Volume 1, Issue 15, 2022

Infectious Diseases Watch

April 11, 2022

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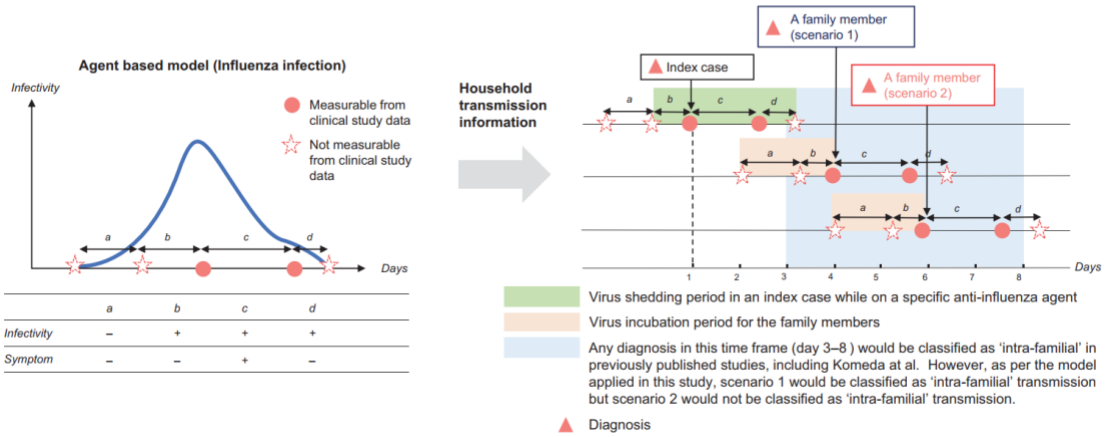
General Infectious Disease

Comparison of Intra-Familial Transmission of Influenza Virus From Index Patients Treated With Baloxavir Marboxil or Oseltamivir Using an Influenza Transmission Model and a Health Insurance Claims Database Clin Infect Dis published online February 1, 2022

doi.org/10.1093/cid/ciac068

The investigators identified index case (IC) as the first family member diagnosed with influenza during the 2018–19 influenza season and classified the families into baloxavir (BXM) or oseltamivir (OTV) group per the drug dispensed to ICs. Using a novel influenza intra-familial infection model, they simulated the duration of influenza infection in ICs based on agent-specific virus shedding periods. Intra-familial infections were defined as non-IC family members infected during the agent-specific viral shedding period in ICs. The virus incubation periods in the non-IC family members were considered to exclude secondary infections from potentially external exposure. The primary endpoint was proportion of families with intra-familial infections. For between-group comparisons, they used a multivariate logistic regression model.

The median proportion of families with intra-familial transmission was 9.57% and 19.35% in the BXM (N = 84,672) and OTV (N = 62,004) groups, respectively. The multivariate odds ratio of 1.73 (2.5th–97.5th percentiles, 1.68–1.77) indicated a substantially higher incidence of intra-familial infections in the OTV group versus the BXM group. Subgroup analyses by ICs' age category, virus type, and month of onset revealed similar trends favoring BXM.



Comments: In this study, the odds of developing intra-familial infection were substantially higher in the OTV group compared with the BXM group, suggesting that BXM is more effective in suppressing influenza intrafamilial infections. This finding is consistent with published literature which has reported better effectiveness of BXM in terms of time to cessation of viral shedding compared with OTV. [N Engl J Med 2018; 379:913–23; Clin Infect Dis 2021; 72:e859–67] The results may not reflect the actual family composition or shared household living, as data are based only on the shared family code without any confirmation whether the family members were actually living in the same household. Future studies are needed to externally valid this study in evaluating transmission outside the household (schools, long-term care facilities, etc.). These results are based on data from a single season with limited cases of type B virus; multi-season studies may shed more light on the impact of yearly variation in virus subtypes, onsets, and infectivity on intra-familial transmission. There was no control group.

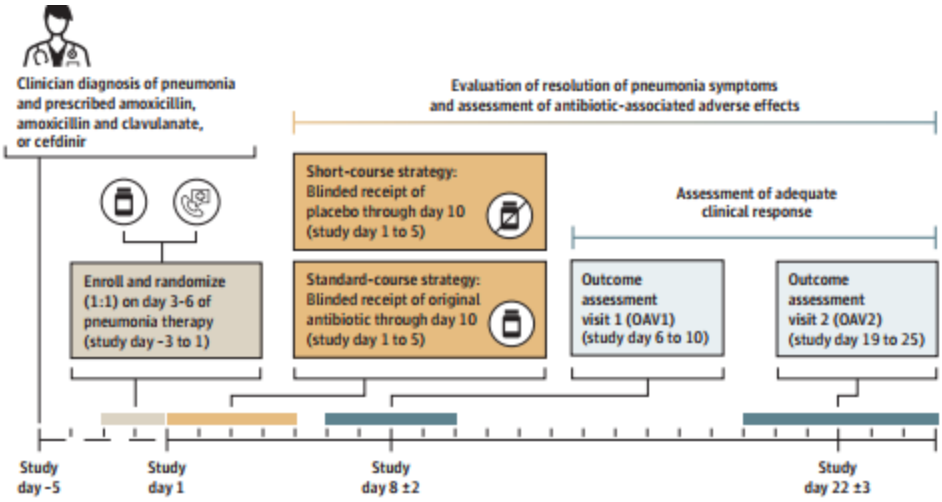
Short- vs Standard-Course Outpatient Antibiotic Therapy for Community-Acquired Pneumonia in Children: The SCOUT-CAP Randomized Clinical Trial

JAMA Pediatr published online January 18, 2022

doi:10.1001/jamapediatrics.2021.5547

This is a randomized double-blind placebo-controlled clinical trial in outpatient clinic, urgent care, or emergency settings in 8 US cities. The objective was to compare a short (5-day) vs standard (10-day) antibiotic treatment strategy for CAP in young children. On day 6 of their originally prescribed therapy, participants were randomized 1:1 to receive 5 days of matching placebo or 5 additional days of the same antibiotic. The primary end point was the end-of-treatment response adjusted for duration of antibiotic risk (RADAR), a composite end point that ranks each child's clinical response, resolution of symptoms, and antibiotic-associated adverse effects in an ordinal desirability of outcome ranking (DOOR). Within each DOOR rank, participants were further ranked by the number of antibiotic days, assuming that shorter antibiotic durations were more desirable. In a subset of children, throat swabs were collected between study days 19 and 25 to quantify antibiotic resistance genes in oropharynx.

