Infectious Diseases Watch

February 21,2022

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General Infectious Diseases

Recommended Adult Immunization Schedule, United States, 2022 **Ann Intern Med** published February 18, 2022 (also in MMWR)

doi:10.7326/M22-0036

Changes to the 2022 Adult Immunization Schedule

1. Hepatitis B vaccination: ACIP recommends universal vaccination of all adults aged 19 through 59 years, and vaccination of adults aged 60 years and older at risk for hepatitis B virus (HBV) infection. Additionally, ACIP recommends vaccination of adults aged 60 years and older requesting protection from HBV without the need to acknowledge a specific risk factor.
2. Influenza vaccination: For the 2021–2022 influenza season, routine annual influenza vaccination is recommended for all persons aged 6 months and older who do not have contraindications. No preferential recommendation is made for one influenza vaccine product over another in persons for whom more than one licensed and recommended product based on patient age and health status is available. A previous severe allergic reaction to influenza vaccine is no longer a contraindication to future receipt of any influenza vaccine. Rather, individuals with a history of severe allergic reaction to an influenza vaccine may have a precaution to receive a different type of influenza vaccine.
3. Pneumococcal vaccination: ACIP recommends routine vaccination against pneumococcal infection for all adults aged 65 years or older. For persons aged 65 years and older who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown, they should receive 1 dose of PCV15 or 1 dose of PCV20. If PCV15 is used, this should be followed by a dose of PPSV23. Persons aged 19 through 64 years with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive 1 dose of PCV15 or 1 dose of PCV20. If PCV15 is used, this should be followed by a dose of PPSV23.
4. Zoster vaccination: In the “Special situations” section under the pregnancy bullet, the language was revised to increase clarity. This bullet now states, “There is currently no ACIP recommendation for RZV use in pregnancy. Consider delaying RZV until after pregnancy.” Additionally, the immunocompromising conditions bullet was revised to reflect the new ACIP recommendations for zoster vaccination. This bullet now states “RZV is recommended for use in persons aged 19 years and older who are or will be immunodeficient or immunosuppressed because of disease or therapy.”

Table 1 Recommended Adult Immunization Schedule by Age Group, United States, 2022

Vaccine	19–26 years	27–49 years	50–64 years	≥65 years
Influenza inactivated (IIV4) or **Influenza recombinant** (RIV4)	1 dose annually			
or	or			
Influenza live, attenuated (LAIV4)	1 dose annually			
Tetanus, diphtheria, pertussis (Tdap or Td)	1 dose Tdap each pregnancy; 1 dose Td/Tdap for wound management (see notes)			
	1 dose Tdap, then Td or Tdap booster every 10 years			
Measles, mumps, rubella (MMR)	1 or 2 doses depending on indication (if born in 1957 or later)			
Varicella (VAR)	2 doses (if born in 1980 or later)		2 doses	
Zoster recombinant (RZV)	2 doses for immunocompromising conditions (see notes)		2 doses	
Human papillomavirus (HPV)	2 or 3 doses depending on age at initial vaccination or condition	27 through 45 years		
Pneumococcal (PCV15, PCV20, PPSV23)	1 dose PCV15 followed by PPSV23 OR 1 dose PCV20 (see notes)			1 dose PCV15 followed by PPSV23 OR 1 dose PCV20
Hepatitis A (HepA)	2 or 3 doses depending on vaccine			
Hepatitis B (HepB)	2, 3, or 4 doses depending on vaccine or condition			
Meningococcal A, C, W, Y (MenACWY)	1 or 2 doses depending on indication, see notes for booster recommendations			
Meningococcal B (MenB)	2 or 3 doses depending on vaccine and indication, see notes for booster recommendations			
	19 through 23 years			
***Haemophilus influenzae* type b** (Hib)	1 or 3 doses depending on indication			

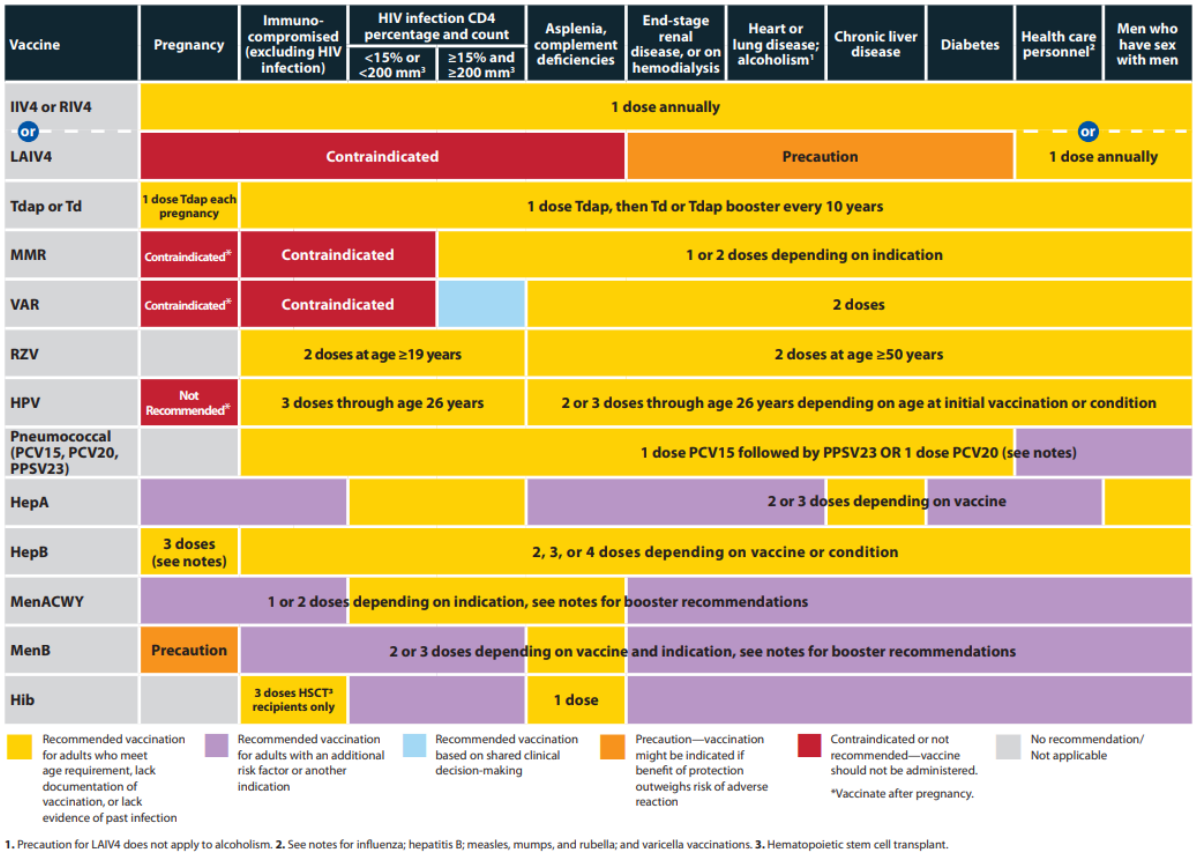
Recommended vaccination for adults who meet age requirement, lack documentation of vaccination, or lack evidence of past infection

Recommended vaccination for adults with an additional risk factor or another indication

Recommended vaccination based on shared clinical decision-making

No recommendation/ Not applicable

Table 2 Recommended Adult Immunization Schedule by Medical Condition or Other Indication, United States, 2022



1. Precaution for LAIV4 does not apply to alcoholism. 2. See notes for influenza; hepatitis B; measles, mumps, and rubella; and varicella vaccinations. 3. Hematopoietic stem cell transplant.

Comment: Probably the biggest change is pneumococcal vaccination if PCV20 is used.

