Infectious Diseases Watch

February 7, 2022

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General Infectious Diseases

Impact of Education and Data Feedback on Antibiotic Prescribing for Urinary Tract Infections in the Emergency Department: An Interrupted Time Series Analysis

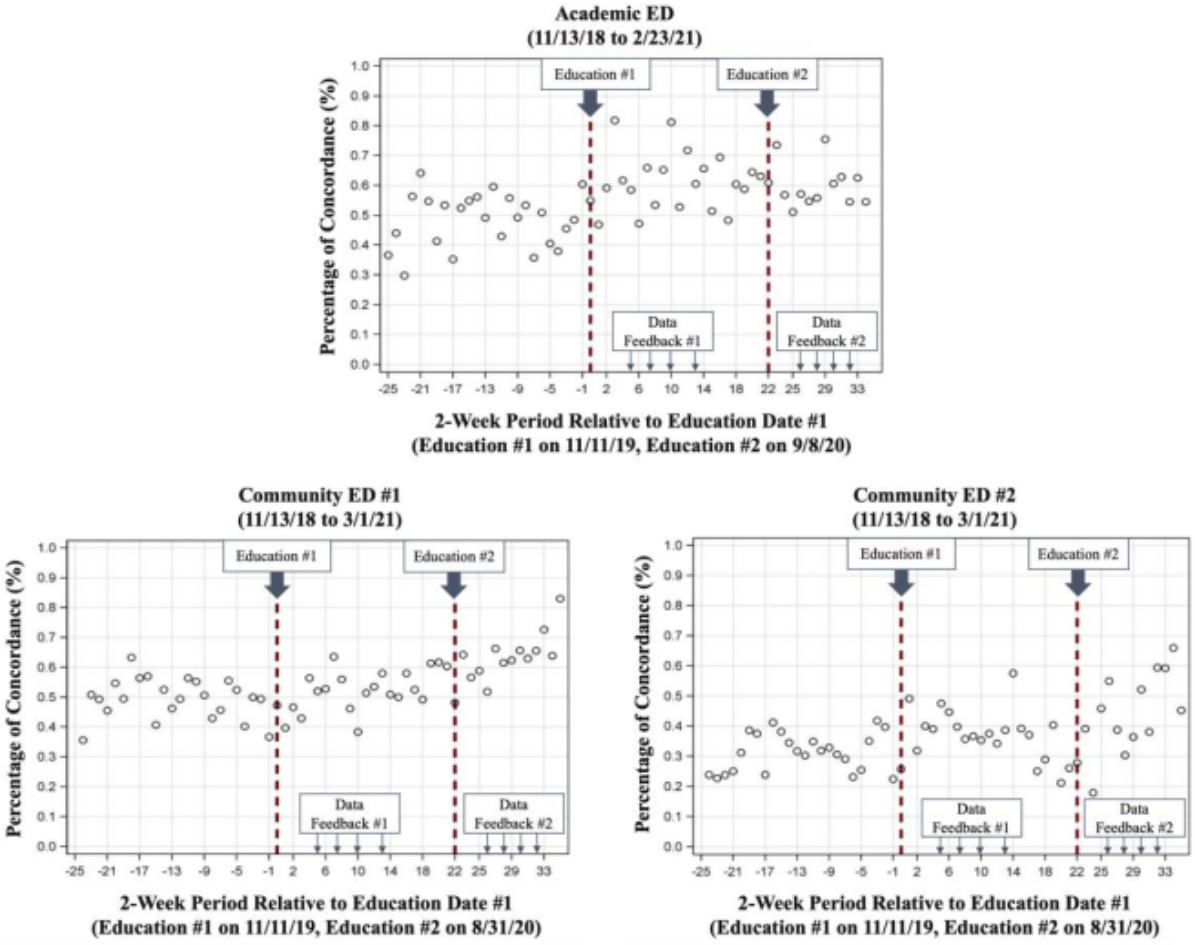
Clin Infect Dis published online February 1, 2022

doi.org/10.1093/cid/ciac073

This study is a quasi-experimental study using an interrupted time series regression analysis with 2-week intervals to assess guideline-concordant prescribing over the pre-intervention period and the two intervention periods. Their strategy (outlined below) was implemented at three North Carolina hospitals with the aim of improving UTI prescribing in the ED setting, where UTIs are often inappropriately treated.

Phase 1 of the intervention included an ED-specific, urinary source antibiogram, ED-specific UTI diagnosis and treatment guidelines, an education session for ED prescribers, and department-specific email feedback on UTI diagnoses, antimicrobial use, and guideline-concordant prescribing. Phase 2 included re-education and provider-specific feedback. Eligible patients included adults with an antibiotic prescription for UTI diagnosed in the ED from 11/13/18 to 3/1/21. Admitted patients were excluded.

Overall, 8,742 distinct patients with 10,426 patient encounters were included in the analysis. Ninety-two percent of all encounters (n=9,583) were diagnosed with cystitis and 8.1% with pyelonephritis (n=843). There was an initial 15% increase in guideline-concordant antibiotic prescribing following Phase 1, compared to the pre-intervention period (incidence rate ratio [IRR], 1.15; 95% confidence interval [CI], 1.03 to 1.29). Although no significant change in guideline-concordant prescribing was seen initially following Phase 2, a 3% increase in guideline-concordant prescriptions was seen with every 2-week interval during Phase 2 (IRR, 1.03; 95% CI, 1.01 to 1.04), compared with Phase 1. By the end of the study period, ED prescribers achieved 56.1% guideline concordance, compared with 42.8% in the pre-intervention period and 49.7% in Phase 1.



Comment: While an education session and dissemination of guideline recommendations provided a small immediate effect, ongoing and sustainable effects were only observed when data was consistently fed back and personalized for prescribers. This study and others highlight the importance of ongoing provider feedback. Studies where provider feedback has been discontinued have seen performance revert to the mean. A limitation of the study was use of ICDF-9 and ICD-10 codes for diagnosis of UTI which does not take into account symptoms and clinical presentation. Phase two was done during the pandemic which did not allow in-person education.

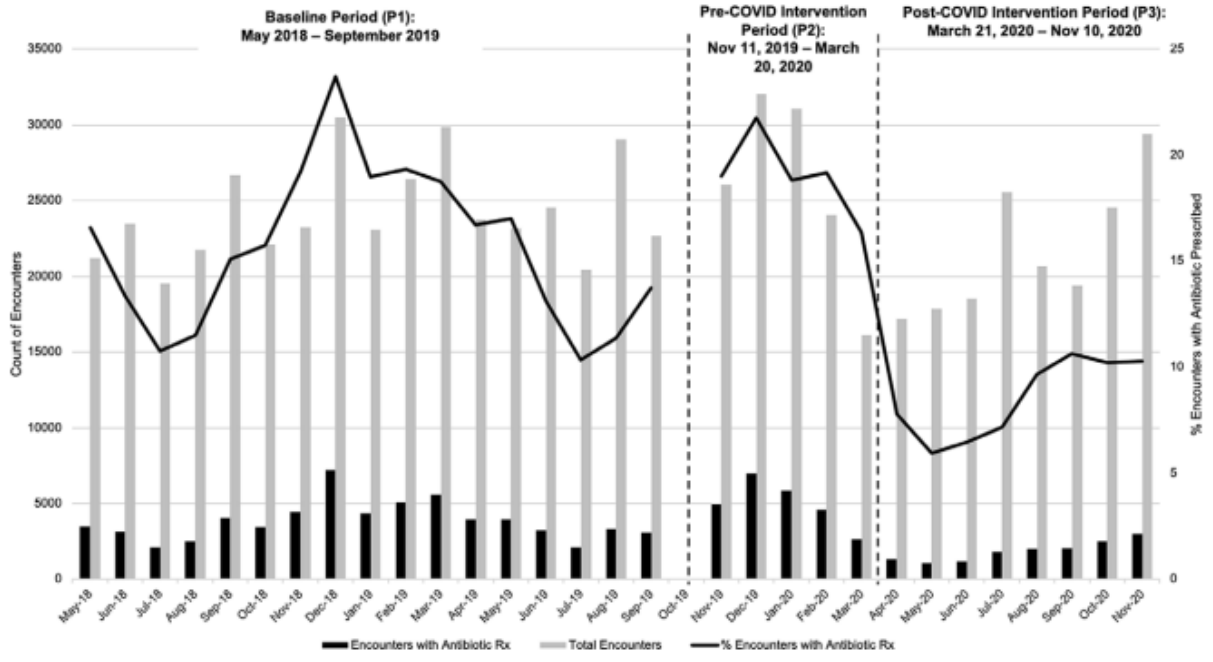
Improvements in appropriate ambulatory antibiotic prescribing using a bundled antibiotic stewardship intervention in general pediatrics practices Infect Control Hosp Epidemiol published online January 31, 2022