A total of 380 healthy children aged 6 to 71 months with nonsevere CAP demonstrating early clinical improvement were enrolled from December 2, 2016, to December 16, 2019. There were no differences between strategies in the DOOR or its individual components. Fewer than 10% of children in either strategy had an inadequate clinical response. The short-course strategy had a 69% (95% CI, 63-75) probability of a more desirable RADAR outcome compared with the standard-course strategy. A total of 171 children were included in the resistome analysis. The median (range) number of antibiotic resistance genes per prokaryotic cell (RGPC) was significantly lower in the short-course strategy compared with the standard-course strategy for total RGPC (1.17 [0.35-2.43] vs 1.33 [0.46-11.08]; *P* = .01) and β-lactamase RGPC (0.55 [0.18-1.24] vs 0.60 [0.21-2.45]; *P* = .03)



Assessments at OAV1 and OAV2			
Rank	Adequate clinical response	Resolution of pneumonia symptoms	Maximal antibiotic-associated adverse effects
1	Yes	Resolved	None
2	Yes	Resolved	Mild
3	Yes	Resolved	Moderate
4	Yes	Resolved	Severe
5	Yes	Persistent symptoms	Any
6	No, ED/clinic visit only	Any	Any
7	No, hospitalization	Any	Any
8	Death from any cause	Any	Any

Comment: In this RCT of 380 children with CAP, a 5-day strategy resulted in similar treatment response with fewer antibiotic days compared with a 10-day strategy. For the primary composite outcome, the 5-day strategy was associated with a 69% probability of a more desirable outcome and a significantly lower abundance of antibiotic resistance genes. Microbiologic testing, such as blood culture, and CXR were not routinely performed as part of study protocol as national guidelines discourage use of these diagnostic tests for pneumonia in the outpatient setting. See next article

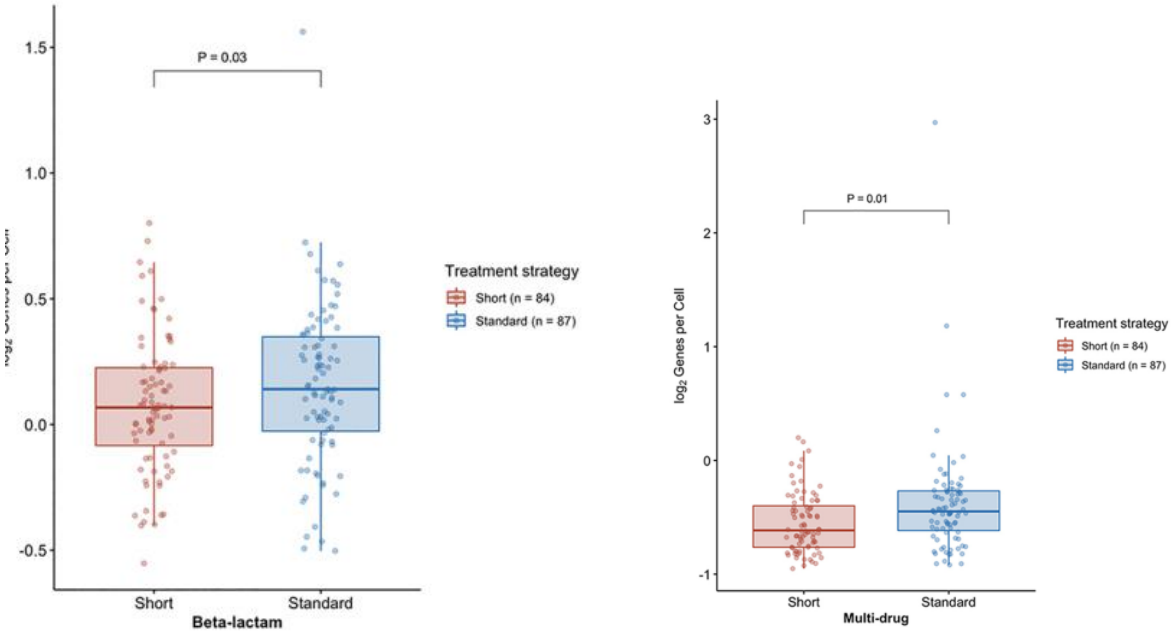
Comparison of the Respiratory Resistomes and Microbiota in Children Receiving Short versus Standard Course Treatment for Community-Acquired Pneumonia

mBio published online April 2022

doi.org/10.1128/mbio.00195-22

The impact of duration of treatment on the respiratory microbiome is limited. Data are from children (n = 171), ages 6 to 71 months, enrolled in the SCOUT-CAP (See article above) Children with CAP were randomized to a short (5 days) versus standard (10 days) beta-lactam treatment strategy. Throat swabs were collected at enrollment and the end of the study and used for shotgun metagenomic sequencing. The number of beta-lactam and multidrug efflux resistance genes per prokaryotic cell (RGPC) was significantly lower in children receiving the short compared to standard treatment strategy at the end of the study (Wilcoxon rank sum test, $P < 0.05$ for each). Wilcoxon effect sizes were small for beta-lactam (r: 0.15; 95% confidence interval [CI], 0.01 to 0.29) and medium for multidrug efflux RGPC (r:0.23; 95% CI, 0.09 to 0.37).

Analyses comparing the resistome at the beginning and end of the trial indicated that in contrast to the standard strategy group, the resistome significantly differed in children receiving the short course strategy. Relative abundances of commensals such as Neisseria subflava were higher in children receiving the standard strategy, and Prevotella species and Veillonella parvula were higher in children receiving the short course strategy. We conclude that children receiving 5 days of beta-lactam therapy for CAP had a significantly lower abundance of antibiotic resistance determinants than those receiving standard 10-day treatment.



Comment: Treatment strategies recommending shorter antibiotic courses for common clinical syndromes have been proposed as a strategy to lower the potential for antibiotic resistance. The investigators in this article examined relationships between the duration of antibiotic treatment and its impact on resistance genes and bacteria in the respiratory microbiome using data from a randomized controlled trial of beta-lactam therapy for pediatric pneumonia. The study design provides evidence of the effectiveness of interventions and minimizes the potential for confounders. Children receiving 5 days of therapy for pneumonia had a lower prevalence of two different types of resistance genes than did those receiving the 10-day treatment. As important, clinical response was equal in both groups. The data also suggest that children receiving longer duration of therapy have a greater abundance of antibiotic resistance genes for a longer period of time than do children receiving shorter duration of therapy. The data in this publication builds on prior studies that where appropriate, shorter duration of therapy provides reduces risk of antimicrobial resistance. The SCOUT-CAP study was limited to otherwise healthy children <6 years with outpatient CAP. Thus, the results of this study may not extend to children with underlying conditions or other populations of children with high levels or prior antibiotic use. The resistome was evaluated at the end of the study, and the duration of follow-up was short (only ~ 1 month after the initiation of antibiotic treatment), and the observed changes in the resistome may be transient.