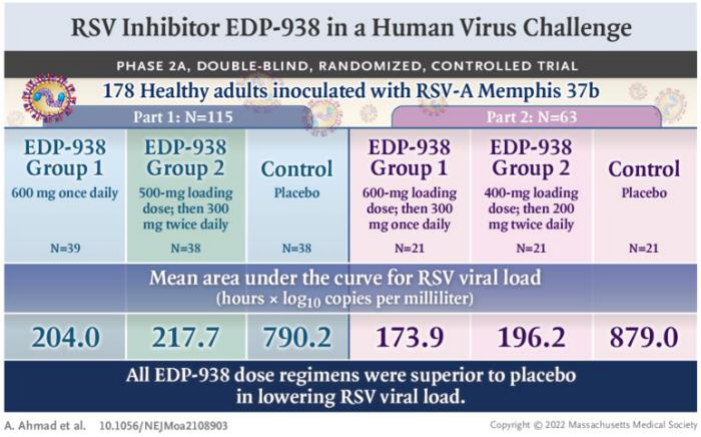
EDP-938, a Respiratory Syncytial Virus Inhibitor, in a Human Virus Challenge N Engl J Med 2022;386:655-66.

DOI: 10.1056/NEJMoa2108903

This is a two-part, phase 2a, randomized, double-blind, placebo-controlled challenge trial. They assigned participants who had been inoculated with RSV-A Memphis 37b to receive EDP-938 or placebo. Different doses of EDP-938 were assessed. Nasal-wash samples were obtained from day 2 until day 12 for assessments. Clinical symptoms were assessed by the participants, and pharmacokinetic profiles were obtained. The primary end point was the area under the curve (AUC) for the RSV viral load, as measured by PCR assay. The key secondary end point was the AUC for the total symptom score.

In part 1 of the trial, 115 participants were assigned to receive EDP-938 (600 mg once daily [600-mg once-daily group] or 300 mg twice daily after a 500-mg loading dose [300-mg twice-daily group]) or placebo. In part 2, a total of 63 participants were assigned to receive EDP-938 (300 mg once daily after a 600-mg loading dose [300-mg once-daily group] or 200 mg twice daily after a 400-mg loading dose [200-mg twice-daily group]) or placebo.

In both parts of the trial, the authors found that the AUC of the viral load, as measured by PCR assay and expressed as hours×$\log_{10}$ copies per milliliter, was lower in the EDP-938 groups than in the placebo group (P<0.001) (e.g., in part 1, the AUC of the viral load was 204.0 in the 600-mg once-daily group, 217.7 in the 300-mg twice-daily group, and 790.2 in the placebo group, corresponding with a viral-load AUC in the 600-mg once-daily group that was 3.9 times as low as that in the placebo group and a viral-load AUC in the 300-mg twice-daily group that was 3.6 times as low as that in the placebo group). The AUC of the mean total symptom score and the mucus weight were also lower in all the EDP-938 groups than in the placebo group. No apparent safety signals were identified.



Comment: Positive results of treatment in previous studies have not always resulted in success in later clinical trials. It has been postulated that the difference in the timing of treatment may be contributing to discrepancy between challenge studies and clinical trials. In challenge studies, the drug is given early, whereas in clinical trials of natural RSV infection, the drug is given when viral titers have peaked, since patients generally present for care 3 to 8 days after symptom onset. The rapid, anamnestic immune response in adults who had been infected with RSV as a child might outcompete the antiviral effects of a drug in clinical trials but is less likely to do so in challenge studies. Even in infants who had not been previously infected with RSV, viral titers are declining at the time of hospitalization, probably because of rapid innate immune response. Thus, disease caused by active virus replication would more likely be affected by treatment in challenge studies than in clinical trials. Another potential factor is a host immune response that contributes to disease through inflammatory mediators. It is possible that later in the course of infection, these responses become less dependent on virus replication, and an antiviral effect is less likely to affect disease in clinical trials. This has some parallels to Covid-19 which has an early viral response phase where antivirals have some efficacy as opposed to the latter inflammatory response phase where antivirals have little efficacy compared to anti-inflammatory drugs. Patients who may be more likely to have a response to later treatment are those with immunosuppression, who often have prolonged virus shedding and progressive disease.

The need for safe and effective treatments for RSV remains high including for adults. RSV accounts for 10.6% of hospitalizations for pneumonia in adults. [N Engl J Med 2005; 352:1749-1759] RSV can cause significant morbidity and mortality in people >65 years of age and immunocompromised adults. Will treatment require both antiviral and anti-inflammatory activity to be effective and would starting treatment after symptom onset add value to challenge studies like Covid-19? The investigators write that “because EDP-938 functions through a different mechanism of action (i.e., inhibition of the viral N protein, which is effective at the stages of

entry into human cells and after entry), it is possible that the window for an intervention with EDP-938 may be longer." In addition to antivirals, there are several promising vaccine candidates.

Strategies for Antibiotic Administration for Bowel Preparation Among Patients Undergoing Elective Colorectal Surgery A Network Meta-analysis JAMA Surg JAMA Surg. 2022; 157:34-41.

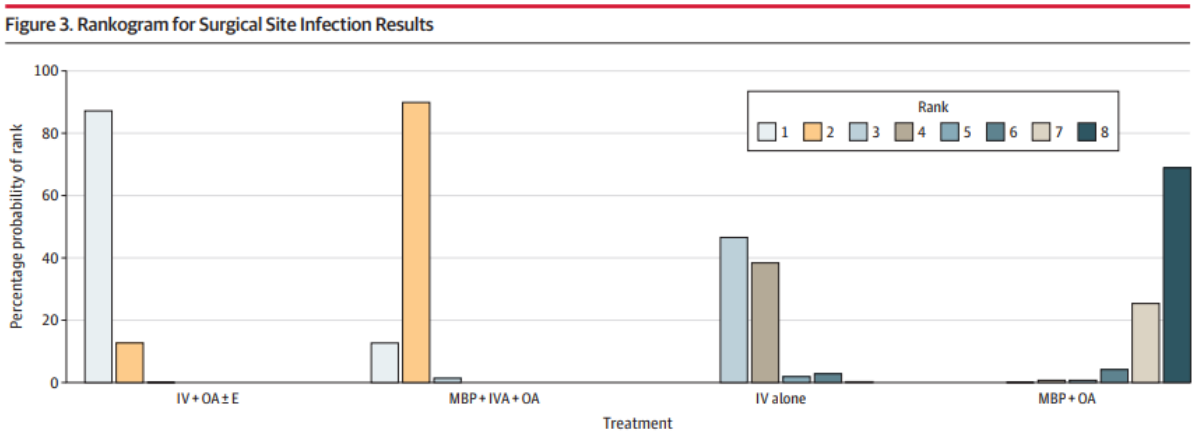
doi:10.1001/jamasurg.2021.5251

The science as to whether a combination of MBP (mechanical bowel prep) and OAB (oral antibiotic prep) or OAB without MBP should be used remain unclear in prevention of SSIs.

Randomized studies of adults undergoing elective colorectal surgery with appropriate aerobic and anaerobic antibiotic cover that reported on incisional SSI or anastomotic leak were selected for inclusion in the analysis. Primary outcomes were incisional SSI and anastomotic leak. Secondary outcomes included other infections, mortality, ileus, and adverse effects of prep.

A total of 35 RCTs that included 8377 patients were identified. Treatments compared IV antibiotics (2762 patients [33%]), IV antibiotics with enema (222 patients [3%]), IV antibiotics with OA with or without enema (628 patients [7%]), MBP with IV antibiotics (2712 patients [32%]), MBP with IV antibiotics with OA (with good IV antibiotic cover in 925 patients [11%] and with good overall antibiotic cover in 375 patients [4%]), MBP with OA (267 patients [3%]), and OA (486 patients [6%]).

The likelihood of incisional SSI was significantly lower for those receiving IV antibiotics with OA with or without enema (rank 1) and MBP with adequate IV antibiotics with OA (rank 2) compared with all other treatment options. The addition of OA to IV antibiotics, both with and without MBP, was associated with a reduction in incisional SSI by greater than 50%. There were minimal differences between treatments in anastomotic leak and in any of the secondary outcomes.



