks before their symptoms began. Three patients were immunocompromised. CDC has not been able to identify how one patient in an unnamed state acquired the virus. That suggests there is ongoing community transmission at least in that state. All cases are all of the West African clade of monkeypox, which is the less severe of the two clades.

Health officials have identified a total of about 400 contacts of 13 patients who also risk becoming infected with monkeypox. So far, health officials have delivered about 1,200 vaccine doses and 100 treatment courses to eight states.

Worldwide cases increased this week, to nearly 800 cases as of Friday. The spread of the virus to at least 31 countries outside Africa.

The vaccine Jynneos, is preferred and has been shown to be safe in older adults, people with H.I.V. or AIDS and those who have received bone marrow transplants and are therefore immunocompromised.

People infected with monkeypox can be vaccinated even a few days after exposure. They can also be treated with one of two drugs approved to treat smallpox, tecovirimat and brincidofovir, which slow the virus.

CDC Case Definitions

Epidemiologic Criteria:

Within 21 days of illness onset:

- Reports having contact with a person or people with a similar appearing rash or who received a diagnosis of confirmed or probable monkeypox **OR**
- Had close or intimate in-person contact with individuals in a social network experiencing monkeypox activity, this includes men who have sex with men (MSM) who meet partners through an online website, app, or social event **OR**
- Traveled outside the US to a country with confirmed cases of monkeypox or where monkeypox is endemic **OR**
- Had contact with a dead or live wild animal or exotic pet that is an African endemic species or used a product derived from such animals

Infection prevention

Personal protective equipment for health care workers caring for a patient with suspected or confirmed monkeypox should include gown, gloves, eye protection (e.g., goggles or face shield) and a NIOSH-approved N95 face mask or higher-level respirator. Patients should be placed in a single-person room with a dedicated bathroom and should wear a well-fitting medical mask if

transported outside their room. An airborne infection isolation room may be used if available but special air handling is not required.

Comment: The WHO has labeled monkeypox a moderate public health risk. WHO does not believe Monkeypox will turn into another pandemic. However, there are still many unanswered questions about the disease, including how exactly it's spreading and whether the suspension of mass smallpox immunization decades ago may somehow have facilitated its transmission. To date most cases being seen in dozens of countries globally are in gay, bisexual or men who have sex with men. If you have a suspected case, contact your local public health authority. If advised collect multiple specimens of multiple types of lesions for preliminary and confirmatory testing as follows: 1) Vigorously swab or brush lesion with two separate sterile, dry polyester or Dacron swabs; 2) Break off the end of the applicator of each swab into a 1.5- or 2-mL screw-capped tube with O-ring or place each entire swab in a separate sterile container. Do not add or store in viral or universal transport media.

COVID-19

COVID-19 News

Novavax COVID vaccine

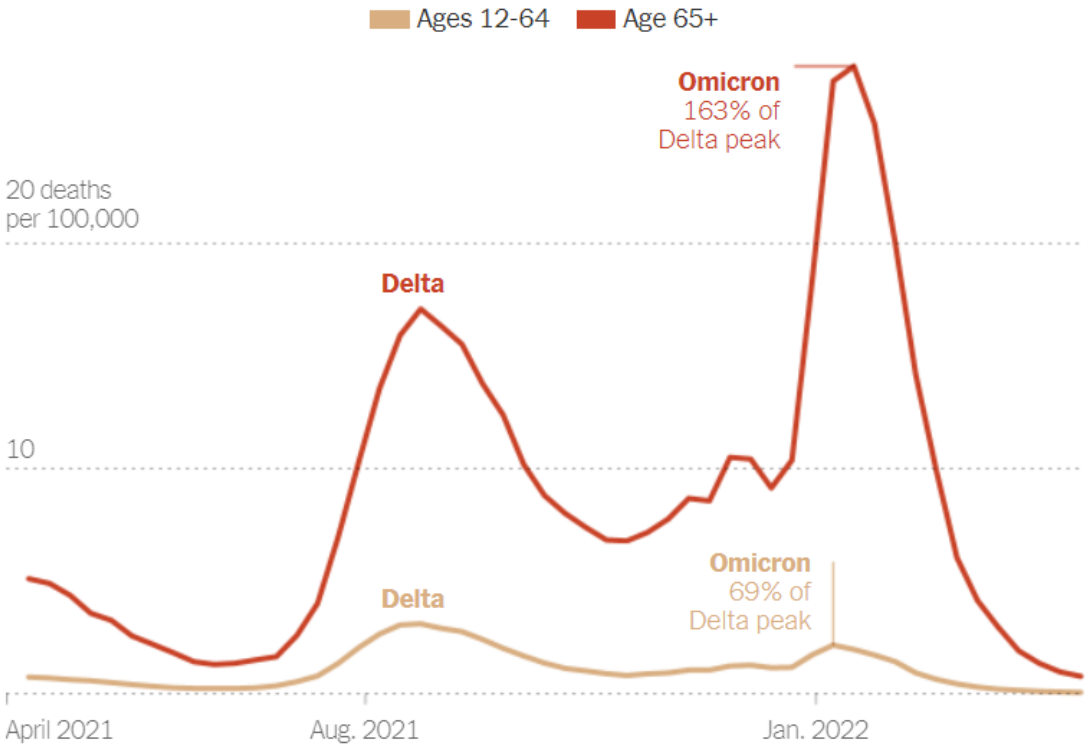
The vaccine is a recombinant nanoparticle protein-based product that contains an adjuvant and is given in two doses 3 weeks apart. The vaccine is made on a more traditional production platform, raising hopes of increased vaccine uptake among Americans who have shied away from newer mRNA vaccines. The vaccine is already used in over 40 countries.