COVID-19

COVID-19 News

FDA: Sotrovimab No Longer Authorized to Treat COVID-19 in Any US Region

According to recent data, the authorized dose of sotrovimab is unlikely to be effective against the Omicron BA.2 subvariant. As of April 5, 2022, the CDC Nowcast data reported that the BA.2 subvariant accounted for more than 50% of cases in all US states and territories.

Comment: FDA advises to use alternative therapies such nirmatrelvir/ritonavir, remdesivir, bebtelovimab and molnupiravir, which are expected to work against the BA.2 subvariant. Based on the article reviewed last week, [ID Watch April 4, 2022] perhaps convalescent plasma may make a comeback for early outpatient treatment in high-risk patients.

White House Rolls Out National Plan to Fight Long COVID April 5, 2022

- Establishing "Centers of Excellence" and evidence-based care models to investigate how best to deliver care to people with long COVID
- Increasing the number and quality of long COVID clinics as well as "robust referral and follow-up systems".
- Promoting provider education and clinical support to help improve, detect, and understand long COVID and related conditions through culturally competent resources
- Ensuring that health insurance coverage for long COVID care is "as accessible as possible"; care for long COVID is required by state Medicaid programs, and Medicare recently expanded coverage for pulmonary rehabilitation services related to long COVID in the 2022 Physician Fee Schedule
- Increasing public awareness of long COVID as a possible cause of disability covered under the Americans with Disabilities Act

Comment: This is welcomed news. We need a standardized definition of Long Covid, and coordination of centers currently engaged in this area. The administration will also help to connect individuals with long COVID with resources and support, including by the CDC-INFO call center and other call centers overseen by CMS, and by connecting older adults and people with disabilities to transportation so they may receive care through the Administration for Community Living's DIAL and Eldercare Locator.

New COVID Combo-Variant XE Found in UK

A new COVID-19 variant has cropped up in the United Kingdom – a combination of the original Omicron strain and its subvariant BA.2 that may be more contagious than BA.2. [getting close to measles!] As of last week, the U.K. Health Security Agency had found 637 cases of the variant, known as XE. XE makes up less than 1% of sequenced cases in the U.K. so far, and there is no evidence yet that the strain leads to more severe disease or less vaccine protection.

Comment: WHO update published March 29 notes XE's high transmissibility and says it may have a growth advantage of 10% over the BA.2 subvariant. To date there is no reason to be alarmed at present.

FDA's Vaccines and Related Biological Products Advisory Committee April 6, 2022

The Vaccines Advisory Committee met virtually on Wednesday. The outside panel largely agreed for the need to tailor future COVID-19 vaccines but the exact path and timeline to do so is still unclear. Here are some take aways:

1. The Advisory Committee met to develop a framework for the nation's COVID-19 booster shot strategy. The FDA has not yet asked members to vote on specific booster recommendations.

2. The committee is weighing whether a new booster should be rolled out this fall. Peter Marks, MD, PhD, director of the FDA's Center for Biologics Evaluation and Research, said during the meeting that although we've seen a major decline in the number of COVID-19 cases in the country, the virus will probably continue to circulate and therefore, we may continue to see waves in the near term. "This is of particular concern as we head into the fall and winter season."

3. Based on this timeline, the FDA will need to determine which strain or strains a new booster should target by June at the latest, so vaccine makers have enough time to manufacture the vaccine(s)

4. The panel did not come up with a concrete plan on boosters, noting it is difficult to predict what strain of the virus the US may be circulating in the fall. The committee will probably meet again in May and June to develop a more detailed proposal for reformulated COVID-19 vaccination.

Comment: Surprisingly the expert panel was not asked to weigh in on the recent FDA/CDC announcement “allowing” a fourth dose or second booster for individuals over age 65 or individuals over age 50 with certain high-risk underlying medical conditions. Clearly, we need a coherent policy on boosters which the public can have confidence in.

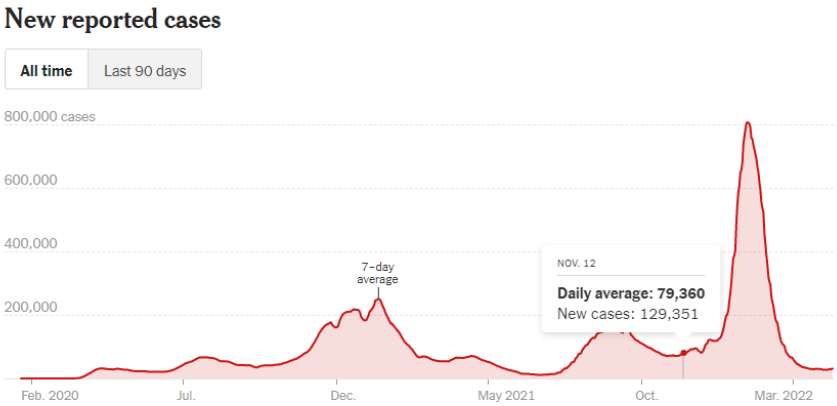
ECDC and EMA issue advice on fourth doses of mRNA COVID-19 vaccines April 7, 2022

The European Centre for Disease Prevention and Control (ECDC) and the European Medicines Agency's (EMA) COVID-19 task force (ETF) have concluded that it is "too early" to consider using a fourth dose of mRNA COVID-19 vaccines (Pfizer and Moderna) in the general population. However, both agencies agreed that a fourth dose (or second booster) can be given to adults 80 years of age and above after reviewing data on the higher risk of severe COVID-19 in this age group and the protection provided by a fourth dose.

The ECDC and EMA also noted that there is currently no clear evidence in the EU that vaccine protection against severe disease is waning substantially in adults aged 60 to 79 years with normal immune systems and thus no clear evidence to support the immediate use of a fourth dose. Nonetheless, both agencies said authorities will continue to monitor data to determine if there is an increasing risk of severe illness among those who are vaccinated, noting that "if the current epidemiological situation changes and new signals emerge, it may become necessary to consider a fourth dose in this age group."