doi:10.1017/ice.2021.534

The investigators performed a before-and-after intervention study to assess the impact of bundled implementation strategies on antibiotic prescribing in 5 primary-care pediatric practices not affiliated with an academic institution. Initially planned a before-and-after intervention study comparing a baseline and intervention period, the pandemic began 3.5 months into their

intervention period so they decided after the intervention to compare 3 study periods: period 1 (P1, baseline, May 2018–September 2019), period 2 (P2, intervention, before the COVID-19 pandemic, November 11, 2019–March 20, 2020), and period 3 (P3, intervention during the COVID-19 pandemic, March 21, 2020–November 10, 2020). Prior to the start of the study, each practice identified a physician champion and operations champion for the project who led the selection and implementation of interventions. Practices chose 2–4 implementation strategies [antibiotic use commitment posters, clinical pathway guidelines, parent education on judicious antibiotic use, EHR templates] to implement in their practice throughout the study intervention period. Study personnel also held in-person or videoconference quarterly meetings with all providers in each practice to review their outcomes and provide peer comparison feedback both across practices enrolled in the study and at the provider level within each practice. Meetings were held in person prior to the COVID-19 pandemic and online during the COVID-19 pandemic. The primary outcome was the percentage of encounters with an antibiotic prescription (stratified by all visits and sick visits only). A secondary outcome was antibiotic prescription appropriateness, measured as the percentage of encounters among children with specific diagnoses and no penicillin allergy that resulted in a guideline-concordant antibiotic prescription for community-acquired pneumonia, streptococcal pharyngitis, otitis media, sinusitis, and skin and soft-tissue infection. Another secondary outcome was the percentage of encounters with a diagnosis of viral upper respiratory tract infection and an antibiotic prescription. A third secondary outcome was the percentage of encounters with an antibiotic prescribed that occurred within 1 week of an initial encounter in which no antibiotic had been prescribed, to serve as a balancing measure for the study.

They demonstrated improvements in guideline-concordant antibiotic use in the pre-COVID-19 intervention period, which was were sustained in the study period during the pandemic (P3): otitis media (P1 72.14% vs P2 81.42% vs P3 86.11%), group A streptococcal pharyngitis (P1 66.13% vs P2 81.56% vs P3 80.44%), pneumonia (P1 70.6% vs P2 76.2% vs P3 100%), sinusitis (P1 76.2% vs P2 83.78% vs P3 82.86%), skin and soft-tissue infections (P1 97.18% vs P2 100% vs P3 100%).



Comment: In this study of a real-world implementation of outpatient antibiotic stewardship bundled implementation strategies in community pediatric practices, the bundled implementation strategies led to significant increases in guideline-concordant antibiotic prescribing for all diagnoses even during the pandemic period. The investigators felt a key part of their study design was allowing practices to choose their own implementation strategies, which increased study participation [ownership] but on the downside it limited their ability to compare effectiveness of specific implementation strategies. Like the study above combining education with audit and feedback was a key strategy. They excluded patients with a penicillin allergy from the calculation of guideline-concordant antibiotic use, which may have limited their ability to see benefit of the penicillin allergy delabeling strategy implemented by 2 of the practices. Practices implemented strategies were for only 6 months.

Association of Exposure to High-risk Antibiotics in Acute Care Hospitals With Multidrug-Resistant Organism Burden in Nursing Homes JAMA Netw Open published online February 1, 2022

doi:10.1001/jamanetworkopen.2021.44959

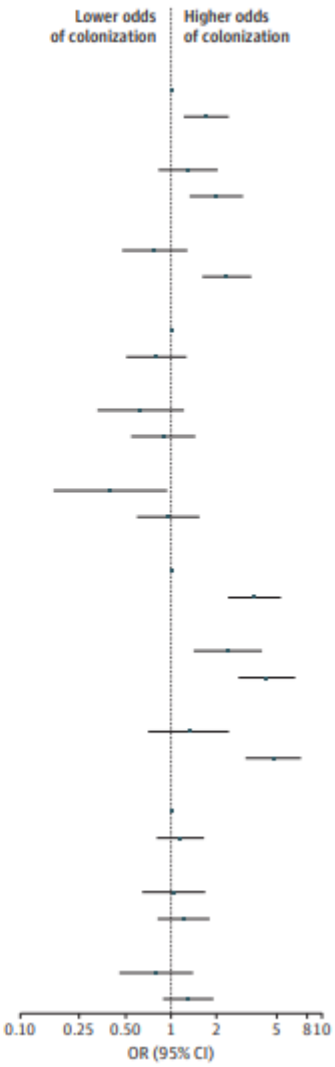
This study examines if recent antibiotic exposures preceding NH stay is associated with MDRO colonization and room environment contamination at NH study enrollment. The study was conducted in 6 NHs in Michigan among NH patients who were enrolled within 14 days of admission. Antibiotic data were abstracted from NH electronic medical records by trained research staff and characterized by class, route, indication, location of therapy initiation, risk for Clostridioides difficile infection (“C diffogenic” agents), and 2019 World Health Organization Access, Watch, and Reserve (AWARE) antibiotic stewardship framework categories. The primary outcomes were MDRO colonization and MDRO room environment contamination at NH study enrollment, measured using standard microbiology methods. Multivariable logistic regression was used to identify whether antibiotic exposure within 60 days was associated with MDRO burden at NH study enrollment.

Of the 642 patients in the study with data on antibiotic exposure (median age, 74.7 years, 57.5% female), 422 (65.7%) had antibiotic exposure prior to enrollment: 368 (57.3%) received 971 hospital-associated antibiotic prescriptions, and 119 (18.5%) received 198 nursing home-associated prescriptions. For antibiotics with documented indications, the most common indications were urinary tract infections (25.1%), skin and skin-structure infections (19.7%), and respiratory tract infections (16.1%). Analysis of antibiotic classification showed that 283 patients (44.1%) received an antibiotic that increased the risk for CDI, and 322 (50.2%) received at least one watch or reserve antibiotic. High-risk, C diffogenic antibiotics and watch and reserve antibiotics were more prevalent among the hospital-associated prescriptions than the nursing home prescriptions.

Overall, 364 patients (56.7%) were colonized with an MDRO, and 437 (68.1%) patient room environments were contaminated with an MDRO upon enrollment in the study. The most common MDROs were VRE, resistant gram-negative bacilli (R-GNB), and MRSA. In multivariable analysis, pre-study enrollment exposure to antibiotics was positively associated with MDRO baseline colonization (odds ratio [OR], 1.70; 95% confidence interval [CI], 1.22 to 2.38) and MDRO environmental contamination (OR, 1.67; 95% CI, 1.17 to 2.39) compared with patients who had not been exposed to antibiotics.

Figure 1. Association of Recent Antibiotic Exposure With Nursing Home Multidrug-Resistant Organism (MDRO) Patient Colonization

Organism/characteristic	Total patients, No.	Patients with MDRO, No. (%)	OR (95% CI)
Any MDRO			
No antibotic history	269	129 (48.0)	1 [Reference]
History of antibiotic exposure	373	235 (63.0)	1.70 (1.22-2.38)
C diffogenic agent classification			
Low-risk exposure	128	70 (54.7)	1.30 (0.83-2.02)
High-risk exposure	245	165 (67.4)	1.99 (1.33-2.96)
WHO AWARE classification			
Access only	94	39 (41.5)	0.78 (0.48-1.28)
Watch or reserve level	279	196 (70.3)	2.32 (1.61-3.36)
MRSA			
No antibotic history	269	47 (17.5)	1 [Reference]
History of antibiotic exposure	373	57 (15.3)	0.80 (0.51-1.26)
C diffogenic agent classification			
Low-risk exposure	128	15 (11.7)	0.63 (0.33-1.21)
High-risk exposure	245	42 (17.1)	0.89 (0.55-1.44)
WHO AWARE classification			
Access only	94	7 (7.5)	0.40 (0.17-0.94)
Watch or reserve level	279	50 (17.9)	0.96 (0.60-1.53)
VRE			
No antibotic history	269	50 (18.6)	1 [Reference]
History of antibiotic exposure	373	164 (44.0)	3.53 (2.38-5.24)
C diffogenic agent classification			
Low-risk exposure	128	43 (33.6)	2.37 (1.42-3.94)
High-risk exposure	245	121 (49.4)	4.26 (2.79-6.51)
WHO AWARE classification			
Access only	94	20 (21.3)	1.31 (0.71-2.39)
Watch or reserve level	279	144 (51.6)	4.70 (3.10-7.12)
R-GNB			
No antibotic history	269	78 (29.0)	1 [Reference]
History of antibiotic exposure	373	127 (34.1)	1.15 (0.81-1.64)
C diffogenic agent classification			
Low-risk exposure	128	39 (30.5)	1.04 (0.65-1.67)
High-risk exposure	245	88 (35.9)	1.21 (0.82-1.79)
WHO AWARE classification			
Access only	94	23 (24.5)	0.80 (0.46-1.39)
Watch or reserve level	279	104 (37.3)	1.29 (0.89-1.89)



Comment: The findings demonstrate hospital antibiotics in this population can have a downstream impact on the burden of MDROs in nursing homes. In addition, this study underscores the potential utility of integrated hospital and NH stewardship programming across the continuum of care on a community basis.