Comments: This review demonstrated that the addition of OA to IV antibiotics were associated with a reduction in incisional SSI by greater than 50%. The results support the addition of OA to IV antibiotics to reduce incisional SSI among patients undergoing elective colorectal surgery. The main weakness of this analysis is the limited number of studies and patients included, with

less than 500 patients for 4 of the bowel preparation options. For SSI, more RCTs examining the role of IV + OA ± E and MBP + IVA + OA among patients undergoing both colon and rectal surgery are indicated. concentration in the colon,2 the impact of OA without MBP on the microflora of the colon requires further study. The result of this trial echoes the result of a Cochrane analysis that combined IV and oral prophylaxis is more effective than IV prophylaxis alone in preventing surgical site infection. [Cochrane Database Syst Rev 2014; 5:CD001181].

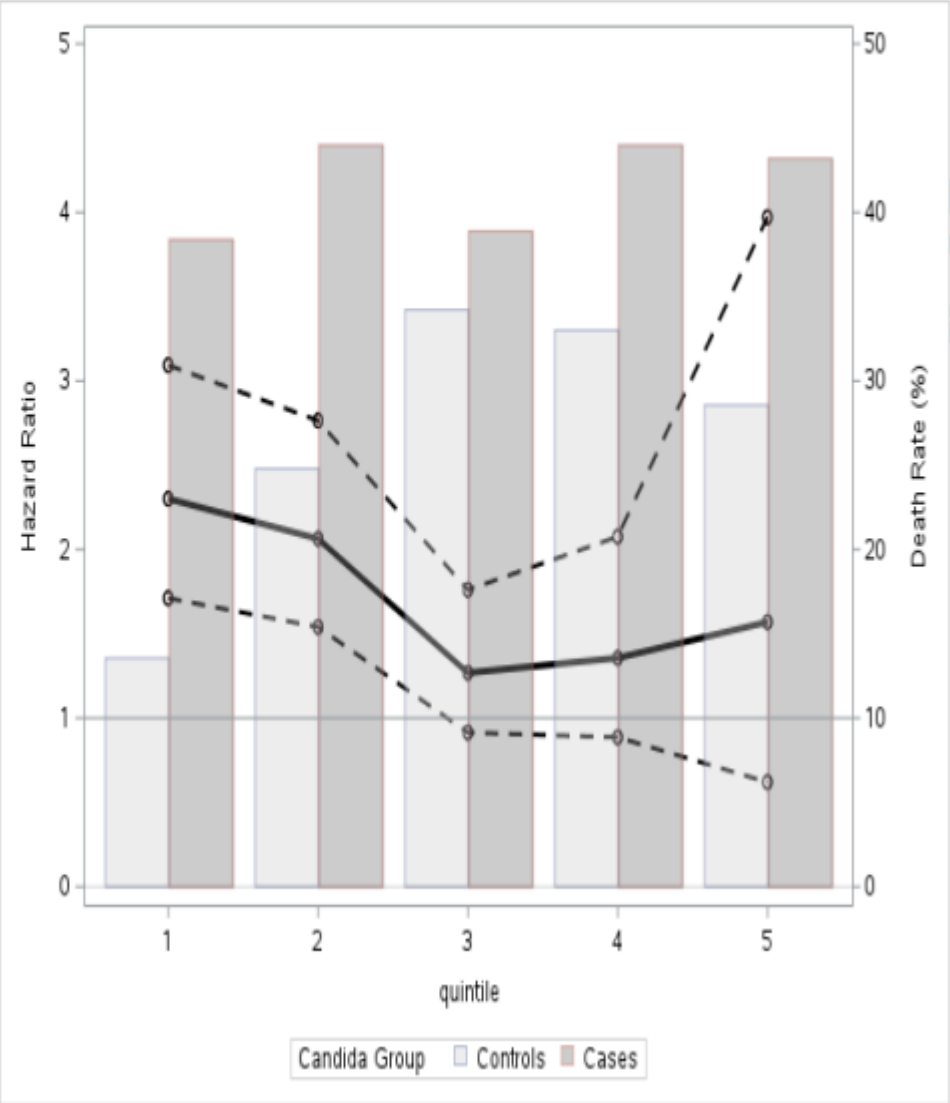
Attributable Mortality of *Candida* Bloodstream Infections in the Modern Era: A Propensity Score Analysis Clin Infect Dis published online January 2, 2022

doi/10.1093/cid/ciac004/6497954

The investigators conducted a retrospective cohort study of adult patients admitted to Barnes Jewish Hospital, a 1,368-bed tertiary care academic hospital. All patients ≥18 years old with a *Candida* spp. isolated from a blood culture from February 2012 to April 2019 were included. They identified 626 adult patients with *Candida* BSI that were frequency-matched with 6,269 control patients that had similar *Candida* BSI risk-factors. The 90-day all-cause mortality attributable to *Candida* BSI was calculated using three methods—propensity score matching, matching by inverse weighting of propensity score, and stratified analysis by quintile.

The 90-day crude mortality was 42% for *Candida* BSI and 17% for frequency-matched controls. Using propensity score matching, the attributable 90-day mortality was 28% with HR of 2.12 (CI 1.98-2.25, p <0.001). In the stratified analysis, the risk for mortality at 90 days was highest in patients in the lowest risk quintile to develop *Candida* BSI (HR 3.13, CI, 2.33-4.19). 69% of untreated patients died versus 35% of treated patients. This same pattern was seen in sensitivity analysis when the covariates with the highest standardized differences were included in the adjusted model.

Figure 1: Hazard ratio for 90-day All-cause Mortality Superimposed on Death Rate (%) p
Score Quintile of Candida BSI Risk



Comment: As other studies have demonstrated Candida BSI continues to have high mortality. Of interest, attributable mortality was more pronounced in patients at lowest risk for *Candida* BSI in part due low percentage of patients receiving treatment. The mortality rate is higher in the analysis than other studies. However, prior trials likely underestimated the mortality as they excluded patients at risk for poor outcomes, and those who died prior to having an opportunity to be screened for study randomization.

COVID-19

COVID-19 News

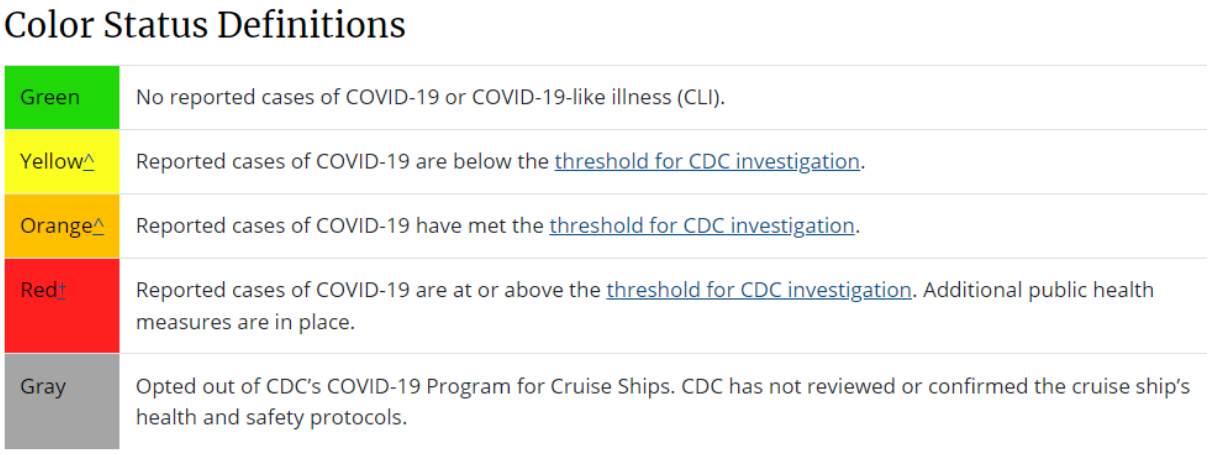
CDC Announces Voluntary COVID Rules for Cruises February 9, 2022
The CDC released new guidelines last Wednesday for a voluntary COVID-19 Program for Cruise Ships, which includes different levels based on the vaccination status of passengers and crew. The levels change how long passengers are recommended to quarantine after coronavirus exposure and masking requirements.