The FDA reviewed trials that included 30,000 patients and were conducted before the Delta and Omicron surges. [80-page report!] Last June, a phase 3 trial found that the vaccine had 90% overall efficacy and was well tolerated, with few serious and adverse events. The FDA said based on efficacy estimates, the vaccine is likely to afford meaningful protection against Omicron, especially against severe disease. FDA examined four cases of myocarditis that occurred within 20 days of receiving the shot. It said the cases raised concerns about a link to the vaccine, similar to associations found earlier with mRNA vaccines. Novavax said natural background levels of myocarditis are expected, with young males known to be at higher risk. It said the difference in the rates between the vaccine and placebo groups was very small (0.007 % and 0.005%, respectively) and that in post-crossover portions of the study, cases were within expected parameters.

Comment: After FDA gave EUA, Moderna and Pfizer's mRNA vaccines also showed an increased risk of myocarditis, but no cases were reported before the vaccines were authorized. The results of the Novavax vaccine came from a study that enrolled subjects mostly in the first part of 2021, before Omicron emerged. However, it is reasonable to assume that the vaccine will provide some meaningful level of protection against Covid-19 due to Omicron, especially severe disease. FDA external panel will review next week.

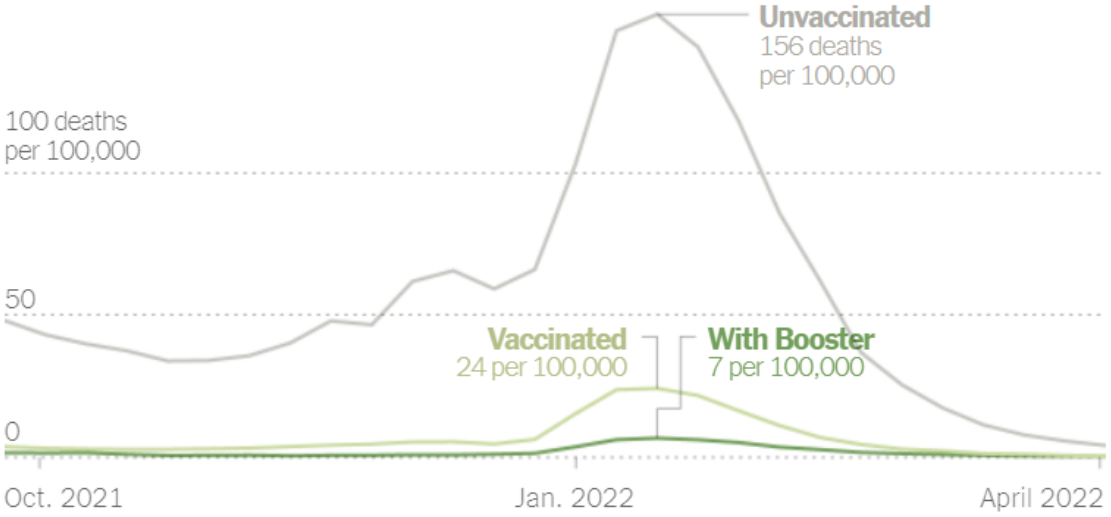
During the Omicron Wave, Death Rates Soared for Older People NY Times June 1, 2022. see graphs below

The Omicron Wave Was Deadlier Than Delta for Older People in the U.S.

