Infectious Diseases Watch

April 25, 2022

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General Infectious Disease

Cefiderocol- Compared to Colistin-Based Regimens for the Treatment of Severe Infections Caused by Carbapenem-Resistant Acinetobacter baumannii

Antimicrob Agents Chemother 2022; 66:e02142-21.

DOI: 10.1128/aac.02142-21

Cefiderocol is a novel siderophore cephalosporin approved by the FDA for treating complicated urinary tract infections and hospital-acquired or ventilator-associated pneumonia caused by carbapenem-resistant Gram-negative bacteria. In a recent randomized trial of cefiderocol (FDC) versus best available therapy for patients with such infections found unexpectedly higher mortality in the subset of patients with carbapenem-resistant *Acinetobacter baumannii* (CRAB) who received FDC — and unexpectedly lower mortality in the control arm, contrary to real-world experience (as well as trials comparing the newer beta-lactam antibiotics with colistin) [CREDIBLE-CR Study]. (Lancet Infect Dis 2021; 21:226–240)

The investigators in this trial conducted a single-center observational study assessing 30-day mortality in 124 patients with CRAB infections treated with FDC-based or colistin-based antimicrobial therapy. Mortality was 55.8% among colistin recipients versus 34.0% among FDC recipients (*P*=0.018). The higher mortality with colistin was seen in patients with CRAB bloodstream infections but not in those with VAP. Multivariate analysis showed septic shock, SOFA score, and age to be independently associated with mortality, while FDC use was protective. As expected, nephrotoxicity was higher in the colistin group.

Interestingly, rates of microbiologic failure trended higher among FDC than colistin recipients (17.4% vs. 6.8%, *P*=0.079). Half (4 of 8) of the cefiderocol microbiological failures developed cefiderocol resistance.

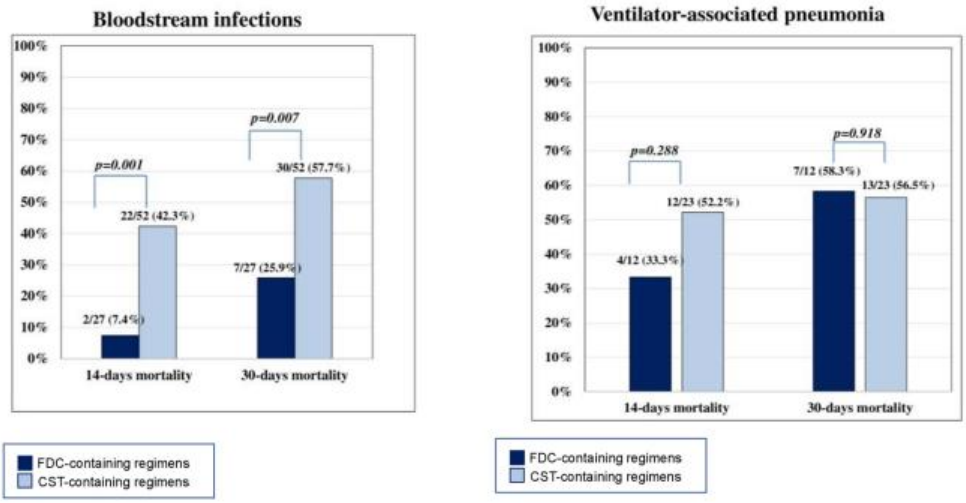


TABLE 5 Cox regression multivariable analysis of factors independently associated with 30-day mortality

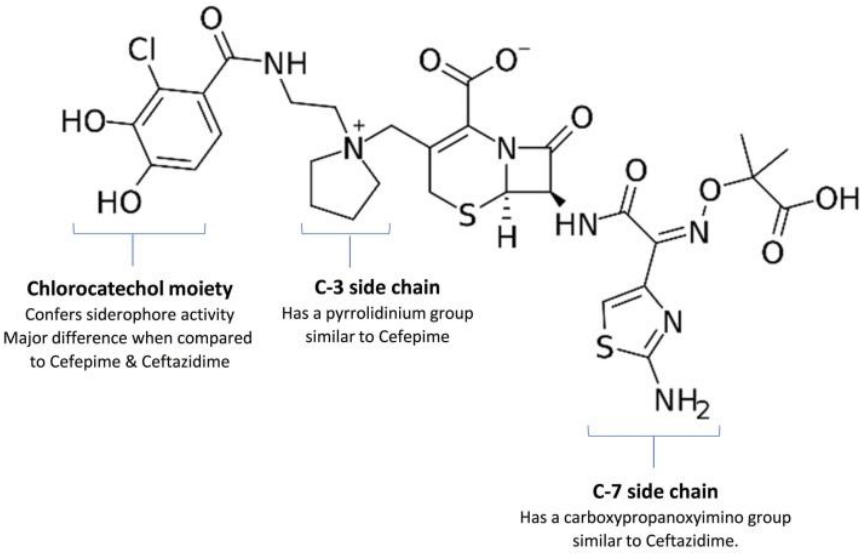
Analysis and factor	aHR[a] (95% CI)	p[b]
Cox regression multivariable analysis		
Septic shock	2.56 (1.11–5.94)	***0.028***
SOFA score	1.15 (1.05–1.27)	***0.003***
Age	1.05 (1.02–1.07)	***0.001***
Cefiderocol-containing regimens (colistin-containing regimens as reference variable)	0.32 (0.18–0.57)	***<0.001***
Propensity score analysis		
Cefiderocol-containing regimens (IPTW-adjusted)	0.44 (0.22–0.66)	***<0.001***

[a]aHR: adjusted hazard ratio.
[b]Boldface italic entries are statistically significant ($P < 0.05$).

Comment: Recent guidance recommends high-dose ampicillin-sulbactam in combination with a second active agent for the treatment of moderate to severe CRAB infections and suggest that FDC may be used in combination for CRAB infections refractory to other antibiotics. (Infectious Diseases Society of America guidance on the treatment of AmpC β-lactamase-producing Enterobacterales, carbapenem-resistant *Acinetobacter baumannii,* and *Stenotrophomonas maltophilia* infections. *Clin Infect Dis* 2021 ciab1013). One challenge in interpreting all these studies is when *A. baumannii* is recovered from the respiratory tract and wounds, is it a true pathogen or is it colonization. There is a lack of robust clinical data supporting the treatment of CRAB infections with any single agent demonstrating *in vitro* activity against CRAB. Interpreting retrospective single-center trials can be challenging, but this study highlights a few important facts. First, newer beta-lactams and newer tetracycline derivative are now replacing colistin due to lower nephrotoxicity and possibly better outcomes. Second, although FDC may represent a step forward in the treatment of CRAB, the emergence of resistance on therapy is a concern. This points to the need for improving dosing and/or multidrug regiments. Further trials are needed. See next article

Cefiderocol: A New Cephalosporin Stratagem Against Multidrug-Resistant Gram-Negative Bacteria Clin Infect Dis 2022; 74:1303–12

doi.org/10.1093/cid/ciab757



This is a nice review paper on current knowledge on use of Cefiderocol (FDC). Below are a few highlights complimenting the AAC article above.

- The catechol moiety on the C-3 position distinguishes FDC from cefepime and ceftazidime and functions as a siderophore, which chelates extracellular iron, forming a cefiderocol-ferric complex. Consequently, while FDC, like other beta-lactams, transits the outer cell membrane by passive diffusion through porins, it is also actively transported into organism by its iron uptake system. Once FDC is transported into the periplasmic space, it dissociates from the iron and binds penicillin-binding proteins (PBP), primarily PBP3, to inhibit peptidoglycan synthesis, causing cell death.
- FDC is resistant to hydrolysis by many beta-lactamases, including most serine carbapenemases and some metallo beta-lactamases, likely due to its C-3 side chain. [see above] Cefiderocol lacks significant activity against gram-positive organisms and anaerobes.
- Overall, FDC retains potent activity against *Enterobacterales*, *Pseudomonas*, and *Acinetobacter* isolates that produce serine-beta-lactamases, cephalosporinases, and oxacillinases. However, although cefiderocol retains activity in the presence of most metallo-beta-lactamases, in vitro data are concerning for reduced potency against New Delhi Metallo-β- Lactamase (NDM)-producing isolates. Additionally, FDC exhibits in vitro activity against *Stenotrophomonas maltophilia*, despite its intrinsic beta-lactam resistance.
- Data suggest cefiderocol resistance is likely mediated by a combination of resistance mechanisms, and the addition of beta-lactamase inhibitors may be sufficient to restore

the drug's activity against some of these mechanisms. FDC resistance also may include mutations in iron transport channels, which inhibit FDCs novel mechanism of entry into bacteria. Unlike other gram-negative bacilli, FDC resistance does not seem to be mediated by porin and efflux mutations.