In updated guidance for travelers, the CDC still says it's best to "avoid" cruise travel and encourages people to be fully vaccinated and boosted against COVID-19 before boarding a cruise ship.
Under the voluntary program, there are three vaccination status levels:

- "Not highly vaccinated" ships, with less than 95% of passengers and crew fully vaccinated
- "Highly vaccinated" ships, with at least 95% of passengers and crew fully vaccinated but less than 95% with up-to-date vaccines, including boosters
- "Vaccination standard of excellence" ships, with 95% of passengers and crew fully vaccinated and boosted

The new program still requires passengers to have a COVID-19 test before embarking. Cruise lines that take part must follow all the new recommendations and notify the CDC of the vaccination status classification for each ship.

Ships in the program are then assigned a color on the CDC's Cruise Ship Color Status page, which shows the number of COVID-19 cases on board. Ships that opt out will receive a "gray" color status.



Color Status Definitions

Green	No reported cases of COVID-19 or COVID-19-like illness (CLI).
Yellow^	Reported cases of COVID-19 are below the threshold for CDC investigation.
Orange^	Reported cases of COVID-19 have met the threshold for CDC investigation.
Red†	Reported cases of COVID-19 are at or above the threshold for CDC investigation. Additional public health measures are in place.
Gray	Opted out of CDC's COVID-19 Program for Cruise Ships. CDC has not reviewed or confirmed the cruise ship's health and safety protocols.

Ships with a green status don't have any reported COVID-19 cases. Those with a yellow status have cases but are below the CDC's threshold for investigation, which is .3% of total passengers and crew. Ships with an orange status are investigated.
If a ship reaches red status -- the highest level of COVID-19 spread that indicates ongoing transmission -- all passengers may be tested during or after the cruise, the CDC says. In addition, masks may be required in indoor settings and crowded outdoor areas.

Quarantine and testing rules also vary by vaccination status. Passengers on ships with the "vaccination standard of excellence" status must do a 5-day quarantine after COVID-19 exposure and wear a mask for 5 more days. In the other two status categories, passengers are required to quarantine for at least 10 days. Travelers who have COVID-19 symptoms must isolate right away and take a COVID-19 test, regardless of vaccination status.

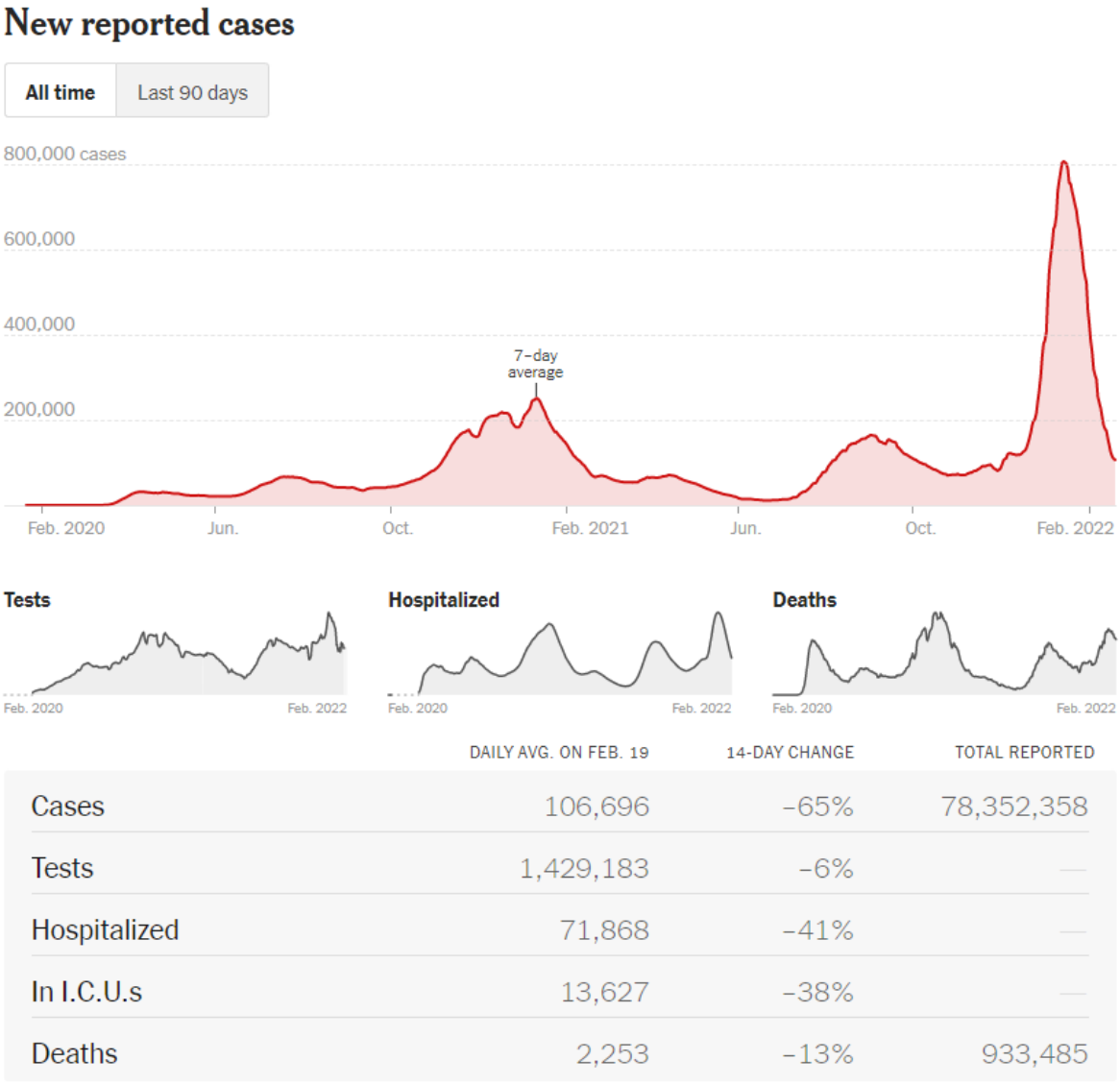
Comment: CDC did lower risk from very high to high. You can go online and check out the ship you may be embarking if the line is participating. This is a step forward for individuals planning on cruising to help decide your level of risk.

Novavax

On Thursday Canada approved Novavax Inc's COVID-19 vaccine for people aged 18 years and older, making it the fifth such shot to be cleared for use in the country. The vaccine's safety and effectiveness in people younger than 18 years have not yet been established, Health Canada said in a statement. Novavax's recombinant protein-subunit vaccine uses a more established technology than mRNA, the novel method used COVID-19 vaccines - from Pfizer and Moderna.

Comment: Novavax's protein-based vaccine, also contains a saponin-based adjuvant. Novavax is currently being reviewed by the FDA and has already received approvals from the European Union and the WHO. As I have written I hope that Novavax vaccine approval could convince as-yet unvaccinated people who are skeptical about the mRNA technology to finally get vaccinated.

