Infectious Diseases Watch

March 14,2022

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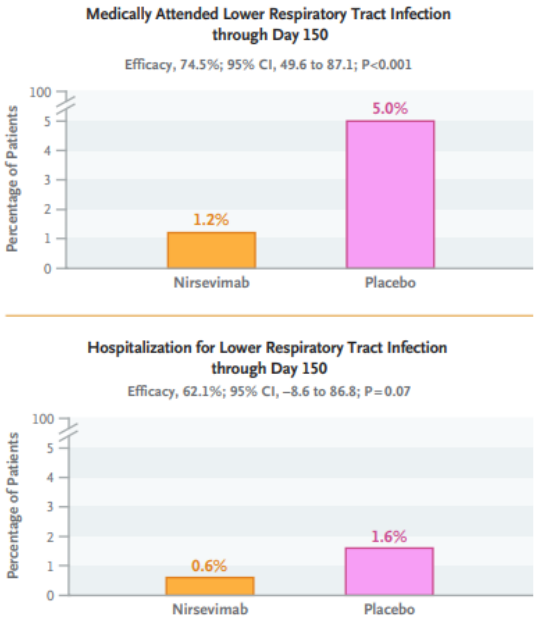
General Infectious Diseases

Nirsevimab for Prevention of RSV in Healthy Late-Preterm and Term Infants N Engl J Med 2022;386:837-46

DOI: 10.1056/NEJMoa2110275

The investigators randomly assigned, in a 2:1 ratio, infants who had been born at a gestational age of at least 35 weeks to receive a single intramuscular injection of nirsevimab or placebo before the start of an RSV season. The primary efficacy end point was medically attended RSV-associated lower respiratory tract infection through 150 days after the injection. The secondary efficacy end point was hospitalization for RSV associated lower respiratory tract infection through 150 days after the injection.

A total of 1490 infants underwent randomization: 994 were assigned to the nirsevimab group and 496 to the placebo group. Medically attended RSV-associated lower respiratory tract infection occurred in 12 infants (1.2%) in the nirsevimab group and in 25 infants (5.0%) in the placebo group; these findings correspond to an efficacy of 74.5% (95% confidence interval [CI], 49.6 to 87.1; P<0.001) for nirsevimab. Hospitalization for RSV-associated lower respiratory tract infection occurred in 6 infants (0.6%) in the nirsevimab group and in 8 infants (1.6%) in the placebo group (efficacy, 62.1%; 95% CI, −8.6 to 86.8; P=0.07). Among infants with data available to day 361, antidrug antibodies after baseline were detected in 58 of 951 (6.1%) in the nirsevimab group and in 5 of 473 (1.1%) in the placebo group. Serious adverse events were reported in 67 of 987 infants (6.8%) who received nirsevimab and in 36 of 491 infants (7.3%) who received placebo. They observed relatively lower efficacy among infants who were 3.0 months of age or younger or who weighed less than 5 kg at the time of the injection.



Comment: Nirsevimab is a recombinant human IgG1 kappa monoclonal antibody that binds the F1 and F2 subunits of the RSV fusion (F) protein at a highly conserved epitope and locks the RSV F protein in the prefusion conformation to block viral entry into the host cell. Nirsevimab shows greater potency at inhibiting RSV than palivizumab in cell-culture and animal models and has an Fc region engineered to have an extended half-life in vivo. Pharmacokinetic data show that nirsevimab levels associated with protection in preclinical studies are maintained through 150 days after administration across age and weight subgroups. RSV has seen a resurgence with the easing of COVID-19 public health measures. This study shows an immunization approach is needed to help mitigate the substantial global burden RSV. In last week's ID Watch I reviewed a study demonstrating that RSV poses a greater risk than influenza to infants. [JAMA Netw Open published online February 28, 2022]

Interim Guidance: 4-Month Rifapentine-Moxifloxacin Regimen for the Treatment of Drug-Susceptible Pulmonary Tuberculosis — United States, 2022

MMWR 2022; 71:285-289

Standard treatment for culture-positive TB required ≥6 months of antibiotics. Sponsored by CDC and conducted in collaboration with the NIH-sponsored ACTG, Study 31/A5349 (https://clinicaltrials.gov/ct2/show/NCT02410772) this international, open label, phase 3 noninferiority clinical trial randomized 2,516 participants at 34 clinical sites in 13 countries. The trial confirmed that a 4-month daily treatment regimen containing high-dose RPT(rifapentine) and MOX(moxifloxacin), as well as INH and PZA, is as effective as (noninferior to) the standard daily 6-month regimen in curing drug-susceptible TB. [N Engl J Med 2021; 384:1705–1718] Based on this trial the CDC just updated guidance.

TABLE 1. Dosing recommendation for a 4-month rifapentine-moxifloxacin regimen for patients aged ≥12 years with pulmonary tuberculosis caused by drug-susceptible organisms — United States, 2022

Medication*	Body weight, kg	Dose	Intensive phase	Continuation phase	Total doses
Rifapentine	≥40	1,200 mg	7 days/wk for 56 doses (8 wks)	7 days/wk for 63 doses (9 wks)	119
Moxifloxacin	≥40	400 mg			
Isoniazid†	≥40	300 mg			
Pyrazinamide	40–<55	1,000 mg		NA	
	≥55–75	1,500 mg			
	>75 kg	2,000 mg			

Abbreviation: NA = not applicable.
* Medications should be administered with food.
† Pyridoxine (vitamin B6), 25–50 mg/day, should be given with isoniazid to all patients.