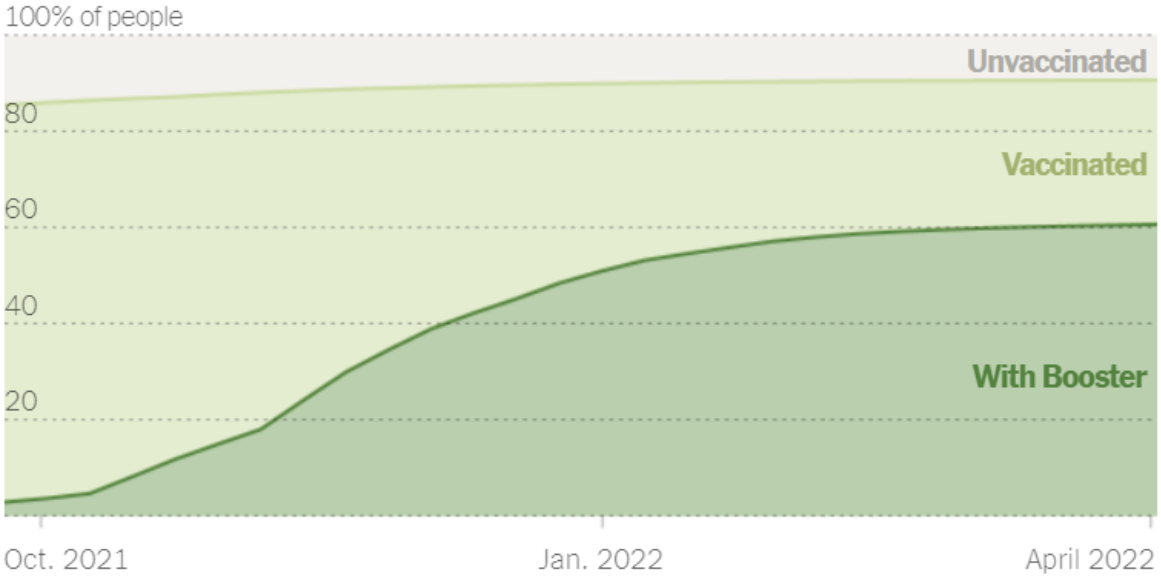


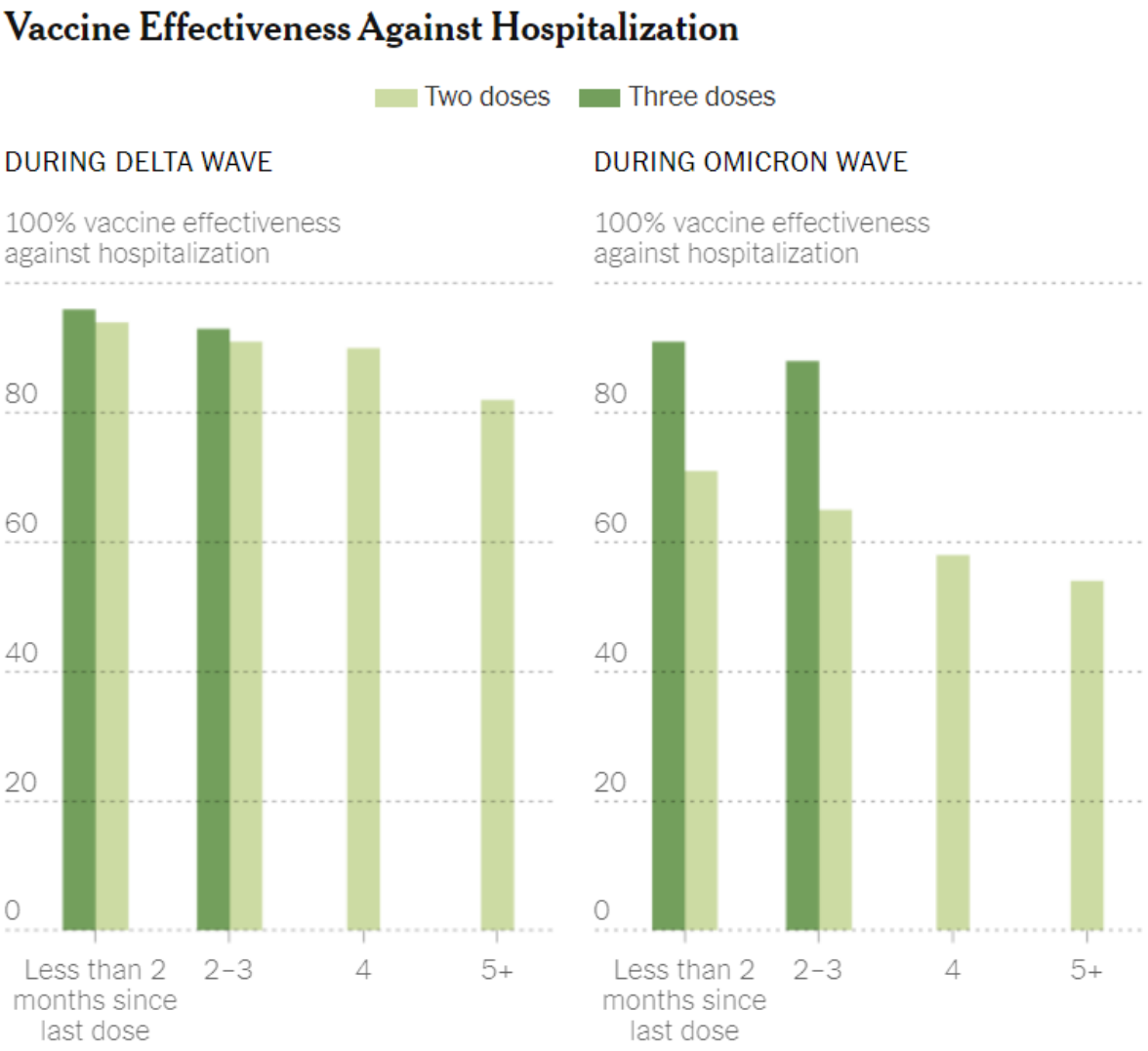
Note: Data is weekly and is as of April 2. Chart includes both fully vaccinated and unvaccinated people; those who only received a part of their primary vaccination series are excluded. • Source: Centers for Disease Control and Prevention

Covid-19 Death Rates for People Age 65+



Vaccination Rates for People Age 65+





Comment: From current data it is clear people over 65 are still at higher risk of dying from Covid-19, but vaccination especially with at least 1 booster greatly decreases chances of severe disease and death. Despite higher levels of vaccination among persons >65, COVID-19 death rates were significantly higher during the Omicron wave. About as many Americans 65 and older died in four months of the Omicron surge as did in six months of the Delta wave, even though the Delta variant, for any one person, tended to cause more severe illness. Although COVID death rates have fallen, older people still account for a disproportionate share. Only 60% of people over 65 have had a booster.

IDSA Covid-19 Guideline Updates

Famotidine

Recommendation 1 (NEW 5/23/2022): Among ambulatory patients with mild-to-moderate COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19 (Conditional recommendation, low certainty of evidence)

Recommendation 2 (UPDATED 5/23/2022): Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19. (Conditional recommendation, low certainty of evidence).

Neutralizing Antibodies for Pre- and Post-Exposure Prophylaxis

- Tixagevimab/cilgavimab (Uvusheld)
    - Recommendation 1 (UPDATED 5/23/2022): In moderately or severely immunocompromised individuals at increased risk for inadequate immune response to COVID-19 vaccine or for persons whom COVID-19 vaccine is not recommended due to a documented serious adverse reaction to the vaccine, the IDSA guideline panel suggests pre-exposure prophylaxis with tixagevimab/cilgavimab rather than no tixagevimab/cilgavimab, when predominant regional variants are susceptible to the agent (Conditional recommendation, Low certainty of evidence)
        - Dosing for tixagevimab/cilgavimab is 300 mg of tixagevimab and 300 mg COVID-19 injections once. As a result of the reduced susceptibility of tixagevimab/cilgavimab to the BA.1 variant, the FDA recommended on February 24, 2022, that the dosage for each mAb in this combination be increased from 150 mg to 300 mg intramuscularly.
- Casirivimab/imdevimab
    - Recommendation 2 (UPDATED 5/23/2022): In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests against postexposure casirivimab/imdevimab, unless predominant regional variants are susceptible to the agent. (Conditional recommendation, Low certainty of evidence)

COVID-19 by the Numbers

The US 7-day average of new COVID-19 cases has **decreased** for the first time since late March, according to the CDC's COVID-19 data tracker weekly review published June 3. COVID-19 cases hit record levels in January amid the omicron surge with a seven-day average of more than 800,000 and consistently fell nationwide through March, CDC data shows. The nation's seven-day case average plateaued at 24,805 on March 29 and rose steadily throughout April and May as highly transmissible omicron subvariants (BA.212.1) spread nationwide.

