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Infectious Diseases Watch

August 8, 2022

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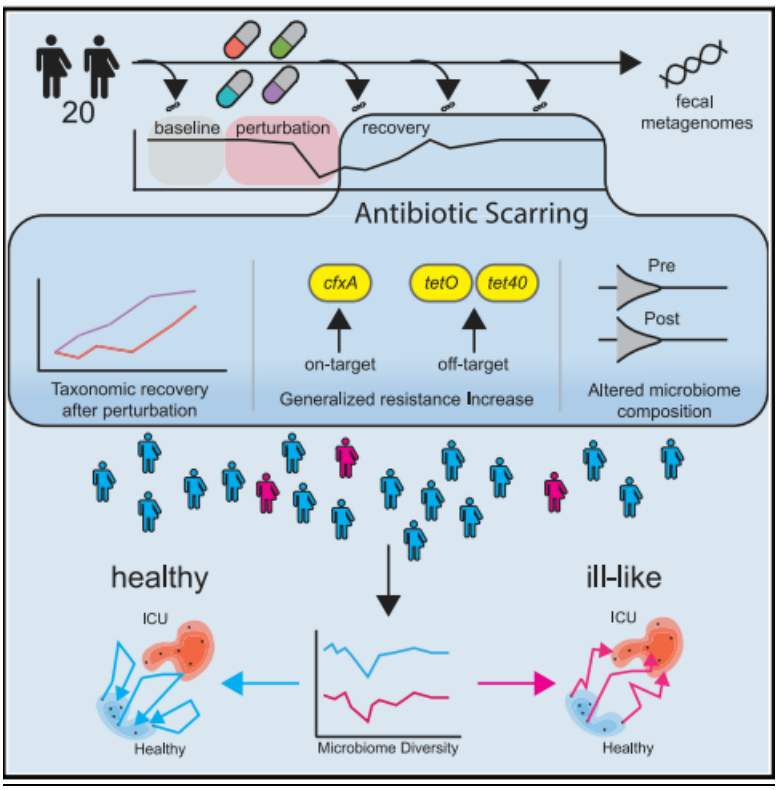
General Infectious Diseases

Acute and persistent effects of commonly used antibiotics on the gut microbiome and resistome in healthy adult Cell Reports April 12,2022

doi.org/10.1016/j.celrep.2022.110649

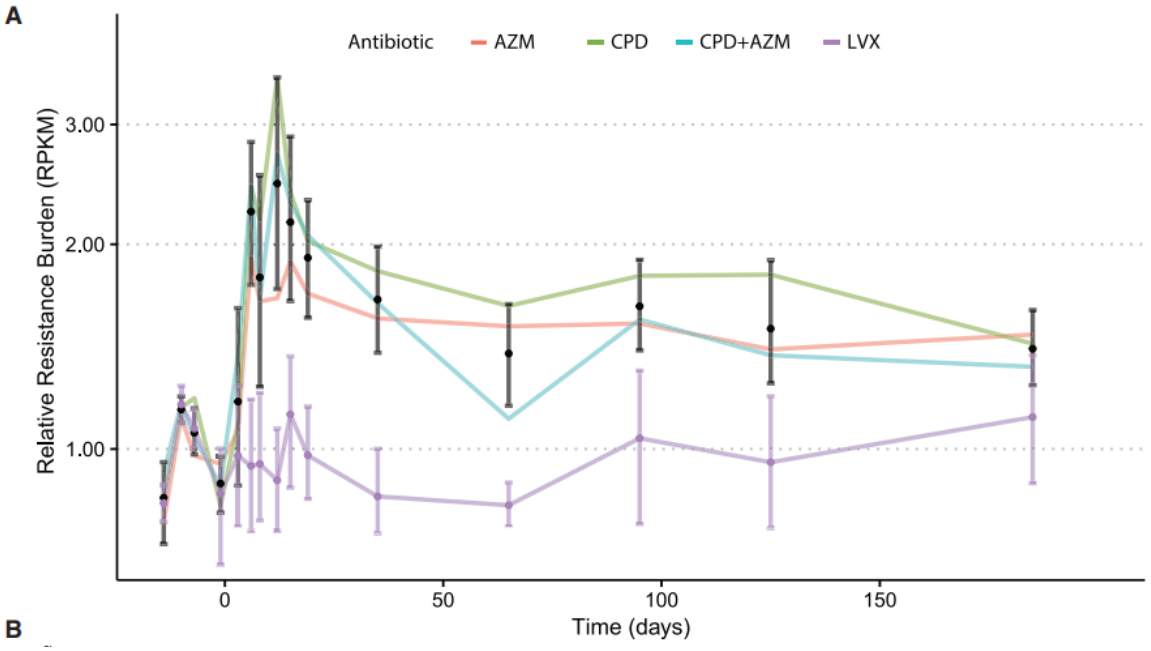


The investigators quantified microbiome dynamics before, during, and 6 months after exposure to 4 commonly used antibiotic regimens. They recruited 20 volunteers, randomized to 1 of 4 groups, to receive (1) azithromycin, (2) levofloxacin, (3) cefpodoxime, or (4) cefpodoxime + azithromycin. They sampled the gut microbiomes at 15 different timepoints, 4 before antibiotics and 11 after.

They found that all the antibiotics decreased the microbiome overall bacterial load (mean reduction of 4.78 log transformed CFU and 2.90 in aerobic and anaerobic bacterial titers respectively) as well as the species richness (Day 6 decreased by a mean of 11.5 when compared to 2 weeks before antibiotics). While most volunteers' microbiome returned to similar

species richness at 2 months, the overall composition and resistome were significantly different. However, those in the azithromycin group exhibited a significant delay in recovery of species richness. The non-azithromycin groups showed a recovery to baseline in CFU/ml counts and species richness by day 19 for both aerobic and anaerobic cultures, but the azithromycin groups (azithromycin and the cefpodoxime + azithromycin) continued to have significantly lower species richness until day 65.

They observed an acute decrease in species richness and culturable bacteria after antibiotics, with most healthy adult microbiomes returning to pre-treatment species richness after 2 months, but with an altered taxonomy, resistome, and metabolic output, as well as an increased antibiotic resistance burden. Azithromycin delays the recovery of species richness, resulting in greater compositional distance. A subset of volunteers experiences a persistent reduction in microbiome diversity after antibiotics and share compositional similarities with patients hospitalized in intensive care units. The resistome, the antimicrobial resistance gene burden increased significantly for those volunteers receiving cefpodoxime, azithromycin, and the combination of the two. Unexpectedly the levofloxacin group did not exhibit a significant change in the resistance burden over time.



Comment: Even short courses of antibiotics demonstrated disturbances in the gut microbiome, and which took months to recover. They also described long-lasting consequences on the resistance gene burden and composition differences of the gut microbiome even when the overall microbial burden recovers. The small treatment group size and 6-month study window of their study limited the ability to discern whether the observed alterations to the taxonomy and resistome persist to longer intervals, although other studies have recorded similar trends years after antibiotic exposure. The ICU comparator group was collected during routine C. difficile surveillance testing, and thus no clinical data were collected that could help identify patient covariates or further explain the variation in antibiotic perturbation in healthy volunteers.

Carbapenem-Resistant enterobacterales in individuals with and without health care risk factors —Emerging infections program, United States, 2012-2015 Am J Infect Cont published online July 27, 2022

doi.org/10.1016/j.ajic.2022.04.003

Active, population-based surveillance was conducted to identify case-patients with cultures positive for Enterobacterales not susceptible to a carbapenem (excluding ertapenem) and resistant to all third-generation cephalosporins tested at 8 US sites from January 2012 to December 2015. Medical records were used to classify cases as health care-associated, or as community-associated (CA) if a patient had no known health care risk factors and a culture was collected < 3 days after hospital admission. Enterobacterales isolates from selected cases were submitted to CDC for whole genome sequencing.

They identified 1499 CRE cases in 1194 case-patients; 149 cases (10%) in 139 case-patients were CA. The incidence of CRE cases per 100,000 population was 2.96 (95% CI: 2.81, 3.11) overall and 0.29 (95% CI: 0.25, 0.35) for CA. The organisms identified most frequently were *K pneumoniae* (53% of cases) and *E. coli* (18%), with *K pneumoniae* accounting for a higher proportion of HC (healthcare-associated) cases and *E coli* for a higher proportion of CA-CRE cases. Most CA-CRE cases were in White persons (73%), females (84%) and identified from urine cultures (98%). Risk factors that predispose patients to UTIs include diabetes, neurological conditions that affect the urinary tract, and urinary tract problems or abnormalities, were frequently identified among our CA-CRE cases. Among the 12 sequenced CA-CRE isolates, 5 (42%) harbored a carbapenemase gene. All carbapenemase enzymes identified were KPC.

Comment: These findings show that a small but notable proportion of CRE occur in persons without health care risk factors. Understanding populations at risk of CA CRE infections, as well as tracking the burden of CRE that is CA into the future, can inform CRE prevention strategies. These data describe cases that were collected from 2012 to 2015, and the epidemiology of CRE in the population under surveillance may have since changed, so findings may not reflect the current epidemiology of CRE. Some studies suggest CA-CRE is increasing. The rates of CA cases could have been underestimated because large private laboratories that mostly serve the outpatient setting did not participate uniformly across all sites. This data was retrospectively abstracted from medical records, and the quality and completeness of such records can vary between health care system and facility types, resulting in differences in reporting of some data elements. In the last issue of ID Watch, the CDC reported on an alarming increase in AMR during Covid-19 with an increase of 35% in CRE.

Association of entry into hospice or palliative care consultation during acute care hospitalization with subsequent antibiotic utilization Cl Microbiol Infect published online August 3, 2022

doi.org/10.1016/j.cmi.2022.07.018

The retrospective cohort study, conducted by researchers with the Iowa City VA Health Care System and the University of Iowa Carver College of Medicine, analyzed a cohort of VA patients who died from January 2014 through December 2019 and had been hospitalized within 6 months prior to death.

The investigators looked at demographics, comorbid conditions, duration of inpatient antibiotics administered, and outpatient antibiotics dispensed. They then compared antibiotic use in hospitalized VA patients placed into palliative care or hospice versus hospitalized patients who did not receive palliative or hospice care.