Comment: The ECDC and EMA noted that they will continue to review available evidence on the effectiveness of COVID-19 vaccines and update their recommendations accordingly. This will certainly add to the confusion around a second booster in the US since the ECDC recommendation is different from the US CDC. In the statement by the ECDC and EMA, they claim the main source of empirical evidence on the potential public health impact of a fourth dose of mRNA vaccines as a second booster in immunocompetent individuals comes from data from Israel, noting that data indicate that a fourth dose of an mRNA vaccine given to immunocompetent individuals at least 4 months after the third dose is able to restore humoral immunity to the level seen after the third dose without raising any new safety concerns. They added further that "only preliminary data from Israel with respect to vaccine effectiveness against severe disease following a fourth dose are currently available. (See article below)

COVID-19 by The Numbers



	DAILY AVG. ON APR. 9	14-DAY CHANGE	TOTAL REPORTED
Cases	30,753	+2%	80,267,553
Tests	794,965	-6%	—
Hospitalized	15,112	-20%	—
In I.C.U.s	2,172	-29%	—
Deaths	565	-29%	983,708

Comment: After two months of declines, reports of new Covid-19 cases in the US have been generally flat in the past two weeks, however, even as case reports have leveled off some, Covid-19 hospitalizations across the country have continued to decrease. Hospitalizations have fallen to an average of roughly 15,000 per day in the past two weeks, the lowest they have been since the first weeks of the pandemic. Deaths also remain on the decline. Around 600 deaths from Covid are being reported each day, a decrease of more than 75 percent from the peak in February amid the Omicron surge. BA.2 now makes up 72% of cases in the US.

COVID-19 Journal Review

Discontinuation of atorvastatin use in hospital is associated with increased risk of mortality in COVID-19 patients

J Hosp Med. 2022; 17:169–175

DOI: 10.1002/jhm.12789

Statins' effects on inflammation, endothelial function, and coagulation, and their upregulation of the ACE2 receptor, are theoretical reasons that they could be beneficial. Studies to date have been inconclusive. [all observational studies] To assess the effect of discontinuing statin therapy, researchers analyzed records of nearly 150,000 adult patients with COVID-19 who were admitted to facilities within a large U.S. healthcare system. [HCA Healthcare] Only patients who were receiving atorvastatin (93% of cohort) were considered in the analysis. Patients were divided into three statin-therapy categories: (1) continuous (home plus in hospital); (2) discontinued (home, but not in hospital); (3) no statins. Logistic regression was performed to assess the association between atorvastatin administration and either mortality or use of mechanical ventilation during the encounter.

Continuous use of atorvastatin (home and in hospital) was associated with a 35% reduction in the odds of mortality compared to patients who received atorvastatin at home but not in hospital (odds ratio [OR]: 0.65, 95% confidence interval [CI]: 0.59–0.72, $p < .001$). Similarly, the odds of ventilation were lower with continuous atorvastatin therapy (OR: 0.70, 95% CI: 0.64–0.77, $p < .001$).

Comment: In analyses adjusted for various potential confounding variables, continuous use of statins was associated with significantly lower mortality than was discontinued use. Odds of mechanical ventilation was also significantly lower with continuous therapy than with discontinued therapy. The investigators attempted to identify those patients who's in-hospital administration of atorvastatin was a continuation of their ongoing use of this medication for other conditions. The authors admitted that due to the nature of their data, they were limited to medication lists reported by the patient or their representative at admission. Such lists are known to often be incomplete or not supplied for a variety of reasons, and thus they say the results should be interpreted with caution. In addition, the overall population who were on a statin were older on average than those patients with no known statin exposure. Although this variable was considered as part of the regression, the younger age of the no-statin group would favor reduced mortality, as age has been consistently identified as a risk factor for COVID-19 mortality. Lastly, although the investigators adjusted for potential confounders, some residual confounders are likely.

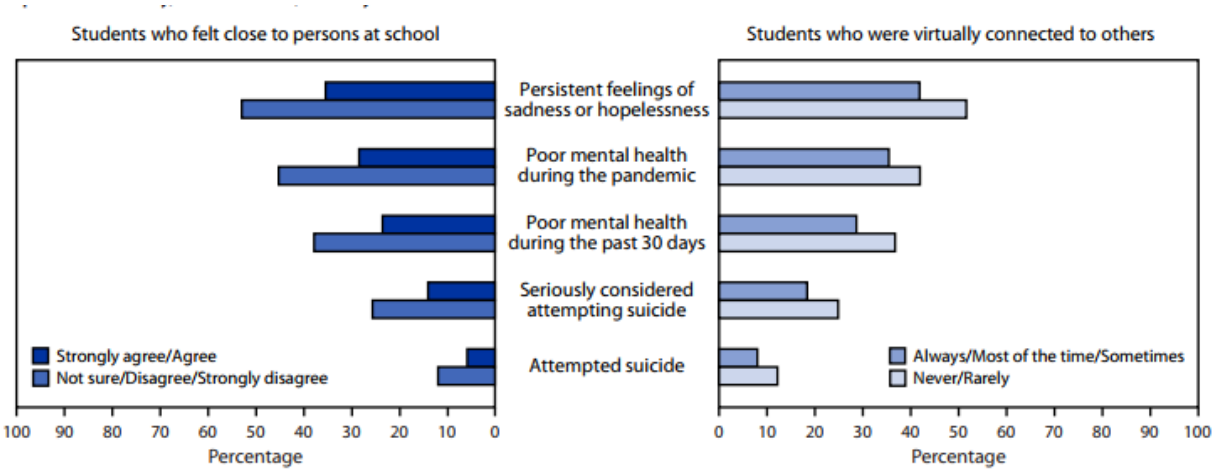
The NIH Covid-19 Guidelines state that patients with COVID-19 who are receiving concomitant medications (e.g., angiotensin-converting enzyme [ACE] inhibitors, angiotensin receptor blockers [ARBs], HMG-CoA reductase inhibitors [statins], systemic or inhaled corticosteroids, nonsteroidal anti-inflammatory drugs, acid-suppressive therapy) for underlying medical conditions **should not discontinue** these medications during acute management of COVID-19

unless discontinuation is otherwise warranted by their clinical condition (AIIa for ACE inhibitors and ARBs; AIII for other medications).

Mental Health, Suicidality, and Connectedness Among High School Students During the COVID-19 Pandemic — Adolescent Behaviors and Experiences Survey, United States, January–June 2021 MMWR 2022; 71:16-21

This report uses data from the 2021 Adolescent Behaviors and Experiences Survey, an online survey of a probability-based, nationally representative sample of US public- and private-school students in grades 9–12 (N = 7,705), to assess US high school students' mental health and suicidality during the COVID-19 pandemic. The study also examines whether mental health and suicidality are associated with feeling close to persons at school and being virtually connected to others during the pandemic.