Hospitalizations

1. The seven-day hospitalization average for May 25-31 was 3,789, a 4.7 percent increase from the previous week's average, but now slightly down. [still cannot tell what percentage are admitted because of Covid-19 or with Covid-19]

Deaths

2. The current seven-day death average is 244, **down** 23.1 percent from the previous week's average. Some historical deaths have been excluded from these counts.

Vaccinations

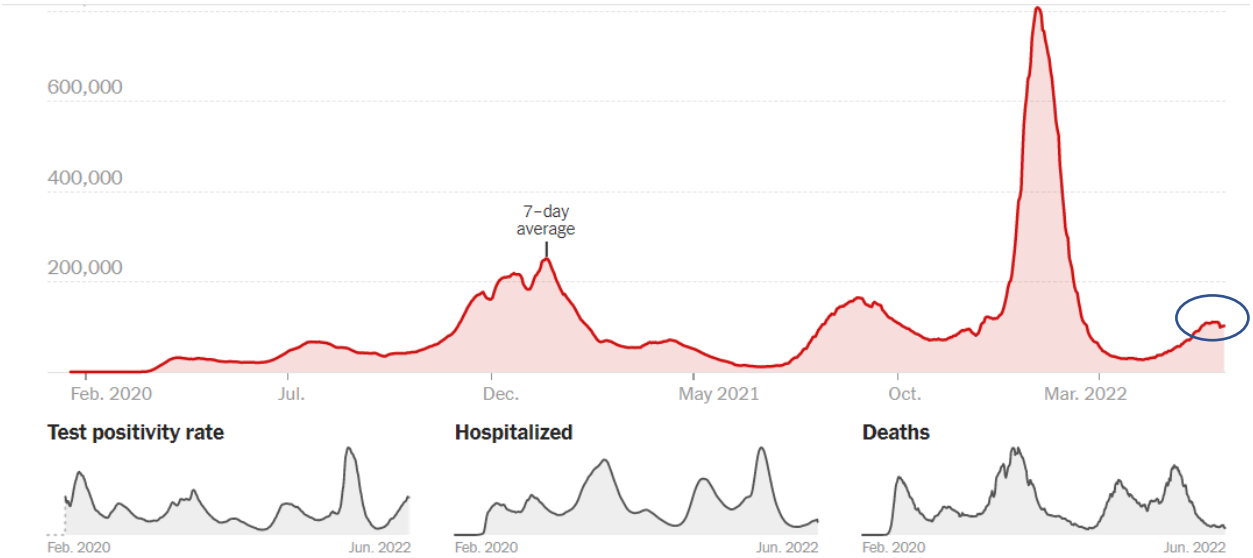
3. The seven-day average number of vaccines administered daily was 343,662 as of June 1, a 9.5 percent decrease from the previous week.

4. As of June 1 about 258.7 million people — 77.9 percent of the U.S. population — have received at least one dose of the COVID-19 vaccine, and more than 221.4 million people, or 66.7 percent of the population, have received both doses.

5. About 103.5 million additional or booster doses in fully vaccinated people have been reported. However, 49 percent of people eligible for a booster dose have not received one.

Variants

6. Based on projections for the week ending May 28, the CDC estimates the BA.2 omicron subvariant accounts for 34.7 percent of U.S. COVID-19 cases, while BA.2.12.1 accounts for 59.1 percent. Other omicron subvariants make up the rest.



	DAILY AVG. ON JUN. 3	14-DAY CHANGE	TOTAL REPORTED
Cases	101,941	-6%	84,618,221
Test positivity	13%	—	—
Hospitalized	24,022	-1%	—
In I.C.U.s	2,537	-2%	—
Deaths	264	-12%	1,004,941

Comment: Good news as areas in the NE and Midwest are now seeing a decline and in other areas this “wave” has been blunted compared to other waves. This is probably due to high community immunity and a milder variant.