COVID-19 by the Numbers

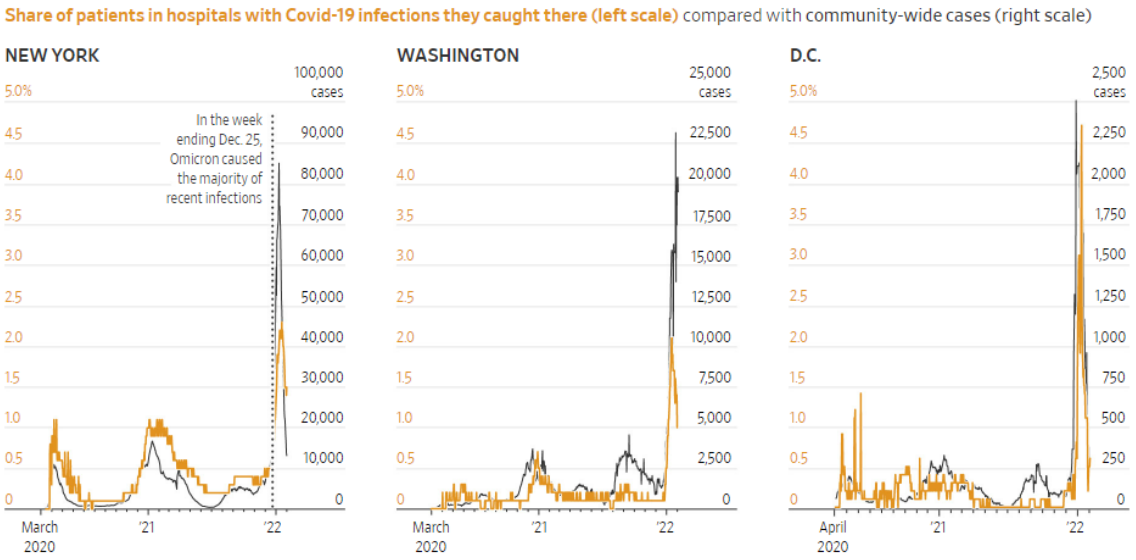


	DAILY AVG. ON FEB. 19	14-DAY CHANGE	TOTAL REPORTED
Cases	106,696	-65%	78,352,358
Tests	1,429,183	-6%	—
Hospitalized	71,868	-41%	—
In I.C.U.s	13,627	-38%	—
Deaths	2,253	-13%	933,485

Comments: All measures continue to show reduced cases, hospitalizations, and deaths. The CDC is looking at changing the focus from cases to more severe measures such as hospitalizations, ICU admissions, and deaths.

As Omicron Surged, Covid-19 Spread Through Patients in Hospitals WSJ February 18, 2022

As the Omicron variant surged across the U.S., it also spread to uninfected non-Covid-19 patients in the hospital. The daily total of patients with Covid-19 that were transmitted in hospitals reached a record of about 4,700 during the Omicron wave in January, according to the analysis of US Department of HHS data. This number compares to around 1,100 patients with hospital-acquired infections during the Delta wave and 2,050 at the height of the pandemic's first winter surge.



Note: Share of hospital's non-Covid patients data through Jan. 31. Total number of hospitals reporting varies by day. Community-wide Covid-19 case figure is a seven-day rolling average. New York data begin March 14, 2020, Washington state data begin Feb. 28, 2020 and D.C. data begin April 1, 2020.
Sources: Department of Health and Human Services (hospital data); Johns Hopkins University (Covid-19 cases); Centers for Disease Control and Prevention (Omicron proportion)

Comment: Hospitals have gone to great lengths to prevent the spread of Covid-19 including screening, limiting visitors, testing all admissions, mandatory Covid-19 vaccinations for HCWs, PPE, and universal masking (usually surgical masks) of HCWs, patients, and visitors. From my perspective I think the analysis likely underestimates the number of Covid-19 cases transmitted in hospitals during the Omicron surge. Nonetheless, the findings show the challenges that facilities face in trying to protect our vulnerable patients. Despite taking these measures the data suggests we may need to do more. Under Journal Review see below how one hospital responded to this challenge. [CID 2.11.22]

Journal Review

Rapid control of hospital-based SARS-CoV-2 Omicron clusters through daily testing and universal use of N95 respirators Clin Infect Dis published online February 11, 2022

doi/10.1093/cid/ciac113/6523822

There has been a significant rise in SARS-CoV-2 cases and a corresponding increase in healthcare associated SARS-CoV-2. [see WSJ report above] In England, the percentage of hospitalized patients with SARS-CoV-2 infections diagnosed >7 days after admission doubled with Omicron. [https://www.england.nhs.uk/statistics/statistical-work-areas/covid-19- hospital-activity] The authors describe a two units cluster of healthcare-associated (HA)-Covid-19. They implemented a protocol requiring N95 masks for all care regardless of Covid status, testing all uninfected patients daily, and limiting rooms to one patient only. The clusters rapidly abated after instituting universal N95 respirators and daily testing.

Comment: The authors postulate that increase HA-Covid-19 infections was attributable to high SARS-CoV-2 in the community which led to increase infections in patients, HCWs, and visitors. Many people may be asymptomatic. In addition, Omicron is 2-3 times more transmissible than

Delta. They point out that although surgical masks decrease viral emissions by about 40-60%, they do not eliminate it. N-95 have the potential to decrease transmission since unlike surgical masks, N-95 the filtration is >95% if properly worn. Broader use of these strategies may prevent HA transmissions.

Effectiveness of Maternal Vaccination with mRNA COVID-19 Vaccine During Pregnancy Against COVID-19–Associated Hospitalization in Infants Aged <6 Months — 17 States, July 2021–January 2022 MMWR February 15, 2022

Using a test-negative, case-control study design, vaccine performance was assessed by comparing the odds of having completed a 2-dose primary mRNA COVID-19 vaccination series during pregnancy among mothers of case-infants and control-infants (those with negative SARS-CoV-2 test results). Participating infants were aged <6 months and admitted outside of their birth hospitalization to one of 20 pediatric hospitals during July 1, 2021–January 17, 2022. During this period, the SARS-CoV-2 Delta variant was the predominant variant in the United States through mid-December, after which Omicron became predominant. Case-infants were hospitalized with COVID-19 as the primary reason for admission or had clinical symptoms consistent with acute COVID-19, and case-infants had a positive SARS-CoV-2 RT-PCR) or antigen test result. No case-infant received a diagnosis of multisystem inflammatory syndrome. Control-infants were those hospitalized with or without COVID-19 symptoms and with negative SARS-CoV-2 RT-PCR or antigen test results. Enrolled control-infants were matched to case-infants by site and were hospitalized within 3–4 weeks of a case-infant's admission date. Baseline demographic characteristics, clinical information, and SARS-CoV-2 testing history were obtained through parent or guardian interviews performed by trained study personnel during hospitalization or after discharge, and electronic medical record review of the infant's record. Mothers were considered vaccinated against COVID-19 if they completed a 2-dose series of either Pfizer or Moderna COVID-19 vaccine.

Eighty-four percent of babies in the study who were hospitalized with Covid-19 were born to people who weren't vaccinated during pregnancy. Among babies with Covid-19 admitted to the ICU, 88% were born to mothers who weren't vaccinated before or during pregnancy. The one baby who died in the study was born to a mother who wasn't vaccinated.

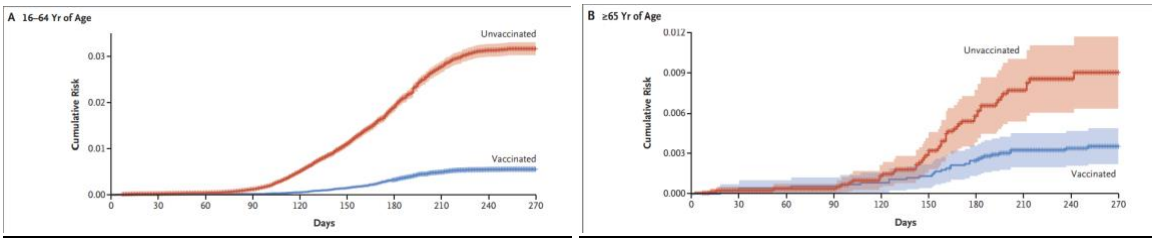
Comment: There is now substantial data that the vaccine protects women from death and serious outcomes including increased for severe disease and preterm delivery. [see last ID Watch] Vaccination during pregnancy has been shown to be safe for mothers and their babies. This study and others also show that vaccinating pregnant women has added benefit of protecting infants from poor outcomes. Unfortunately**,** vaccination rates in pregnant have lagged behind national averages. Around 64% of the U.S. population are currently fully vaccinated, according to the CDC, compared with only 42% of pregnant people as of mid-January. As reported last week in ID Watch, the protection passed to infants from vaccinated mothers could be more durable than that of mothers who were naturally infected by SARS-CoV-2. Unfortunately, VE could not be assessed directly against specific variants. In addition, the sample was too small to assess VE by pregnancy trimester of vaccination, and the small sample size resulted in wide confidence intervals for some estimates that should be interpreted with caution.