- FDC displays linear kinetics. It is primarily renally excreted and does not undergo significant hepatic metabolism. Dose adjustments are required for renal impairment but not for hepatic impairment. There are no recommendations for weight-based dosing in obesity and no data regarding cerebral spinal fluid penetration.
- Complicated UTI Trial (APEKS-cUTI)
    - The APEKS-cUTI study was a phase 2, multicenter, double-blind, parallel-group noninferiority trial that evaluated FDC vs imipenem for the treatment of cUTI (Lancet Infect Dis 2018;18:1319-1328) The clinical response rates were similar between the treatment groups, however, microbiological response at test of cure was higher in the FDC arm (73% vs 56%; difference 17.25%; 6.92% to 27.58%).
- Nosocomial Pneumonia (APEKS-NP Trial)
    - The APEKS-NP study was a phase 3, randomized, double-blind, multicenter, noninferiority trial that compared FDC vs high-dose, extended infusion meropenem for adults with HAP, VAP, or HCAP due to gram-negative pathogens. (Lancet Infect Dis 2021; 21:213-225) FDC was noninferior to high-dose extended infusion meropenem as the primary outcome (all-cause mortality at day 14) was similar in the 2 groups (12.4% FDC vs 11.6% meropenem; adjusted difference, 0.8%; 95% CI, –6.6% to 8.2%). The proportion of patients with clinical cure and microbiological eradication at test of cure was similar in both groups. The most common pathogen was *K. pneumoniae* followed by *P. aeruginosa* and *A. baumannii*.
- CREDIBLE-CR Trial (severe carbapenem-resistant infections) (Lancet Infect Dis 2020; 21:226-240)
    - This is a phase 3, randomized, open-label, multicenter, descriptive study assessing FDC vs clinician-directed best available therapy (BAT) in adults with serious carbapenem-resistant (CR) gram-negative infections. Investigators included patients hospitalized with HAP, VAP, HCAP, BSI, cUTI, or sepsis caused by a suspected or proven CR gram-negative pathogen. For patients with nosocomial pneumonia, BSI, or sepsis, the primary end point was clinical cure after treatment completion (7 days ± 2 days after end of therapy). The primary end point for patients with cUTI was microbiological eradication at test of cure.
    - A total of 152 patients were randomized to receive FDC (n = 101) or BAT (n = 51). The most common diagnosis was nosocomial pneumonia (n = 67, 45%) followed by BSI/sepsis (n = 47, 31%) and cUTI (n = 36, 24%). The primary analysis included 118 patients (FDC n = 80, BAT n = 38) who had a confirmed carbapenem-resistant infection. In the FDC group, 83% (66 of 80) of patients received monotherapy, while in the BAT arm, 71% (27 of 38) received combination therapy (the majority of which were colistin-based regimens). The most common CR pathogens were *A. baumannii*, *K. pneumoniae*, and *P. aeruginosa* (FDC MIC90 of 1 µg/mL, 4 µg/mL, and 2 µg/mL, respectively).
    - Clinical cure at test of cure was similar in each group for those with nosocomial pneumonia (FDC 50% [20 of 40], 95% CI, 33.8% to 66.2%; BAT 53% [10 of 19], 95% CI, 28.9% to 75.6%) and BSI or sepsis (FDC 43% [10 of 23], 95% CI, 23.2% to 65.5%; BAT 43% [6 of 14], 95% CI, 17.7% to 71.1%). For patients with cUTI, microbiological eradication at test of cure was 53% (9 of 17, 95% CI, 27.8% to

77.0%) in the FDC group and 20% (1 of 5, 95% CI, 0.5% to 71.6%) in the BAT group.

- The surprise was more patients died in the FDC arm compared with those treated with BAT (33.7% [34 of 101] vs 18.3% [9 of 49]). Post hoc all-cause mortality in the FDC arm was higher at day 28 (difference 6.4%; 95% CI, –8.6% to 19.2%) and at day 49 (difference 13.3%; 95% CI, –2.5% to 27.8%)
- Most of the treatment failure deaths in the FDC arm occurred in patients with *Acinetobacter* infections (13 of 16) compared with only 1 death (1 of 4) in the BAT arm. Fifteen patients who received FDC had evidence suggesting treatment emergent in vitro resistance, with a 4-fold increase in cefiderocol MIC from baseline; 10 of these patients experienced treatment failure. See article above
- **Comment:** This was an open-labeled design. The sample size was small, and there was an imbalance between the groups.

Drug Name	ESBL activity	KPC activity	NDM activity	OXA activity	*Pseudomonas*	*Acinetobacter*	*Stenotrophomonas*
Ceftazidime-avibactam	Yes	Yes	No	Yes	Yes	No	No
Ceftolozane-tazobactam	Yes	No	No	No	Yes	No	No
Imipenem-relebactam	Yes	Yes	No	No	Yes	No	No
Eravacycline	Yes	Yes	Yes	Yes	No	Yes	Yes
Plazomicin	Yes	Yes	Yes	Yes	Variable	No	No
Cefiderocol	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Livermore DM, et al. *Antimicrob Agents Chemother.* 2016;60:3840.
Stewart A, et al. *Antimicrob Agents Chemother.* 2018;62:e01195.
Otsuka Y. *Chem Pharm Bull.* 2020;68:182-190.

This is a chart I made for ID Week 2020 presentation as a reference

Final Comments: The surprising results on increased mortality in the CREDIBLE-CR trial casts a shadow on the role of FDC in treating certain CR gram-negative organisms. The FDA approved FDC based on the APEKS-cUTI and APEKS-NP trials. The EMA (the European FDA) approved FDC use for aerobic gram-negative infections with “limited treatment” options. Despite the CREDIBLE-CR trial other trials suggest cefiderocol is a promising alternative agent for some carbapenem-resistant infections, but its role in the management of CR *Pseudomonas* and *Acinetobacter* infections needs further study. The emergence of resistance on therapy is also a concern.

COVID-19

COVID-19 News

RSV, Influenza, and COVID-19

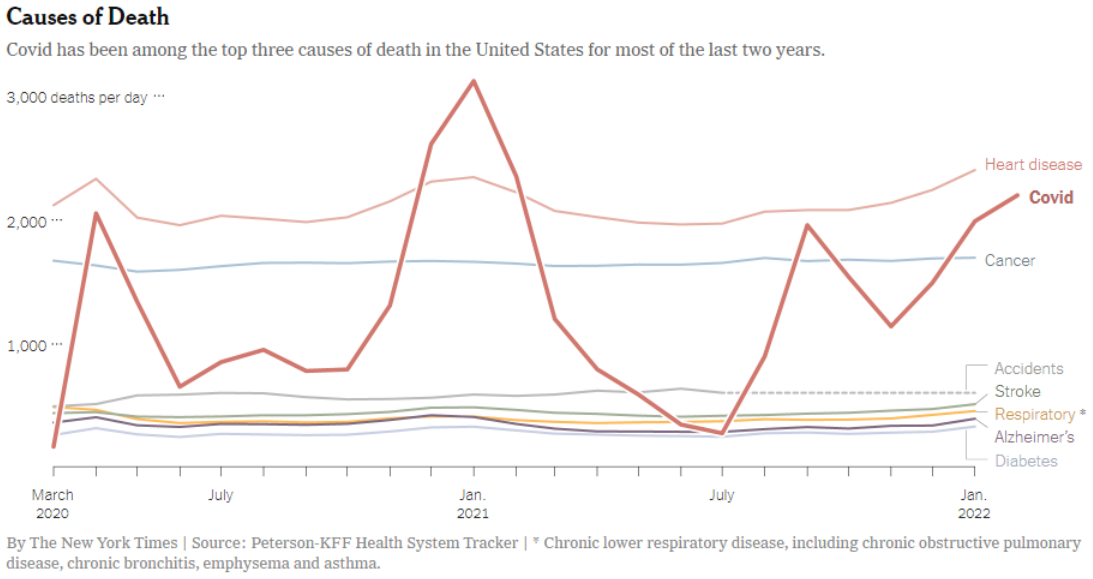
Age	RSV (per 100,000)*	Flu (per 100,000)*	COVID-19 (per 100,000)**
<1 year	2381	181	89
1	710	86	
2	395	62	
3	211	48	
4	111	41	
5-6	72	40	32
7-11	36	23	
12-17	39	17	66

