Infectious Diseases Watch

Israel Edition

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General Infectious Diseases

Risk for Asymptomatic Household Transmission of *Clostridioides difficile* Infection Associated with Recently Hospitalized Family Members Emerg Infect Dis 2022; 28:932-939

doi.org/10.3201/eid2805.212023

In an analysis of US Commercial Claims and Medicare data on >195 million individuals from 2001 to 2017, the investigators compared monthly incidence of CDI in households where a family member had been hospitalized and discharged home within 60 days to that in households without a recently hospitalized member. They were specifically interested in the risk posed to household members by patients who are discharged without a CDI diagnosis and who are not diagnosed with CDI after discharge. They separated enrollees into categories for ages 0–17, 18–40, 41–65, and >65 years. They also categorized antimicrobial drugs into separate risk strata for high-CDI-risk antibiotics (clindamycin, fluoroquinolones, cephalosporins, carbapenems, ampicillin/ sulbactam, piperacillin/tazobactam, and later-generation cephalosporins) or low-CDI-risk antibiotics (penicillin, macrolides, sulfonamides, trimethoprim, tetracyclines, and first-generation cephalosporins). They also identified patients taking PPIs within 30 days before the CDI index date.

Of almost 225,000 CDI cases, about 3,900 represented a potential acquisition from an asymptomatic, recently hospitalized family member. The CDI incidence rate was approximately 73% higher for individuals exposed to an asymptomatic recently hospitalized family member than for those without such exposure. Further, CDI incidence in the exposed family members progressively increased in relation to duration of hospitalization. Results were similar but less pronounced if the exposure window was increased from 60 to 90 days. Known CDI risk factors also were associated with greater incidence. Antimicrobial drug exposure was associated with an increased CDI incidence rate; for low-CDI-risk antibiotics the IRR was 2.69 (95% CI 2.59–2.79), and for high-CDI-risk antibiotics IRR was 8.83 (95% CI 8.63–9.03). PPI usage was also associated with statistically significant CDI incidence, an IRR of 2.23 (95% CI 2.15–2.30). CDI incidence increased with age; relative to ages 0–17 years the IRR continuously increased from 1.71 (95% CI 1.65–1.78) for ages 18–40 years to 9.32 (95% CI 8.92–9.73) for ages >65 years.

Table 4. Results of regression analysis of incidence rate ratio for *Clostridioides difficile* infection using quasi-Poisson model and 60-day exposure window in study of asymptomatic *C. difficile* transmission among household members, United States*

Variable	IRR (95% CI)
No. days member was hospitalized within 60 d	
0	Referent
1–3	1.30 (1.19–1.41)
4–10	1.46 (1.32–1.62)
11–20	1.79 (1.43–2.23)
21–30	2.17 (1.48–3.18)
>30	2.45 (1.66–3.60)
Age group, y	
0–17	Referent
18–40	1.71 (1.65–1.78)
41–65	2.97 (2.86–3.08)
>65	9.32 (8.92–9.73)
Sex	
M	Referent
F	1.30 (1.28–1.33)
Outpatient antimicrobial drug use within 60 d	
None	Referent
Low-risk drugs	2.69 (2.59–2.79)
High-risk drugs	8.83 (8.63–9.03)
PPI use within 30 d	2.23 (2.15–2.30)
Infant <2 y in family	1.51 (1.44–1.58)

Comment: Hospitalized patients can remain asymptomatically colonized with C. difficile after discharge. (Clin Microbiol Rev. 2018;31: e00021-17) This patient population could represent a reservoir of CDI outside healthcare settings. In this study, they found that persons exposed to recently hospitalized family members were at substantially increased risk for CDI within 60 days after the family member's hospital discharge. This study identified a previously underappreciated potential CDI reservoir outside healthcare settings. A limitation of the study includes reliance on administrative claim data to identify CDI cases and lack of microbiological data confirming transmission. The results, however, suggests a potential route of community spread of C difficile. This brings up the role of home environmental cleaning after the patient returns home.

Pharmacist-Driven Transitions of Care Practice Model for Prescribing Oral Antimicrobials at Hospital Discharge

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doi:10.1001/jamanetworkopen.2022.11331

This was a quality improvement study using a nonrandomized stepped-wedge design with 3 study phases from September 1, 2018, to August 31, 2019. Seventeen distinct medicine, surgery, and specialty units from a health system in Michigan participated, including 1 academic tertiary hospital and 4 community hospitals. Hospitalized adults who had urinary, respiratory, skin and/or soft tissue, and intra-abdominal infections and were prescribed antimicrobials at discharge were included in the analysis. Data were analyzed from February 18, 2020, to February 28, 2022.

Clinical pharmacists engaged in a new standard of care for antimicrobial stewardship practices during TOC (transitions of care) by identifying patients to be discharged with a prescription for

oral antibiotics and collaborating with primary teams to prescribe “optimal therapy.” Academic and community hospitals used both ASP and clinical pharmacists in a multidisciplinary rounding model to discuss, document, and facilitate order entry of the antibiotic prescription at discharge. The primary end point was frequency of optimized antimicrobial prescription at discharge. Health system guidelines were developed from national guidelines and best practices for short-course therapies were used to evaluate optimal therapy. Safety end points included ADEs, 30-day unplanned office and/or emergency department visits, 30-day readmissions, and 30- and 90-day mortality. Antimicrobial-related ADEs were categorized as mild to moderate or as severe. Severe ADEs that were assessed to 90 days included *C difficile* infection and isolation (from any clinical culture) of a new multidrug-resistant organism, whereas anaphylaxis and/or angioedema, kidney failure, acute hepatic failure, torsades de pointes, seizure, and serious hematologic toxic effects were measured to 30 days.