Effectiveness of the BNT162b2 Vaccine after Recovery from Covid-19 N Engl J Med published online February 16, 2022

DOI: 10.1056/NEJMoa2119497

This observational study began on March 1, 2021, after the Israeli Ministry of Health approved COVID-19 vaccination for all patients who had recovered from COVID-19 3 or more months before. All participants had recovered from a primary SARS-CoV-2 infection from August 23, 2020 (190 days before the study period) to May 31, 2021 (90 days after study initiation). Average patient age was 39.3 years (range, 16 to 110).

A total of 149,032 patients who had recovered from SARS-CoV-2 infection met the eligibility criteria. Of these patients, 83,356 (56%) received subsequent vaccination during the 270-day study period. Reinfection occurred in 354 of the vaccinated patients (0.4%, 2.46 cases per 100,000 persons per day) and in 2168 of 65,676 unvaccinated patients (3.3%, 10.21 cases per 100,000 persons per day). Vaccine effectiveness was estimated at 82% (95% confidence interval [CI], 80 to 84) among patients who were 16 to 64 years of age and 60% (95% CI, 36 to 76) among those 65 years of age or older. No significant difference in vaccine effectiveness was found for one dose as compared with two doses. The study included the Delta variant surge.



Comment: Among patients who had recovered from Covid-19, the receipt of at least one dose of the Pfizer vaccine was associated with a significantly lower risk of recurrent infection. They found that the receipt of more than one vaccine dose was not associated with greater effectiveness. However, they noted that only 19% of the vaccinated patients received more than one vaccine dose during the study period. However, given the previous exposure to the virus, it seems that the primary vaccine dose in recovered patients provided a more robust and longer immunogenic response than the first dose alone in patients without previous Covid-19. These results are consistent with the findings from a previous study conducted in Italy. [First-dose mRNA vaccination is sufficient to reactivate immunological memory to SARS-CoV-2 in subjects who have recovered from COVID-19. J Clin Invest 2021; 131(12):e149150] Limitation of this study is that reinfections were identified on the basis of a positive result on PCR assay, a procedure that would miss patients who were reinfected but were unaware of their infection or those who decided to avoid PCR testing, which would be more likely in mild cases. See next article

Protection against SARS-CoV-2 after Covid-19 Vaccination and Previous Infection N Engl J Med published online February 16, 2022

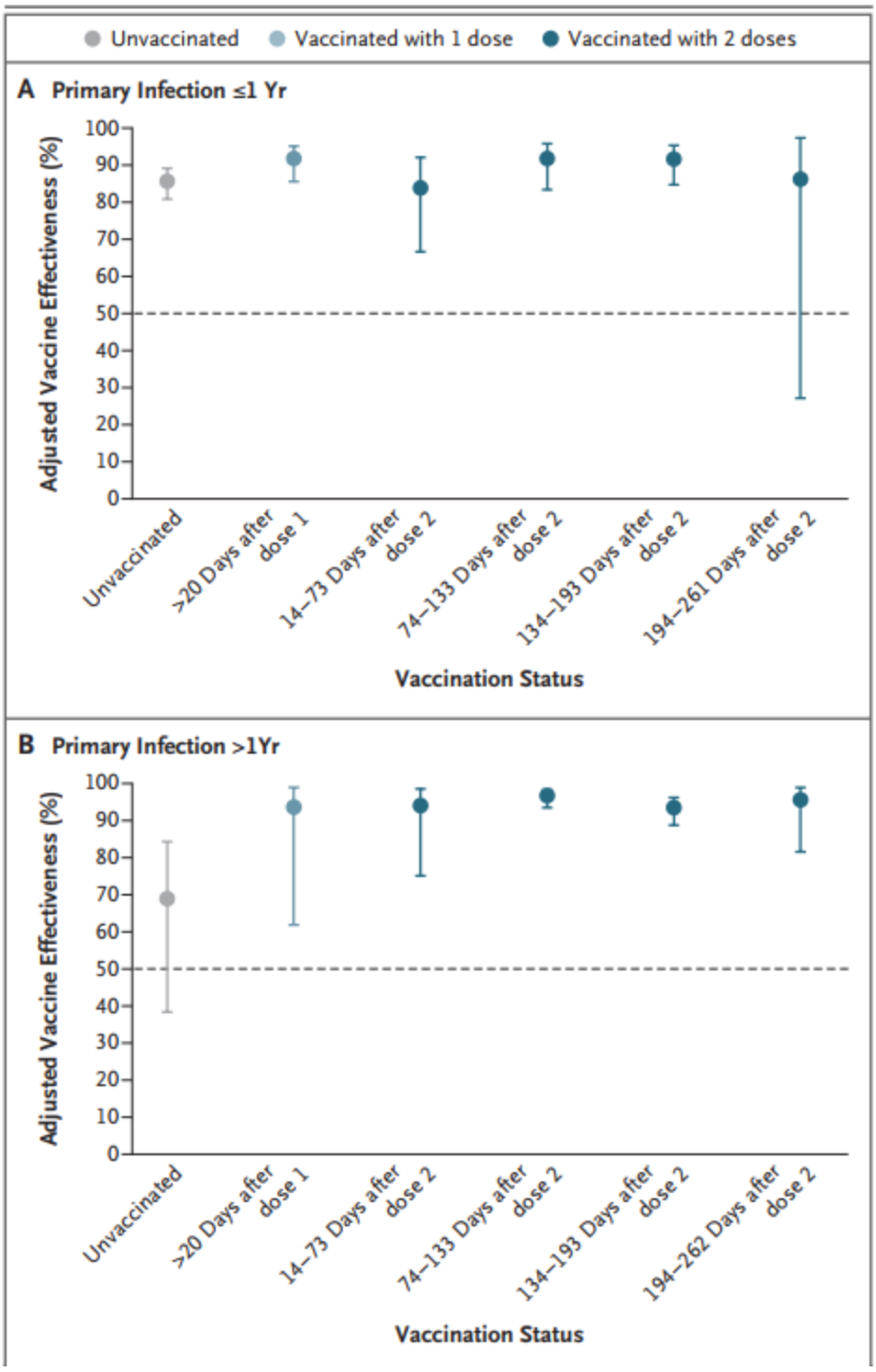
DOI: 10.1056/NEJMoa2118691

This is a prospective study led by UK Health Security Agency researchers to evaluate the effectiveness and duration of COVID-19 vaccination in a group of asymptomatic UK healthcare workers who underwent testing for infection every 2 weeks, as well as monthly antibody testing.

The team compared the time to SARS-CoV-2 infection among unvaccinated participants and those who received the Pfizer or AstraZeneca vaccine up to 10 months before, stratified by whether they had been previously infected. Median age was 46 years, and 84% were women.

Among 35,768 participants, 27% had recovered from COVID-19, as evidenced by the presence of SARS-CoV-2 antibodies. Nearly all participants (97%) had received two vaccine doses; 78% of them had received the Pfizer vaccine with a long interval (6 weeks or more) between doses, while 9% received the same vaccine with a short interval (less than 6 weeks) between doses, and 8% had received the AstraZeneca vaccine.

From December 7, 2020, to September 21, 2021, there were 2,747 primary SARS-CoV-2 infections and 210 reinfections. Among COVID-19–naïve participants in the long-interval Pfizer group, adjusted vaccine effectiveness fell from 85% 14 to 73 days after the second dose to 51% at a median of 201 days. Effectiveness was not significantly different between the long- and short-interval groups. Among AstraZeneca vaccine recipients, adjusted vaccine effectiveness was 58% after the second dose, much lower than among Pfizer vaccinees. Unvaccinated participants saw waning of infection-acquired immunity after 1 year, although efficacy stayed higher than 90% in those who were vaccinated after infection, even in those infected more than 18 months before.