Comment: This CDC report now recommends a 4-month regimen consisting of 8 weeks of daily treatment with RPT, isoniazid (INH), pyrazinamide, and MOX, followed by 9-weeks of daily treatment with RPT, INH, and MOX in patients with drug-susceptible tuberculosis. The regimen is intended for administration in settings where mycobacterial cultures, molecular and phenotypic drug susceptibility testing (DST), radiographic studies and other diagnostic tools, infrastructure for adverse event monitoring, patient-centered clinical care, and coordination with public health for case management are available. If drug resistance to INH, RIF, PZA, or any FQ is detected by any testing method in baseline or follow-up specimens, the 4-month regimen should be stopped, and patients should be started on an appropriate treatment regimen that accounts for the identified drug resistance pattern. HCPs should carefully review a patient's clinical history, concurrent medications, social determinants of health, and risk factors for adverse drug reactions when making the decision to use this regime. For patients with cavitary disease, a positive culture at the end of 2 months especially if diabetic, HIV, or immunosuppressed, longer duration of therapy may be appropriate. The other consideration is use routine FQ and potential side effects.

Shorter Treatment for Nonsevere Tuberculosis in African and Indian Children N Engl J Med 2022; 386:911-22

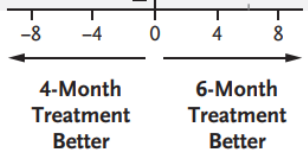
DOI: 10.1056/NEJMoa2104535

The investigators conducted an open-label, treatment-shortening, noninferiority trial involving children with nonsevere, symptomatic, presumably drug-susceptible, smear-negative tuberculosis in Uganda, Zambia, South Africa, and India. Children younger than 16 years of age were randomly assigned to 4 16 weeks or 6 24 weeks of standard first-line antituberculosis treatment with pediatric fixed-dose combinations as recommended by the WHO. Specifically, all the participants initially received 8 weeks of standard therapy with isoniazid, rifampin and pyrazinamide (fixed-dose combination formulation), with or without ethambutol according to local guidelines (intensive phase). This treatment was followed by standard therapy with isoniazid and rifampin (continuation phase) in a fixed-dose combination for either 8 weeks in the 4-month group (intervention) or 16 weeks in the 6-month group (control). All anti-TB treatment was administered 7 days per week The primary efficacy outcome was unfavorable status (composite of treatment failure [extension, change, or restart of treatment or tuberculosis recurrence], loss to follow-up during treatment, or death) by 72 weeks, with the exclusion of participants who did not complete 4 months of treatment (modified

intention-to-treat population). A noninferiority margin of 6 percentage points was used. The primary safety outcome was an adverse event of grade 3 or higher during treatment and up to 30 days after treatment. Children were seen at screening, at enrollment (randomization), and at weeks 2, 4, 8, 12, 16, 20, 24, 28, 36, 48, 60, and 72. Screening procedures included history taking to identify contacts with persons with tuberculosis and an evaluation of symptoms associated with tuberculosis; performance of a PPD or interferon γ–release assay, where available; radiography of the chest; and obtaining at least two respiratory samples (gastric aspirate, expectorated sputum, or induced sputum) for smear microscopy, Xpert MTB/RIF assay (Xpert, Cepheid), mycobacterial culture, and drug susceptibility testing. In children with peripheral lymph-node tuberculosis, a fine-needle aspirate was obtained.

A total of 1204 children underwent randomization (602 in each group). The median age of the participants was 3.5 years, 11% had human immunodeficiency virus infection, and only 14% had microbiological confirmed tuberculosis. They did, however, adapt the pediatric consensus algorithm for diagnosis of intrathoracic tuberculosis. [Clin Infect Dis 2015; 61:Suppl 3:S179-S187] Retention by 72 weeks was 95%, and adherence to the assigned treatment was 94%. [amazing] A total of 16 participants (3%) in the 4-month group had a primary-outcome event, as compared with 18 (3%) in the 6-month group (adjusted difference, -0.4 percentage points; 95% confidence interval, -2.2 to 1.5). The noninferiority of 4 months of treatment was consistent across the intention-to-treat, per-protocol, and key secondary analyses, including when the analysis was restricted to the 958 participants (80%) independently adjudicated to have tuberculosis at baseline. A total of 95 participants (8%) had an adverse event of grade 3 or higher, including 15 adverse drug reactions (11 hepatic events, all but 2 of which occurred within the first 8 weeks, when the treatments were the same in the two groups).

	No. of Patients	4-Month Treatment	6-Month Treatment	Risk Difference (95% CI)
		no. of participants with event/total no. (%)		*percentage points*
Primary outcome				
Modified intention-to-treat population	1145	16/572 (3)	18/573 (3)	−0.3 (−2.3 to 1.6)
Per-protocol population	1121	14/563 (2)	17/558 (3)	−0.6 (−2.5 to 1.4)
Intention-to-treat population	1204	44/602 (7)	44/602 (7)	0 (−2.9 to 2.9)
Key secondary outcome				
Modified intention-to-treat population	910	10/450 (2)	13/460 (3)	−0.6 (−2.6 to 1.4)
Per-protocol population	895	8/445 (2)	13/450 (3)	−1.1 (−3.1 to 0.9)