COVID-19

COVID-19 News

FDA fully approves Moderna COVID vaccine

FDA granted full approval to the mRNA COVID-19 vaccine made by Moderna, approved for use in adults 18 and older as a two-dose vaccine with shots administered 1 month apart.

Comment: This was not unexpected and a long time coming.

Pfizer vaccine in children <5

Pfizer asked the FDA on Tuesday to authorize two doses of their vaccine for children younger than five while the companies continue to research whether three doses would be more effective for that age group.

Comment: This is a highly unusual since it appears federal regulators pressed Pfizer to submit a request for emergency authorization, even though two doses failed to produce the hoped-for immune response among children aged two to four in a clinical trial. [see COVID-19 Briefing December 20, 2021] Only children between six months and two years old demonstrated an immune response comparable to that of older teenagers and young adults, the standard for a successful trial. The doses were one-tenth the strength of adult doses. The disappointing trial results prompted Pfizer to test a third low dose of the shot in this age group. But rather than wait until the end of March for those to come in, federal regulators decided to encourage Pfizer to apply for authorization of a two-dose regimen in order to get a head start on the vaccination effort.

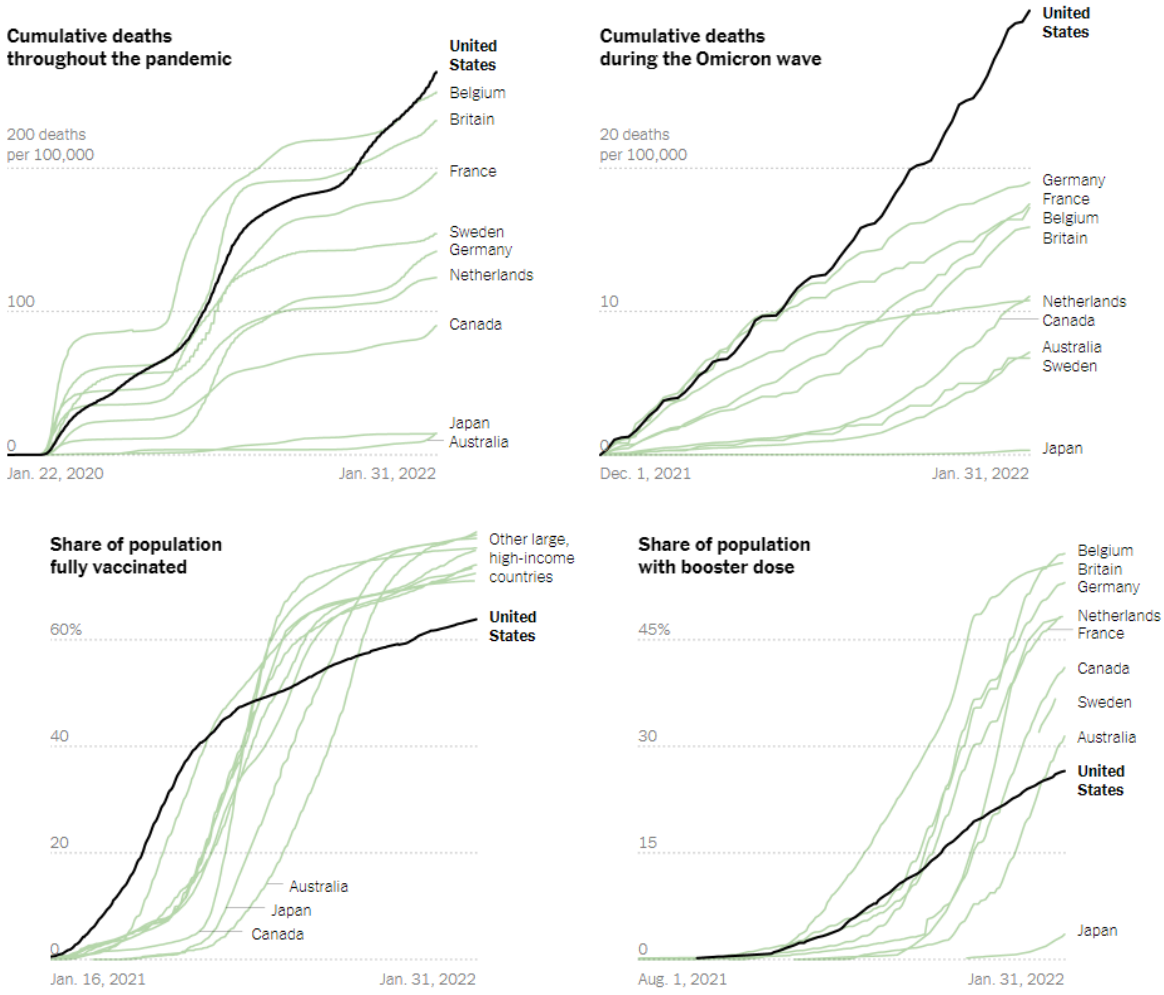
An emergency meeting of the FDA's Advisory Group is scheduled for February 15th. This approach suggests a short circuit the normal process. To me it doesn't make sense to approve a two-dose vaccine with the hope the third dose would improve response and convince parents to vaccinate their children. I hope Pfizer can provide updated vaccination data. The pace of vaccination for children between 5 and 11 remains even lower than public health experts had feared. Roughly only 30 percent of children 5-11 have received at least one dose, according to the CDC data. According to the Kaiser study only about 30% of parents currently are willing to vaccinate their child < age 5.

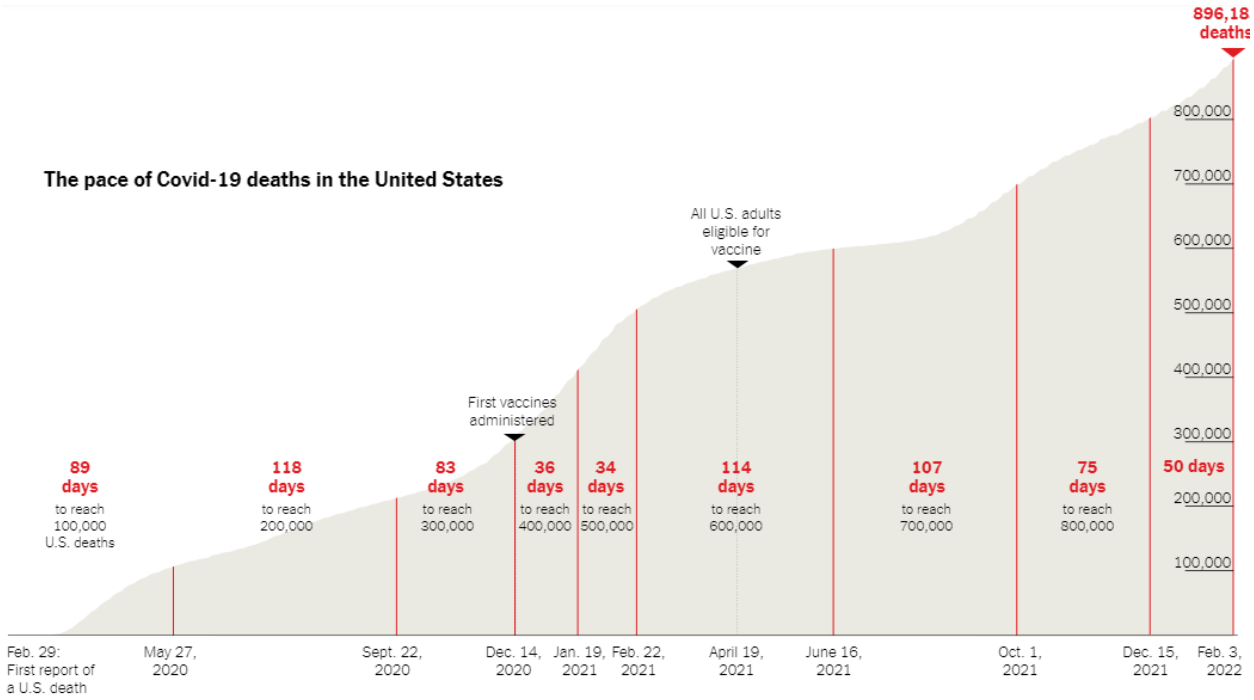
Novavax

Last Monday Novavax announced it has officially submitted an EUA request to the FDA for its protein-based coronavirus vaccine, which is different from the mRNA technology in Pfizer and Moderna's vaccines. [NEJM online 12.15.21-see COVID-19 Briefing December 16, 2021] In this publicatio0n Novavax VE was >90% and for the prevention of moderate-to-severe disease.

Comment: For those who are vaccine hesitant about mRNA and adenovirus platforms, the availability of a well understood protein-based vaccine may persuade some vaccine hesitant individuals. This would be the 4th approve vaccine in the US.