Unvaccinated
Vaccinated with 1 dose
Vaccinated with 2 doses
A Primary Infection ≤1 Yr
Adjusted Vaccine Effectiveness (%)
100
90
80
70
60
50
40
30
20
10
0
Unvaccinated
>20 Days after dose 1
14–73 Days after dose 2
74–133 Days after dose 2
134–193 Days after dose 2
194–261 Days after dose 2
Vaccination Status
B Primary Infection >1Yr
Adjusted Vaccine Effectiveness (%)
100
90
80
70
60
50
40
30
20
10
0
Unvaccinated
>20 Days after dose 1
14–73 Days after dose 2
74–133 Days after dose 2
134–193 Days after dose 2
194–262 Days after dose 2
Vaccination Status

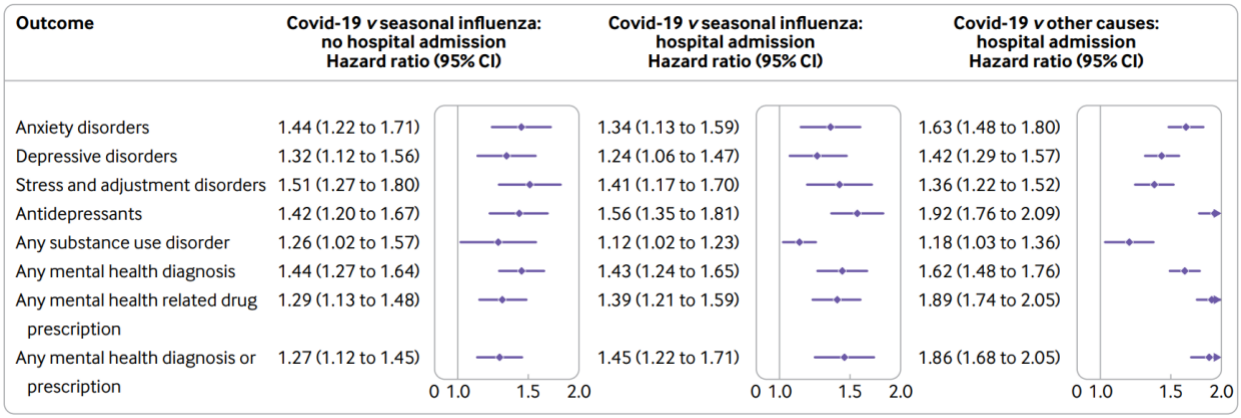
Comment: Of the more than 35,000 healthcare workers in the U.K. the investigators found that previous infection plus vaccination provided substantial protection for more than a year after the initial infection. An important limitation of this study is the relatively small number of participants who contributed follow-up data on key vaccination exposures; these participants included those who were unvaccinated, those who received the AstraZeneca vaccine, and those who received the Pfizer vaccine with a short interval between doses. The immune response may vary depending on which SARS-CoV-2 strain caused natural infection and whether natural infection or vaccination occurred first. The article and the one above demonstrates the highest and most durable protection were observed in participants who received one or two doses of vaccine after a primary infection. These studies were performed before Omicron.

Risks of mental health outcomes in people with Covid-19: cohort study BMJ published online February 17, 2022

doi.org/10.1136/ bmj-2021-068993

The investigators performed a comprehensive in-depth evaluation of the risks of mental health disorders in people with Covid-19 at one year. Cohort comprising 153,848 people who survived the first 30 days of SARS-CoV-2 infection, and two control groups: a contemporary group (n=5,637,840) with no evidence of SARS-CoV-2, and a historical control group (n=5,859,251) that predated the covid-19 pandemic.

People with Covid-19 show increased risks of incident mental health disorders (e.g., anxiety disorders, depressive disorders, stress and adjustment disorders, opioid use disorders, other (non-opioid) substance use disorders, neurocognitive decline, and sleep disorders) compared with contemporary controls without SARS-CoV-2 or historical controls before the pandemic. The risks of mental health disorders were evident even among those who were not admitted to hospital and were highest in those who were admitted to hospital for Covid-19 during the acute phase of the disease. People with Covid-19 showed higher risks of mental health disorders than people with seasonal influenza; people admitted to hospital for Covid-19 showed increased risks of mental health disorders compared with those admitted to hospital for any other causes. Investigators also found that Covid patients were 80 percent more likely to develop cognitive problems like brain fog, confusion and forgetfulness than those who didn't have Covid. After having Covid, people were 55 percent more likely to be taking prescribed antidepressants and 65 percent more likely to be taking prescribed anti-anxiety medications than contemporaries without Covid.



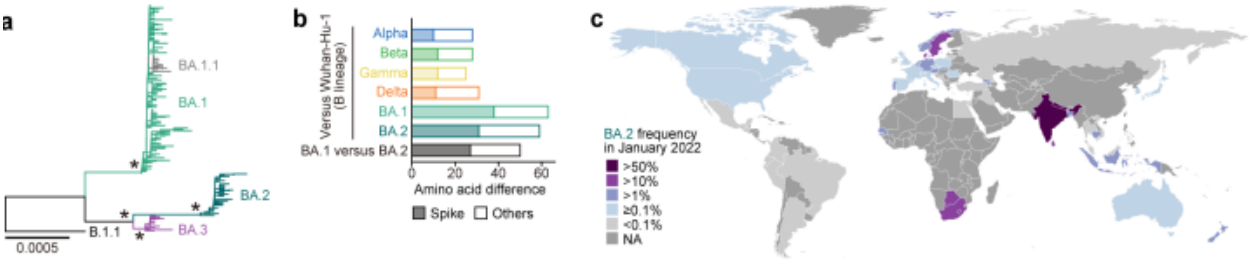
Comment: Altogether, these findings suggest that people with Covid-19 are experiencing increased rates of mental health outcomes, which could have far-reaching consequences. The increased risk of opioid use is of particular concern, especially considering the high rates of opioid use disorders pre-pandemic. [which was getting better pre-pandemic] The increased risks of mental health outcomes in people with Covid-19 is another unintended consequence which demands greater attention now to address much more serious downstream consequences in the future.

Virological characteristics of SARS-CoV-2 BA.2 variant bioRxiv posted February 14, 2022

doi.org/10.1101/2022.02.14.480335

As of February 2022, Omicron is classified into three main lineages, BA.1, BA.2, BA.3, and a sublineage of BA.1, BA1.1, which harbors the R346K substitution in S. BA.1 differs from BA.2 by 50 amino acids, which is approximately twice as much as the numbers of amino acid differences between four VOCs (Alpha, Beta, Gamma and Delta) and Wuhan-Hu-1[ancestral strain]. Phylodynamics analysis suggests that BA.1 emerged first, followed by BA.2 and BA.3.

Statistical analysis shows that the effective reproduction number of BA.2 is 1.4-fold higher than that of BA.1. Neutralization experiments show that the vaccine-induced humoral immunity fails to function against BA.2 like BA.1, and notably, the antigenicity of BA.2 is different from BA.1. Cell culture experiments show that BA.2 is more replicative in human nasal epithelial cells and more fusogenic than BA.1. Furthermore, infection experiments using hamsters show that BA.2 is more pathogenic than BA.1. The investigators suggest that the risk of BA.2 for global health is potentially higher than that of BA.1. These laboratory studies suggest BA.2 appears to potentially escape the immunity induced by vaccines, but a booster shot restores protection, making illness after infection about 74% less likely. Also, “BA.2 is may be resistant to some treatments, including sotrovimab.



Comment: The experimental data suggest the possibility that BA.2 may be of more concerned variant to global health. Currently, both BA.2 and BA.1 are recognized together as Omicron, and these are almost indistinguishable. Based on these findings, the investigators propose that BA.2 should be recognized as a unique variant of concern, and this SARS-CoV-2 variant should be monitored in greater detail. In US based on CCD genomic surveillance BA.2 makes up about 5% of Omicron.

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19 N Engl J Med published online February 16, 2022

DOI: 10.1056/NEJMoa2118542

This is a phase 2–3 double-blind, randomized, controlled trial in which symptomatic, unvaccinated, nonhospitalized adults at high risk for progression to severe coronavirus disease 2019 (Covid-19) were assigned in a 1:1 ratio to receive either 300 mg of nirmatrelvir plus 100 mg of ritonavir or placebo every 12 hours for 5 days. Covid-19–related hospitalization or death from any cause through day 28, viral load, and safety were evaluated.