Of the 101,208 patients who died during the study period, 9,808 were in hospice care and 40,796 received a palliative care consult, and they were matched to 50,604 patients without palliative or hospice care.

Within 14 days of placement or consultation, 41% (4,040/9,808) of hospice patients and 48% (19,735/40,796) of palliative care patients received at least one antibiotic, while 25% (2,420/9,808) of matched non-hospice and 27% (10,991/40,796) of matched non-palliative care patients received antibiotics. Entry into hospice was independently associated with a 12% absolute increase in antibiotic prescribing (as measured by days of therapy) and entry into palliative care was associated with a 17% absolute increase during the 14 days post-entry versus pre-entry period.

Comment: This study confirms prior studies that documented continued antibiotic use at the end of life. More needs to be done to improve stewardship in patients in hospice or palliative care.

AMR Registry

An AMR Registry has been developed by nonprofit clinical data-sharing organization Vivli, which when fully operationalized will allow researchers from academic settings, governments, and multilateral organizations like the WHO to access raw antibiotic susceptibility data collected by pharmaceutical and biotech companies through a single, centralized online platform. To date, the AMR Register has received data sets from seven companies, covering resistance data on 925,000 bacterial isolates collected in more than 80 countries from 2004 through 2020.

Comment: The hope is that the susceptibility data shared through the AMR Register will enable researchers to map global patterns of resistance, identify new antibiotic-resistant pathogens, and develop policies that could halt their spread. In the US only the state of Illinois has an MDR Registry.

Bacteria that Causes Rare Disease Melioidosis Discovered in U.S. Environmental Samples CDC July 27, 2022

CDC has identified for the first time in domestic environmental samples the bacteria that causes a rare and serious disease called melioidosis. The bacteria, *Burkholderia pseudomallei* or *B. pseudomallei*, was identified through sampling of soil and water in the Gulf Coast region of Mississippi. Two unrelated individuals living in close geographic proximity in the Gulf Coast region of the southern United States became sick with melioidosis two years apart—in 2020 and 2022— prompting state health officials and CDC to take samples and test household products, soil, and water in and around both patients' homes. Three of the samples taken from soil and puddle water in 2022 tested positive at CDC for *B. pseudomallei*, indicating bacteria from the environment was the likely source of infection for both individuals and has been present in the area since at least 2020.

Comment: An average of 12 cases of melioidosis are diagnosed in the US each year, most have occurred in people with recent travel to a country where this bacteria is endemic. *B. pseudomallei* has historically been found in tropical and sub-tropical areas such as South and Southeast Asia, northern Australia, and parts of Central and South America and Puerto Rico. Melioidosis has a wide range of nonspecific symptoms like fever, joint pain, and headaches and can cause conditions that include pneumonia, abscess formation, or blood infections. Worldwide, melioidosis is fatal in 10 – 50% of those infected.

Per CDC, individuals living in the Gulf Coast of Mississippi and who have health conditions that may put them at higher risk—such as diabetes, chronic kidney disease, chronic lung disease, or excessive alcohol use— should take precautions to protect themselves:

- Avoid contact with soil or muddy water, particularly after heavy rains, and protect open wounds with waterproof dressings.
- Wear waterproof boots when gardening, doing yard work, or doing agricultural work, which can prevent infection through the feet and lower legs—particularly after flooding or storms.
- Wear gloves to protect the hands when working directly with soil.

? another potential emerging pathogen! ☹

Polio and Wastewater Surveillance

Polio has been detected in New York wastewater sample. The samples were taken in June and July in two counties north of New York City. The state confirmed the first U.S. case of the disease in nearly a decade in an unvaccinated Rockland County, N.Y., man on July 21. There was no indication that the infected man was the source found in the wastewater samples, and the investigation into the origin is ongoing.

Comment: In the past for every one case of paralytic polio observed, there may be hundreds of other people infected. Health officials are urging those unvaccinated for polio, including children by 2 months of age, those who are pregnant and those who have not previously completed their vaccine series to get vaccinated immediately with IPV. The vaccination against polio in the Rockland religious community is only ~60%. One the many negative health impacts due to Covid-19 is decrease pediatric vaccination rates. See Covid-19 News below

Monkeypox

CDC to Make Monkeypox Nationally Notifiable Condition

US Declares Monkeypox Outbreak a National Health Emergency

The CDC said last Wednesday it plans to make monkeypox disease a nationally notifiable condition. The designation, which is set to take effect on August 1st, updates criteria for reporting of data on cases by states to the agency and would allow the agency to monitor and respond to monkeypox even after the current outbreak recedes. States will be required to

report confirmed or probable monkeypox cases within 24 hours. The CDC asked for data to be shared even before the investigation of a case was completed.

Officials from HHS and FDA declared the ongoing monkeypox outbreak in the US a public health emergency, paving the way for an increase in funding for tests, vaccines, and treatments for Monkeypox.

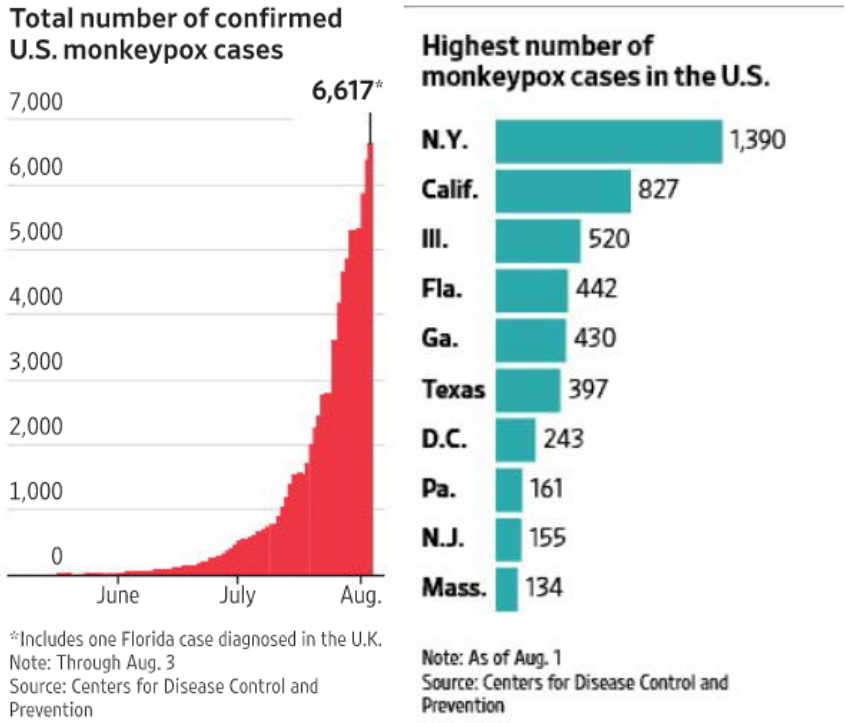
Comment: Given the rise in cases, CDC's action to make this a reportable disease is appropriate and needed to better understand transmission and effective interventions. The US is now aligned with WHO in declaring Monkeypox a health emergency.

In addition, the FDA was considering authorizing fractional dosing of Jynneos, the only vaccine approved for use against monkeypox in the US. Intradermal injection at one-fifth the dose strength, as opposed to intramuscular injection, would stretch the supply of vaccine, which has been in high demand in virus hot spots such as New York City, Chicago, and San Francisco. HHS has previously said the federal government has ordered 6.9 million doses of Jynneos, but the bulk of the vaccines will not be available until 2023! See below

US has Surpassed Spain as the Country with the Most Cases

CDC officials have finally declared monkeypox a public-health emergency. [da!] NY and CA lead the way. To date, there have been more than 7000 confirmed or suspected cases in the US. Epidemiologists said the virus is exploiting close-knit social and sexual networks, but knowledge of how the virus is spreading in this current outbreak remains incomplete! The WHO declared monkey-pox a global health emergency and says monkeypox is most commonly spread through close contact with an infected person's rash, lesions and bodily fluids. The virus can also spread via fabrics and other materials, and through prolonged exposure to an infected person's saliva or mucus. Airborne, transmission of the virus hasn't been considered to be of significant concern by public-health experts, but some early research suggests it could be possible in certain conditions through very small droplets that remain suspended in the air over long distances and time. A person can spread monkeypox until all their lesions have scabbed and the scabs have fallen off. Public-health officials have advised potentially infectious people to remain isolated for the duration of their illness. Monkeypox symptoms typically last two to four weeks.

The WHO noted that cases rose 18.7% last week, with Europe and the Americas reporting the bulk of cases over the past month. [See graphs below] In the last week of July, the US saw the largest spike in cases. (See above) Together 10 countries account for 89% of the world's cases, including the US (5,175 cases [now over 7000]), Spain (4,298), Germany (2,677), the United Kingdom (2,546), France (1,955), Brazil (1,369), the Netherlands (879), Canada (803), Portugal (633), and Italy (479). Of all case-patients with available data, 98.8% are men, and the median age is 37. Men 18 to 44 years old represent 76.7% of cases in the global outbreak. Among cases with known data on sexual orientation, 97.5% identified as men who have sex with men (MSM), and 1% identified as bisexual. Thirty-seven percent of cases with known HIV status were HIV-positive. Sexual contact is the likely transmission event for 91.5% of patients, and 339 cases were reported in healthcare workers. Most health workers, however, were infected in the community and not through workplace exposure. <10% of cases have been hospitalized almost all for pain control.



Comment: Many public health officials around the US say we were too slow at responding to the outbreak when it first emerged and continue to take insufficient action to stem the spread of the virus. [see Perspective in last ID Watch] CDC has said they have been working with partners to help put information in the hands of people who may be at highest risk for contracting monkeypox. The CDC released updated data confirming the monkeypox outbreak is concentrated among men who have had sex with several men, and issued more detailed recommendations on how to avoid exposure to the disease.

Among 291 men surveyed, 40% reported that they had two to four partners and 14% reported five to nine partners in the three weeks before developing monkeypox, according to the report. About 19% reported 10 or more partners during that period, the CDC said Friday. And among 86 men who reported information, 28% said they had had group sex, which is defined as sex with more than two people, at a festival, group sex event or sex party, based on the report. The research was conducted from May 17 through July 22.