*Averaged across years 2003-2010
**December 2020-January 2022

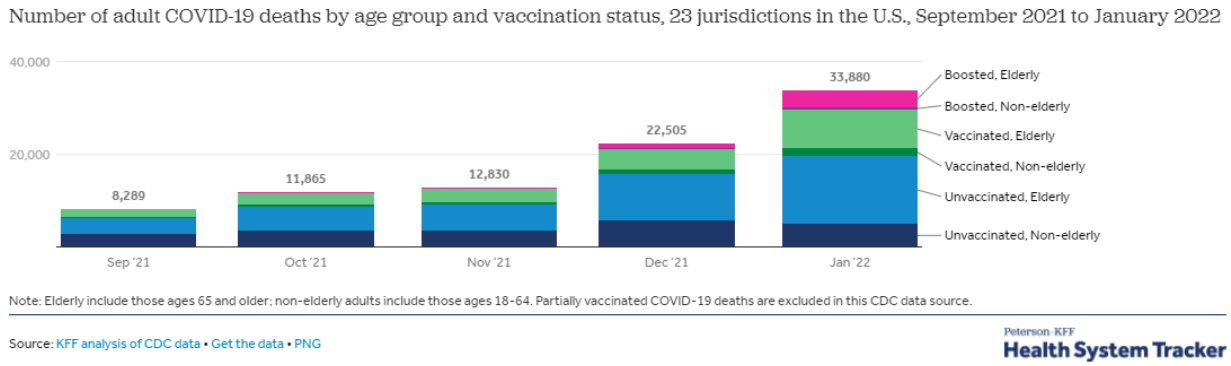
Annual rate of hospitalizations for viral diseases per 100,000 children in the United States. Table created by Katelyn Jetelina/YLE, based on data from two sources: RSV/Flu from Goldstein et al and COVID19 from CDC's COVIDNet.

Comment: I included this table to remind everyone as we move to hopefully the endemic phase of Covid-19 that we need to be mindful of other respiratory viruses and the potential impact in children and adolescents.

Peterson KFF Tracker April 21, 2022



Comment: As of mid-April 2022, nearly 1 million people in the U.S. have died of COVID-19. In this analysis, they estimate the number of adult deaths that could have been prevented by timely vaccination. They found that approximately 234,000 deaths since June 2021 could have been prevented with primary series vaccination. These vaccine-preventable deaths represent 60% of all adult COVID-19 deaths since June 2021, and a quarter (24%) of the nearly 1 million COVID-19 deaths since the pandemic began. They used the CDC studies of vaccine effectiveness for the primary vaccine series against death to estimate the number of deaths among unvaccinated adults that most likely would not have been prevented by vaccination.



Comment: CDC estimates that in February and March of 2022 unvaccinated people were 10 times more likely to die from COVID-19 than people vaccinated with at least a primary series, on an age-adjusted basis. Unvaccinated people were 20 times more likely to die from COVID-19 than people with a booster dose.

Since a national data are not available for the share of deaths that are among unvaccinated people, this analysis assumed that CDC's 25 jurisdictions are nationally representative. These jurisdictions include several large and geographically diverse states, representing 66% of the population. However, the data from the 25 jurisdictions do not include deaths among partially vaccinated people, and so they assigned deaths among partially vaccinated people equally to the "vaccinated" and "unvaccinated" groups. Another potential limitation arises on how they apply vaccine effectiveness. CDC reports that earlier in the Omicron wave, vaccines (primary mRNA series without a booster dose) were 79% effective at preventing ventilator support or in-hospital death, but, to my knowledge, CDC has not yet published an estimate of vaccine effectiveness against death alone. Additionally, the vaccine effectiveness estimates that they used were for the whole population, but unvaccinated people tend to be younger, on average, and therefore vaccine effectiveness may have been different for this group compared to the adult population as a whole.

CDC/ACIP Meeting April 20, 2022

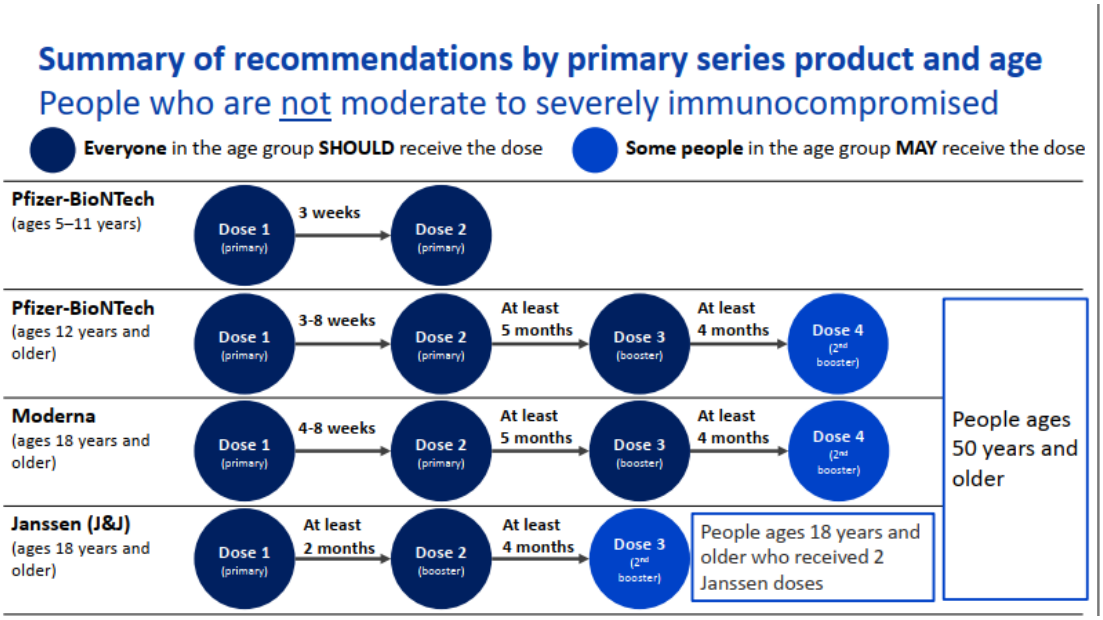
Though all Americans aged 50 and older are now eligible to get a second booster of COVID-19 vaccine, the CDC's ACIP said some groups may benefit more than others from the second booster. The immunocompromised, those who live with the immunocompromised, and those at great risk for severe COVID-19, should probably consider getting a fourth dose of mRNA vaccine—a second booster—as soon as possible. But people who have had COVID-19 within