Overall, 37.1% of students experienced poor mental health during the pandemic, and 31.1% experienced poor mental health during the preceding 30 days. In addition, during the 12 months before the survey, 44.2% experienced persistent feelings of sadness or hopelessness, 19.9% had seriously considered attempting suicide, and 9.0% had attempted suicide. Compared with those who did not feel close to persons at school, students who felt close to persons at school had a significantly lower prevalence of poor mental health during the pandemic (28.4% versus 45.2%) and during the past 30 days (23.5% versus 37.8%), persistent feelings of sadness or hopelessness (35.4% versus 52.9%), having seriously considered attempting suicide (14.0% versus 25.6%), and having attempted suicide (5.8% versus 11.9%). The same pattern was observed among students who were virtually connected to others during the pandemic (i.e., with family, friends, or other groups by using a computer, telephone, or other device) versus those who were not.



Comment: More than one in three high school students (37.1%) experienced poor mental health during the COVID-19 pandemic. In addition, 44.2% of students experienced persistent feelings of sadness or hopelessness, almost 20% seriously considered suicide, and 9.0% attempted suicide during the 12 months before the survey. The prevalence of poor mental health and suicidality was high across students of all sex, sexual identity, and racial and

ethnic groups; however, poor mental health, persistent feelings of sadness or hopelessness, and suicidal thoughts and behaviors were less prevalent among those who felt close to persons at school and were virtually connected with others during the pandemic. Mental health issues among youths are an important public health concern during the ongoing COVID-19 pandemic. During the COVID-19 pandemic, students' feelings of being connected to school were likely reduced by extensive school closures and transitions to virtual learning. Efforts to improve connectedness to schools, peers, and family are critical to protecting the mental health and well-being of our children.

Comparative Effectiveness of Single vs Repeated Rapid SARS-CoV-2 Antigen Testing Among Asymptomatic Individuals in a Workplace Setting JAMA Netw Open published online March18, 2022

doi:10.1001/jamanetworkopen.2022.3073

The investigators sought to analyze the comparative effectiveness and estimated accuracy of an employee screening program using single vs repeated antigen tests compared with RT-PCR among asymptomatic individuals. Antigen testing of midturbinate nasal swab specimens was performed by trained personnel using Sofia2 SARS Antigen Fluorescent Immunoassay (Quidel Corporation), LumiraDX (Abbott), and BinaxNow (Abbott) rapid antigen tests from November 27, 2020, to October 21, 2021. Individuals with any symptoms of COVID-19 were excluded from screening.

A total of 179,127 rapid SARS-CoV-2 antigen tests were performed, with a 0.35% positivity rate (623 positive antigen test results) between November 2020 and October 2021. Of 623 total positive test results, 238 (38%) were confirmed to be true positive and 385 (62%) false positive by PCR. Of the 623 tests with positive results, 569 (91%) were followed by a second rapid antigen test. Of 224 sets of tests with concordant results (2 separate but consecutive antigen tests with positive results), PCR results were positive for 207 (92%). When the result of the first antigen test was positive and the result of the second antigen test was negative (n = 345), PCR results were negative for 328 (95%). The overall estimated accuracy of a second antigen test was 94%.

Comment: The results of this study demonstrated that when a repeated rapid antigen test was offered to participants of an employee screening program, the estimated accuracy increased from 38% to 92% for true-positive results as determined by PCR for SARS-CoV-2. These findings may have important implications for how rapid antigen tests can be deployed for more accurate results, especially in a setting where the time to results is important and where widespread PCR testing may not be available. As expected, test results appeared to be more accurate when community infection rates were higher and, therefore, the pretest probability was higher. The diagnostic value of a second antigen test remained high regardless of pretest probability. The study was only for employees who were asymptomatic and were being screened as part of a workplace testing program. As other studies have demonstrated, a single antigen test has a lower sensitivity compared to PCR for detecting infection in asymptomatic individuals. As employers consider the best use of onsite or at-home rapid antigen testing, a second antigen test may be useful for more accurate diagnosis of COVID-19 infection and for guiding intervention. On the other hand, as reported in last week's ID Watch, in symptomatic

persons infected with SARS-CoV-2 there is a correlation between a positive rapid Ag with positive viral culture and the potential for transmission of SARS-CoV-2 infection.

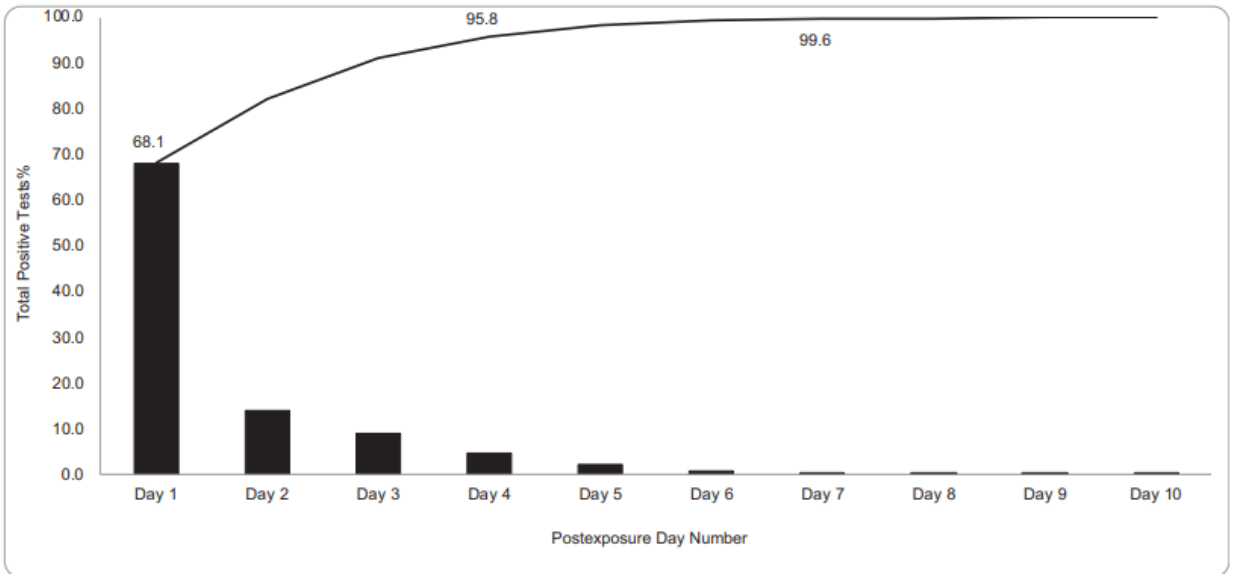
A Test-to-Stay (TTS) Modified Quarantine Program for COVID-19 in Schools

Pediatrics 2022; 149: e2021055727

doi/10.1542/peds.2021-055727/1277857

For the 2020–2021 academic year, MA implemented an opt-in TTS program, in which students exposed to COVID-19 in school are tested each school day with a rapid antigen test. If negative, students may participate in school-related activities that day. Testing occurs daily for a duration of 7 calendar days after exposure. This article reports the results from the first 13 weeks of the program.