After releasing the data, the CDC also issued more specific warnings and recommendations for reducing the risk of monkeypox than its earlier guidelines. The CDC also extended its recommendations to anyone sexually active, not just those who suspect they are infected. In addition to advising people to limit their number of sex partners, the CDC recommended wearing latex, polyurethane or nitrile gloves, and changing or cleaning clothes, bedding, towels and sex toys after sex.

There is still inadequate vaccine and antivirals (tecovirimat) to meet the needs (see below), but supplies are increasing. In a recent report, the shortage of vaccines was caused in part because HHS failed early on to ask that bulk stocks of the vaccine it already owned be bottled for distribution. Here is an interesting statistic**: The US leads in deaths due to Covid-19 and now leads in number of cases of Monkeypox. Why?**

Tecovirimat and the Treatment of Monkeypox — Past, Present, and Future Considerations N Engl J Med published online August 4, 2022

DOI: 10.1056/NEJMp2210125

The authors are from the FDA, NIH, and CDC. However, the views expressed in this article are those of the authors and do not necessarily represent those of the FDA, the CDC, or the NIH. The authors try explaining their decision to treat tecovirimat as an investigational drug.

In the current situation, there is a drug — tecovirimat, available for clinical use under an expanded-access protocol (https://www.cdc.gov/poxvirus/ monkeypox/clinicians/obtaining - tecovirimat.html) — that might conceivably speed resolution of monkeypox illness and improve outcomes yet poses the same conundrum: how to manage compassionate access to a drug whose safety and efficacy in humans have not been fully established. The FDA approved tecovirimat as a smallpox treatment in 2018, based on safety data in people and efficacy data in primates — which, for the purposes of the trial, were infected with monkeypox. The so-called animal rule allows the agency to approve drugs when testing them in people would be unethical.] Health officials have designated tecovirimat, also called Tpoxx, an "investigational drug," which they say means it cannot be released from the strategic national stockpile without a series of bureaucratic steps. The FDA has simplified the process as of late.

The Department of HHS on Thursday declared monkeypox a national health emergency. But Secretary Xavier Becerra did not take an additional step that would have allowed the FDA to grant EUAs for vaccines and treatments, as the agency did during the Covid-19 pandemic. The article while acknowledging that animal data is promising and that the drug seemed safe in healthy patients, they wrote that, without large clinical trials, "we will not know whether tecovirimat would benefit, harm or have no effect on people with monkeypox disease." Currently, they claim it is unclear if or how well this drug works for monkeypox patients. They go on to say that providing tecovirimat only as an investigational drug provides data from patients who use this drug. They believe this will ultimately help us understand who will benefit most, what the true benefits are and any potential unintended consequences. They "recognize that monkeypox can cause severe disease and that tecovirimat has been shown to have

efficacy in animal models of monkeypox and an acceptable safety profile in healthy people. Therefore, while RCTs are under development, the Centers for Disease Control and Prevention (CDC) and the FDA have worked together to streamline the expanded-access process by reducing paperwork and data collection, and we will continue to fine-tune these mechanisms with input from health care providers using this process. In parallel, we believe that it remains critical to conduct RCTs in the United States to determine whether tecovirimat is a safe and effective treatment for monkeypox disease, especially given the disease's clinical presentation in the current outbreak." They conclude: "The CDC, the FDA, and the NIH will continue to work together to provide access to tecovirimat for compassionate use while appropriately evaluating its safety and efficacy in RCTs."

Comment: The paperwork and bureaucracy of gaining access to tecovirimat is challenging given the growing public health emergency in the US with monkeypox. As I understand, the law gives the agency considerable flexibility to use scientific assessments to ensure those in need get the medications that can help them. HHS could have allowed the FDA to grant EUA for treatments. This would ensure greater access for those who truly need the drug and cut down on the paperwork and still be able to track outcomes and adverse events. RCTs can continue as we did for Covid-19. The number of new cases is exploding and represents an underestimate of the true numbers.

A nice review on anti-virals against Monkeypox has been published online **in Clin Infect Dis July 29, 2022 [doi.org/10.1093/cid/ciac622]** In this review, they explore three antiviral agents with activity against monkeypox and other orthopoxviruses: cidofovir, brincidofovir, and tecovirimat. Cidofovir, and its prodrug brincidofovir, are inhibitors of DNA replication with a broad spectrum of activity against multiple families of double-stranded DNA viruses. Tecovirimat has more specific activity against orthopoxviruses and inhibits the formation of the extracellular enveloped virus necessary for cell-to-cell transmission. See below They conclude that given their favorable tolerability profile, tecovirimat and brincidofovir are preferred therapeutic options over cidofovir.

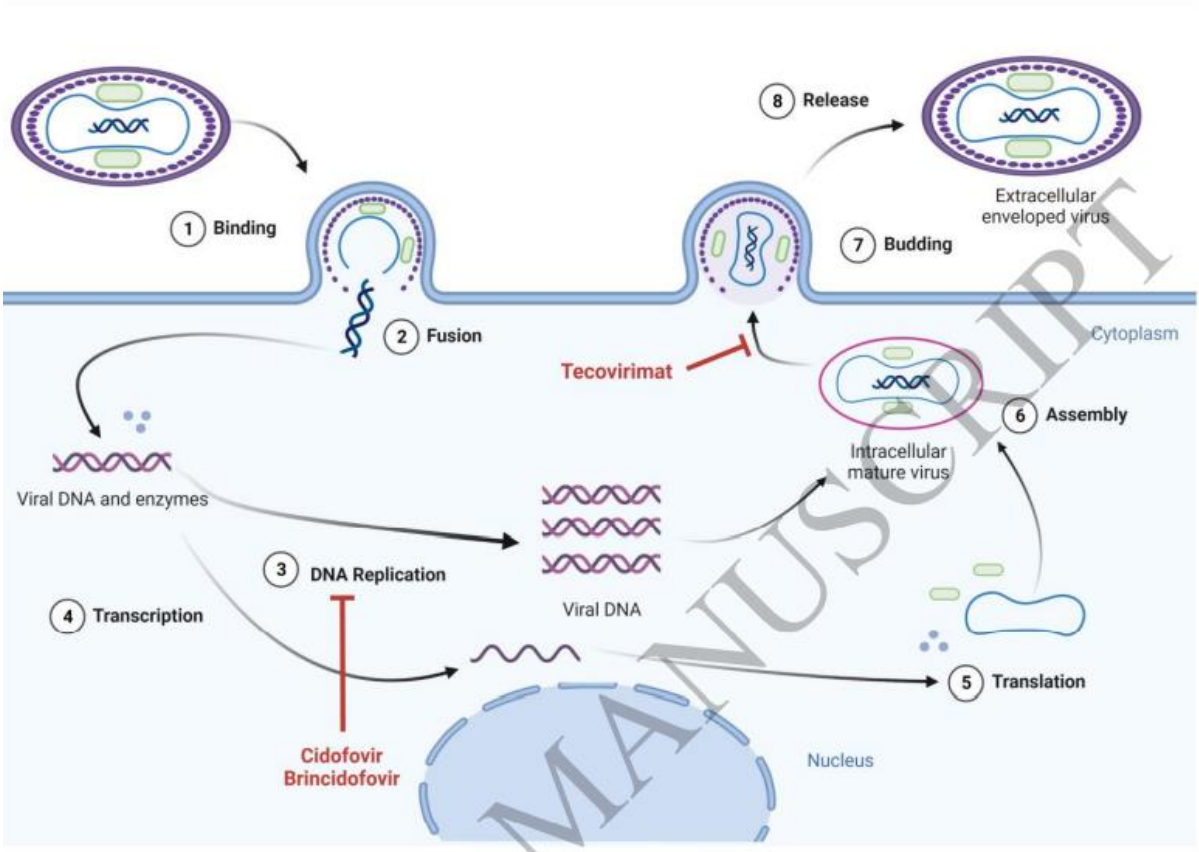


Figure 3
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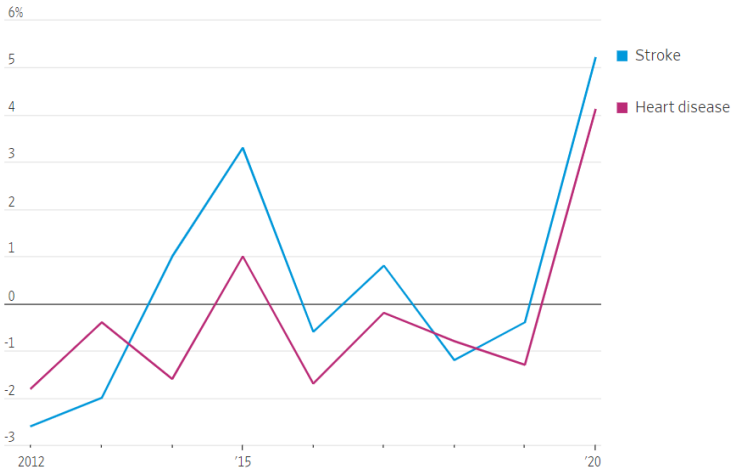
COVID-19