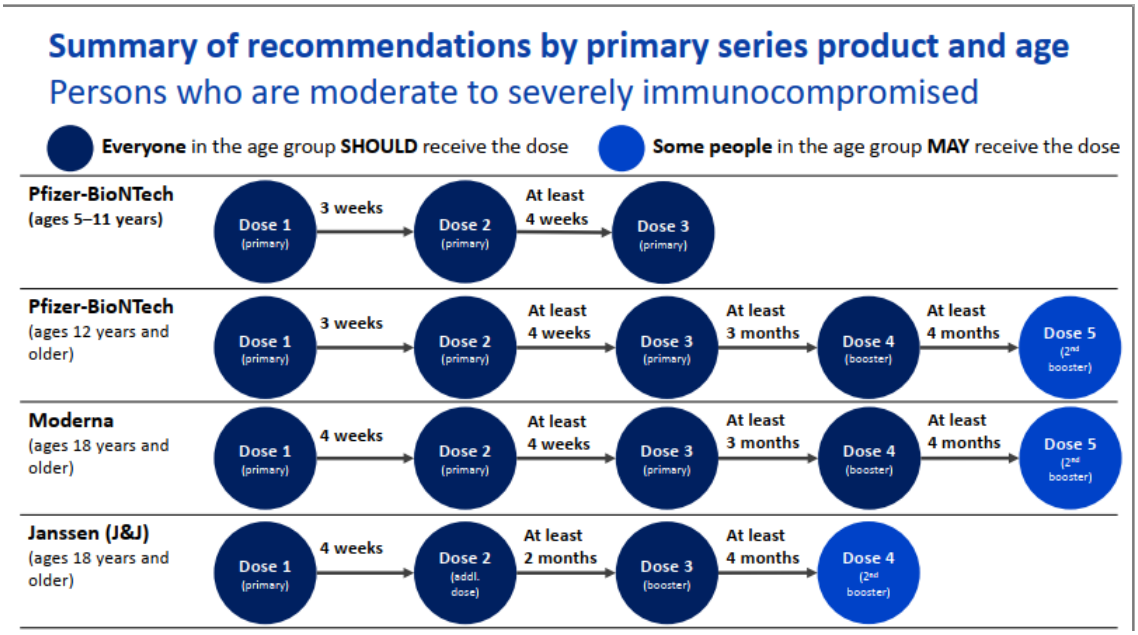
the last 3 months and older—but healthy—adults who want to wait until the fall to get a booster are likely okay to take a wait-and-see approach. The booster dose should reduce severe disease rather than prevent transmission or infection.

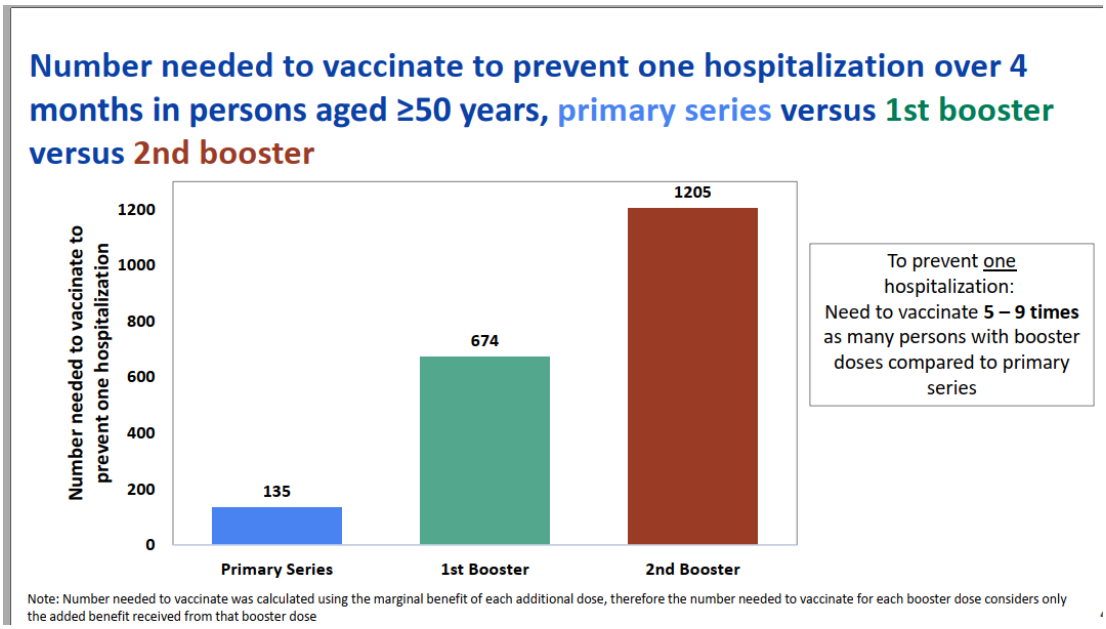
ACIP members voiced concerns about booster fatigue and creating the impression that a vaccination program that required large swathes of the population to get boosted every 4 to 6 months would be viewed as unsuccessful. They also emphasize that the primary series of vaccines, the first two doses, remained the most important in terms of preventing deaths.

No votes were cast today as ACIP members discussed these questions.

According to the CDC, 4.3 million people 50 and older have received a fourth dose. The CDC COVID Data Tracker shows that 66% of Americans are fully vaccinated against COVID-19, 77.4% have received at least one dose of vaccine, and 45.5% of those eligible have received their first booster dose. See representative slides below




Summary of recommendations by primary series product and age
Persons who are moderate to severely immunocompromised
Everyone in the age group SHOULD receive the dose
Some people in the age group MAY receive the dose
Pfizer-BioNTech (ages 5–11 years)
Dose 1 (primary)
3 weeks
Dose 2 (primary)
At least 4 weeks
Dose 3 (primary)
Pfizer-BioNTech (ages 12 years and older)
Dose 1 (primary)
3 weeks
Dose 2 (primary)
At least 4 weeks
Dose 3 (primary)
At least 3 months
Dose 4 (booster)
At least 4 months
Dose 5 (2nd booster)
Moderna (ages 18 years and older)
Dose 1 (primary)
4 weeks
Dose 2 (primary)
At least 4 weeks
Dose 3 (primary)
At least 3 months
Dose 4 (booster)
At least 4 months
Dose 5 (2nd booster)
Janssen (J&J) (ages 18 years and older)
Dose 1 (primary)
4 weeks
Dose 2 (addl. dose)
At least 2 months
Dose 3 (booster)
At least 4 months
Dose 4 (2nd booster)


Number needed to vaccinate to prevent one hospitalization over 4 months in persons aged ≥50 years, primary series versus 1st booster versus 2nd booster
Number needed to vaccinate to prevent one hospitalization
1200
1000
800
600
400
200
0
135
674
1205
Primary Series
1st Booster
2nd Booster
To prevent one hospitalization:
Need to vaccinate 5 – 9 times as many persons with booster doses compared to primary series
Note: Number needed to vaccinate was calculated using the marginal benefit of each additional dose, therefore the number needed to vaccinate for each booster dose considers only the added benefit received from that booster dose

Benefit and risk balance for COVID-19 vaccine booster doses

Comment: I think you can see some of the data around a second boosters, but the effects of a second booster is less than the first booster and the effects are short-lived. You can see the number to vaccinate to prevent 1 hospitalization is very high. The last slide is a nice graphic on risks and benefits.

Infectious Diseases Society of America (IDSA) Keep Masking Up April 21, 2022

IDSA agrees with the CDC's recommendation that everyone wear well-fitting, high-quality masks in indoor public settings when COVID-19 community levels are high. IDSA recommends masks also be worn on public transportation systems, although the federal mask mandate has been lifted.

IDSA further emphasizes that the authority to implement community mitigation measures, such as mask requirements, during a public health emergency must rest with public health authorities like CDC and state and local health officials.