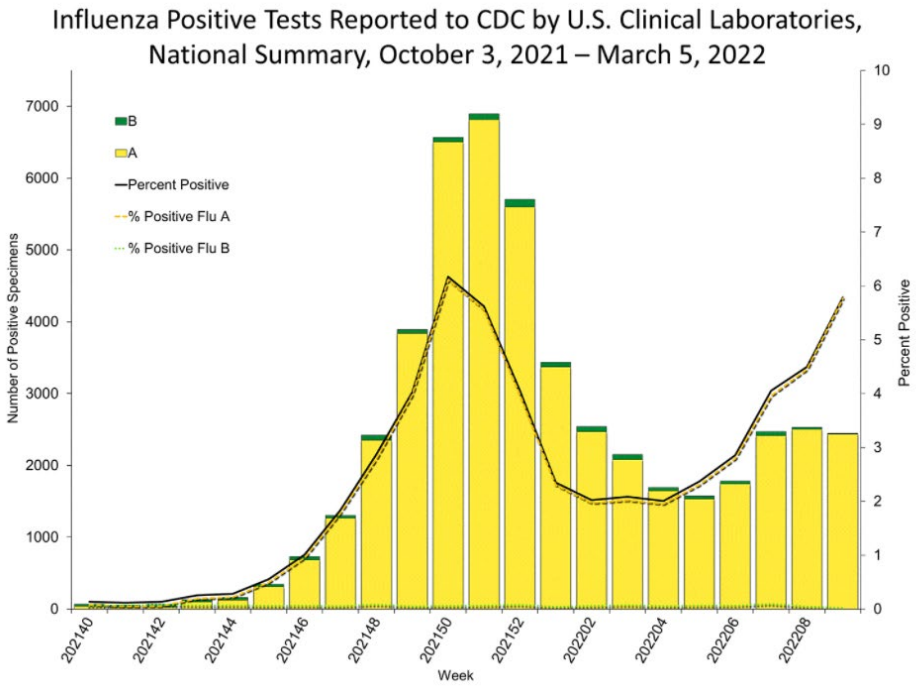


Comment: Four months of antituberculosis treatment was noninferior to 6 months of treatment in children with drug-susceptible, nonsevere, smear-negative tuberculosis. Shortening treatment for drug-susceptible tuberculosis is a key goal for both adults and children. Early trials

showed that it was possible to shorten the treatment duration in adult. [See above] Most children with tuberculosis have paucibacillary disease [paucibacillary tuberculosis is define as disease with a sputum-smear grade of less than 2+ (<1 acid-fast bacillus per field) or noncavity disease) and nonsevere disease (Nonsevere tuberculosis included respiratory tuberculosis confined to one lobe (opacification of <1 lobe) with no cavities, no signs of miliary tuberculosis, no complex pleural effusion) with low rates of microbiologic tuberculosis confirmation in routine care. Given only 14% had microbiological confirmation, drug susceptibility was limited.

Influenza Update

- Influenza activity is increasing in most of the country.
- The highest influenza percent positivity levels were seen in states in the central and south-central regions of the country.
- Most influenza viruses detected are A(H3N2). H3N2 viruses identified so far this season are genetically closely related to the vaccine virus. However, antigenic data show that the majority of the H3N2 viruses characterized are antigenically different from the vaccine reference viruses. While the number of B/Victoria viruses circulating this season is small, most of the B/Victoria viruses characterized are antigenically similar to the vaccine reference virus.



Comment: Now that Covid-19 cases have dropped, will other respiratory viruses fill the gap for the next 1-2 months. Some areas of the US have seen an increase. Below is an initial estimate of VE so far this season.

Interim Estimates of 2021–22 Seasonal Influenza Vaccine Effectiveness — United States, February 2022 MMWR 2022; 71:365-370

Based on data from 3,636 children, adolescents, and adults with acute respiratory infection during October 4, 2021–February 12, 2022, seasonal influenza vaccination did not reduce the risk for outpatient respiratory illness caused by influenza A(H3N2) viruses that have predominated so far this season.

Comment: These findings are consistent with previous evidence of low to no protection against outpatient infection with A(H3N2) subclade 2a.2 viruses from an investigation of an influenza outbreak on a university campus during October–November 2021. Compared with influenza vaccination during 2020–21, influenza vaccination coverage is lower so far this season in certain groups, including some groups who are at high risk for severe influenza or complications from influenza, such as persons who are pregnant, infants, and preschool-aged children, as well as persons from racial and ethnic minority groups. Although influenza virus circulation and laboratory-confirmed influenza associated hospitalizations declined from late December 2021 through January 2022 some regions of the United States have now seen increases in influenza activity.

COVID-19

COVID-19 News

A Roadmap for Living with Covid March 2022

1. Expand the focus of U.S. preparedness and response from COVID-19 to major respiratory viruses, including flu and RSV infection, with the interim goal to reduce annual deaths below the worst influenza season of the last decade.

2. Create, maintain and disseminate a transparent infectious disease dashboard to guide the public and policymakers at national, state and local levels on the introduction, modification and lifting of public health measures.

3. Strengthen testing, surveillance and data infrastructure**.** This includes production capacity for 1 billion at-home rapid tests per month, test-to-treat infrastructure that links testing to medical consults and treatment, and the establishment of infrastructure to rapidly collect and analyze data on population immunity.

4. Regulate the improvement and monitoring of indoor air quality**.** The group calls for the administration to direct the Environmental Protection Agency and Occupational Safety and Health Administration to create standards that protect workers from inhalation exposure.

5. Direct and fund HHS, including the NIH and FDA, to accelerate the development of new, more effective therapeutics, particularly multi-drug oral antivirals and next-generation vaccines that offer better, broader and longer-lasting protection. The authors want the administration to direct and fund HHS to achieve a vaccination rate of at least 85 percent by the end of 2022, which would include CMS reimbursing clinicians for discussing vaccinations with patients who are insured by Medicare and Medicare.

6. Shift the goal of U.S. contributions to the global vaccination effort from stopping infections through population vaccination coverage alone to improving the distribution and administration infrastructure necessary to fully vaccinate the most vulnerable.

7. Strengthen research on long COVID-19**.** The authors urge for coordinated and expanded research to answer questions on its frequency, risk factors, prognosis and benefits of vaccines and therapies for long COVID-19 within the next year, along with support for individuals experiencing the condition.

8. Create a permanent cadre of community health workers who will support populations highly susceptible to adverse outcomes from respiratory viruses.