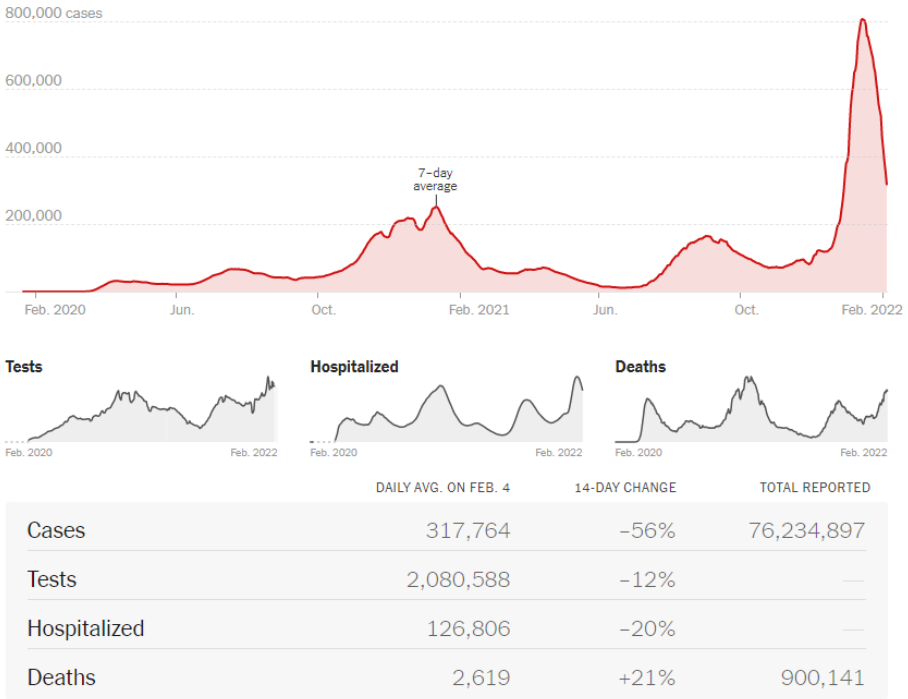
COVID-19 by The Numbers-Deaths >900,000





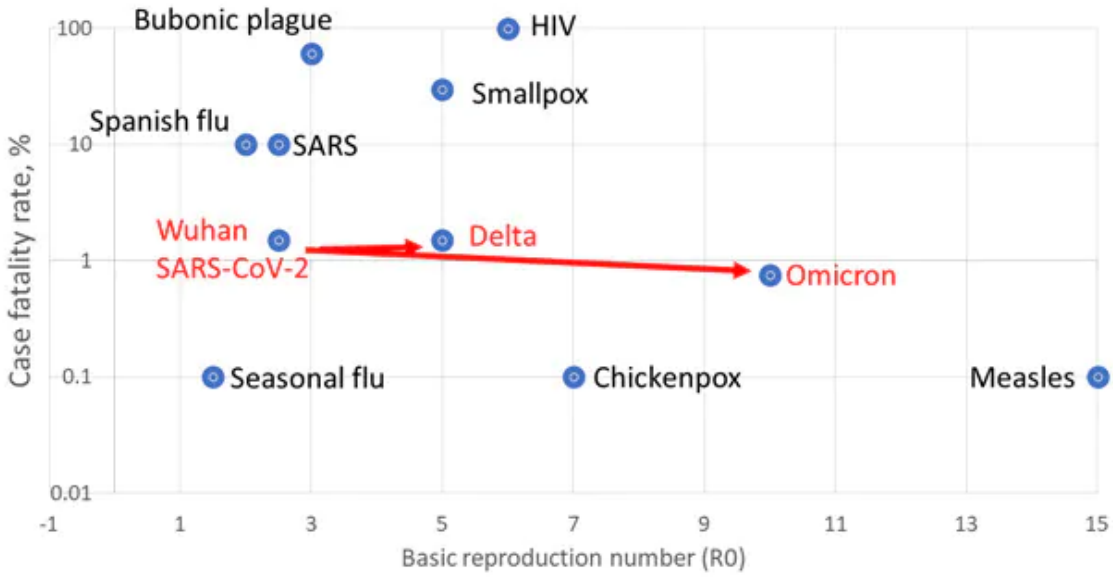
Comment: The US leads all countries in cumulative deaths and last in fully vaccinated in high-income countries! [see Lancet article below]

January 5, 2022



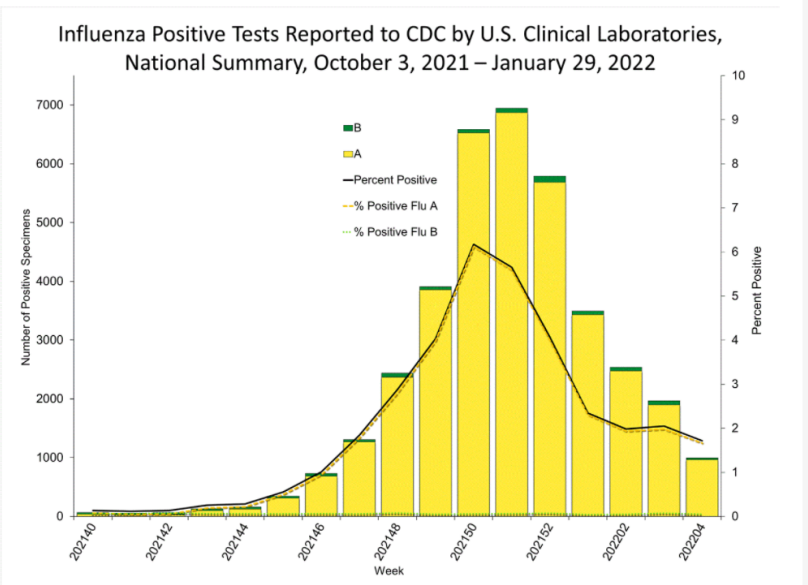
Comment: Overall cases and hospitalizations are decreasing with deaths a delayed indicator.

Updated R0



Influenza Update

- Influenza activity has decreased in recent weeks, but sporadic activity continues across the country.
- The majority of influenza viruses detected are A(H3N2). Most of the H3N2 viruses identified so far this season are genetically closely related to the vaccine virus. Some viruses show antigenic differences that developed as H3N2 viruses have continued to evolve.



Comment: US flu levels dropped further and dipped below the national baseline last week. Hospitalizations declined slightly again, and no new pediatric flu deaths were reported, keeping the season's total at five. We are now in February which traditionally is the peak for influenza. To date it appears that Omicron is outcompeting other respiratory viruses. Amazing!

Journal and Publication Review

A Literature Review and Meta-Analysis of the Effects of Lockdowns on COVID-19 Mortality Studies in Applied Economics series John Hopkins SAE./No.200/January 2022

This systematic review and meta-analysis were designed to determine whether there is evidence to support the belief that “lockdowns” reduce COVID-19 mortality. Lockdowns are defined as the imposition of at least one compulsory, non-pharmaceutical intervention (NPI).

NPIs are any government mandate that directly restrict peoples’ possibilities, such as policies that limit internal movement, close schools, and businesses, and ban international travel. This study employed a systematic search and screening procedure in which 18,590 studies are identified that could potentially address the belief posed. After three levels of screening, 34 studies ultimately qualified. Of those 34 eligible studies, 24 qualified for inclusion in the meta-analysis.

They were separated into three groups: lockdown stringency index studies, shelter-in-place order (SIPO) studies, and specific NPI studies. An analysis of each of these three groups support the conclusion that lockdowns have had little to no effect on COVID-19 mortality. More specifically, stringency index studies find that lockdowns in Europe and the United States only reduced COVID-19 mortality by 0.2% on average. SIPOs were also ineffective, only reducing