Covid-19 News

Covid-19 and Impact on US Health

Heart Disease and Stroke

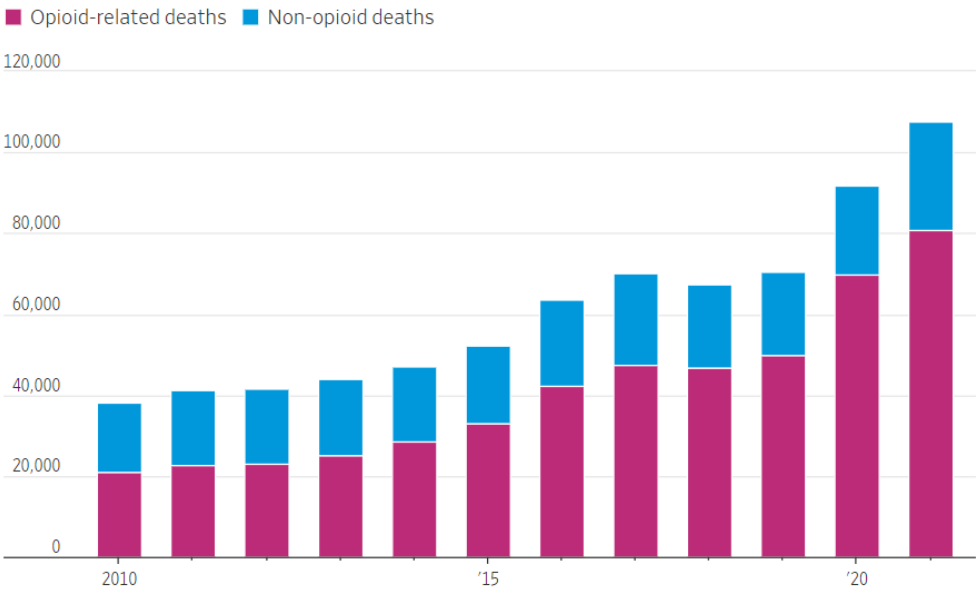
Change in U.S. deaths from previous year, accounting for age change



Source: Stephen Sidney, Kaiser Permanente Northern California Division of Research

Drug and Alcohol Use

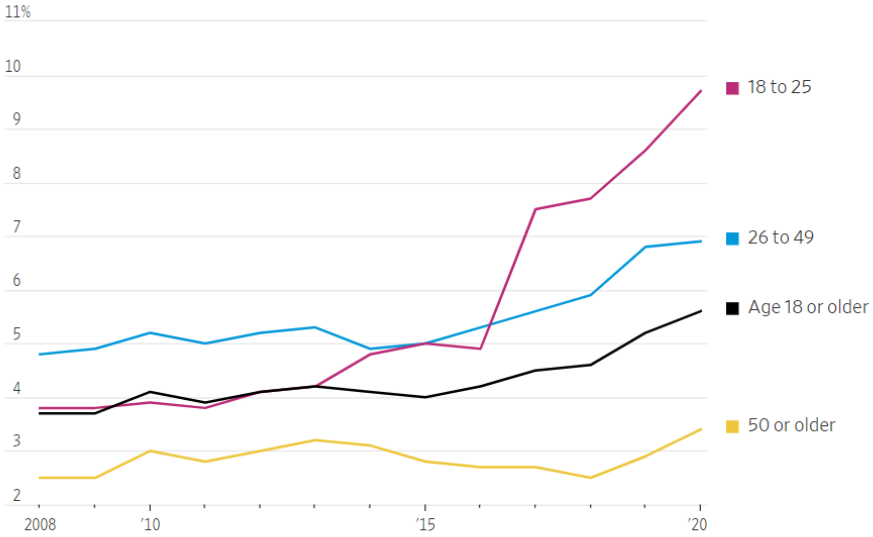
Drug-overdose deaths in the U.S.



Note: 2021 data is provisional.
Source: Centers for Disease Control and Prevention

Mental Health

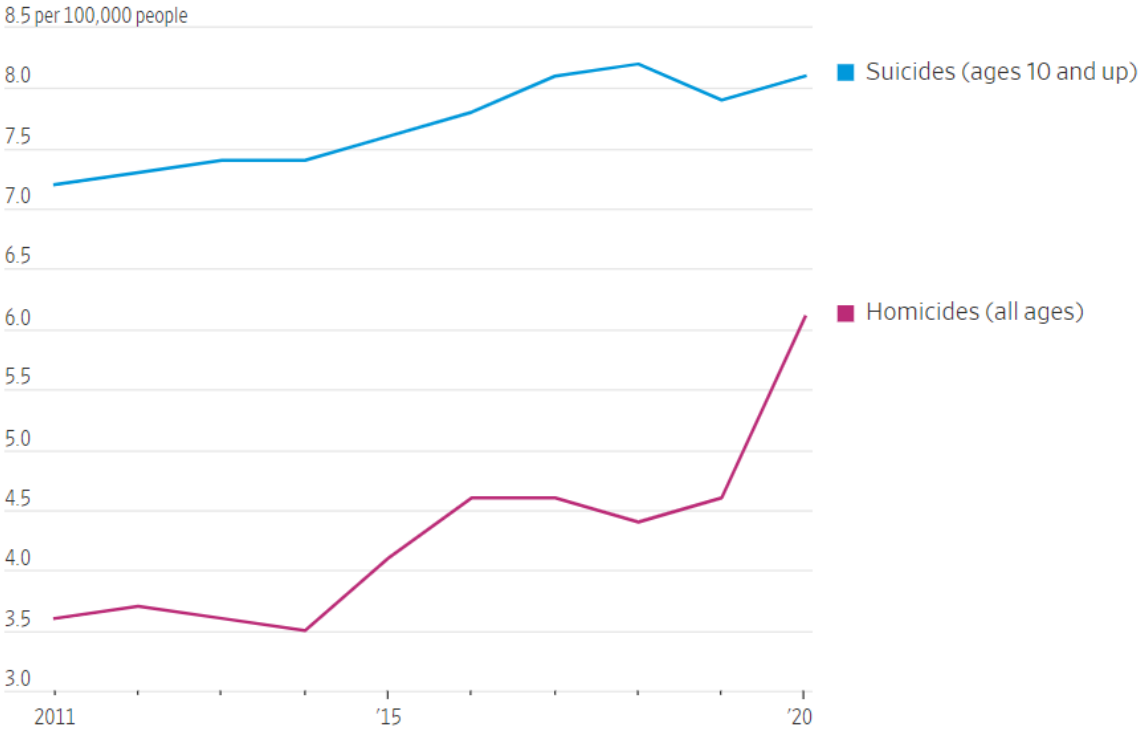
Serious mental illness in the past year among U.S. adults



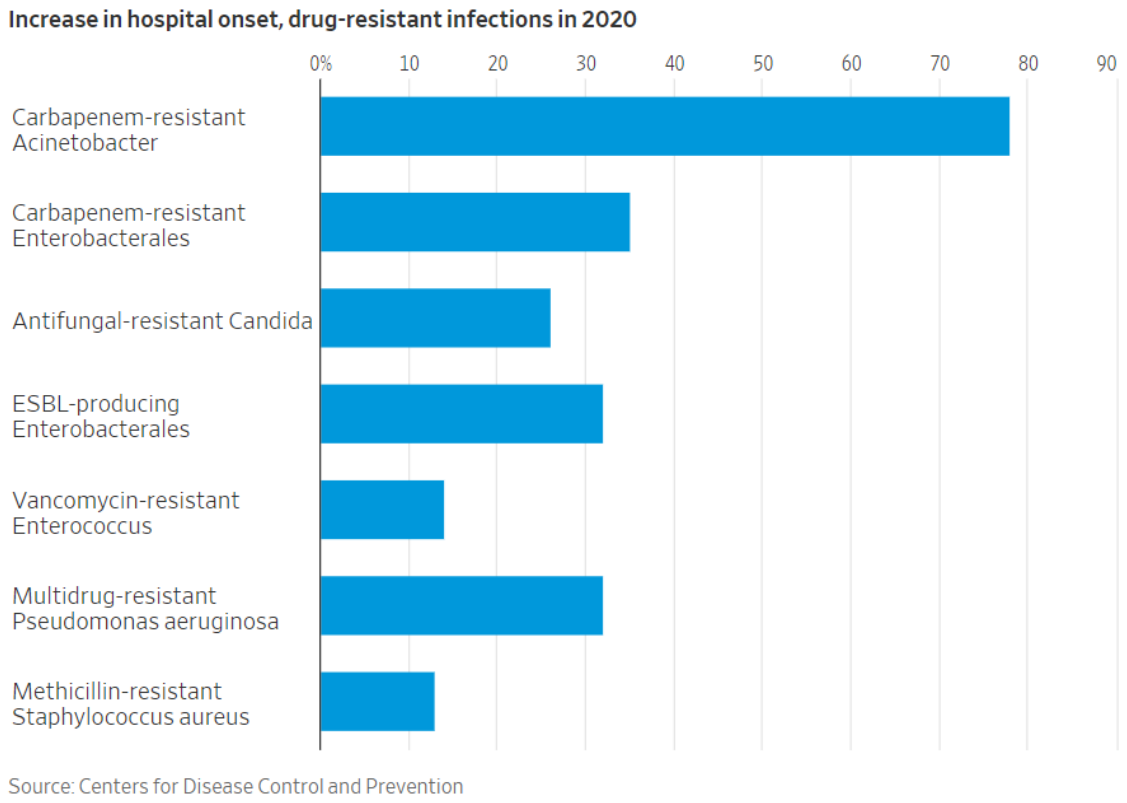
Note: Because of methodological changes in 2020, caution should be used when comparing that estimate to prior years.
Source:Substance Abuse and Mental Health Services Administration