9. Expand and support the healthcare workforce**.** Calls to action include greater pay, health benefits, tuition assistance, loan forgiveness and safe working conditions for workers. The group wants industrywide incentives to accelerate the adoption of automation for routine paperwork and chores, and the extension and expansion of temporary regulatory flexibilities that allowed healthcare organizations to operate telehealth and hospital-at-home programs throughout the pandemic.

10. Create a new post to fight biosecurity pandemic threats**.** The yet-to-be post, deputy assistant to the president for national security affairs and biosecurity, would sit within the National Security Council and be responsible for the preparation and response to any biosecurity and pandemic threats, including foreign and domestic sources of anti-science misinformation.

11. Redesign U.S. public health communications to regain public trust in a fast-moving, deeply polarized environment to promote the best health outcomes for Americans. The proposed redesign includes the creation of a Joint Information and Communication Center to oversee the sharing of infectious disease data, and infrastructure for dissemination of public health messages.

12. Roll out policies and programs to enable schools and childcare facilities to remain open and safe for in-person learning and care without need for special public health mitigation measures. These measures include improved air filtration and expanded school nurse programs.

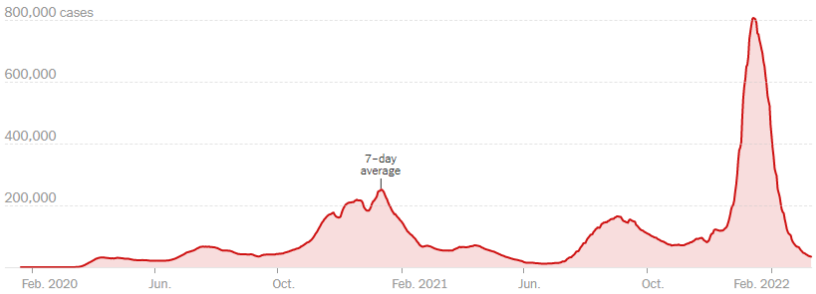
Comment: There is a lot to like in this roadmap. The key is to execute and sustain!

WHO Panel Endorses COVID-19 Booster Shots

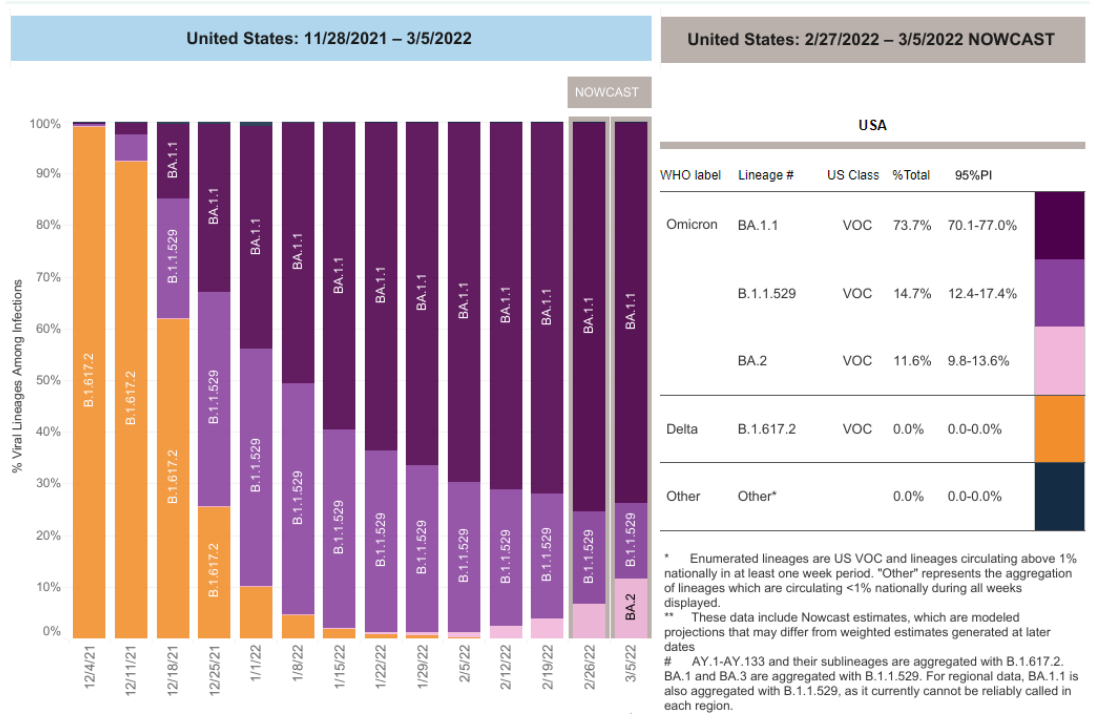
An expert group convened by the WHO said last Tuesday it now strongly supports urgent and broad access to booster doses of COVID-19 vaccine amid the global spread of the Omicron variant. This is a reversal from last year when the WHO said boosters weren't necessary for healthy people and contributed to vaccine inequity.

Comment: This is an appropriate reversal given evidence around the Omicron variant.

COVID-19 by the Numbers



	DAILY AVG. ON MAR. 12	14-DAY CHANGE	TOTAL REPORTED
Cases	34,232	-48%	79,411,749
Tests	970,075	-10%	—
Hospitalized	30,164	-43%	—
In I.C.U.s	5,461	-46%	—
Deaths	1,297	-31%	966,218



Comment: The graphs speak for itself as numbers across the US continue to decline. There has been an increase in BA.2 up to 11.6%.

Journal Review

COVID-19 Incidence Among 6th-12th Grade Students by Vaccination Status

Pediatrics published online February 22, 2022

DOI: 10.1542/peds.2022-056230

In this study, researchers in North Carolina used a private secondary school (grades 6–12) with 1128 students to assess risk for SARS-CoV-2 infection and symptomatic COVID-19 according to vaccination status. The study was conducted during a high level of SARS-CoV-2 Delta transmission, starting on August 1, 2021, and continuing to November 12, 2021. School nurses monitored vaccination status, infections, and exposures. Symptomatic students were required to undergo testing. The school required indoor masking, and all classes were in person.