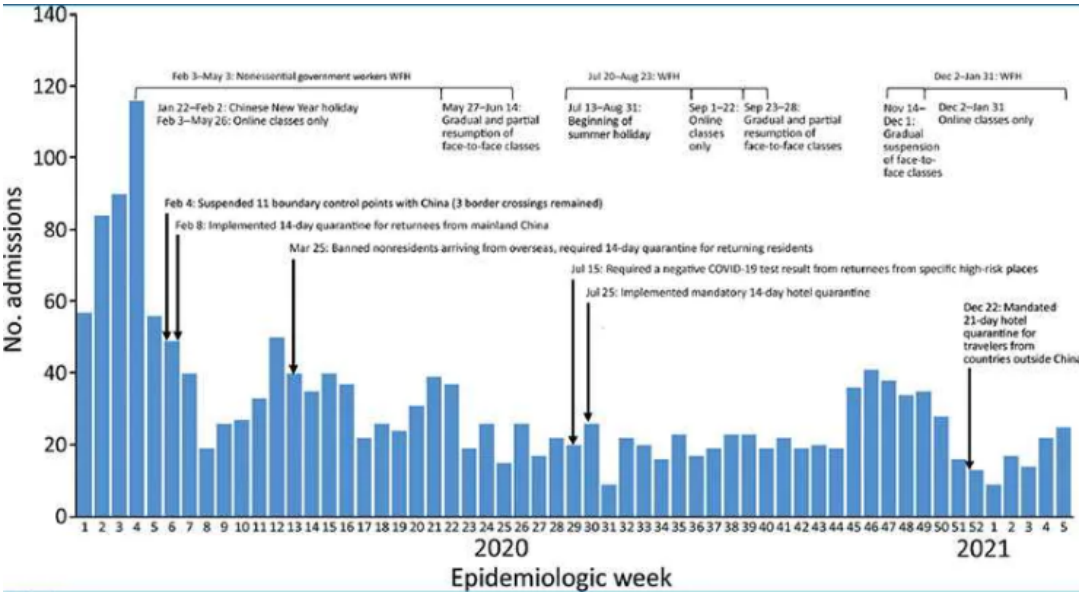
COVID-19 mortality by 2.9% on average. Studies that looked at only SIPO orders found they reduced COVID-19 mortality by 5.1%, but studies that looked at shelter-in-place orders along with other lockdown measures found that shelter-in-place orders actually increased COVID-19 mortality by 2.8%. They concluded lockdowns actually limited peoples' access to safe (outdoor) places such as beaches, parks, and zoos, or included outdoor mask mandates or strict outdoor gathering restrictions, pushing people to meet at less safe (indoor) places. The researchers also examined studies that focused on specific lockdown measures and found that the only intervention that reduced COVID-19 mortality was the closure of non-essential businesses, which reduced mortality by 10.6%, but this effect was likely driven by the closure of bars. Overall NPI studies found no broad-based evidence of noticeable effects on COVID-19 mortality.

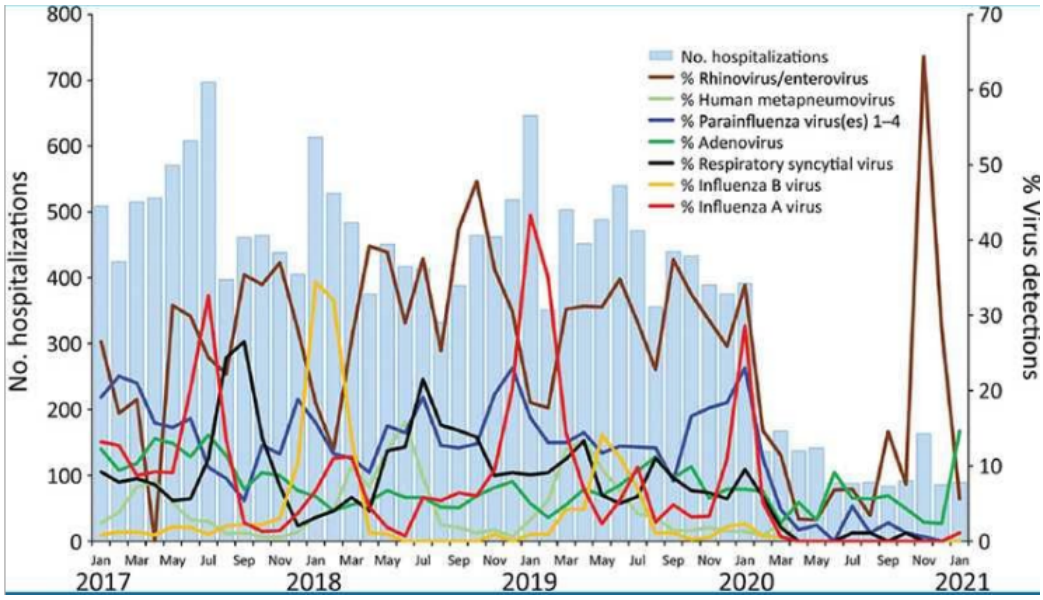
Comment: For most, this report was a surprise and under reported. Researchers also pointed out other unintended consequences of lockdowns, such as rising unemployment, reduced schooling, an increase in domestic violence incidents, increase in suicides, and surging drug overdoses. From May 2020 to April 2021, the US recorded 100,306 drug overdose deaths, a 28.5% increase from the 78,056 deaths that were recorded in the previous 12-month period, according to CDC data. A study from the National Commission on COVID-19 and Criminal Justice last year found that domestic violence incidents increased 8.1% in the U.S. after lockdown orders were issued. The report concludes "these costs to society must be compared to the benefits of lockdowns, which our meta-analysis has shown are marginal at best. Such a standard benefit-cost calculation leads to a strong conclusion: lockdowns should be rejected out of hand as a pandemic policy instrument." A few limitations of this report deserve comment. First they excluding certain studies in 2020 based on modeling which showed a positive impact on mortality so as to avoid biases as well as those on by "time-dependent factors" like seasonality. In addition, papers that looked at early lockdowns such as in China, which suppressed COVID-19 to very low death rates, were also not included. I think in the start of the pandemic we had few tools at our disposal, and we used the 1918 experience to guide us with good intentions. We must now go back and look the science and balance the science with other societal needs given the fact we have many more tools in our toolbox.

Effects of Nonpharmaceutical COVID-19 Interventions on Pediatric Hospitalizations for Other Respiratory Virus Infections, Hong Kong Emerg Infect Dis 2022;28:62-68.

This review set out to determine the effects of nonpharmaceutical interventions (NPIs) for coronavirus disease on pediatric hospitalizations for infection with respiratory viruses other than SARS-CoV-2. They analyzed hospital data for 2017–2021. Compared with 2017–2019, age-specific hospitalization rates associated with respiratory viruses greatly decreased in 2020, when NPIs were in place. Also, when NPIs were in place, rates of hospitalization decreased among children of all ages for infection with influenza A and B viruses, RSV, adenovirus, parainfluenza viruses, human metapneumovirus, and rhinovirus/enterovirus. Regression models adjusted for age and seasonality indicated that hospitalization rates for acute febrile illness/respiratory symptoms of any cause were reduced by 76% and by 85%– 99% for hospitalization for infection with these viruses. Of interest, implementing NPIs and reopening schools were associated with only a small increase in hospitalizations for rhinovirus/enterovirus infections. Using UTI hospitalizations as a control, for which hospitalizations in 2020 were about the same as in previous years, we cannot conclude that the reduced hospitalizations for acute

febrile illness/respiratory symptoms and respiratory viruses in 2020 resulted from avoidance of public hospitals during the COVID-19 pandemic.





Comment: NPIs in Hong Kong were clearly associated with reduced pediatric hospitalizations for respiratory viruses. Their observation that school resumption did not affect rates of hospitalization for infection with other respiratory viruses, except rhinovirus, is consistent with modeling studies of SARS-CoV-2 that predicted that school closures alone would prevent only 2%–4% of deaths. As I have written on multiple occasions, school closure during the COVID-19 pandemic carries high social and economic costs across communities and has the most severe effect on the most vulnerable and especially in disadvantaged populations. Schools should be considered an essential service that should be kept open with appropriate mitigations measures in place. The wearing of face masks in Hong Kong was remarkable including among young children very different from the US. In this review of the effects of school closure and school resumption, they had data only on pediatric hospitalizations and did not study the effects

of school closures or resumptions on infections and hospitalizations of adults especially considering the potential of household contacts.

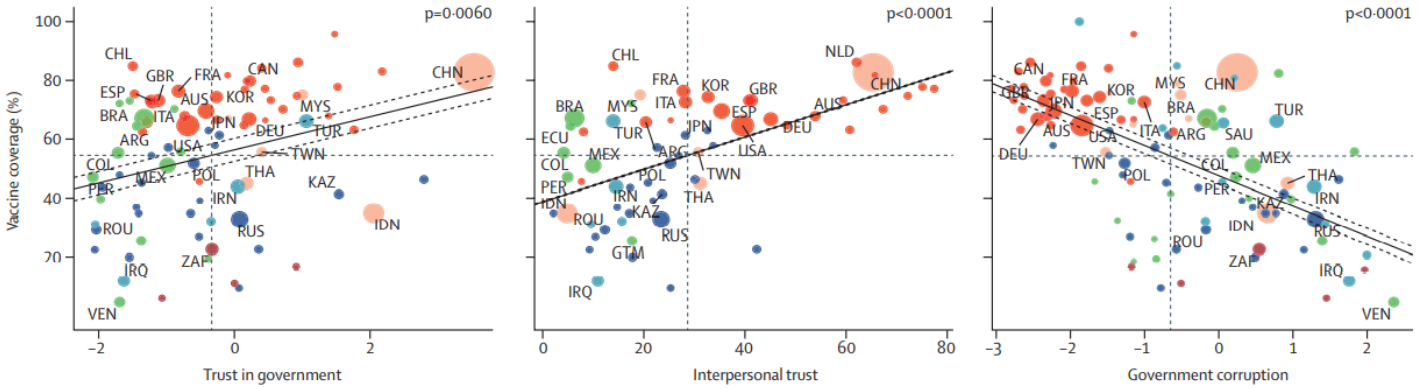
Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021 Lancet published online February 1, 2022

doi.org/10.1016/ S0140-6736(22)00172-6

The authors start with the statement: “National rates of COVID-19 infection and fatality have varied dramatically since the onset of the pandemic. Understanding the conditions associated with this cross-country variation is essential to guiding investment in more effective preparedness and response for future pandemics.”