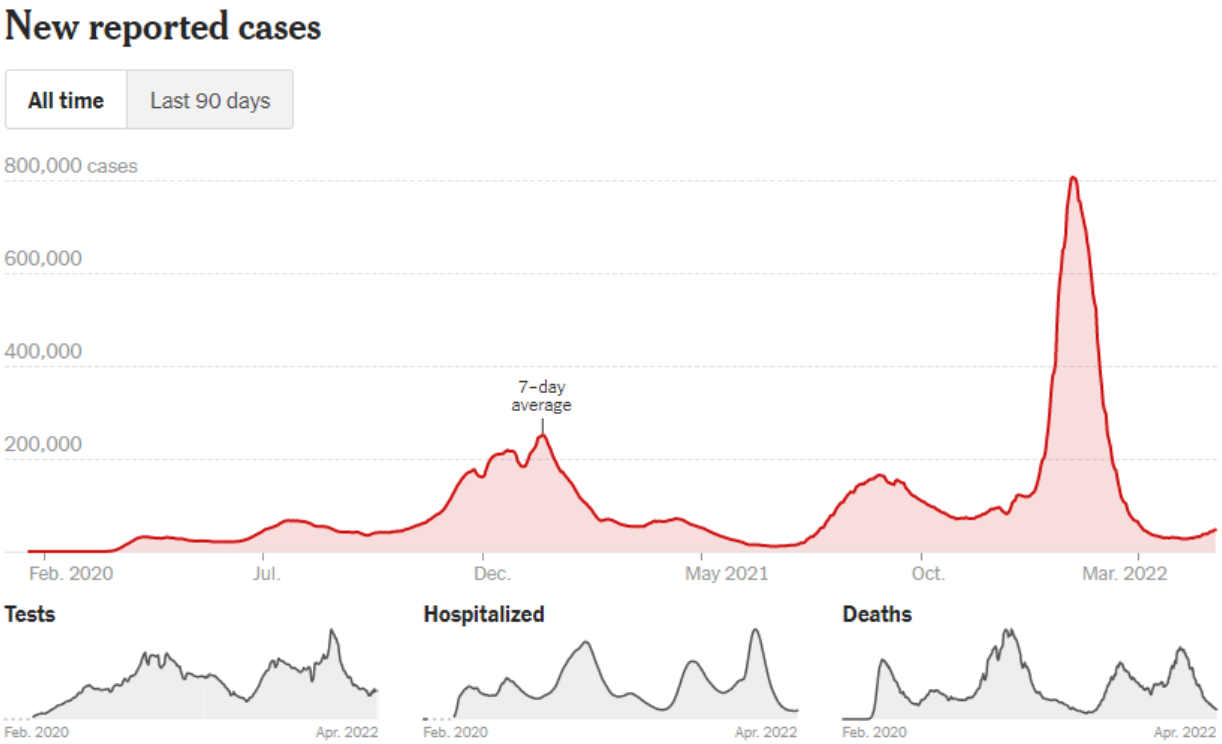
Factors the public should consider when deciding whether to wear a mask include personal health risk, community COVID-19 levels and the guidance of public health officials. Wearing a mask indoors in public settings offers protections both for you and those you encounter.

Many people in our communities remain at risk for severe disease from COVID-19. Children under 5 still cannot get vaccinated. While vaccination significantly lowers everyone's risk of severe disease, people with weakened immune systems, chronic diseases or those who are older still have some risk even when vaccinated.

The nation's infectious diseases experts and most public health officials still encourage people to wear masks in certain settings. As the pandemic continues to evolve, the public should be prepared for updated guidance.

Comment: This statement seems very reasonable and consistent with comments I have written in ID Watch over the last several months. See comments below in review of article from PNAS.

COVID-19 by the Numbers

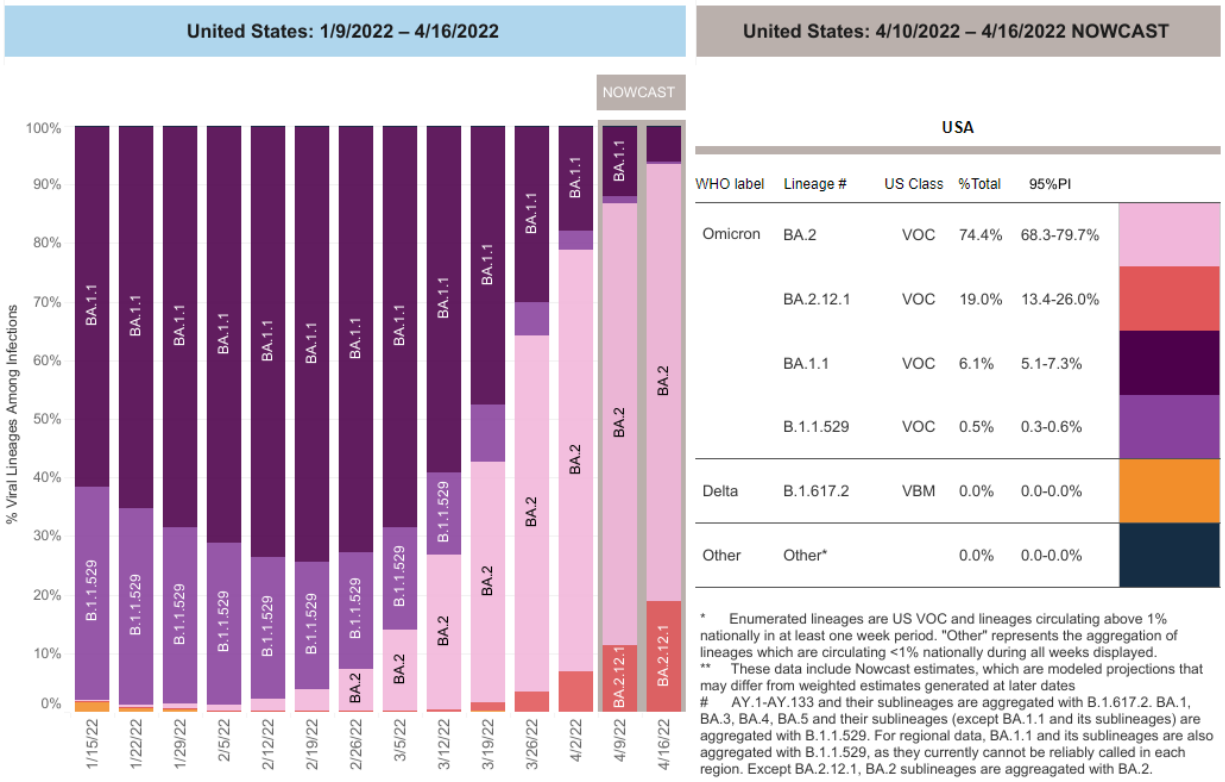


	DAILY AVG. ON APR. 23	14-DAY CHANGE	TOTAL REPORTED
Cases	46,582	+51%	80,855,787
Tests	813,142	+17%	—
Hospitalized	15,468	+3%	—
In I.C.U.s	1,900	-12%	—
Deaths	370	-34%	989,678

Comments:

- Cases have increased in a majority of states and territories during the past two weeks, but the increases are sharpest in the Northeast and Midwest. However, the average number of reported cases announced per day in the U.S. still remains at its lowest level since the summer of 2021. Given the increasing number of home tests some cases may

go unreported in official tallies, suggests that the current volume of cases is likely an undercount.
- Public health experts believe that two new subvariants may be contributing to this growth. Both evolved from the BA.2 subvariant. (See below)
- Hospitalizations also remain low.
- Deaths continue to decline.



COVID-19 Journal Review

SARS-CoV-2 mRNA vaccine effectiveness in healthcare workers by dosing interval and time since vaccination: test negative design, British Columbia, Canada OFID published April 15, 2022

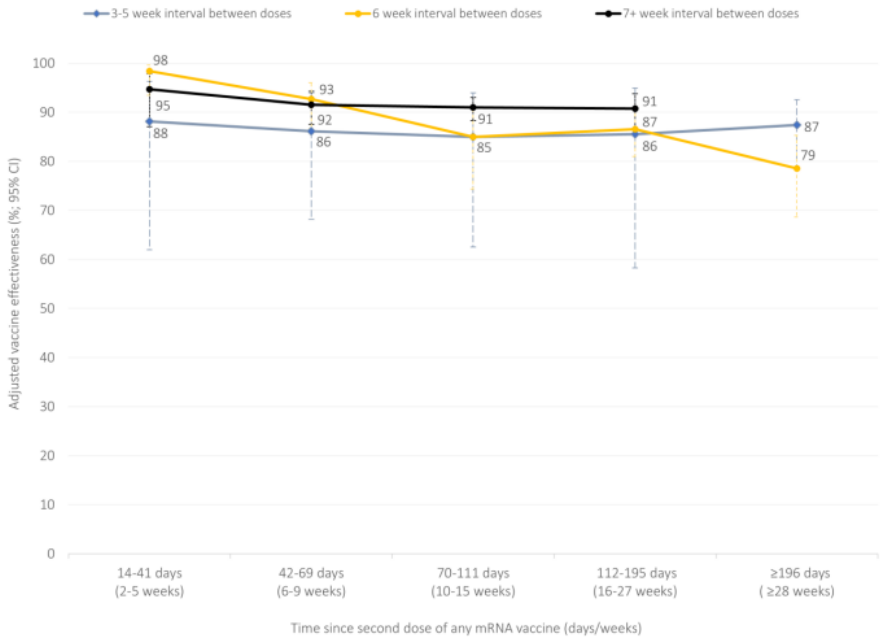
doi.org/10.1093/ofid/ofac178

Researchers from the BC Centre for Disease Control, Communicable Diseases and Immunization Services used a test-negative design to evaluate the odds of vaccination in HCWs and controls matched in a 6:1 ratio to COVID-19 test date. mRNA vaccination was considered receipt of the first dose 21 or more days before the test date or the second dose at least 14 days before.