A total of 2298 schools signed up for TTS, and 504,167 individuals out of a total population of 860,457 consented. During the first 13 weeks with complete data, 1959 schools activated the program at least once for 102,373 individual, exposed students. Out of 328,271 tests performed, 2943 positive cases were identified (per person positivity rate, 2.9%, 95% confidence interval, 2.8–3.0). A minimum of 325,328 and a maximum of 497,150 days of in person school were saved through participation in the program.



Comment: Unvaccinated students in school districts without the capacity to implement TTS, and students in TTS districts who have barriers to opt into these programs, may not have equal access to in-person learning. Many TTS programs limit activities for participants during their observation period, ranging from allowing only classroom-based activities to allowing extracurricular and after-school activities if masking and distancing can be maintained. In a commentary the authors point out that households with lower incomes are more likely to rely on after-school programs, introducing additional barriers to these services when TTS programs allow in-person classroom participation but limit participation in after-school activities. Finally, I

believe public health agencies can contribute by ensuring schools have adequate contact tracing and testing services.

Incidence Rates and Clinical Outcomes of SARS-CoV-2 Infection With the Omicron and Delta Variants in Children Younger Than 5 Years in the US JAMA Pediatr published online April 1, 2022

doi:10.1001/jamapediatrics.2022.0945

This is a cohort study (September 1, 2021-January 31, 2022) using the TriNetX Analytics Platform to access aggregated and deidentified electronic health records of 90 million patients from 66 health care organizations. This dataset includes patients which represented 28% of the US population from 50 states covering diverse geographic, age, race, income, and insurance groups. Self-identified race and ethnicity were included owing to their association with SARS-CoV-2 infection risk and outcomes.

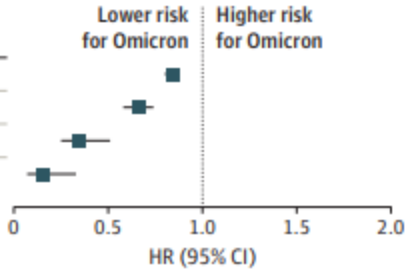
The study population contained 3 cohorts of children younger than 5 years with no prior SARS-CoV-2 infection: (1) Omicron cohort, who contracted SARS-CoV-2 infection between December 26, 2021, and January 25, 2022; (2) Delta cohort, who contracted SARS-CoV-2 infection between September 1, 2021, and November 15, 2021; and (3) Delta2 cohort, who contracted SARS-CoV-2 infection between November 16 and November 30, 2021. Delta2 cohort was developed to control for later time periods and shorter infection window. They examined monthly incidence rates of SARS-CoV-2 infection (new cases per 1000 persons per day) between September 1, 2021, and January 31, 2022, among children without prior infections, stratified by 2 age groups (0-2 and 3-4 years). They tested whether severe clinical outcomes differed between Omicron and Delta cohorts and between Delta2 and Delta cohorts. Cohorts were propensity-score matched for demographics. Risk of death, emergency department visits, hospitalizations, intensive care unit (ICU) admissions, and the need for mechanical ventilation within 14 days after initial SARS-CoV-2 infection were compared between matched cohorts using hazard ratios (HRs) and 95% CIs.

The monthly incidence rate of SARS-CoV-2 infections was mostly stable (1.0-1.5 cases per 1000 persons per day) between September and November 2021 (Delta-predominant period) but rapidly increased to 2.4 to 5.6 cases per 1000 persons per day in December 2021, coincident with the emergence of Omicron variant. Monthly incidence rate of SARS-CoV-2 infections peaked at 8.6 cases per 1000 persons per day in the first half of January 2022 (Omicron-predominant period) and 8.2 in the second half of January 2022. Incidence rate of Omicron infection was higher in children aged 0 to 2 years than in those aged 3 to 4 years. Omicron cohort was younger and with fewer comorbidities than Delta cohort, but differences were controlled for after matching. Risks for severe clinical outcomes in children infected with Omicron variant were significantly lower than those in the matched Delta cohort, whereas the risks for severe clinical outcomes in Delta2 cohort did not differ from those in Delta cohort. There were fewer than 10 deaths in all cohorts!

Figure. Comparison of Risks of Clinical Outcomes of SARS-CoV-2 Infection in Children Younger Than 5 Years

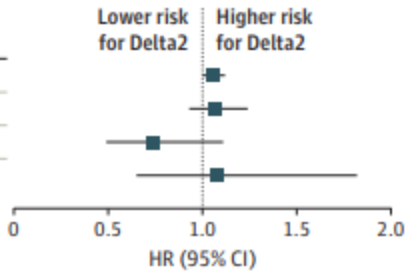
A Omicron vs Delta cohorts

Outcome	Matched Omicron cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	4637 (20.36)	5602 (24.60)	0.84 (0.80-0.87)
Hospitalizations	401 (1.76)	741 (3.25)	0.66 (0.58-0.74)
ICU admissions	38 (0.17)	115 (0.51)	0.35 (0.25-0.51)
Mechanical ventilation	10 (0.04)	51 (0.22)	0.15 (0.07-0.33)



B Delta2 vs Delta cohorts

Outcome	Matched Delta2 cohort, No. (%)	Matched Delta cohort, No. (%)	HR (95% CI)
ED visits	2740 (26.33)	2614 (25.12)	1.06 (1.00–1.12)
Hospitalizations	371 (3.56)	360 (3.46)	1.07 (0.93–1.24)
ICU admissions	40 (0.38)	55 (0.53)	0.74 (0.49–1.11)
Mechanical ventilation	30 (0.29)	28 (0.27)	1.08 (0.65–1.82)



Comment: Results of this cohort study suggest that the incidence rate of SARS-CoV-2 infection with Omicron variant was 6 to 8 times that of Delta variant in children younger than 5 years, but severe clinical outcomes were less frequent than with Delta variant. Study limitations include potential biases introduced by the observational and retrospective analyses of electronic health records and the need for validation of the results from other data.