They looked at daily SARS-CoV-2 infections and COVID-19 deaths for 177 countries and territories and 181 subnational locations extracted from the Institute for Health Metrics and Evaluation’s modelling database. Cumulative infection rate and infection-fatality ratio (IFR) were estimated and standardized for environmental, demographic, biological, and economic factors. For infections, they included factors associated with environmental seasonality (measured as the relative risk of pneumonia), population density, gross domestic product (GDP) per capita, proportion of the population living below 100 m, and a proxy for previous exposure to other betacoronaviruses. They analyzed measures of pandemic preparedness. 12 indicators of preparedness and response and seven indicators of health system capacity were considered, in addition to ten other demographic, social, and political conditions that previous research suggests might be relevant. Associations with both incidence and mortality from SARS-CoV-2 infections were investigated. They controlled for demographic, biological, economic, and environmental variables associated with COVID-19 outcomes, including population age structure and environmental seasonality, population density, national income, and population health risks, to identify contextual factors subject to policy control.

Pandemic-preparedness indices, which aim to measure health security capacity, were not meaningfully associated with standardized infection rates or IFRs. Measures of trust in the government and interpersonal trust, as well as less government corruption, had larger, statistically significant associations with lower standardized infection rates. High levels of government and interpersonal trust, as well as less government corruption, were also associated with higher COVID-19 vaccine coverage among middle-income and high-income countries where vaccine availability was more widespread, and lower corruption was associated with greater reductions in mobility.



Comment: The investigators found that a given country's level of distrust had strong associations with its coronavirus infection rate. Yes, trust in one's government and fellow citizens, as measured in leading surveys, correlates with better pandemic outcomes overall! One reason for their finding may be that trust of both types is also associated with higher vaccination rates and greater compliance with recommended NPIs. Politics has further eroded our trust in our government. In addition Americans' confidence in their government is increasingly partisan.

This may explain why the US leads the high incomes countries in deaths due to COVID-19. [see above] At this point in the pandemic, Americans are more confident in their physicians and front-line health workers than in the CDC or politicians. Trust in state governors has fallen the most. The need for timely, accurate, credible, and consistent information that is tailored to specific audiences cannot be overstated. US officials have struggled to maintain this standard in the current pandemic. There is also a strong need to coordinate a patchwork of state and federal public health authorities.

Prevalence and Durability of SARS-CoV-2 Antibodies Among Unvaccinated US Adults by History of COVID-19 JAMA published online February 3, 2022

doi:10.1001/jama.2022.1393

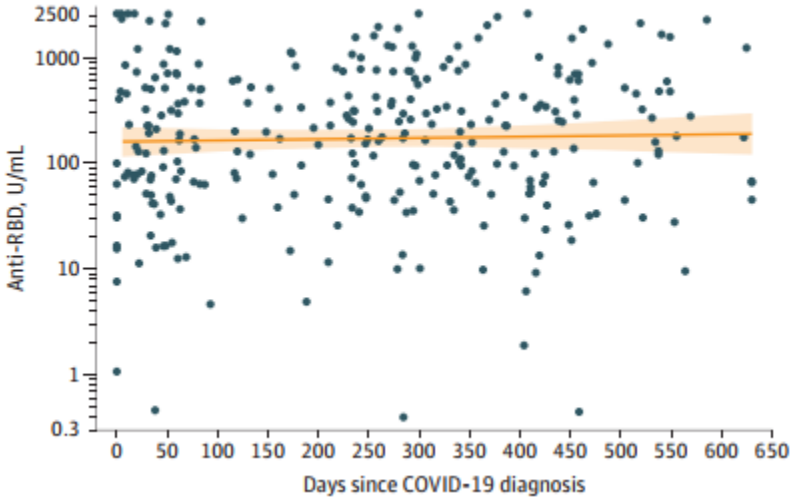
The prevalence of natural immunity remains unknown. Among individuals who develop antibodies [natural immunity], durability of this response beyond 6 months remains unknown. The investigators in this paper set out to characterize natural immunity and long-term durability among unvaccinated individuals who have anti–spike antibodies.

Healthy adults who reported no SARS-CoV-2 vaccination were recruited via 1 public Twitter post and 1 public Facebook advertisement between September 11, 2021, and October 8, 2021. Participants completed an online questionnaire about demographics, COVID-19 status, and mask use. They used a weighted random sampling (relative weights based on the estimated unvaccinated US population by age, race and ethnicity, and education, They created 3 equally sized sample groups among those who reported a test-confirmed COVID-19 infection ("COVID-confirmed"), believed they had COVID-19 but were never tested ("COVID-unconfirmed"),

and did not believe they ever had COVID-19 and never tested positive ("no-COVID"). Qualitative detection of antibodies against the SARSCoV-2 antinucleocapsid (N) protein and semiquantitative detection of antibodies against the SARS-CoV-2 spike protein receptor-binding domain (RBD) were collected.

Of 1580 individuals invited to undergo serologic testing, 816 (52%) did so between September 24, 2021, and November 5, 2021. Participants had a mean age of 48.0 years, 421 (52%) were women, and 669 (82%) were White. Fourteen percent reported routine mask use in public. Among 295 reported COVID-confirmed participants, 293 (99%) tested positive for anti-RBD antibodies (≥250 U/mL, 44%; ≥500 U/mL, 27%; ≥1000 U/mL, 15%). A median of 8.7 (IQR, 1.9-12.9; range, 0-20) months passed since reported COVID-19 diagnosis. The median anti-RBD level among those who tested positive was 205 (IQR, 61-535) U/mL. There was no evidence of association between time after infection and antibody titer (0.8% increase [95% CI, –2.4% to 4.2%] per month, *P* = .62). Among 275 reported COVID-unconfirmed participants, only 152 (55%) tested positive for anti-RBD antibodies (≥250 U/mL, 18%; ≥500 U/mL, 12%; ≥1000 U/mL, 6%). Among 246 reported no-COVID participants, 11% tested positive for anti-RBD antibodies (≥250 U/mL, 2%; ≥500 U/mL, 2%; ≥1000 U/mL, 2%).

Figure. Anti-Spike RBD Levels by Time Since COVID-19 Diagnosis



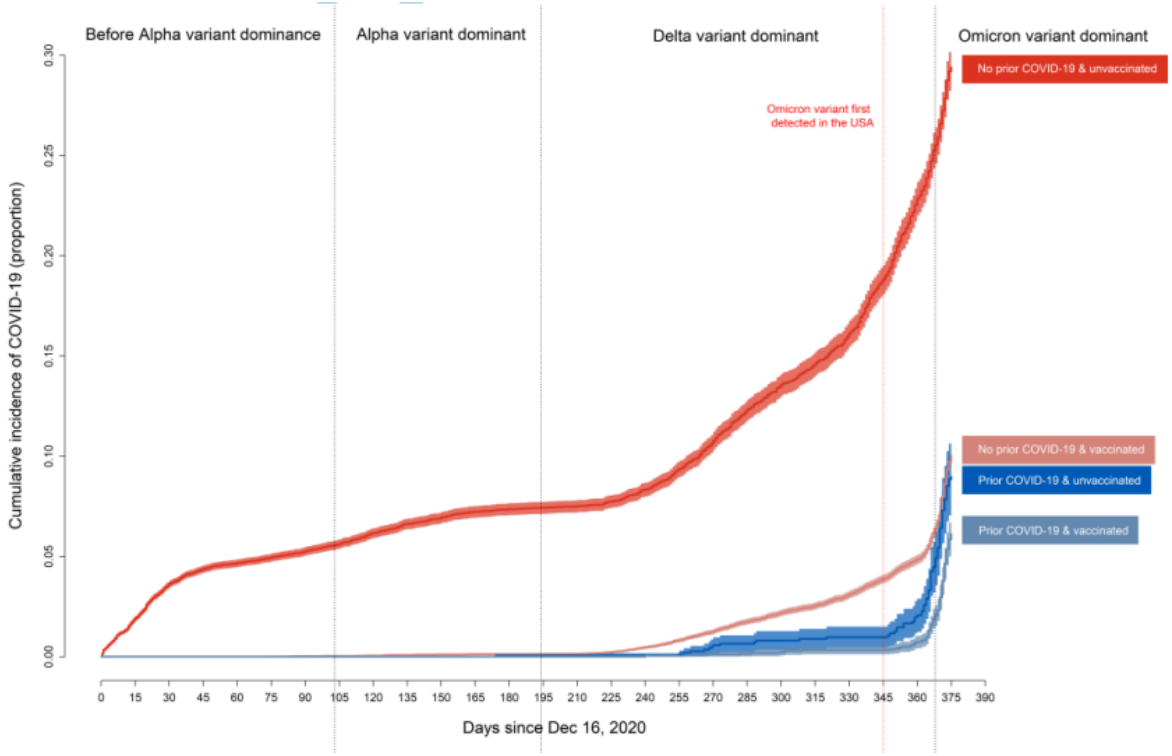
Comment: One of the key findings was anti-RBD levels were detected up to 20 months, extending previous 6-month durability data. In addition, about half of unvaccinated adults who thought they had COVID-19 were proven wrong by antibody tests. The sample size was small and largely white, young, and healthy. The study lacked information on breakthrough infections. Nonetheless natural immunity in unvaccinated healthy US adults up to 20 months after confirmed COVID-19 infection is encouraging. it is unclear how these antibody levels correlate with protection against future SARS-CoV-2 infections, particularly with emerging variants such as Omicron.