Tests were conducted from January 17 to October 2, 2021, a span that included the dominance of the Delta variant. Mean follow-up was 49 days for the single-dose group and 89 days for two-dose recipients. Over 80% of HCWs were women, and controls were about a decade older than cases. Among vaccinated HCWs, 92% of single-dose and 83% of two-dose recipients were given the Pfizer vaccine.

Of all vaccinees, 1,265 received one dose of COVID-19 vaccine, while 1,246 received two. Among two-dose recipients, 12% received their second dose 3 to 5 weeks after the first, while 31% did so at 6 weeks, and 58% at 7 or more weeks. Over the study period, Canada's National Advisory Committee on Immunization changed recommended dosing intervals, ranging from 3 to 4 weeks to 16 weeks, as conditions evolved.

After adjustment, mRNA VE against infection was 71% for one dose at a median of 7 weeks and 90% for two doses at 13 weeks. Seven months after the second dose, VE was still greater than 80%. Two-dose VE was consistently 5% to 7% higher when given at least 7 weeks apart than after a 3- to 5-week interval.



Comment: The findings did not demonstrate significant waning immunity, even in the Delta era, however, this study was before the Omicron surge. Protection was enhanced by the Canadian decision to extend the interval between first and second doses reinforcing other studies. This study only involved HCWs. However, this study also has limitations, mainly related to its observational design and use of surveillance-based data subject to misclassified, missing or incomplete information.

Global Prevalence of Post COVID-19 Condition or Long COVID: A Meta-Analysis and Systematic Review J Infect Dis published online April 16, 2022

doi.org/10.1093/infdis/jiac136

Investigators conducted a systematic review including fifty studies identified in the review, and 41 were included in a quantitative synthesis, and 31 reporting overall prevalence were included in the meta-analysis.

The 50 studies included a total of 1,680,003 COVID-19 patients, including those who were hospitalized (67,161 patients from 22 studies), nonhospitalized (4,165 from 5 studies), and any COVID-19 patients, regardless of hospitalization status (1,608,677 from 23 studies).

This analysis found the prevalence of long COVID at 1 month at 37%, while it was 25% at 2 months and 32% at 3 months. Estimated global prevalence of long COVID was 43% (95% confidence interval [CI], 39% to 46%), although estimates ranged from 9% to 81%, which the investigators said may be attributable to differences in sex, region, study population, definition, and follow-up.

Long COVID prevalence among hospitalized patients was 54% (95% CI, 44% to 63%), while it was 34% (95% CI, 25% to 46%) for outpatients. Regionally, estimated pooled prevalence of lingering COVID-19 symptoms was 51% (95% CI, 37% to 65%) in Asia, 44% (95% CI, 32% to 56%) in Europe, 31% (95% CI, 21% to 43%) in North America, and 31% (95% CI, 22% to 43%) in the United States.

Worldwide, estimated prevalence of long COVID was 37% (95% CI, 26% to 49%) 1 month after diagnosis, 25% (95% CI, 15% to 38%) at 2 months, 32% (95% CI, 14% to 57%) at 3 months, and 49% (95% CI, 40% to 59%) at 4 months. The most common symptoms were fatigue (23%), followed by memory problems (14%), shortness of breath (13%), sleep problems (11%), and joint pain (10%).

Overall, the meta-analysis showed that a higher percentage of women reported long COVID symptoms than men (49% vs 37%, respectively) and that preexisting asthma was a predisposing factor for lingering symptoms.

Comment: Findings from the study show that the prevalence of long COVID is substantial, the health effects of infection seem to be prolonged. Risk factors not included and not identified in the meta-analyzed included severe initial illness, older age, and underlying conditions such as obesity and hypothyroidism. In addition to the PICO and 16 PRISMA search (July 2021), they updated their search twice (August 2021 and March 2022) in an effort to ensure this analysis was up to date. The effects observed for hospitalized COVID-19 positive individuals are likely attributed to hospitalization (e.g., critical care myopathy), which may partially explain and confound the observed differences between hospitalized and non-hospitalized prevalence of post COVID-19 condition. While this review included studies across 16+ countries, data from multiple regions are largely absent, notably, Africa, Central America, Oceania, and he Caribbean. Few children were included in these studies. Post COVID-19 condition's impact on population health and the labor force is enormous. Research is critical in helping us understand the pathophysiology of long Covid and come up with effective interventions.

Intramuscular AZD7442 (Tixagevimab– Cilgavimab) for Prevention of Covid-19 N Engl J Med published online April 20, 2022

DOI: 10.1056/NEJMoa2116620

The investigators enrolled 5,197 COVID-naïve adults at elevated risk for inadequate immune response to COVID-19 vaccination and/or exposure to SARS-CoV-2 at 87 sites from November 21, 2020, to March 22, 2021, before the rise of the Delta and Omicron variants.

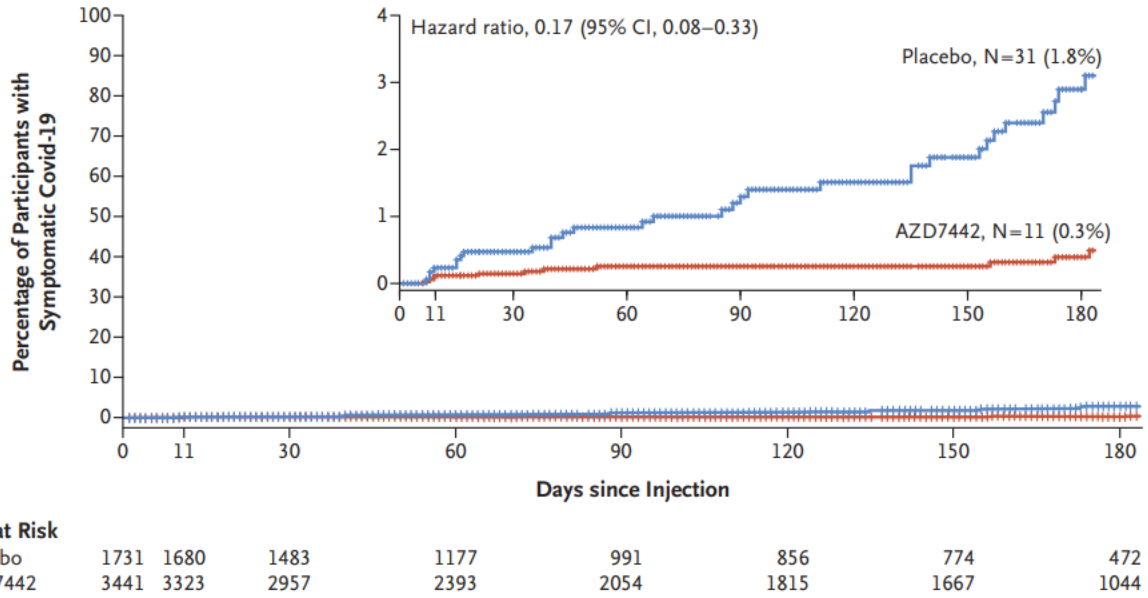
The researchers randomly assigned participants in a 2:1 ratio to receive one intramuscular 300-milligram dose of either Evusheld (3,460) or a saline placebo (1,737) and contacted them weekly about any COVID-19 symptoms for up to 183 days.