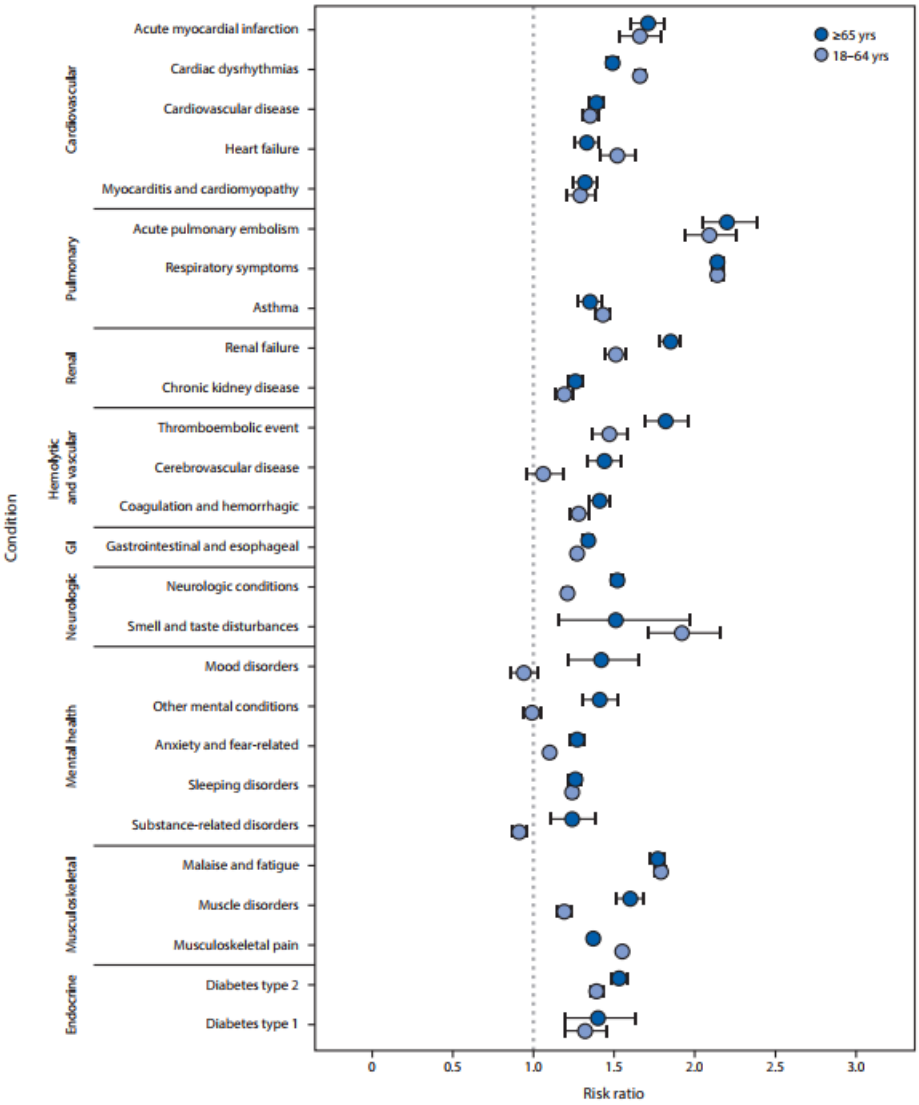
COVID-19 Journal Review

Post-COVID Conditions Among Adult COVID-19 Survivors Aged 18–64 and ≥65 Years — United States, March 2020–November 2021 MMWR 2022; 71:713-717

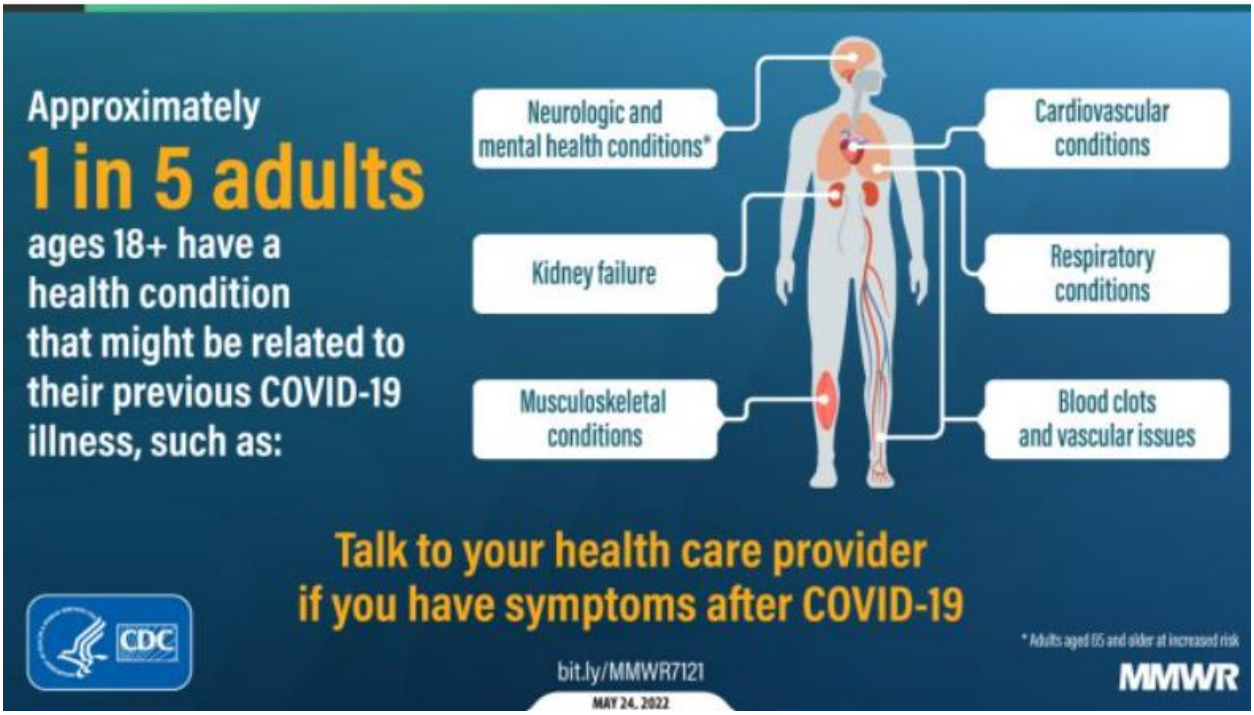
EHR data (Cerner) during March 2020–November 2021, for persons in the United States aged ≥18 years were used to assess the incidence of 26 conditions often attributable to post-COVID (hereafter also referred to as incident conditions) among patients who had received a previous COVID-19 diagnosis (case-patients) compared with the incidence among matched patients without evidence of COVID-19 in the EHR (control patients). The analysis was stratified by two age groups (persons aged 18–64 and ≥65 years). Patients were followed for 30–365 days after the index encounter until one or more incident conditions were observed or through October 31, 2021 (whichever occurred first).

Among all patients aged ≥18 years, 38% of case-patients experienced an incident condition compared with 16% of controls; conditions affected multiple systems, and included cardiovascular, pulmonary, hematologic, renal, endocrine, gastrointestinal, musculoskeletal, neurologic, and psychiatric signs and symptoms.

By age group, the highest risk ratios (RRs) were for acute pulmonary embolism (RR = 2.1 and 2.2 among persons aged 18–64 and ≥65 years, respectively) and respiratory signs and symptoms (RR = 2.1 in both age groups). Among those aged 18–64 years, 35.4% of case-patients experienced an incident condition compared with 14.6% of controls. Among those aged ≥65 years, 45.4% of case-patients experienced an incident condition compared with 18.5% of controls. These findings translate to one in five COVID-19 survivors aged 18–64 years, and one in four survivors aged ≥65 years experiencing an incident condition that might be attributable to previous COVID-19. COVID-19 survivors aged ≥65 years in this study were at increased risk for neurologic conditions, as well as for four of five mental health conditions (mood disorders, other mental conditions, anxiety, and substance-related disorders). Neurocognitive symptoms have been reported to persist for up to 1 year after acute infection and might persist longer.



Abbreviation: GI = gastrointestinal.