Protection by a Fourth Dose of BNT162b2 against Omicron in Israel N Engl J Med published online April 5, 2022

DOI: 10.1056/NEJMoa2201570

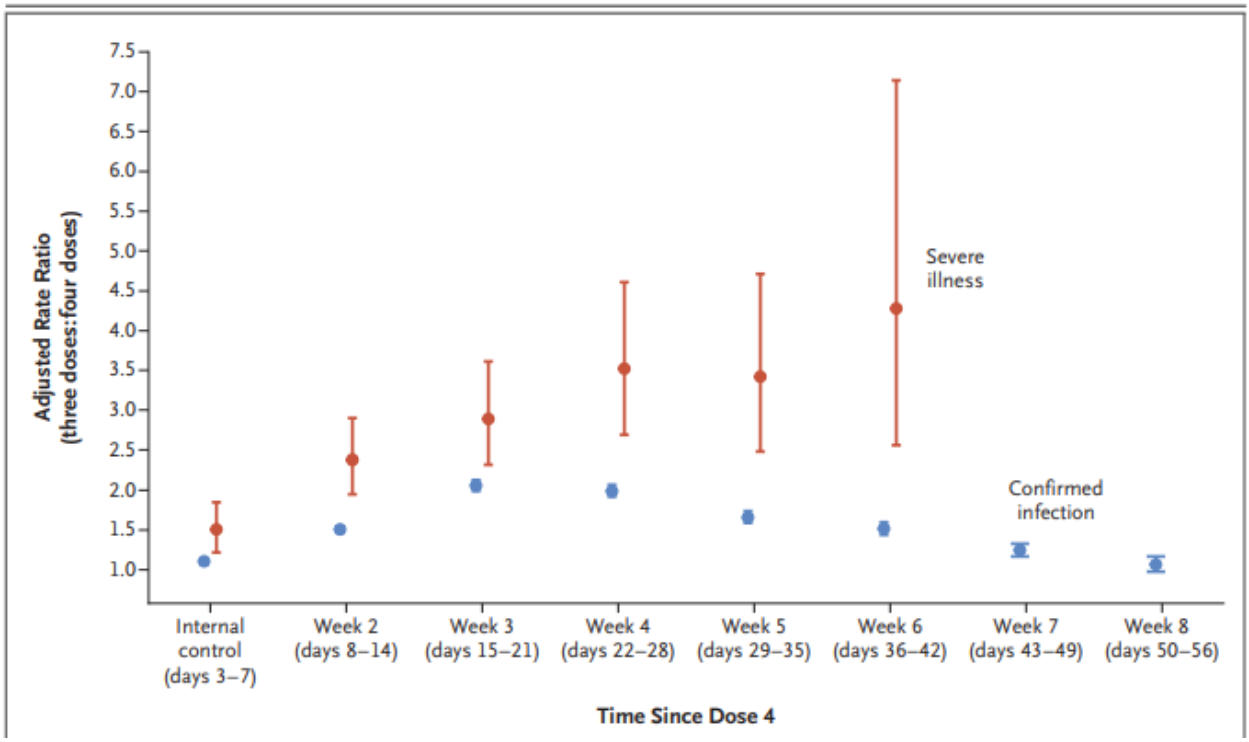
This study involved data from 1,252,331 people aged 60 years and older, who became eligible for a fourth COVID-19 shot [second booster] in Israel on January 2, 2022. The study period ran from January 10th to February 18th for severe illness and to March 2nd for infection. For the estimation of rates, we used quasi-Poisson regression with adjustment for age, sex, demographic group, and calendar day

The unadjusted rate of COVID-19 infections per 100,000 person-days among people who had received a fourth vaccine dose 8 days before was 1.5, compared with 3.9 in those who had received three doses and 4.2 in controls who had received a fourth dose 3 to 7 days before.

After adjustment, the rate of severe COVID-19 in the fourth week after receipt of the fourth vaccine dose was lower than that of the three-dose group by a factor of 3.5 (95% confidence interval [CI], 2.7 to 4.6) and lower than that in controls by a factor of 2.3 (95% CI, 1.7 to 3.3).

Vaccine protection against severe infection was stable for 6 weeks after the fourth dose. The unadjusted rate of severe COVID-19 infection per 100,000 person-days was 177 in fourth-dose recipients, 361 in the three-dose group, and 388 in controls.

The adjusted rate of infection among those who had received a fourth dose 4 weeks earlier was lower than that in the three-dose group by a factor of 2.0 (95% CI, 1.9 to 2.1) and lower than that of controls by a factor of 1.8 (95% CI, 1.7 to 1.9).



The higher the rate ratio, the greater the protection conferred by the fourth dose of vaccine

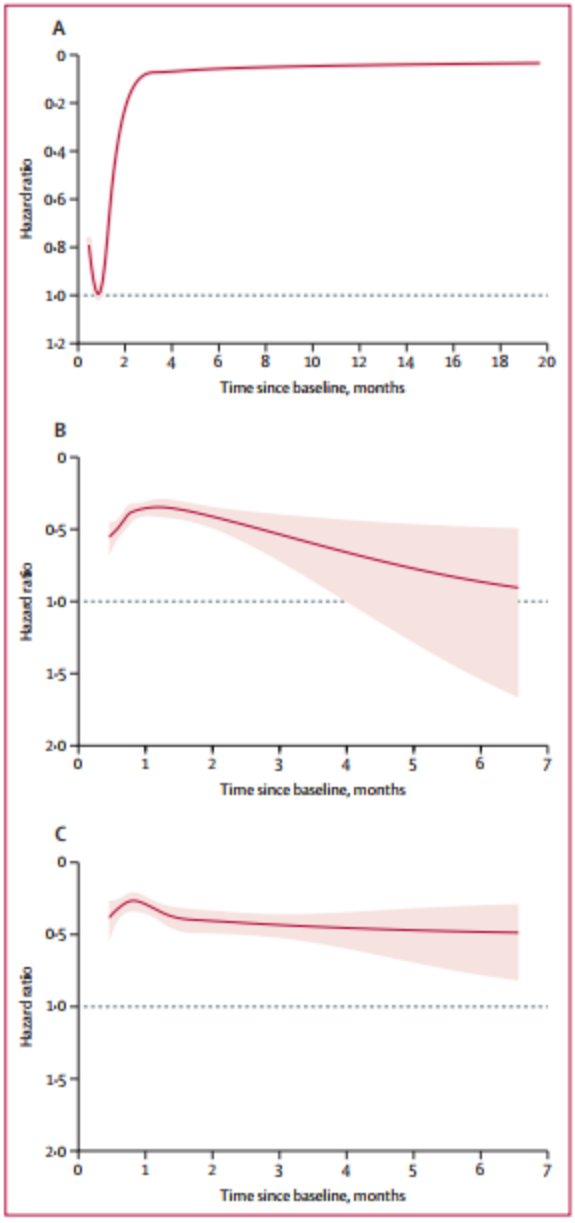
Comment: This study is from different investigators from pre-publication article reviewed last week in ID Watch. This study provides evidence for the effectiveness of a fourth vaccine dose against severe illness caused by the omicron variant, as compared with a third dose administered more than 4 months earlier in persons >60. For confirmed infection, however, a fourth dose appeared to provide only short-term protection and a modest absolute benefit. [1 in 42,000 risk reduction] Although their analysis attempted to address biases such as confounding, some sources of bias may not have been measured or adequately controlled for — for example, behavioral differences between persons who received the fourth dose and those who did not. For severe illness, differences in the prevalence of coexisting conditions could potentially have affected the results; however, this information is not recorded in the national database, and therefore we did not adjust for such differences.

Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden Lancet Infect Dis published online March 31, 2022

doi.org/10.1016/S1473-3099(22)00143-8

This is a retrospective cohort study, comparing three cohorts using the Swedish nationwide registers. Cohort 1 included unvaccinated individuals with natural immunity matched pairwise on birth year and sex to unvaccinated individuals without natural immunity at baseline. Cohort 2 and cohort 3 included individuals vaccinated with one dose (one-dose hybrid immunity) or two doses (two-dose hybrid immunity) of a COVID-19 vaccine, respectively, after a previous infection, matched pairwise on birth year and sex to individuals with natural immunity at baseline. Outcomes of this study were documented SARS-CoV-2 infection from March 20, 2020, until Oct 4, 2021, and inpatient hospitalization with COVID-19 as main diagnosis from March 30, 2020, until September 5, 2021.

This study based on the total population of Sweden showed that natural immunity was associated with a 95% lower risk of SARS-CoV-2 reinfection and an 87% lower risk of COVID-19 hospitalization than no immunity, for up to 20 months. In head-to-head comparisons, hybrid immunity induced by either one or two doses of a COVID-19 vaccine was associated with an additional risk reduction of SARS-CoV-2 reinfection compared with natural immunity for up to 9 months, although with small absolute differences. Furthermore, one-dose hybrid immunity was associated with an additional 94% lower risk of COVID-19 hospitalization, and two-dose hybrid immunity with an additional 90% lower risk of COVID-19 hospitalization, than natural immunity, although the number of hospitalizations were few.



Risk of SARS-CoV-2 infection in individuals with natural immunity compared with individuals without immunity (A), and risk of these outcomes in individuals with one-dose hybrid immunity (B) and two-dose hybrid immunity (C) compared with individuals with natural immunity

Comment: The risk of SARS-CoV-2 reinfection and COVID-19 hospitalization is low in individuals with a previous infection. Vaccination after recovering from a previous infection might result in additional risk reduction against reinfection and hospitalization for up to 9 months, but the differences in absolute risk appear small. The associated protection from natural immunity was lower in older individuals. Because these individuals have higher risk of critical illness and death from COVID-19 boosting their level of protection is important. Since this was an observational trial this limits the possibility to draw causal inferences, since there might be

unknown confounding or bias not accounted. In the analysis of hybrid immunity versus natural immunity, it is possible that vaccinated individuals with symptoms of infection may be more prone to self-testing than individuals that remain unvaccinated after a documented infection. Baseline date was not the same in all cohorts, which could mean that variations in infection pressure and dominating SARS-CoV-2 variants during follow-up influenced the results, although the investigators adjusted all models for baseline date. Unfortunately, they could not evaluate how different variants of SARS-CoV-2 influenced the associations, as they did not have access to such data on an individual level. See next article

SARS-CoV-2 Naturally Acquired Immunity vs. Vaccine-induced Immunity, Reinfections versus Breakthrough Infections: a Retrospective Cohort Study Clin Infect Dis published online April 5, 2022

doi/10.1093/cid/ciac262/6563799

The investigators examined the long-term protection of naturally acquired immunity compared to vaccine induced immunity. This was a retrospective observational study of almost 125,000 persons comparing two groups: SARS-CoV-2 naïve individuals who received a two-dose Pfizer vaccine versus previously infected individuals who had not been vaccinated. The applied two multivariate logistic regression models evaluating four outcomes: infection, symptomatic disease, hospitalization and death between June 1 to August 14, 2021, when Delta was the predominant variant.

SARS-Co-2 naïve vaccinees had a 13-fold (CI, 8.08-21.11) increased risk for breakthrough infections with Delta compared to unvaccinated-previously-infected individuals when the first event (infection of vaccination) occurred during January and February 2021. The increased risk was significant for symptomatic disease as well. When they went back and analyzed infection to occur at any time between March 2020 to February 2021 there was evidence of waning naturally acquired immunity, but SARS-CoV-2 naïve vaccinees still had a 54.96-fold (CI, 4.85-7.33) increase of breakthrough infection and a 7.13-fold (CI, 5.51-9.21) increased risk of symptomatic disease.

Comment: This analysis demonstrated that naturally acquired immunity affords longer lasting and stronger protection against infection and symptomatic disease due to the Delta variant of SARS-CoV-2, compared to the Pfizer two-dose vaccine-induced immunity. Since Delta variant was the dominant strain in Israel during the outcome period, the decreased long-term protection of the vaccine compared to that afforded by previous infection cannot be ascertained against other strains, including Omicron. Second, their analysis addressed protection afforded solely by the Pfizer vaccine, and therefore does not address other vaccines or long-term protection following a third dose. Another concern is that the frequency of PCR testing differed between groups, meaning that one group manifested different health seeking behavior during the pandemic and therefore is potentially more diagnosed rather than more infected. To address that potential detection bias, the investigators conducted a sensitivity analysis where the number of PCR tests undertaken throughout the pandemic was adjusted for, as a proxy for COVID-19-related health seeking behavior. The findings demonstrated that this adjustment did not change the results. What can we take away from this and other studies [many reviewed in ID Watch and the Covid-19 Briefing]? To me it is time we adjust our vaccination strategy to include natural immunity. While I am at it, why haven't we officially changed the recommendation on dosing interval for primary vaccination from 3-4 weeks to 2 months?