Necessity of COVID-19 Vaccination in Persons Who Have Already Had COVID-19 Clin Infect Dis published online January 22, 2022

doi/10.1093/cid/ciac022/6507165

Employees of Cleveland Clinic working in Ohio on Dec 16, 2020, the day COVID-19 vaccination was started, were included. Anyone who tested positive for COVID-19 at least once before the study start date was considered previously infected. One was considered vaccinated 14 days after receiving the second dose of a COVID-19 mRNA vaccine. The cumulative incidence of COVID-19, symptomatic COVID-19, and hospitalizations for COVID-19, were examined over the next year.

They reported on 52238 employees, 4718 (9%) were previously infected, and 36922 (71%) were vaccinated by the study's end. A total of 7851 (15%) employees acquired COVID-19 during the study, of which 4675 (60%) were symptomatic infections and 133 (1.7%) required hospitalization for COVID-19. Not surprisingly the cumulative incidence of COVID-19 was substantially higher throughout for those previously uninfected who remained unvaccinated than for all other groups, lower for the vaccinated than unvaccinated, and lower for those previously infected than those not. Incidence of COVID-19 increased dramatically in all groups after the Omicron variant emerged. Previously infected, until the emergence of the Omicron variant, the cumulative incidence of COVID- 19 was not significantly different between those vaccinated and unvaccinated, even at almost a year of follow-up. Among those not previously infected, the cumulative incidence of COVID-19 remained negligible for those vaccinated up to 8 months into the study, following which there was a steady increase in infections. The incidence of COVID-19 increased dramatically with the Omicron variant's emergence, regardless of whether subjects were previously infected or not, and vaccinated or not. Findings for both are similar to that of COVID-19 infection overall, in that the group at highest risk was previously uninfected subjects who remained unvaccinated. In multivariable Cox proportional hazards regression, both prior COVID-19 and vaccination were independently associated with significantly lower risk of COVID-19. Among previously infected subjects, a lower risk of COVID-19 overall was not demonstrated compared to vaccination (after several months), but vaccination was associated with a significantly lower risk of symptomatic COVID-19 in both the pre-Omicron (HR 0.60, 95% CI 0.40–0.90) and Omicron (HR 0.36, 95% CI 0.23–0.57) phases.



Comment: Both previous infection and vaccination provide substantial protection against COVID-19. Vaccination of previously infected individuals does not provide additional protection against COVID-19 for several months, but after that provides significant protection at least against symptomatic COVID-19 probably by boosting of waning natural immunity. They did not have a policy of asymptomatic employee screening, previously infected subjects who remained asymptomatic might have been misclassified as previously uninfected, thereby potentially underestimating the protective effect of prior infection. Healthcare employee population included no children and few elderly subjects, and only a small minority would have been immunocompromised limiting generalizability. This study and many more conclude that the group at the highest risk remains the unvaccinated. [see below MMWR on LA] It has also become increasingly clear that natural immunity from prior infection does provide some level of protection against reinfection and severe disease. As the investigators point out protection from both natural immunity and vaccine-induced immunity can wane over time and has proven to be less potent against Omicron. As recent articles reviewed in Infectious Diseases Watch [including the one above] suggest that natural immunity should be factored into COVID-19 vaccination recommendations.

Transmission of SARS-CoV-2 2 Omicron VOC subvariants BA.1 and BA.2: 3 Evidence from Danish Households

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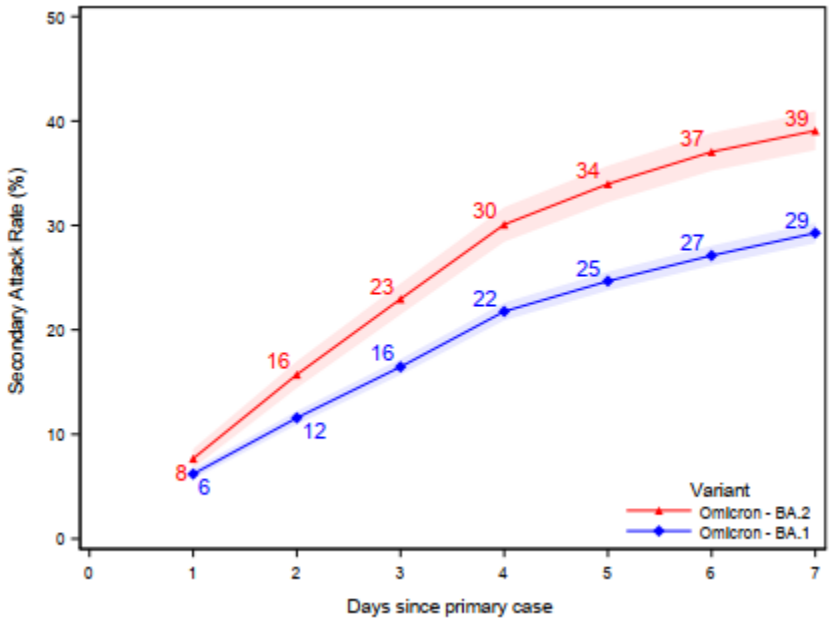
The group examined secondary attack rates in households that had a primary case between Dec 20, 2021, and Jan 11, 2022, looking at differences in transmission between BA.2, BA.1 (the

original Omicron variant), unknown, and Delta variants. Of the households, 2,122 had an initial BA.2 case, and 6,419 had a primary BA.1 case.

They found that the secondary attack rate was substantially higher for BA.2 than BA.1, estimating that the rate was 39% for BA.2 and 29% for BA.1. When the investigators looked at susceptibility differences, they found that BA.2 was associated with increased susceptibility in unvaccinated people, fully vaccinated people, and those who had received boosters compared with BA.1. However, they found that booster-vaccinated individuals had a reduced susceptibility and transmissibility for both BA.1 and BA.2 compared to fully vaccinated individuals. Therefore, the pattern of increased transmissibility in BA.2 households was not observed for fully vaccinated and booster-vaccinated primary cases, where the OR of transmission was below 1 for BA.2 compared to BA.1.



Comment: It is important to sort out the difference between the two Omicron variants, because BA.2 looks different than BA.1, differing by about 40 mutations. The investigators noted that BA.2 increased rapidly in Denmark, rising from 0% of sequences samples on December 6, 2021, to 47% of sequenced samples on January 11, 2022.

They concluded that BA.2 is inherently substantially more transmissible than BA.1, and that it also possesses immune-evasive properties that further reduce the protective effect of vaccination against infection, but do not increase its transmissibility from vaccinated individuals with breakthrough infections. The BA.2 variant findings also suggest 3-dose vaccination protects well against symptomatic infection, which goes against any increased immune evasion. BA.2's increased transmissibility may prolong the Omicron wave in some places. Nearly half of all states in the US have confirmed the presence of the Omicron subvariant BA.2.