Comment: These findings translate to one in five COVID-19 survivors aged 18–64 years, and one in four survivors aged ≥65 years experiencing an incident condition that might be attributable to previous COVID-19. The most common incident conditions in both age groups were respiratory symptoms and musculoskeletal pain.

There are some significant weaknesses in this study:

1. Patient data were limited to those seen at facilities serviced by Cerner during January 2020–November 2021; therefore, the findings might not be representative of the entire U.S. adult population and does not account for Omicron
2. The incidence of new conditions after an acute COVID-19 infection is biased toward a population that is seeking care, either as a follow-up to a previous complaint (including COVID-19) or for another medical complaint.
3. COVID-19 vaccination status was <u>not</u> considered in this analysis, nor were potentially confounding factors (e.g., SARS-CoV-2 variant, sex, race, ethnicity, health care entity, or geographic region), because data were not available, were inconsistent, or included a high proportion of missing or unknown values. This has been a consistent weakness in many of the CDC studies. This highlights how behind we are in data collection across different data sets and not having common dictionaries.
4. ICD-10-CM codes were used to identify COVID-19 case-patients, and misclassification is possible. We all know the challenges of using administrative data.
5. The study only assessed conditions thought to be attributable to COVID-19 or post-COVID illness, which might have biased RRs away from the null. (pointed out in article)

The authors are careful-they say might be related to prior Covid-19 infection. The next question is this long Covid defined by the term used to describe an array of symptoms that can last for months or longer after the initial Covid infection and/or identified post-Covid health problems

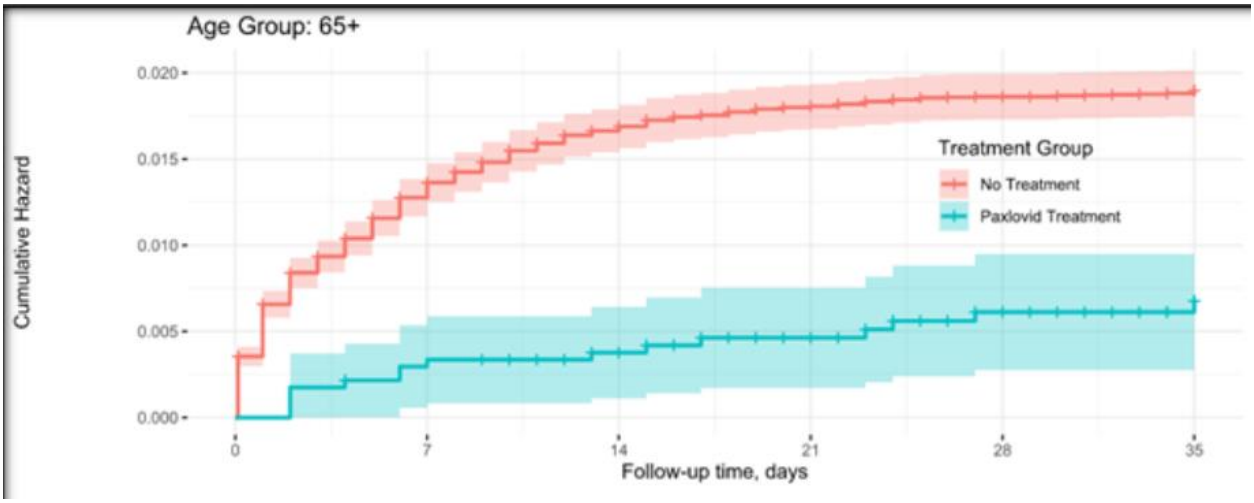
that are not really long Covid? Nonetheless, we need to use common definitions and develop data sets with common dictionaries that are complete. Now that we know that Covid-19 can lead to serious long-term problems we need to develop strategies to reduce the risk of long Covid and other complications.

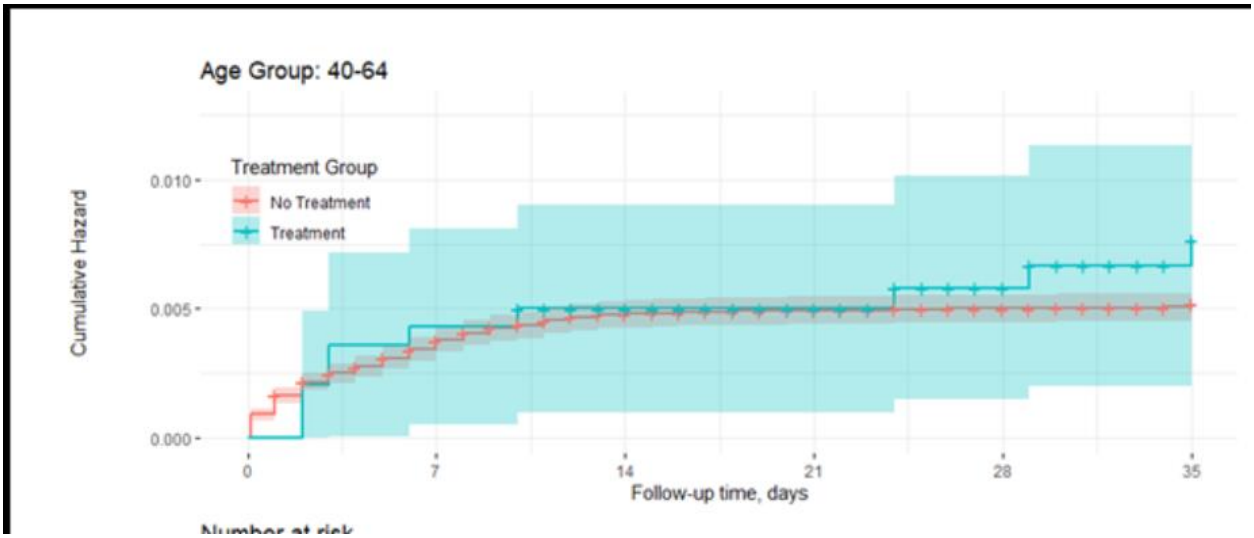
Oral Nirmatrelvir and Severe Covid-19 Outcomes During the Omicron Surge Res Square posted June 1, 2022. article suggested by Josh Septimus

doi.org/10.21203/rs.3.rs-1705061/v1

This study included all Clalit Health Services members in Israel, 40 years of age and older, with confirmed Covid-19 infection during the omicron surge (January 9-March 10, 2022) that were defined as high-risk for severe disease. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between nirmatrelvir treatment and hospitalizations and deaths due to Covid-19, with adjustment for individual sociodemographic factors, coexisting conditions, and prior Covid-19 immunity status.