By November 2021, nearly 74% of students had been vaccinated. Twenty unvaccinated students (6.7%) and 7 vaccinated students (0.8%) reported infections during the study period.

The respective numbers for symptomatic infections were 16 (5.4%) and 5 (0.6%). Only 2 of the 27 total infections were classified as resulting from in-school transmission.

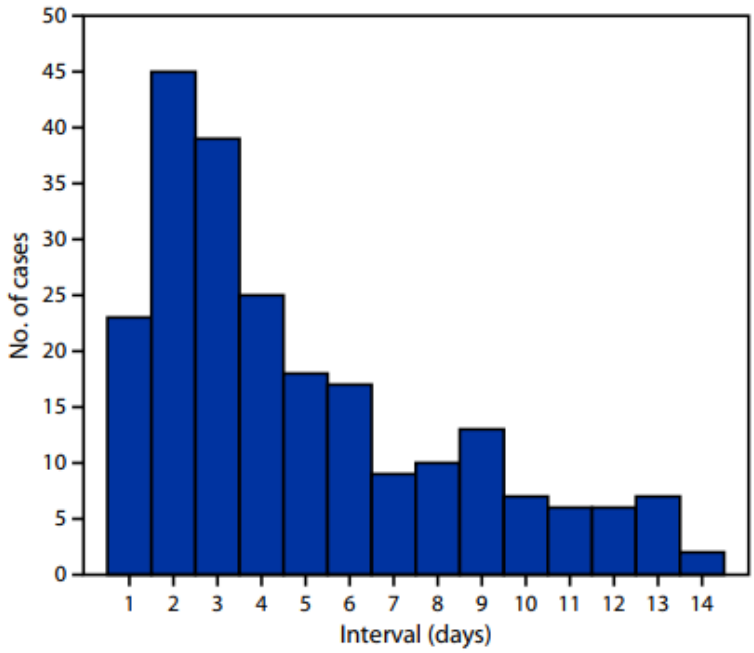
Comment: The vaccination rate in this school system if much higher than what is reported nationally. The differential rate of infection between vaccinated versus unvaccinated makes a strong case for vaccination. The low transmission rate in this school (masks were required indoors) also support the value of vaccination plus NPIs such as masks during periods of high community transmission. This study was completed before Omicron.

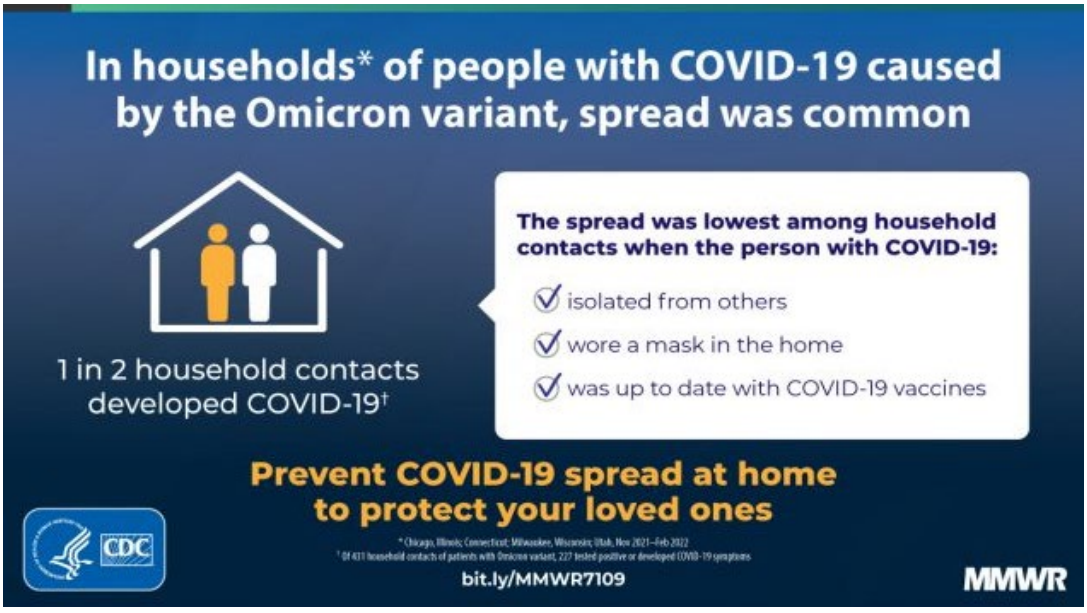
SARS-CoV-2 B.1.1.529 (Omicron) Variant Transmission Within Households — Four U.S. Jurisdictions, November 2021–February 2022 MMWR March 4, 2022

To investigate the effectiveness of prevention strategies in household settings, CDC partnered with four US jurisdictions to describe Omicron household transmission during November 2021–February 2022. Persons with sequence-confirmed Omicron infection and their household contacts were interviewed.