See article below

Age-adjusted rates of firearms deaths

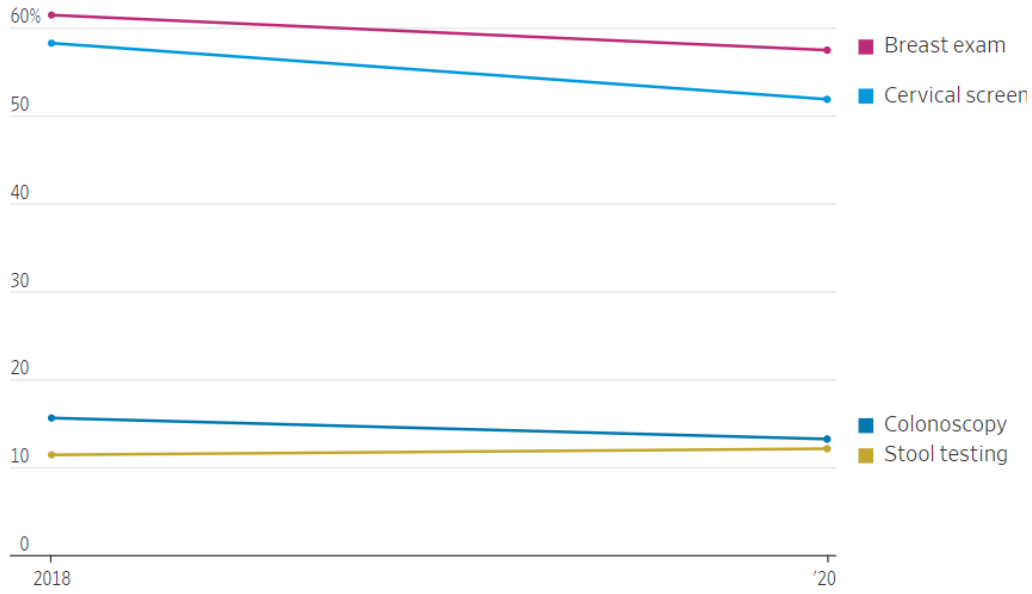


Source: Centers for Disease Control and Prevention



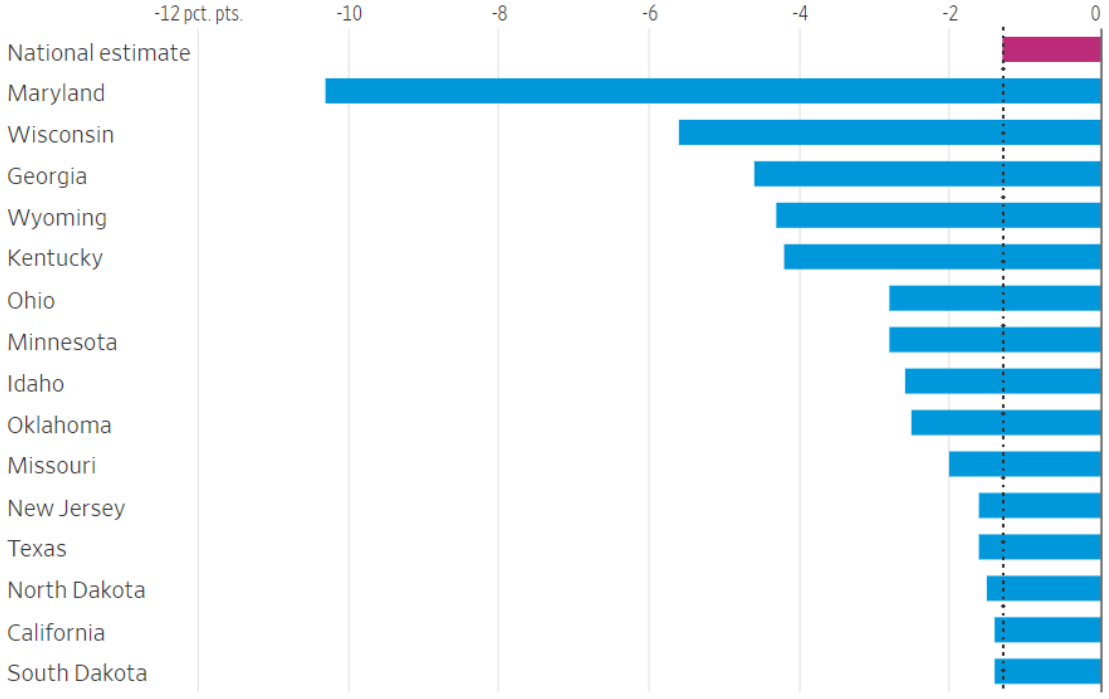
See last week's ID Watch

Percentage of eligible people who underwent cancer screening within the past year



Note: Estimates were adjusted for age, sex, state and education.
Source: Fedewa, et al., JAMA Network Open, June 2022, American Cancer Society

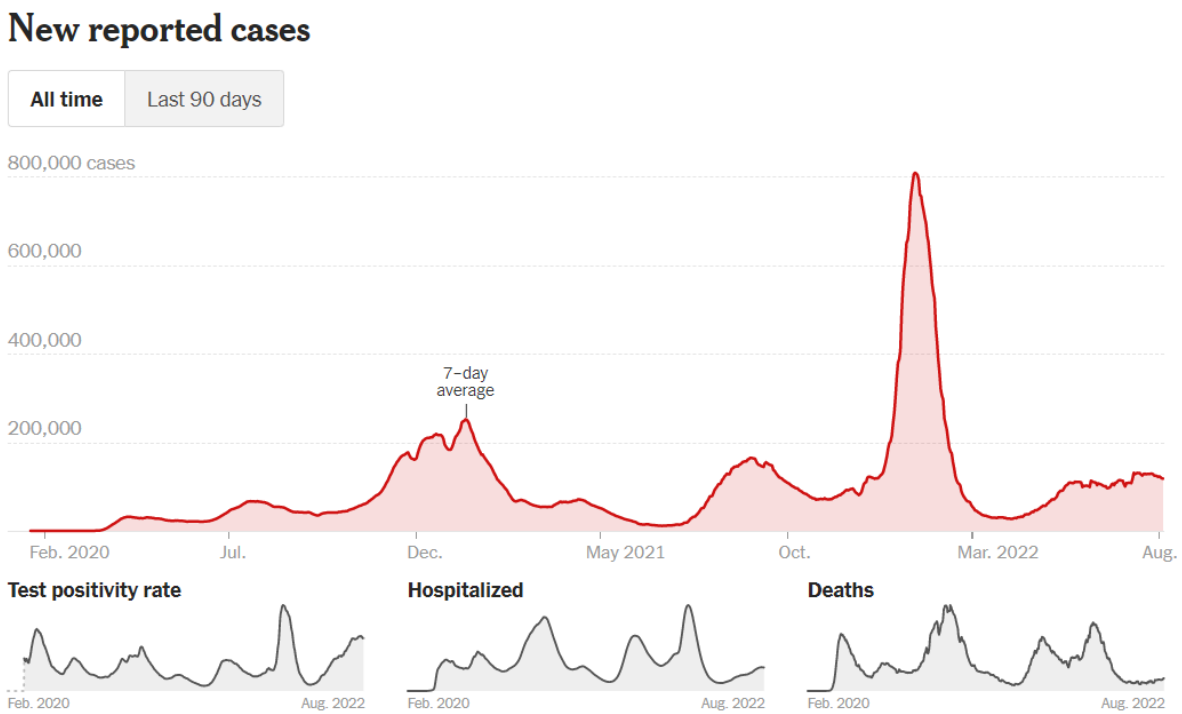
Largest declines in kindergarten vaccination rates for measles, mumps and rubella, 2020-21



Source: Centers for Disease Control and Prevention

Comment: These graphs tell a very disturbing pattern-The downstream effects of the Covid-19 pandemic's influence has impacted nearly every aspect of health in America in a negative way.

COVID-19 by the Numbers



Comment: Daily case counts have begun to trend downward in recent days, accompanied by similar declines in test positivity and hospitalizations so far this month. Hospitalizations have also decreased this week after increasing steadily from April through July. Deaths, a delayed indicator, inched up in recent weeks, but remain much lower than they have been at most points in the pandemic. The current surge with BA.5 may have peaked. The big question what lies ahead as we move into the fall and winter. Could this be the beginning of the end? I hope so, but this virus has been unpredictable, and we cannot let our guard down. I will remind everyone that the pandemic of 1918 lasted two years.

COVID-19 Journal Review

The Impact of the COVID-19 Pandemic on Adolescent Mental Health and Substance Use J Adolescent Health published online July 12, 2022

doi.org/10.1016/j.jadohealth.2022.05.025

Data were from Baseline (2018) and Wave 3 (2020; mean age =14.8; 50% female) of 1,188 adolescents recruited from 12 Texas public middle schools as part of a randomized controlled trial. Participants were primarily Black (23%), Latinx (41%), Asian (11%), and White (9%). They assessed mental health and substance use (Baseline and Wave 3) and pandemic-related physical interaction, loneliness, stress, family conflict, and economic situation (Wave 3)

COVID-19-induced stress and loneliness were linked to depression (beta = 0.074, p ≤ .001; beta =0.132, p ≤ .001) and anxiety (beta =0.061, p = .001; beta = 0.088, p ≤ .001) among ethnically diverse adolescents. Adolescents who did not limit their physical interactions due to COVID-19 had fewer symptoms of depression (beta = -0.036, p = .03); additionally, adolescents who did not restrict their socializing were substantially more likely to report using a variety of substances (e.g., for episodic heavy drinking; odds ratio =1.81, p = .001). Increased use of a food bank was linked to depression (beta = 0.063, p ≤ .001) and a negative change in financial situation was linked to increased alcohol use (odds ratio = 0.70, p = .04) among adolescents. After controlling for prepandemic psychopathology and race/ethnicity, COVID-19 induced isolation, loneliness, stress, and economic challenges were linked to poor mental health and substance misuse.

Comment: In this study of 1,188 ethnically diverse adolescents, the stress and isolation caused by the COVID-19 pandemic was associated with psychosocial health problems, even after accounting for prepandemic health. This generation of adolescents will benefit from interventions designed to mitigate these mental and behavioral health impacts. The results of this study mirror other studies on the impact of COVID-19 on adolescents, indicating increases in depression, anxiety, isolation, and stress. [Youth Adolesc. 2021; 50: 44-57] There are several limitations. First, all data were based on adolescent self-report. Next the measure of substance misuse was limited to only the past-year use. Future studies should consider more recent misuse and the intensity of misuse. See impact on mental health above during the pandemic

Association Between Vaccination and Acute Myocardial Infarction and Ischemic Stroke After COVID-19 Infection JAMA published online July 22, 2022

doi:10.1001/jama.2022.12992

Full vaccination against COVID-19 was associated with a reduced risk of acute myocardial infarction (MI) and ischemic stroke as secondary complications of acute infection.