109,213 participants were eligible for nirmatrelvir (Paxlovid) therapy during the two-month study period. Among the 42,819 eligible patients aged 65 years and above, 2,504 were treated with nirmatrelvir. Hospitalizations due to Covid-19 occurred in 14 out of the treated and 762 of the untreated patients: adjusted HR 0.33 (95% CI, 0.19 to 0.55). Death due to Covid-19 occurred in 2 treated and 151 untreated patients; adjusted HR: 0.19 (95% CI, 0.05 to 0.76). Among the 66,394 eligible patients 40 to 64 years of age, 1,435 were treated with nirmatrelvir. Hospitalizations due to Covid-19 occurred in 9 treated and 334 untreated patients: adjusted HR 0.78 (95% CI, 0.40 to 1.53). Death due to Covid-19 occurred in 1 treated and 13 untreated patients; adjusted HR: 1.64 (95% CI, 0.40 to 12.95). However, immunosuppression was significantly associated with hospitalizations in the 40-64 age group.



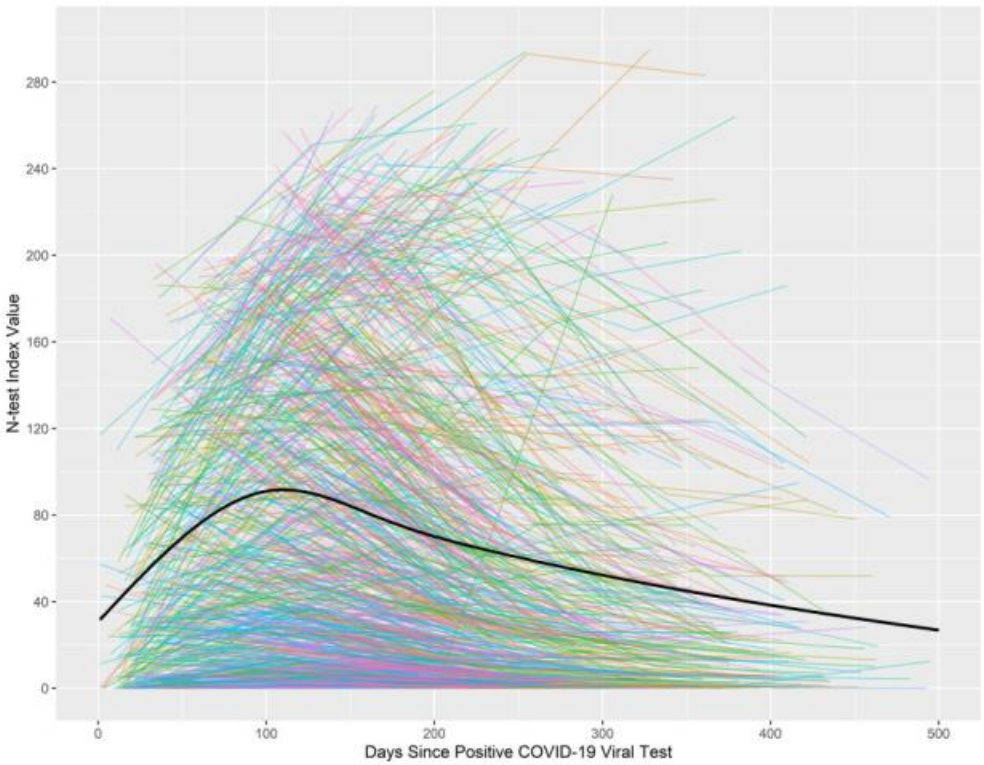


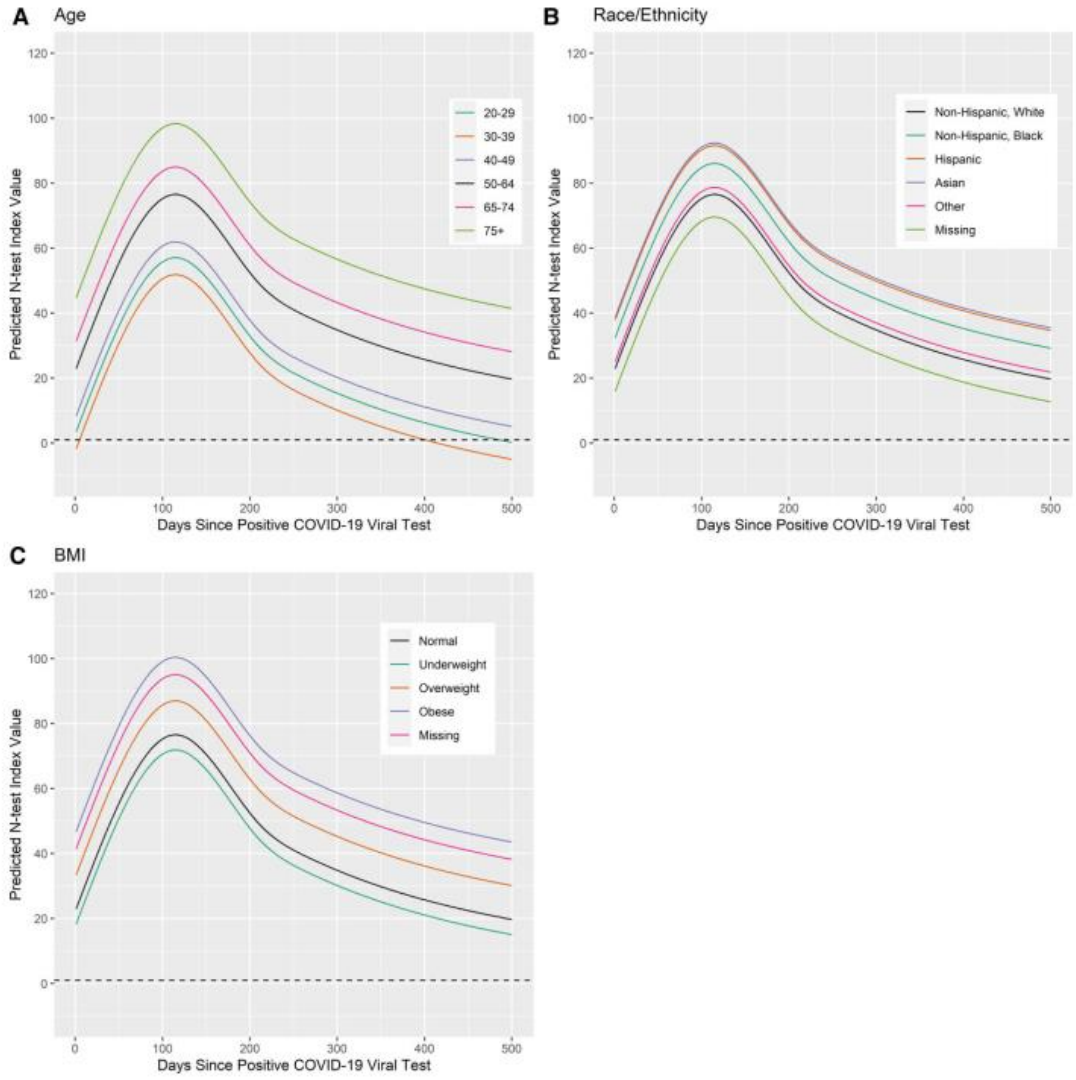
Comment: Nirmatrelvir therapy was associated with a 67% reduction in Covid-19 hospitalizations and an 81% reduction in Covid-19 mortality in patients 65 years and above. However, no significant benefit in avoidance of severe Covid-19 outcomes was shown in younger adults (40-64). Senior citizens who had no prior immunity - meaning they were neither vaccinated nor recovered from a previous COVID case - saw an 86% drop in hospitalizations with nirmatrelvir. Those who had prior immunity also benefited, but at a lower rate of 60%. In patients ages 40-64, however, regardless of their prior immunity, the data showed no significant benefit in reducing hospitalization. Prior studies lacked data on the clinical efficacy of nirmatrelvir against the omicron variant. The investigators noted limitations that may have biased their findings, such as lack of data on the symptoms patients presented, which may have impacted their course of treatment, or patients' degrees of prior immunity. Another potential limitation is the heterogeneity of degrees of immunity in the subgroup with prior immunity. This group included patients with infection-induced, vaccine-induced, and hybrid-induced immunity, disregarding any waning of such immunity over time. Nonetheless, this study looked at both immune and nonimmune (original trial all nonimmune) and defined which age group is likely to benefit. Not everyone needs nirmatrelvir!

Antibody Duration After Infection From SARS-CoV-2 in the Texas Coronavirus Antibody Response Survey J Infect Dis published online May 6, 2022

Researchers examined data from over 57,000 volunteers across the state of Texas over the age of 20 who were enrolled in the Texas CARES survey, which began in October of 2020 with the goal of assessing COVID-19 antibody status over time among a population of adults and children in Texas. Texas CARES consists of a prospective convenience sample of individuals, were are longitudinally tested for SARS-CoV-2 antibody status every 3 months for a total of 3 time points from 1 October 