Omicron transmission occurred in 124 (67.8%) of 183 households. Among 431 household contacts, 227 were classified as having a case of COVID-19 (attack rate [AR] = 52.7%). The Ars among household contacts of index patients who had received a COVID-19 booster dose, of fully vaccinated index patients who completed their COVID-19 primary series within the previous 5 months, and of unvaccinated index patients were 42.7% (47 of 110), 43.6% (17 of 39), and 63.9% (69 of 108), respectively. The AR was lower among household contacts of index patients who isolated (41.2%, 99 of 240) compared with those of index patients who did not isolate (67.5%, 112 of 166) (p-value <0.01). Similarly, the AR was lower among household contacts of index patients who ever wore a mask at home during their potentially infectious period (39.5%, 88 of 223) compared with those of index patients who never wore a mask at home (68.9%, 124 of 180) (p-value <0.01)

FIGURE 1. Interval*,† between index patient onset date and household contact onset date — four U.S. jurisdictions, November 2021–February 2022





Comment: In a study of household transmission in four US jurisdictions, Omicron infection resulted in high transmission among household contacts, particularly among those who lived with index patients who were not vaccinated or who did not take measures to reduce the risk of transmission to household contacts. This investigation used a convenience sample of persons with sequence-confirmed Omicron infections, and participation in this investigation was voluntary. The small sample size, especially for certain stratum specific ARs, may limit overall

generalizability of the results. In addition, the investigation relied primarily on self-reported data. Vaccination status was not always verified, and the analysis did not account for potential variations in prevention practices e.g., frequency of mask use. The interval analysis reflected time between dates of a positive test result or symptom onset, not date of infection, and did not account for duration of symptoms and prevention strategies, such as frequency of mask use as stated above.

SARS-CoV-2 is associated with changes in brain structure in UK Biobank Nature published online March 78, 2022

doi.org/10.1038/s41586-022-04569-5

Oxford investigators administered cognitive tests to and scanned the brains of 785 visitors to the UK Biobank imaging centers two times an average of 38 months apart. Of the 785 participants, 401 (51%) were diagnosed as having COVID-19 between their scans, from March 2020 to April 2021. The remaining 384 participants were age- and sex-matched controls. Patients were aged 51 to 81 years. Fifteen COVID-19 patients were hospitalized, and two received critical care. Relative to their nonhospital peers, hospitalized patients were, on average, older and had higher blood pressure and weight and were more likely to have diabetes and to be men.

Among COVID-19 survivors, an average of 141 days elapsed between diagnosis and the second brain scan. Changes in these patients included a reduction in gray matter thickness in the orbitofrontal cortex (associated with sense of smell) and the parahippocampal gyrus (associated with memory of events). Scans also revealed evidence of brain-tissue damage in areas linked with the olfactory cortex (tied to smell), a reduction in whole-brain volume, and an increase in cerebrospinal fluid volume. Cognitive decline was also evident between the two scans, as shown by atrophy of the cerebellum. A control analysis on patients with non-COVID pneumonia showed that these brain changes were specific to COVID-19 rather than the generic effects of a respiratory disease.

The investigators noted that the imaging differences between the two groups were modest, at about 2% of average baseline values. The typical annual loss of gray matter each year due to aging is 0.2% to 0.3%. The infected participants also showed on average larger cognitive decline between the two timepoints. Importantly, these imaging and cognitive longitudinal effects were still seen after excluding the 15 cases who had been hospitalized.

Comment: Although previous research suggests that COVID-19 may cause brain abnormalities and cognitive dysfunction, most studies have involved hospitalized patients with severe illness and have been limited to post-COVID imaging data. To my knowledge, this is the first longitudinal imaging study of SARS-CoV-2 where participants were initially scanned *before* any had been infected. The findings may indicate COVID-related brain degeneration from either the olfactory pathways, nervous system inflammation, or a lack of sensory input resulting from a loss of smell calling for studies on the future vulnerability of the affected brain areas in these

patients. Olfactory—whether neuronal or supporting—cells concentrated in the olfactory epithelium are also particularly vulnerable to coronaviruses infection, and this seems to be also the case specifically with SARS-CoV-2. [see last ID Watch] Whether this deleterious impact can be partially reversed, or whether these effects will persist needs to be studied.

One-Year Trajectory of Cognitive Changes in Older Survivors of COVID-19 in Wuhan, China A Longitudinal Cohort Study JAMA Neurol published online March 8, 2022

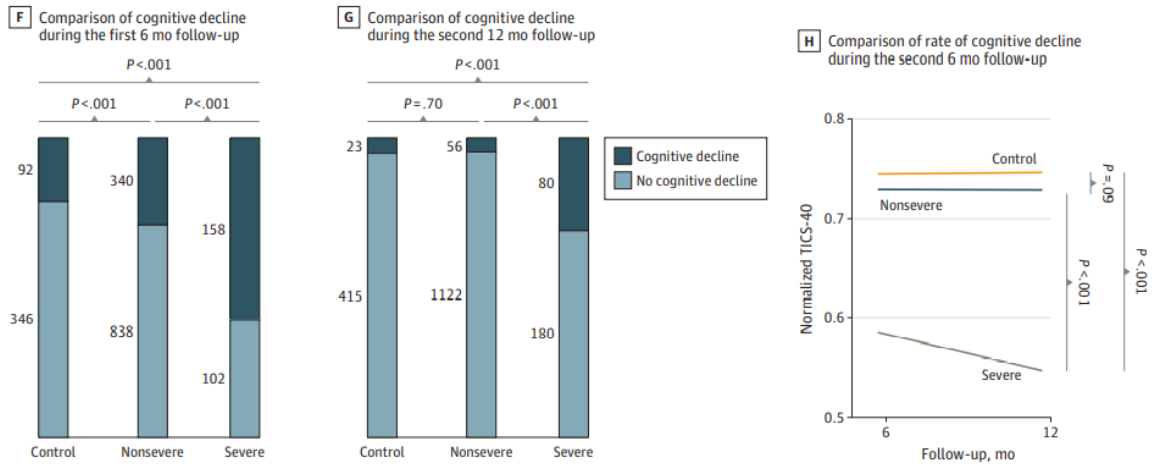
doi:10.1001/jamaneurol.2022.0461

This cohort study recruited 3233 COVID-19 survivors 60 years and older who were discharged from 3 COVID-19–designated hospitals in Wuhan, China, from February 10 to April 10, 2020. Their uninfected spouses (N = 466) were recruited as a control population. Follow-up monitoring cognitive functioning and decline took place at 6 and 12 months. A total of 1438 COVID-19 survivors and 438 control individuals were included in the final follow-up. COVID-19 was categorized as severe or nonsevere following the ATS guidelines.