A total of 2246 patients underwent randomization; 1120 patients received nirmatrelvir plus ritonavir (nirmatrelvir group) and 1126 received placebo (placebo group). An interim analysis of 774 patients treated within 3 days of symptom onset showed that nirmatrelvir recipients' incidence of COVID-related hospitalization or death by day 28 was 6.32 percentage points lower than in the placebo group (95% confidence interval [CI], -9.04 to -3.59; relative risk reduction [RR], 89.1%). Three of 389 nirmatrelvir patients (0.77%) were hospitalized, but none died. In contrast, 27 of 385 placebo patients (7.01%) were hospitalized, and 7 of them died. The final analysis of 1,379 patients showed similar efficacy, with a difference in incidence of 5.81 percentage points (95% CI, -7.78 to -3.84) and a relative RR of 88.9%. All 13 deaths were among placebo recipients.

The SARS-CoV-2 viral load was lower in the nirmatrelvir than in the placebo group at day 5 of treatment. Treatment-emergent adverse events occurred in similar proportions in both groups (22.6% with nirmatrelvir vs 23.9% with placebo). Serious adverse events occurred in 1.6% of the nirmatrelvir group, compared with 6.6% in the placebo group, and adverse events leading to treatment discontinuation occurred in 2.1% vs. 4.2%, respectively.

Comment: The results are clear, but nonetheless an editorial points out it is worth considering the difference between absolute and relative risk reduction. Although the relative risk reductions were large and similar across most subgroups (at about 89%), those at lower risk had a very small absolute benefit. In patients who were SARS-CoV-2 seronegative at baseline, the

absolute risk reduction was about 10 percentage points. However, in those who were SARS-CoV-2 seropositive at baseline, either because they had been infected in the past or had already undergone seroconversion from their current infection, the absolute risk reduction was about 1 percentage point. This trial was performed between mid-July and early December 2021, a period when the delta variant was most likely responsible for most infections. Currently nirmatrelvir is in short supply. This article provides some guidance: the absolute benefit will accrue primarily to patients at highest risk for disease progression, particularly those with multiple and serious coexisting conditions and those unable to mount sufficient immune responses. We do not yet know how nirmatrelvir plus ritonavir will perform as new variants, such as Omicron, but there is no reason to believe nirmatrelvir will not work against Omicron.

Oral famotidine versus placebo in non-hospitalised patients with COVID-19: a randomised, double-blind, data-intense, phase 2 clinical trial Gut published online February 2022.

This is a RCT double-blind, placebo-controlled, phase 2 clinical trial enrolling symptomatic unvaccinated adult outpatients with confirmed COVID-19 between January 2021 and April 2021 from two US centers. Patients self-administered 80 mg famotidine (n=28) or placebo (n=27) orally three times a day for 14 consecutive days. Endpoints were time to (primary) or rate of (secondary) symptom resolution, and resolution of inflammation (exploratory).

Of 55 patients in the intention-to-treat group (median age 35 years (IQR: 20); 35 women (64%); 18 African American (33%); 14 Hispanic (26%)), 52 (95%) completed the trial, submitting 1358 electronic symptom surveys. Time to symptom resolution was not statistically improved ($p=0.4$). Rate of symptom resolution was improved for patients taking famotidine ($p<0.0001$). Estimated 50% reduction of overall baseline symptom scores were achieved at 8.2 days (95% CI: 7 to 9.8 days) for famotidine and 11.4 days (95% CI: 10.3 to 12.6 days) for placebo treated patients. Differences were independent of patient sex, race or ethnicity. Five self-limiting adverse events occurred (famotidine, n=2 (40%); placebo, n=3 (60%)). On day 7, fewer patients on famotidine had detectable interferon alpha plasma levels ($p=0.04$). Plasma immunoglobulin type G levels to SARS-CoV-2 nucleocapsid core protein were similar between both arms.

Comment: Famotidine is a selective histamine H2-receptor (H2R) antagonist which has been shown to reduce type-I interferon release from SARS-CoV-2-infected epithelial cells in a TLR3-dependent manner. Famotidine intake as an antacid has been associated with improved clinical outcome in several retrospective cohort studies of hospitalized patients. In a case series of unvaccinated outpatients with moderate COVID-19, oral famotidine at 80 mg three times a day was well tolerated and associated with rapid symptomatic and physiological improvement. [Gut 2020; 69:1592–7]. Famotidine, as a result, has been frequently prescribed to non-hospitalized patients with COVID-19, without robust clinical trial data supporting biological or clinical efficacy. In this trial famotidine was safe and well tolerated in outpatients with mild to moderate COVID-19. Famotidine led to earlier resolution of symptoms and inflammation without reducing anti-SARS-CoV-2 immunity. However, the numbers are small. Additional randomized trials are badly needed.

Efficacy of Ivermectin Treatment on Disease Progression Among Adults With Mild to Moderate COVID-19 and Comorbidities JAMA Intern Med published online February 18, 2022

doi:10.1001/jamainternmed.2022.0189

The investigators conducted an open-label, randomized clinical trial on the use of ivermectin in the first week of COVID-19 symptom onset in hospitalized adults 50 years and older with mild or moderate illness and underlying medical conditions in Malaysia. The study took place from May 31 to Oct 25, 2021. Average patient age was 62.5 years, 54.5% were women, 51.8% had received two doses of a COVID-19 vaccine, 75.3% had high blood pressure, 53.5% had diabetes, 37.6% had abnormal cholesterol levels, and 23.9% were obese. Patients were randomly assigned in a 1:1 ratio to receive oral ivermectin daily for 5 days plus standard care (241 patients) or standard care only (249). Standard care consisted of treatment of symptoms and monitoring of clinical findings, laboratory test results, and chest imaging for signs of disease progression. Severe disease was defined as hypoxia (low oxygen levels) requiring the use of supplemental oxygen to maintain oxygen saturation at 95% or higher. The sample size was calculated based on a superiority trial design and primary outcome measure. The expected rate of primary outcome was 17.5% in the control group, according to previous local data of high-risk patients who presented with mild to moderate disease.11 A 50% reduction of primary outcome, or a 9% rate difference between intervention and control groups, was considered clinically important. This trial required 462 patients to be adequately powered.

Fifty-two of 241 patients in the ivermectin group (21.6%) and 43 of 249 patients in the standard-care-only group (17.3%) became severely ill (relative risk [RR], 1.25; 95% confidence interval [CI], 0.87 to 1.80). There were no significant differences between the two groups in time to symptom resolution or rates of mechanical ventilation, intensive care unit (ICU) admission, 28-day in-hospital death, or adverse events. Four ivermectin recipients (1.7%) required mechanical ventilation, compared with 10 (4.0%) in the standard-care group (RR, 0.41; 95% CI, 0.13 to 1.30). Six patients (2.4%) in the ivermectin group were admitted to an ICU, versus 8 (3.2%) in the control group (RR, 0.78; 95% CI, 0.27 to 2.20), and 3 ivermectin recipients (1.2%) and 10 controls (4.0%) died by 28 days (RR, 0.31; 95% CI, 0.09 to 1.11). Forty-four patients (9.0%) had 55 adverse events, 33 of them in the ivermectin group. The most common adverse event was diarrhea, occurring in 14 (5.8%) in the ivermectin group and 4 (1.6%) in the standard-care group.

Comment: In this RCT of early ivermectin treatment for adults with mild to moderate COVID-19 and comorbidities, the investigators found no evidence that ivermectin was effective in preventing progression to severe disease. These findings are similar to the results of the IVERCOR-COVID-19 trial, which found that ivermectin was ineffective in reducing the risk of hospitalization. [BMC Infect Dis. 2021;21(1):635] This study was not designed to assess the effects of ivermectin on mortality from COVID-19. Second, the generalizability of these findings may be limited by the older study population, although younger and healthier individuals with low risk of severe disease are even less likely to benefit from ivermectin.