2020 to 30 August 2021. Participants included adult retail/business employees, K -12th grade and university educators and students, and patients and employees from Health Resources and Services Administration designated Federally Qualified Health Centers. The current report focuses on individuals from Texas CARES who were 20 years of age and older, reported only 1 positive COVID-19 diagnosis with a date of diagnosis, and had at least 1 valid nucleocapsid (N) antibody test (N-test) result and at least 1 nonzero N-test value after their first reported COVID-19–positive diagnosis through 30 August 2021. Most volunteers self-reported a COVID-19 infection before October of 2020. The results differed from person to person based on their age, body mass index (BMI), smoking or vaping use, and the severity of infection; however, all volunteers showed a similar decrease in antibodies.

The research shows that the level of antibodies in those previously infected increases for the first 100 days post-infection and then gradually declines over the next 500 days and beyond. The trajectory of each individual's antibody duration is shown in Figure 1 below; each line represents an individual's trajectory in the study, and the black curve represents the model-based predicted average curve. This mixed linear model with only the restricted cubic spline representation of time since COVID-19– positive and participant-specific random effect was highly significant (LRT = 433.0, df = 4, P, .001). The general pattern of the N-test values over time shows a rapid increase over the first few months (90–100 days; Figure 1).


N-test Index Value
280
240
200
160
120
80
40
0
0
100
200
300
400
500
Days Since Positive COVID-19 Viral Test



Comment: These results are promising because we now have a good estimate of how long some antibodies last after a COVID-19 infection. The results of this study are just another step in understanding the virus's impact. They demonstrate antibodies after infection can last for almost a year and half. It's important to understand that being vaccinated against the virus still offers the best protection against infection, reinfection, or hospitalization. Neutralizing antibodies do wane over time making reinfection more common, but memory B and T cells still protect against severe disease and death. This is a cohort study and nonrandom and self-selection biases may be seen. Given the large cohort size allowed the investigators to control for covariates. COVID-19 infection dates were self-reported so attendant limitations in self reporting must be recognized. It is possible that people incorrectly reported infection or dates of infection. As mitigation behaviors, such as mask use and social distancing, become more relaxed, and more variants emerge, estimating and predicting the duration of antibodies becomes increasingly more important. Previous research out of Texas CARES found children previously infected with COVID-19 had circulating antibodies that lasted for at least seven months.