Trained raters interviewed COVID-19 patients at 12 months over the phone to evaluate cognition using the Chinese version of Telephone Interview of Cognitive Status-40 (TICS-40), which includes 10 variables and has a maximum of 40 points. A score of 20 or lower was considered indicative of mild cognitive impairment (MCI), while a score of 12 or lower indicated dementia, and a decrease of 3 points or more was considered clinically meaningful cognitive decline.

Of the COVID-19 patients. 48.1% were men, median age was 69 years, and none had a history of dementia. The control group was 50.7% men, and the median age was 67 years. The incidence of impaired cognition among COVID-19 survivors was 12.5% 12 months after hospital release. COVID-19 survivors had lower TICS-40 scores than controls at both 6 months (median, 29 vs 30 points) and 12 months (29 vs 31). Severely ill patients had lower TICS-40 scores than those with milder illness and controls (median score, 24 vs 30 vs 31) at 6 months; at 12 months, they had lower scores than controls (22.5 vs 31). Patients with mild or moderate illness and controls differed in IQCODE scores but not TICS-40 over follow-up.

Among severely ill COVID-19 patients, 10.0% had dementia and 26.5% had MCI at 6 months. At 12 months, 15.0% had dementia and 26.2% had MCI, much higher than in those with milder illness (dementia, 0.8%; MCI, 5.4%) and controls (dementia, 0.7%; MCI, 5.0%). Survivors of mild or moderate COVID-19 and controls had similar incidences of dementia and MCI at both 6 and 12 months. Severe illness was tied to a higher risk of early-onset cognitive decline (odds ratio [OR], 4.9; 95% confidence interval [CI], 3.3 to 7.2), late-onset cognitive decline (OR, 7.6; 95% CI, 3.6 to 16.0), and progressive cognitive decline (OR, 19.0; 95% CI, 9.1 to 39.5), while milder COVID-19 was associated with a higher risk of early-onset cognitive decline (OR, 1.7; 95% CI, 1.3 to 2.3) after adjusting for age, sex, educational attainment, body mass index (BMI), and underlying illnesses. The prevalence of progressive decline was 21.2% with severe COVID-19, 1.2% with non-severe COVID-19, and 2.3% in controls.



Comment: The findings suggest that long-term cognitive decline is common after SARS-CoV-2 infection, indicating the necessity of evaluating the impact of the COVID-19 pandemic on the future dementia burden worldwide. Telephone questionnaires were used to follow up on the cognitive functions of participants. This method of follow-up may not be as accurate as face-to-face interviews, although telephone-based questionnaires have been validated. Second, the lack of cognitive information before SARS-CoV-2 infection is an inherent limitation of this study that may lead to an overestimation of the impact of COVID-19 on postinfection cognitive decline.

Hospitalizations and Mortality From Non–SARS-CoV-2 Causes Among Medicare Beneficiaries at US Hospitals During the SARS-CoV-2 Pandemic JAMA Netw Open published online March 9, 2022

doi:10.1001/jamanetworkopen.2022.1754

This is a retrospective cohort study from January 2019 through September 2021 using 100% of national Medicare claims, including 4626 US hospitals. Participants included 8,448,758 individuals with non–COVID-19 medical admissions with fee-for-service Medicare insurance.

Admissions for non–SARS-CoV-2 diagnoses fell sharply in March and April 2020 and remained lower through September 2021. Mortality rates after hospitalization were substantially higher, especially for Black individuals, Hispanic individuals, and those with low socioeconomic status, and the increases in mortality were greater in lowerquality hospitals and hospitals with high caseloads of SARS-CoV-2.

The prolonged increases in mortality rates after hospitalization for non–SARS-CoV-2 illnesses suggest a need for improved access to hospital care for individuals with non–SARSCoV-2 illnesses. Perhaps the most striking finding from the study was that increased mortality was observed in hospitals with more COVID-19–related admissions, confirming the far-reaching consequences of COVID-19–related strain on the health care system. The same has been seen for HAIs. The COVID-19 pandemic has strained health systems around the world in unprecedented ways, with all health systems grappling with limitations and burnout in staffing

(physicians, nurses, respiratory therapists, and pharmacists), supplies (medications, tests, ventilators, masks, high-flow oxygen machines, and vaccines), and space (hospital beds, subacute nursing facility beds, and dialysis units). During the pandemic's inpatient surges, COVID-19–specific mortality was already known to increase. [Ann Intern Med. 2021;174(9):1240-1251 reviewed last year in the COVID-19 Briefing] This study confirms the concern many of us have feared: elderly patients admitted to hospitals with diagnoses other than COVID-19 are more likely to die during surges, even after adjusting for patient and hospital characteristics. This work is important because it quantifies a very serious source of harm that is not captured by the daily COVID-19 case or death statistics.

Efficacy of Antiviral Agents against the SARS-CoV-2 Omicron Subvariant BA.2 N Engl J Med published online March 9, 2022

DOI: 10.1056/NEJMc2201933

As compared with the ancestral strain, the sublineage BA.2 of the omicron variant has 16 amino acid substitutions in the receptor-binding domain of the spike (S) protein of SARS-CoV-2, which is the primary target for monoclonal antibody–based therapy. The BA.2 and BA.1 variants share 12 of these 16 substitutions; however, BA.2 has four substitutions in the receptor-binding domain (i.e., S371F, T376A, D405N, and R408S) that differ from those in BA.1.
These findings suggest that there may be differences in the effectiveness of monoclonal antibodies against these different omicron sublineages. This investigators examined the neutralizing ability of therapeutic monoclonal antibodies that have been approved by the FDA individually and in combination, against the omicron BA.2 as well as antivirals. live-virus focus reduction neutralization test (FRNT) was employed.