Over 73% of participants were at elevated risk of infection owing to age > 60, obesity, impaired immunity, or a high risk for vaccine-related adverse events, and 77.5% had congestive heart failure, chronic obstructive pulmonary disease, or chronic kidney or liver disease. A Poisson regression with robust variance was used as the primary efficacy analysis model to estimate the relative risk of the incidence of symptomatic infection in the AZD7442 group as compared with the placebo group.

Among Evusheld recipients, 1,161 (34%) were vaccinated against COVID-19, as were 853 (49%) in the placebo group. Average age was 53.5 years, 43.4% were age 60 or older, 46.1% were women, 14.5% were Hispanic, 17.3% were Black, and 73.0% were White. Of all participants, 52.5% were considered at increased risk of SARS-CoV-2 exposure, including HCWs, meatpackers, military personnel, students living in dorms, and others living closely together in Belgium, France, Spain, the United Kingdom, and the United States.

Symptomatic COVID-19 infection occurred in 0.2% of 3,460 Evusheld recipients, compared with 1.0% of 1,731 placebo recipients (relative risk reduction, 76.7%; 95% confidence interval [CI], 46.0% to 90.0%). After a median of 6 months, the relative risk reduction was 82.8% (95% CI, 65.8% to 91.4%). Among individuals at increased risk for COVID-19 infection or exposure, relative risk reductions (80.7% and 82.6%, respectively) were comparable to that in the overall population in the primary efficacy analysis (76.7%). Serum concentrations of Evusheld remained high for 6 months after receipt. Five cases of severe or critical Covid-19 and two Covid-19– related deaths occurred, all in the placebo group.

Among the 3,460 Evusheld recipients, 35.3% reported at least one adverse event, most mild or moderate, compared with 34.2% of 1,736 placebo recipients. The most common adverse event was a reaction at the injection site, which occurred in 2.4% in the Evusheld group and 2.1% of placebo recipients.



Comment: In December 2021, the FDA authorized Evusheld to prevent COVID-19 in people with moderately to severely impaired immunity and those in whom vaccination is not recommended. On February 24, 2022 the FDA recommended increasing the dose to 600 mg owing to the emergence of the Omicron BA.1 subvariant. There were too few events to statistically assess the benefit of AZD7442 in preventing severe disease in these groups. In addition, due to the low number of events in smaller but important subgroups, including immunocompromised persons, the efficacy in these groups could not be estimated. The introduction of vaccines in participating countries may have affected the incidence of SARS-CoV-2 infection during the trial.

SARS-CoV-2 Vaccination and Myocarditis in a Nordic Cohort Study of 23 Million Residents JAMA Cardiol published online April 20, 2022

doi:10.1001/jamacardio.2022.0583

Investigators from the Norwegian Institute of Public Health studied the incidence of myocarditis and pericarditis among residents of Denmark, Finland, Norway, and Sweden aged 12 and older before vaccination or 28 days after the first or second vaccine doses.

Eighty-one percent of participants were vaccinated by study end. All were followed from December 27, 2020, to October 5, 2021. Among all participants, 1,077 and 1,149 developed myocarditis and pericarditis, respectively, before or after vaccination.

One-hundred-five participants developed myocarditis after the first dose of the Pfizer vaccine, and 115 did so after the second. Among Moderna recipients, 15 developed myocarditis after the first dose, as did 60 after the second. Of recipients of two doses of the same vaccine (homologous vaccination), the second dose was tied to a 75% elevated risk of myocarditis for Pfizer (adjusted incidence rate ratio [IRR], 1.75; 95% confidence interval [CI], 1.43 to 2.14) and a more than sixfold increased risk for Moderna (IRR, 6.57; 95% CI, 4.64 to 9.28).

The investigators noted 9.7 myocarditis cases per 100,000 person-years for unvaccinated males and 4.3 per 100,000 for females. Among all participants aged 16 to 24, myocarditis rates were 18.8 and 4.4 per 100,000 person-years for males and females, respectively. Adjusted IRRs in homologous vaccinated males aged 16 to 24 were 5.31 (95% CI, 3.68 to 7.68) after a second dose of Pfizer and 13.83 (95% CI, 8.08 to 23.68) for Moderna. An estimated 5.55 (95% CI, 3.70 to 7.39) excess myocarditis cases per 100,000 vaccinees occurred after the second dose of Pfizer, compared with 18.39 (95% CI, 9.05 to 27.72) after Moderna. Pericarditis rates were similar.

Comments: Results of this large cohort study indicated that both first and second doses of mRNA vaccines were associated with increased risk of myocarditis and pericarditis. For individuals receiving 2 doses of the same vaccine, risk of myocarditis was highest among young males (aged 16-24 years) after the second dose. The data here are compatible with 4 to 7 excess events within 28 days per 100,000 vaccinees after a second dose of Pfizer, and 9 to 28 excess events within 28 days per 100,000 vaccinees after a second dose of Moderna. The risk of myocarditis associated with vaccination against SARS-CoV-2 must be balanced against the benefits of these vaccines. A recent study [reviewed in ID Watch] looked at risk after a third dose and found the risk of myocarditis is lower compared to second dose.

The risk of COVID vaccine-related myocarditis is still low and most feel outweighed by the benefits of vaccination. In an editorial the authors stated: "At the individual level, immunization prevents not only COVID-19–related myocarditis but also severe disease, hospitalization, long-term complications after COVID-19 infection, and death." "At the population level, immunization helps to decrease community spread, decrease the chances of new variants emerging, protect people who are immunocompromised, and ensure how health care system can continue to provide for our communities."

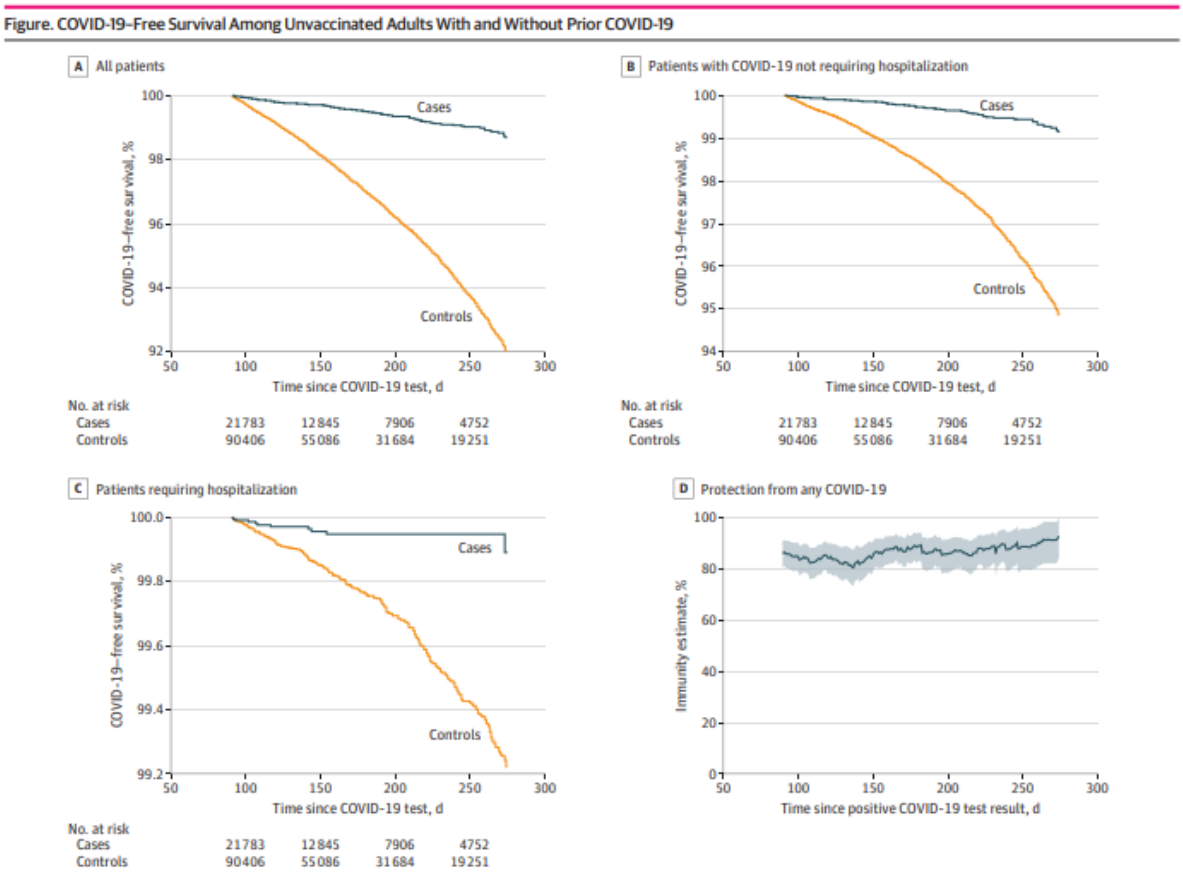
Rates of COVID-19 Among Unvaccinated Adults With Prior COVID-19 JAMA Netw Open published 2022;5(4):e227650 April 20, 2022