These cardiovascular events were significantly reduced in the 31 to 120 days after COVID-19 diagnosis for the fully vaccinated compared with those not vaccinated:

- Composite of hospitalizations for acute MI and ischemic stroke: adjusted HR 0.42 (95% CI 0.29-0.62)
- Acute MI: adjusted HR 0.48 (95% CI 0.25-0.94)
- Ischemic stroke: adjusted HR 0.40 (95% CI 0.26-0.63)

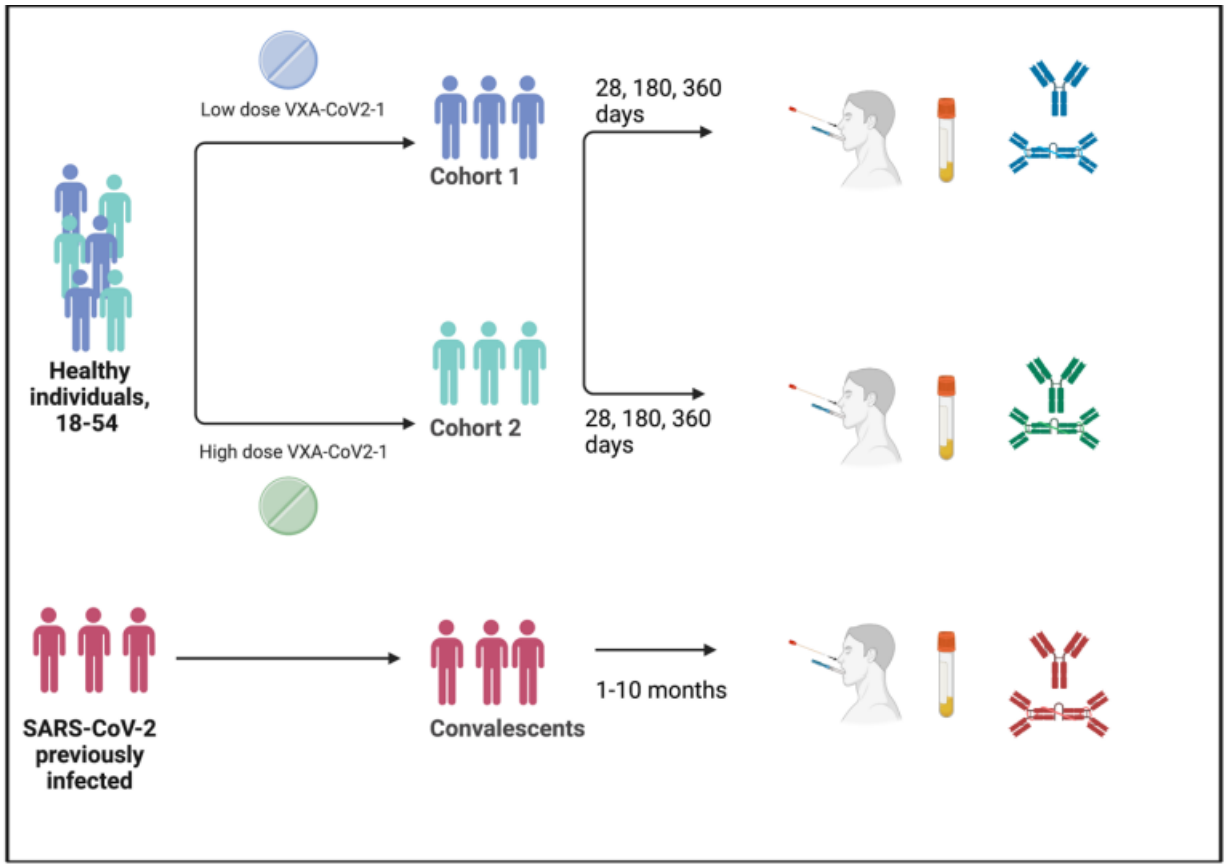
The reduction in post-COVID heart attacks and strokes among the fully vaccinated was observed across various subgroups. However, it did not reach statistical significance for people with a previous history of outcome events or for those with severe or critical COVID-19.

Comment: The findings support vaccination, especially for those with risk factors for cardiovascular diseases. It had been unclear if vaccines against SARS-CoV-2 prevent secondary complications of COVID-19. A potential limitation included that diagnosis codes for reimbursement were used to capture outcome events; therefore, some diagnostic inaccuracies may exist. Also, there were imbalances in patient characteristics by vaccination status. A model was applied to offset the effect of such imbalances, but the possibility of unobserved bias remains.

SARS-CoV-2 oral tablet vaccination induces neutralizing mucosal IgA in a phase 1 open label trial medRxiv posted July 19, 2022

doi.org/10.1101/2022.07.16.22277601

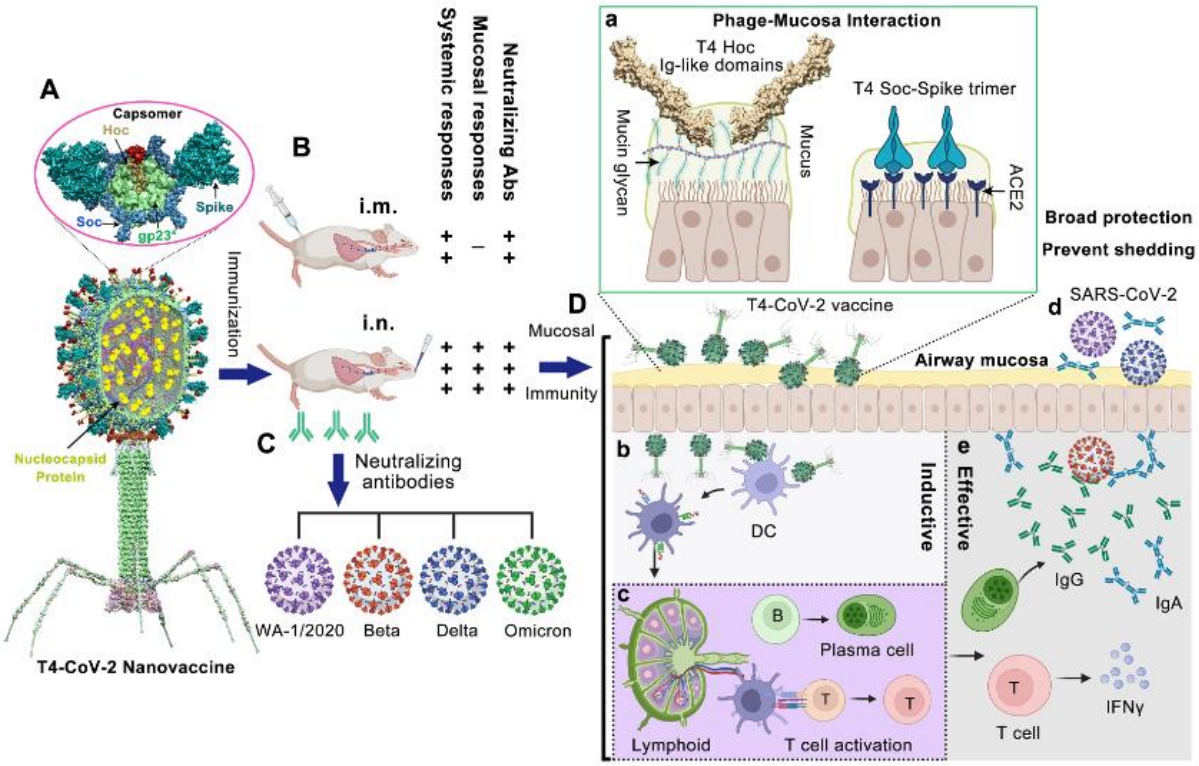
The investigators conducted a single-site, dose-ranging, open-label clinical trial of an oral SARS-CoV-2 vaccine to determine safety and immunogenicity.[Phase 1] The tablet vaccine is comprised of a non-replicating adenoviral vector expressing the SARS-CoV-2 Spike and Nucleocapsid genes and a double-stranded RNA adjuvant. 35 adult subjects meeting inclusion/exclusion criteria received a single low (1x1010 IU) or high (5x1010 IU) dose and 5 subjects received two low doses. Nasal, saliva and serum samples were assessed for the presence of IgA, IgG and surrogate neutralizing antibodies. Convalescent subjects between 1-8 months post infection were recruited to give nasal, saliva, and serum samples for comparison.



No serum neutralizing antibodies were observed, but modest IgA responses were seen in serum post immunization. The majority of vaccine recipients had an increase in mucosal secretory IgA which was highly cross-reactive against all coronaviruses tested [highly cross-reactive to omicron and delta variants of SARS-CoV-2 as well as previously shown that both the saliva and nasal samples at day 29 post vaccination were cross-reactive to other human alpha and beta coronaviruses] and persisted up to 360 days. Furthermore, the nasal IgA induced by vaccination has superior neutralizing activity compared to convalescent nasal samples.

Comment: Oral vaccine platform increases adaptive immune responses at mucosal surfaces, which are important sites of entry for respiratory pathogens such as SARS-CoV-2 and potentially important sites for long-term low level viral replication of SARS-CoV-2. Mucosal IgA, due to its polymeric nature and ability to translocate, is also more likely to hinder transmission [Nature Reviews Immunology. 2006;6(2):148-58; Sci Transl Med. 2021;13(577]; a vaccine that could decrease asymptomatic transmission could alleviate outbreaks. This vaccine was tested before mRNA vaccines were readily available. Currently, the majority of people in the US have been immunized with an mRNA vaccine and/or have natural immunity, and it's unclear how this vaccine would perform in such a population. Given that mRNA vaccines induce potent, but transient serum responses, it is hopeful that this vaccine would complement the mRNA vaccines. The vaccine was well tolerated. I found this report intriguing and would like to see larger phase 3 trials to confirm. An intranasal vaccine is also under development. See next article

A Bacteriophage-Based, Highly Efficacious, Needle- and Adjuvant-Free, Mucosal COVID-19 Vaccine mBio published online July 28, 2022



Investigators report on a noninfectious, bacteriophage T4-based, multicomponent, needle- and adjuvant-free, mucosal vaccine harboring engineered Spike trimers on capsid exterior and

nucleocapsid protein in the interior. Intranasal administration of two doses of this T4 SARS-CoV-2 vaccine 21 days apart induced robust mucosal immunity, in addition to strong systemic humoral and cellular immune responses. The intranasal vaccine induced broad virus neutralization antibody titers against multiple variants, Th1-biased cytokine responses, strong CD41 and CD81 T cell immunity, and high secretory IgA titers in sera and bronchoalveolar lavage specimens from vaccinated mice. All of these responses were much stronger in intranasally vaccinated mice than those induced by the injected vaccine. Furthermore, the nasal vaccine provided complete protection and sterilizing immunity against the mouse-adapted SARS-CoV-2 MA10 strain, the ancestral WA-1/2020 strain, and the most lethal Delta variant in both BALB/c and human angiotensin converting enzyme (hACE2) knock-in transgenic mouse models.