While two monoclonal antibody combinations– tixagevimab/cilgavimab (Evusheld) and casirivimab/imdevimab (REGEN-COV) – showed neutralizing activity against the Omicron subvariant BA.2, both required substantially higher concentrations to produce a response in patients with COVID-19. S309 (the precursor of sotrovimab), which has been shown to have lower neutralizing activity against omicron/BA.1 and omicron/BA.1.1 than against the ancestral strain and other variants of concern had even less neutralizing activity against omicron/BA.2 in this study The susceptibilities of Omicron/BA.2 to the antivirals remdesivir, molnupiravir, and nirmatrelvir, were similar to those of the ancestral strain and other VOC. As reported above, BA.2 now accounts for 11.6% of strains in the US.

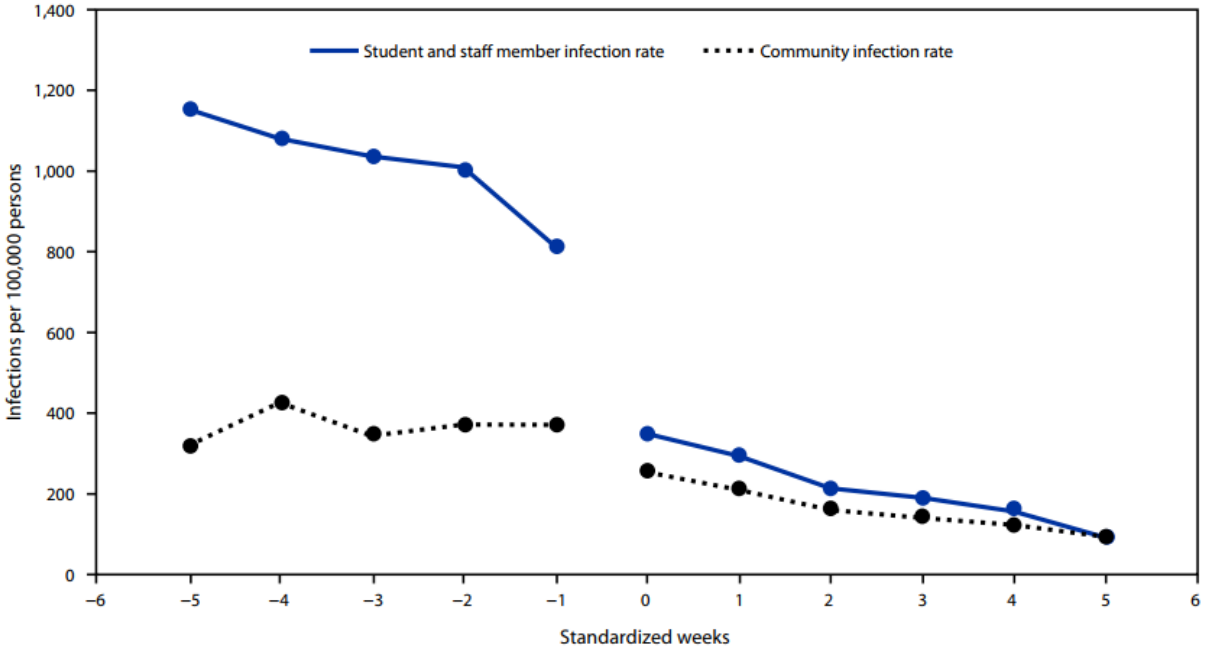
Comment: This study highlights the challenges around MCA and new variants; however, antivirals remain activity regardless of variant consistent with their mechanisms of action. It is imperative that we increase supply of antivirals and develop mechanisms to identity high risk individuals in the first 5 days who will benefit.

SARS-CoV-2 Incidence in K–12 School Districts with Mask-Required Versus Mask-Optional Policies — Arkansas, August–October 2021 MMWR 2022; 71:384-389

The investigators compared the rates of COVID-19 cases at 233 public school districts in Arkansas between August 23, 2021 and October 16, 2022. About a third had full mask mandates, a fifth required masks in certain settings or groups, and half had no mask requirements. They also looked at COVID-19 rates in the surrounding community, social and economic status, and staff and student vaccination rates.

During the study period, statewide COVID-19 community transmission levels declined from substantial to moderate, and vaccination coverage increased, but still low. Average weekly district-level case rates among students and staff were consistently higher than community case rates and decreased over time from 745 cases per 100,000 people in late August and early September to 137 cases per 100,000 people in mid-October. During the same time, vaccination coverage increased from 13.5% to 18.6% among staff and older students.

The research team found that districts with full mask mandates had lower COVID-19 rates, relative to the case rates in the surrounding community, than districts without mandates. Overall, districts with full mask requirements had 23% lower COVID-19 rates, compared with districts with no requirements, including 24% lower among staff and 23% lower among students. The researchers also found that partial masking policies didn't help as much as full mask mandates. Among 26 districts that switched from a no-mask policy to a full or partial requirement during the study period, case rates dropped more than would have been expected based on community cases at the time, the study authors wrote. A week after a mask policy was put in place, case rates among students and staff decreased significantly.



Comment: Like other studies like this there are several importance weaknesses**.** Since it was done from August to October, investigators aren't sure whether the same results would be the same once the Omicron variant became the dominant variant given higher risk of transmission. Vaccination coverage was <20% among staff and older students. What's more, the study couldn't account for other prevention efforts at schools, such as quarantine rules, classroom

ventilation, and whether people followed physical distancing guidelines. Future studies could match nearby schools in the same community that had different masking policies to study their effects. Compliance with an existing mask policy was not directly observed or otherwise evaluated. Unlike other studies, transmission was higher among students and staff than the community. Nonetheless in areas with high COVID-19 community levels, masks can be an important part of a multicomponent prevention strategy in K-12 settings.