doi:10.1001/jamanetworkopen.2022.7650

This cohort study used data from patients tested for SARS-CoV-2 at 1300 sites of care in 6 western US states in the Providence health care system between October 1, 2020, and November 21, 2021. Patients who were unvaccinated for and had symptoms consistent with COVID-19 at the time of testing were included. Beginning 90 days after their initial SARS-CoV-2 (NAAT), patients were monitored for subsequent COVID-19, as determined by a positive SARS-CoV-2 NAAT result in the presence of symptoms. They performed Cox proportional hazards regression to analyze COVID-19–free survival among patients with prior COVID-19 (positive for SARS-CoV-2 on their initial test [cases]) compared with patients who tested negative for SARS-CoV-2 on their initial test (controls), adjusting for age, sex, and race and ethnicity (based on medical record documentation).

They investigators identified 24,043 cases and 97,572 controls; 2762 controls (2.8%) developed COVID-19 compared with 98 cases (0.4%). In the survival model, the HR among cases for developing COVID-19 was 0.15 (95% CI, 0.13- 0.18); for hospitalization for COVID-19, 0.12 (95% CI, 0.08-0.18); and for COVID-19 not requiring hospitalization, 0.17 (95% CI, 0.13-0.21). Prior COVID-19 was associated with protection of 85% against any recurrent COVID-19, 88% against hospitalization for COVID-19, and 83% against COVID-19 not requiring hospitalization.

Protection remained stable over the study period with no attenuation up to 9 months from initial infection.



Comment: The findings that patients with prior COVID-19 had 88% protection against hospitalization for COVID-19 and 83% protection against COVID-19 not requiring hospitalization suggest that natural immunity was associated with similar protection against mild and severe disease compared to mRNA vaccines. However, this study was done before Omicron. Limitations include possible COVID-19 testing or vaccination at outside health care facilities, but undetected infection should have been balanced between cases and controls. Patients who have recovered from COVID-19 may behave differently from those without immunity, potentially confounding results.

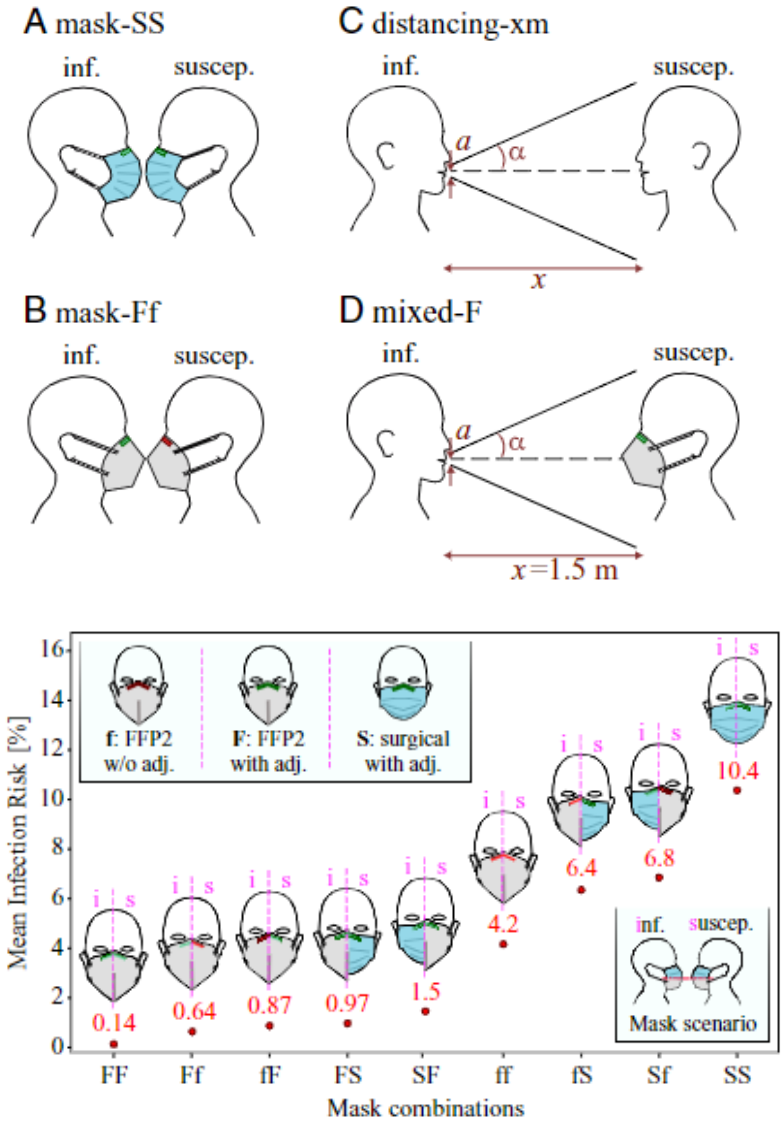
An upper bound on one-to-one exposure to infectious human respiratory particles PNAS 2021 118: e2110117118

doi.org/10.1073/pnas.2110117118

The investigators used the concept of an upper bound for one-to-one exposure to infectious human respiratory particles and apply it to SARS-CoV-2. To calculate exposure and infection risk, they used a comprehensive database on respiratory particle size distribution; exhalation flow physics; leakage from face masks of various types and fits measured on human subjects;

consideration of ambient particle shrinkage due to evaporation; and rehydration, inhalability, and deposition in the susceptible airways.

They found for a typical SARS-CoV-2 viral load and infectious dose, that social distancing alone, even at 3.0 m between two speaking individuals, leads to a 90% for risk of infection after a few minutes. If only the susceptible wears a face mask with the infected person speaking at a distance of 1.5 m, the risk varies significantly; that is, with a surgical mask, the risk of infection reaches 90% after 30 min, and, but with an FFP2 mask [N95], it remains at only about 20% even after 1 h. When both wear a surgical mask, while the infected one is speaking, the risk of infection remains below 30% even after 1 h, but, when both wear a well-fitting FFP2 mask, it is 0.4%.



Comment: Since the judge rejected the national mandate for travelers taking public transportation last week, I pulled this paper from several months ago to highlight how this may impact transmission. I am not an attorney, but I am uncomfortable with the legal system

impacting public health policy. What this paper concludes is that wearing appropriate masks in the community provides excellent protection for others and oneself and makes social distancing less important. Wearing a well-fitting, high-quality mask correctly offers the wearer a high degree of protection, even if other people in proximity aren't masked and/or infected. This may be like airports, planes, and trains as the mask mandate has been lifted. If you are high-risk, first be up to date with vaccinations. Next, decide what risk you are willing to take. If you are immunocompromised, have multiple high-risk underlying medical conditions, and elderly you may wish to continue to wear a high-grade mask indoors especially in crowded, poorly ventilated areas. Also consider people in your community who remain at risk for severe disease from COVID-19.