Comment: This modular, needle-free, phage T4 mucosal vaccine delivery platform is a promising candidate for designing efficacious mucosal vaccines against other respiratory infections and for emergency preparedness against emerging epidemic and pandemic pathogens. The immune responses stimulated by the T4 based COVID-19 vaccine were broad and included the following: Th1 and Th2 derived IgG and IgA antibodies in sera, virus-neutralizing antibodies, CD41 helper and effector T cells and CD81 killer T cells, Th1-biased cytokines, and mucosal IgG and sIgA antibodies in BALF. The T4-CoV-2 vaccine appears safe and stable. A noninfectious phage T4-CoV-2 vaccine with no tropism to human cells and no use of adjuvants or chemical stimulants represent significant advantages. Phase 1 human clinical trials are needed to translate the vaccine into reality.

Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

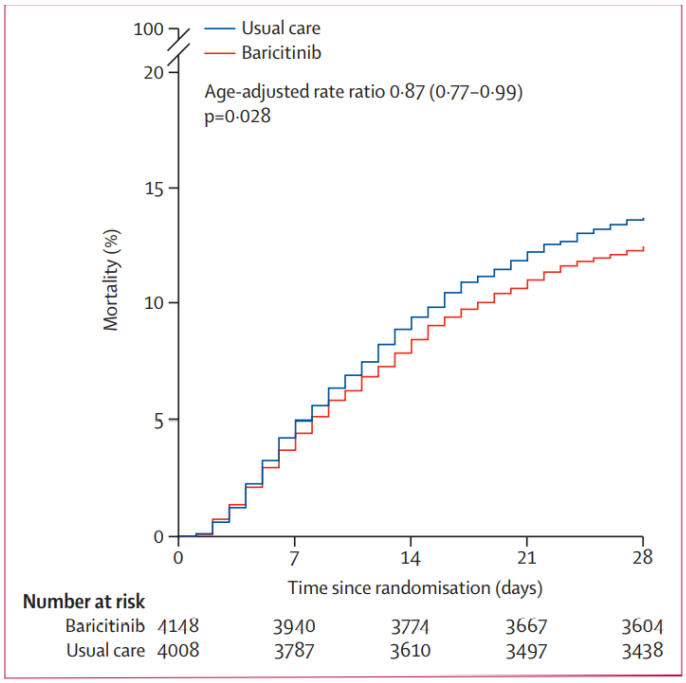
Lancet 2022; 400: 359–68

This is a randomized, controlled, open-label, platform trial (Randomised Evaluation of COVID-19 Therapy [RECOVERY]), which assessed multiple possible treatments in patients hospitalized with COVID-19 in the UK. Eligible and consenting patients were randomly allocated (1:1) to either usual standard of care alone (usual care group) or usual care plus baricitinib 4 mg once daily by mouth for 10 days or until discharge if sooner (baricitinib group). The primary outcome was 28-day mortality assessed in the intention-to-treat population. A meta-analysis was done, which included the results from the RECOVERY trial and all previous randomized controlled trials of baricitinib or other JAK inhibitor in patients hospitalized with COVID-19.

At randomization, 95% of patients were already receiving corticosteroids and 23% were receiving tocilizumab (with planned use within the next 24 h recorded for a further 9%). Overall, 514 (12%) of 4148 patients allocated to baricitinib versus 546 (14%) of 4008 patients allocated to usual care died within 28 days (age-adjusted rate ratio 0·87; 95% CI 0·77−0·99; p=0·028). This 13% proportional reduction in mortality was somewhat smaller than that seen in a meta-analysis of eight previous trials of a JAK inhibitor (involving 3732 patients and 425 deaths), in which allocation to a JAK inhibitor was associated with a 43% proportional reduction in mortality (rate ratio 0·57; 95% CI 0·45–0·72).

Including the results from RECOVERY in an updated meta-analysis of all nine completed trials (involving 11,888 randomly assigned patients and 1485 deaths) allocation to baricitinib or

another JAK inhibitor was associated with a 20% proportional reduction in mortality (rate ratio 0·80; 95% CI 0·72–0·89; p<0.0001).



	Deaths/patients randomly assigned (%)		Observed minus expected deaths		Rate ratio of death rates (95% CI)
	JAK inhibitor group	Control group	(O–E)*	Var (O–E)	
Murugesan†	0/50 (0%)	0/50 (0%)	0·0	0·0	
Cao and colleagues†	0/20 (0%)	3/21 (14%)	−1·5	0·7	0·13 (0·01–1·31)
RUXCOVID†	9/287 (3%)	(3/145) ×2‡ (2%)	1·0	2·6	1·48 (0·44–4·99)
Guimarães and colleagues†	4/144 (3%)	8/145 (6%)	−2·0	2·9	0·50 (0·16–1·60)
COV-BARRIER (critically ill)	20/51 (39%)	29/50 (58%)	−4·7	6·4	0·47 (0·22–1·03)
RUXCOVID-DEVENT†	90/164 (55%)	(36/47) ×4‡ (77%)	−7·9	8·8	0·41 (0·21–0·79)
ACTT2	24/515 (5%)	37/518 (7%)	−6·4	14·4	0·64 (0·38–1·07)
COV-BARRIER	62/764 (8%)	100/761 (13%)	−19·2	36·2	0·59 (0·43–0·82)
Subtotal: 8 trials	**209/1995 (10%)**	**327/2023 (16%)**	**−40·7**	**72·0**	**0·57 (0·45–0·72)**
RECOVERY	514/4148 (12%)	546/4008 (14%)	−35·7	264·3	0·87 (0·77–0·99)
All trials	**723/6143 (12%)**	**873/6031 (14%)**	**−76·3**	**336·3**	**0·80 (0·72–0·89)**
Heterogeneity between RECOVERY and previous trials: χ^2_1=10·5 (p=0·0012)					p<0·0001

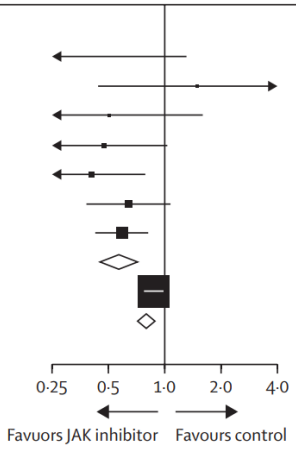


Figure 4: **Meta-analysis of mortality in randomised controlled trials of a JAK inhibitor in patients hospitalised with COVID-19**

Comment: On Nov 19, 2020, the FDA granted EUA for baricitinib in combination with remdesivir, which was revised on July 28, 2021, to no longer require co-administration with remdesivir. On May 10, 2022, the FDA issued a new indication for the use of baricitinib in adults hospitalized with COVID-19 requiring supplemental oxygen, non-invasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation. The NIH guidelines were updated in February 2022 recommend the use of baricitinib for patients on dexamethasone who have rapidly increasing oxygen needs and systemic inflammation. In January 2022, the WHO updated their COVID-19 therapeutics guidelines to include a strong recommendation for the use

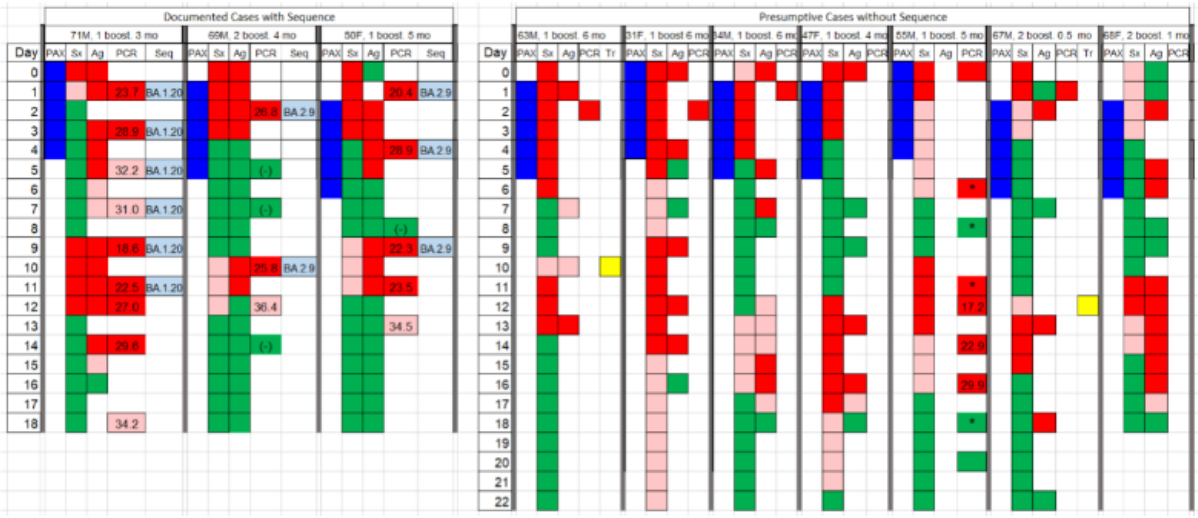
of baricitinib as an alternative to an IL-6 receptor blocker, in combination with corticosteroids, in patients with severe or critical COVID-19. In April IDSA updated their COVID-19 guidelines on baricitinib**.** Among hospitalized adults with severe COVID-19, the IDSA panel suggests baricitinib with corticosteroids rather than no baricitinib. The results from the RECOVERY trial and this meta-analysis support the evidence that baricitinib can reduce mortality and other adverse clinical outcomes in patients hospitalized with COVID-19 and support the co-administration of baricitinib with dexamethasone or an IL-6 receptor blocker.