SARS-CoV-2 Omicron Variant Neutralization after mRNA-1273 Booster Vaccination N Engl J Med published online January 26, 2022

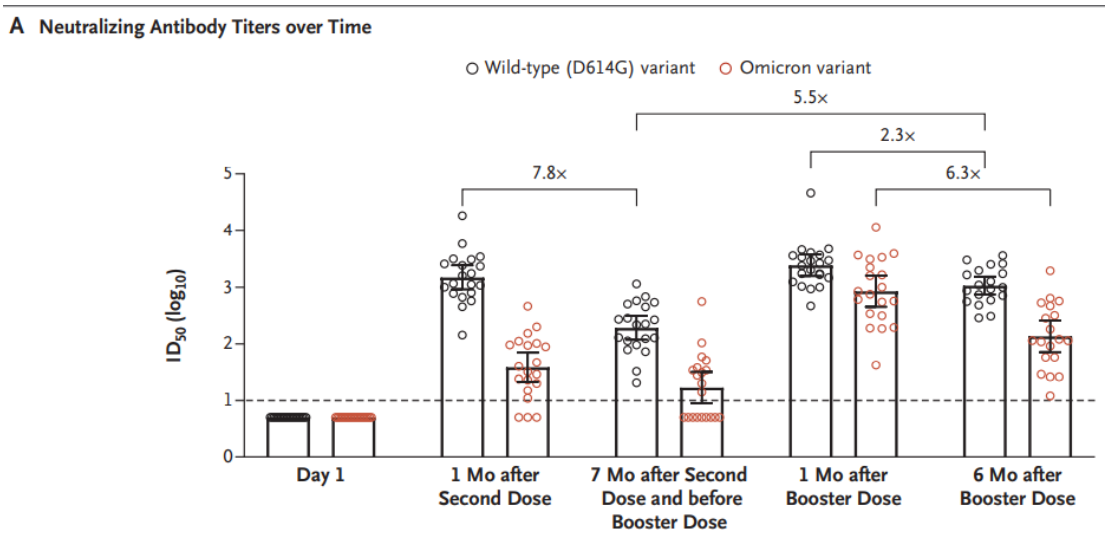
DOI: 10.1056/NEJMc2119912

The investigators measured Omicron variant neutralization using serum samples from participants who had received the two-dose Moderna vaccine regimen in the Coronavirus Efficacy (COVE) phase 2 and 3 trials of that vaccine. Participants were randomly assigned to receive either a third dose of the prototypical Moderna vaccine (the version available under an emergency use authorization for US adults), a 1:1 mix of the authorized vaccine and Beta variant messenger RNAs (mRNAs), or a 1:1 mix of Beta and Delta mRNAs.

The Moderna vaccine induced detectable antibodies against Omicron in 85% of participants 1 month after the second dose. The 50% inhibitory dilution (ID_{50}) geometric mean titer was 35.0 times lower against Omicron than against the wild-type strain. Independently performed live-virus focus-reduction and pseudovirus neutralization tests yielded similar results. Seven months after primary vaccine series completion, anti-Omicron antibodies were found in only 55% of participants, along with ID_{50} geometric mean titers 8.4 times lower than those against the wild-type virus.

A 50-micrograms (μg) booster dose of the prototypical Moderna COVID-19 vaccine was tied to ID_{50} geometric mean titers against Omicron that were 20.0 times higher than those measured 1 month after the second dose; these levels were 2.9 times lower than those against the wild-type virus. Six months after a vaccine booster dose, concentrations of neutralizing antibodies against the Omicron variant were 6.3 times lower than peak levels measured 1 month after the booster. But all participants still had detectable neutralizing antibody concentrations. Neutralizing antibody levels against Omicron fell faster than those against the wild-type virus 6 months after the COVID-19 booster, similar to the drop against the wild-type strain after the second Moderna dose. The booster dose was linked with longer durability of wild-type virus neutralization, which was 2.3 times lower 6 months after the booster injection than at 1 month after the booster.

The 100-μg booster doses of all three Moderna vaccines produced comparable ID_{50} geometric mean titers against Omicron; these levels were 2.5 to 2.6 times higher than those measured after the 50-μg booster dose of the prototypical Moderna vaccine and 1.4 to 1.5 times higher than peak concentrations against the wild-type virus 1 month after the second dose in the COVE trial. The strong boosting of neutralization against Omicron was similar to that against Delta and Beta.



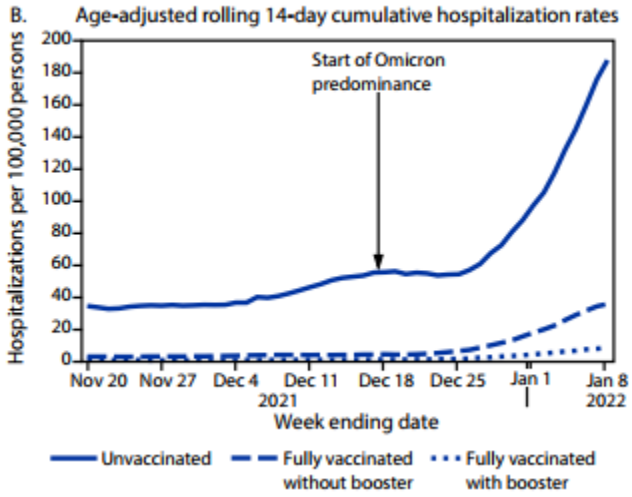
Comment: These results showed that after the primary two-dose series of the Moderna vaccine, neutralization titers against the omicron variant were 35.0 times lower than those against the D614G variant. These lower titers could lead to an increased risk of breakthrough infection. However, a booster dose of the Moderna vaccine increased neutralization titers against the omicron variant that were 20.0 times higher than those assessed after the second dose of vaccine, and at these titers should reduce the risk of breakthrough infection. The decline in neutralization of the omicron variant 6 months after the booster injection was similar to the decline in neutralization titers against the D614G variant 7 months after the second dose. This is the nature of neutralizing antibodies, but T and B cell responses remain intact and does prevent against severe disease and death. This study had small sample sets that may not reflect neutralization in a more diverse population.

SARS-CoV-2 Infection and Hospitalization Among Adults Aged ≥18 Years, by Vaccination Status, Before and During SARS-CoV-2 B.1.1.529 (Omicron) Variant Predominance — Los Angeles County, California, November 7, 2021–January 8, 2022 MMWR February 1, 2022

LACDPH (LA County Department of Public Health) conducted a cross-sectional analysis of LAC residents aged ≥18 years with laboratory-confirmed SARS-CoV-2 infection (a positive SARS-CoV-2 result from a PCR or antigen test) during November 7, 2021– January 8, 2022. Persons were considered fully vaccinated ≥14 days after receipt of the final dose in the primary series of Pfizer, Moderna, or J&J vaccine and considered unvaccinated if <14 days had elapsed since receipt of the first dose in the primary series of an mRNA or J&J vaccine. Fully vaccinated persons who received a booster were considered fully vaccinated with a booster ≥14 days after the date of the booster. Infections occurring in partially vaccinated persons (persons who had received the first dose in a 2-dose series >14 days earlier, but who were either missing a second dose or <14 days had elapsed since receipt of the second dose) were excluded because of small sample size. Demographic and clinical characteristics of SARS-CoV-2 infections were compared by vaccination status.

Unvaccinated adults were 23 times more likely to be hospitalized with COVID-19 during the Omicron wave than adults who were vaccinated and boosted and found by far the highest rates

of cases and hospitalizations among unvaccinated people, followed by vaccinated but not boosted people, with vaccinated and boosted people having the most protection. The study also found that hospitalizations were 5.3 times higher among the unvaccinated than vaccinated but not boosted.



Comment: This is another study supporting the importance of being "up to date" with COVID-19 vaccination in protecting against SARS-CoV-2 infection and hospitalization. Vaccination data for persons who lived in LAC at the time of their laboratory-confirmed infection, but who were vaccinated outside of California, were unavailable, leading to misclassification of their vaccination status. Some boosters might have been misclassified as first doses, and the persons receiving these might have been incorrectly classified as partially vaccinated and excluded. COVID-19–associated hospitalizations were determined based on hospital admission and SARS-CoV-2 test dates alone, potentially leading to the inclusion of incidental positive SARS-CoV-2 test results in patients whose hospitalizations were not caused by COVID-19.

Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection — California, February–December 2021

MMWR published online February 4, 2022

This report used a test-negative design case-control study to randomly enroll selected California residents who had received a test result for SARS-CoV-2 during February 18–December 1, 2021. Face mask or respirator use was assessed among 652 case-participants (residents who had received positive test results for SARS-CoV-2) and 1,176 matched control-participants (residents who had received negative test results for SARS-CoV-2) who self-reported being in indoor public settings during the 2 weeks preceding testing and who reported no known contact with anyone with confirmed or suspected SARS-CoV-2 infection during this time.

Always using a face mask or respirator in indoor public settings was associated with lower adjusted odds of a positive test result compared with never wearing a face mask or respirator in these settings (adjusted odds ratio [aOR] = 0.44; 95% CI = 0.24–0.82). Among 534 participants who specified the type of face covering they typically used, wearing N95/KN95 respirators (aOR = 0.17; 95% CI = 0.05–0.64) or surgical masks (aOR = 0.34; 95% CI = 0.13–0.90) was

associated with significantly lower adjusted odds of a positive test result compared with not wearing any face mask or respirator.

Comment: In addition to being "up to date" with recommended COVID-19 vaccinations, consistently wearing a face mask or respirator in certain indoor public settings provides additional protection from infection. These data from real-world settings reinforce the importance of consistently wearing the right face masks or respirators preferably a KN95/N95 to reduce the risk of acquisition of SARS-CoV-2 infection among high-risk population. This study did not account for other preventive behaviors that could influence risk for acquiring infection, including adherence to other NPIs like physical distancing recommendations, ventilation etc. Estimates do not account for face mask or respirator fit or the correctness of face mask or respirator wearing.