Rapid Relapse of Symptomatic Omicron SARS-CoV-2 Infection Following Early Suppression with Nirmatrelvir/Ritonavir Res Square posted May 23, 2022

doi.org/10.21203/rs.3.rs-1588371/v3

The authors describe relapse of COVID-19 symptoms and SARS-CoV-2 viral load following nirmatrelvir/ritonavir (NM/R) in 10 non-immunocompromised patients aged 31 to 71-years-old. Most patients improved rapidly after treatment with NM/R and had negative antigen or PCR tests prior to relapse on Days 9-12 of their illness. Relapse symptoms were described most frequently as cold symptoms, though some patients experiencing a recurrence of fatigue and headache. All relapses resolved without additional antiviral treatment. Viral load during relapse was comparable to levels during initial infection. Sequencing in three patients indicated that relapse was not due to a treatment-emergent mutation or infection with a different viral strain. One symptomatic and one presymptomatic patient transmitted SARS-CoV-2 to family members during relapse. The presence of high viral load[Ct] and the occurrence of two transmission events suggest that patients with relapse should isolate until antigen testing is negative.

Time course of SARS-CoV-2 infection and COVID-19 symptoms. Day 0 was the first day of positive tests or symptoms. Shown are the time periods for administration of NM/R (Pax), symptoms (Sx), antigen tests (Ag), PCR (Ct values when available), subvariant classification (Seq), and transmission (Tr). Symptoms and test results are color coded as follows: green, asymptomatic or negative test; red, symptomatic or abnormal test (positive antigen test or PCR Ct <30); pink, mild or improving symptoms, faint antigen test, or PCR Ct >30; yellow, the first possible day of transmission during rebound. * Cue test in 55M.



Comment: Additional work is required to determine the frequency, duration, and spectrum of rebound symptoms. This study also supports isolation if a person relapses after NM/R. Should NM/R be given longer?

Development of Resistance-Associated Mutations After Sotrovimab Administration in High-risk Individuals Infected With the SARS-CoV-2 Omicron Variant JAMA published online August 1, 2022

doi:10.1001/jama.2022.13854

Investigators at the Amsterdam University Medical Centers assessed COVID-19 Omicron samples from 18 patients with impaired immune systems in January and February 2022. Participants were treated with one 500-milligram infusion of sotrovimab 1 to 23 days after diagnosis and tested for viral mutations via nasal-throat swabs on the day of treatment and 7 and 28 days later. Swabs from 14 patients were also tested 4 days before the infusion and up to 52 days after.

The average patient age was 60.9 years, and 83% had compromised immune systems due to underlying medical conditions or use of an immune-suppressing drug. According to genomic analysis, 17 patients were infected with the Omicron BA.1 subvariant, while 1 had BA.2.

Ten patients (56%) developed a total of nine receptor-binding domain mutations at two spike-protein positions 3 to 31 days after sotrovimab receipt, while no such mutations were seen in Omicron samples from the general population. Participants with mutations took a significantly

longer time to clear the virus than those without mutations (average, 32.0 vs 19.6 days; hazard ratio, 0.11).

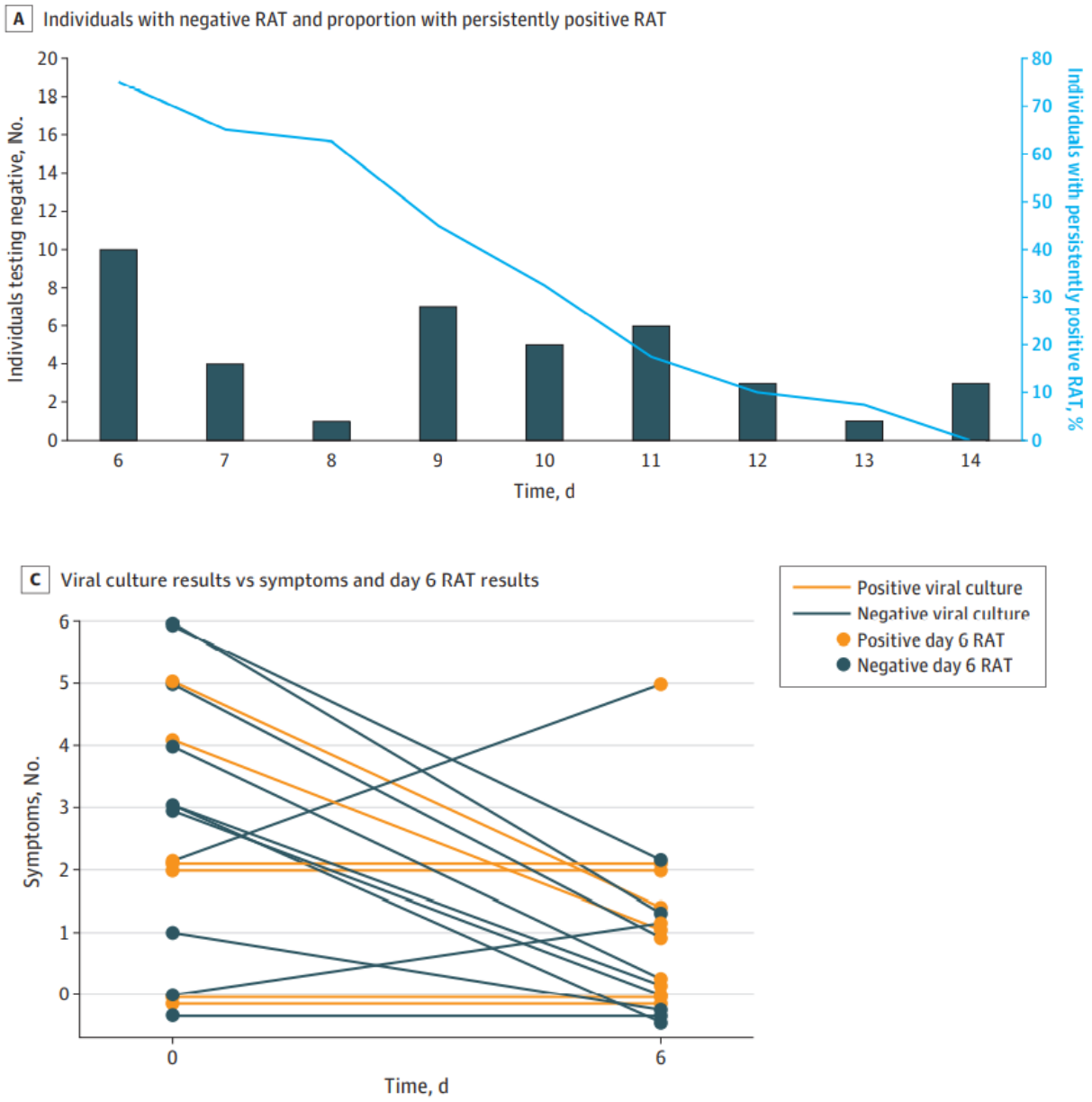
Comment: Spike-protein mutations at the positions found in this study have been tied to a 27- to 279-fold decrease in susceptibility to sotrovimab. The present findings add to the emerging evidence that treatment of high-risk patients with a single monoclonal antibody is associated with mutations especially in immunocompromised patients who are at risk for prolonged infection. [N Engl J Med. 2022;386(15):1477-1479]. Further studies investigating combination monoclonal antibody therapy and continuous genomic surveillance in immunocompromised patients are warranted to address the expanding antigenic diversity and subsequent emergence of resistance during COVID-19 treatment. This study is a relatively small sample size, and lacked a control group.

Duration of Symptoms and Association With Positive Home Rapid Antigen Test Results After Infection With SARS-CoV-2 JAMA Netw Open 2022;5(8):e2225331.

doi:10.1001/jamanetworkopen.2022.25331

Starting on day 6, individuals newly testing positive tests for SARS-CoV-2 completed an online demographic survey, daily symptom logs, and RAT self-testing. Day 0 was the day of positive SARS-CoV-2 test or symptom onset, whichever came first. On day-6, anterior nasal and separate oral swabs were collected sand 17 individuals (42.5%) for viral culture. A *t* test was used to compare means, using 1-tailed $P < .05$ to signify statistical significance; R^2 was used to explore linear associations between independent variables age, time since last vaccination, and cycle threshold value from initial polymerase chain reaction tests with the dependent variable day of first negative RAT result.

The investigators enrolled 40 individuals (mean [SD] age, 34 [9.5] years; 23 [57.5%] women and 17 [42.5%] men). Of these, 36 (90.0%) had received a primary vaccine series and first booster dose. None required hospitalization. In this period, 96% to 99% of sequenced were Omicron BA.1. Only 10 participants (25.0%) had a negative RAT result on day 6, and all had negative results by day 14. There were no correlations between day of first negative RAT result and age ($R^2 = 0$), time since last vaccine ($R^2 = 0.05$), or cycle threshold value at diagnosis ($R^2 = 0.03$). The mean (SD) day of first negative RAT result in the 7 never-symptomatic participants vs the 33 ever-symptomatic participants was 8.1 (3.0) vs 9.3 (2.4) ($P = .14$). Positive RAT results were frequent (61 of 90 tests [68%]) on days 6 to 14 among individuals reporting no symptoms that same day. 17 individuals were tested for viral culture on day 6, 12 of whom also had a positive RAT result. Of the 12, 6 had positive culture results (5 anterior nasal and 1 oral). None had positive results from both sites. No individuals with a negative day-6 RAT result had positive cultures. Of the 6 individuals with positive cultures, 2 reported improving symptoms and 2 reported unchanged symptoms, whereas 2 never reported symptoms. Seven of the 9 reporting no symptoms on day 6 (78%) had negative culture results.



Comment: In individuals with newly diagnosed with COVID-19, 75% continued to have positive RAT results, while 35% had culturable virus on day 6. Everyone with a negative day-6 RAT result had a negative viral culture. However, only 50% of those with a positive RAT result had culturable virus. This study demonstrates a requirement of a negative RAT result may unduly extend isolation for those who are no longer infectious. On the other hand, a recommendation to end isolation based solely on the presence of improving symptoms risks releasing culture-positive, potentially infectious individuals prematurely, underscoring the importance of proper mask wearing and avoidance of high-risk transmission venues through day 10. This is a small sample of mostly young, vaccinated, nonhospitalized individuals.