A total of 800 patients prescribed oral antimicrobials at hospital discharge were included in the analysis. 400 in the preintervention period and 400 in the postintervention period. The most common diagnoses were pneumonia (264 [33.0%]), upper respiratory tract infection and/or acute exacerbation of chronic obstructive pulmonary disease (214 [26.8%]), and UTIs (203 [25.4%]). Patients in the postintervention group were more likely to have an optimal antimicrobial prescription (time-adjusted generalized estimating equation odds ratio, 5.63 [95% CI, 3.69-8.60]). The absolute increase in optimal prescribing in the postintervention group was consistent in both academic (37.4% [95% CI, 27.5%-46.7%]) and community (43.2% [95% CI, 32.4%-52.8%]) TOC models. There were no differences in clinical resolution or mortality. However, fewer severe antimicrobial-related adverse effects (time-adjusted generalized estimating equation odds ratio, 0.40 [95% CI, 0.18-0.88]) were identified in the postintervention (13 [3.2%]) compared with the preintervention (36 [9.0%]) groups.

Prescription component	Patient group, No./total No. (%)		Absolute difference, % (95% CI)	Time-adjusted GEE OR (95% CI)
	Preintervention	Postintervention		
Overall	144/400 (36.0)	326/400 (81.5)	45.5 (39.2 to51.3)	5.63 (3.69 to 8.60)
Group 1	14/25 (56.0)	185/225 (82.2)	26.2 (7.0 to 45.8)	1.09 (0.59 to 2.01)
Group 2	59/150 (39.3)	103/125 (82.4)	43.1 (32.2 to 52.7)	3.93 (1.72 to 8.99)
Group 3	71/225 (31.6)	38/50 (76.0)	44.4 (30.0 to 56.5)	5.53 (1.59 to 19.23)
Community hospitals	86/275 (31.3)	73/98 (74.5)	43.2 (32.4 to 52.8)	4.28 (2.10 to 8.69)
Academic hospital	58/125 (46.4)	253/302 (83.8)	37.4 (27.5 to 46.7)	3.27 (1.87 to 5.72)
Components of nonoptimal prescribing throughout antimicrobial therapy course				
Prolonged duration[a]	177/400 (44.2)	37/400 (9.2)	−35.0 (−40.2 to −29.2)	0.17 (0.11 to 0.26)
Treatment for asymptomatic bacteriuria[a]	37/400 (9.2)	10/400 (2.5)	−6.8 (−10.0 to −3.4)	0.31 (0.11 to 0.86)
Nonbacterial upper respiratory tract infection[a]	7/400 (1.7)	1/400 (0.3)	−1.5 (−3.0 to 0)	0.15 (0.03 to 0.86)
Non-guideline-concordant selection[b]	81/400 (20.2)	24/400 (6.0)	−14.3 (−18.8 to −9.6)	0.28 (0.10 to 0.78)
Suboptimal dose[c]	23/400 (5.7)	4/400 (1.0)	−4.8 (−7.3 to −2.2)	0.11 (0.03 to 0.43)
Organism resistant to antimicrobial agent[b]	8/400 (2.0)	2/400 (0.5)	−1.5 (−3.2 to 0.2)	0.37 (0.07 to 2.09)
Duration too short[c]	6/400 (1.5)	6/400 (1.5)	0 (−1.8 to 1.8)	0.63 (0.10 to 4.11)

Comment: The findings of this quality improvement study suggest that providing resources to add additional review and intervention on antimicrobial discharge therapies can lead to improvements in the quality and safety of antimicrobial prescriptions. Several other studies have highlighted the importance of ASP on transition of cases including discharges. However**,** there are several limitations in the nonrandomized design of this study, including biases due to maturation and Hawthorne effect and regression to the mean.

COVID-19

COVID-19 News

CDC Restates Recommendation for Masks on Planes, Trains

US health officials on May 3rd restated their recommendation that Americans wear masks on planes, trains and buses, despite a court ruling last month that struck down a national mask mandate on public transportation.

Americans aged 2 and older should wear a well-fitting mask while on public transportation, including in airports and train stations, the CDC recommended, citing the current spread of SARS-CoV-2 and projections of future COVID-19 trends.

Comment: Given a "bump" in new cases and the transmissibility of BA.2, it is advisable especially for high-risk individuals to consider wearing a high quality and appropriately fitting masks on public transportation and in crowded indoor settings.

Latest COVID Subvariants

COVID-19 cases and hospitalizations have increase again in the US, but deaths have continued to come down. The "bump" is nowhere near the Omicron surge of last winter. Cases admitted to the hospital may be with Covid-19 or for Covid-19. Public health officials are monitoring several new Omicron subvariants that are contributing to the case numbers. In some parts of the U.S., a spinoff of the BA.2 subvariant called BA.2.12.1 may be the main culprit. In other countries, Omicron subvariants called BA.4 and BA.5 are driving up cases especially in South Africa. All three subvariants appear to be spreading more quickly than BA.2 and creating their own COVID-19 waves. BA.2.12.1 is growing about 25% faster than BA.2. It now makes up about 37% of new cases across the US, according to the latest CDC date. BA.2 makes up about 62% of new cases, down from 70% the week before.

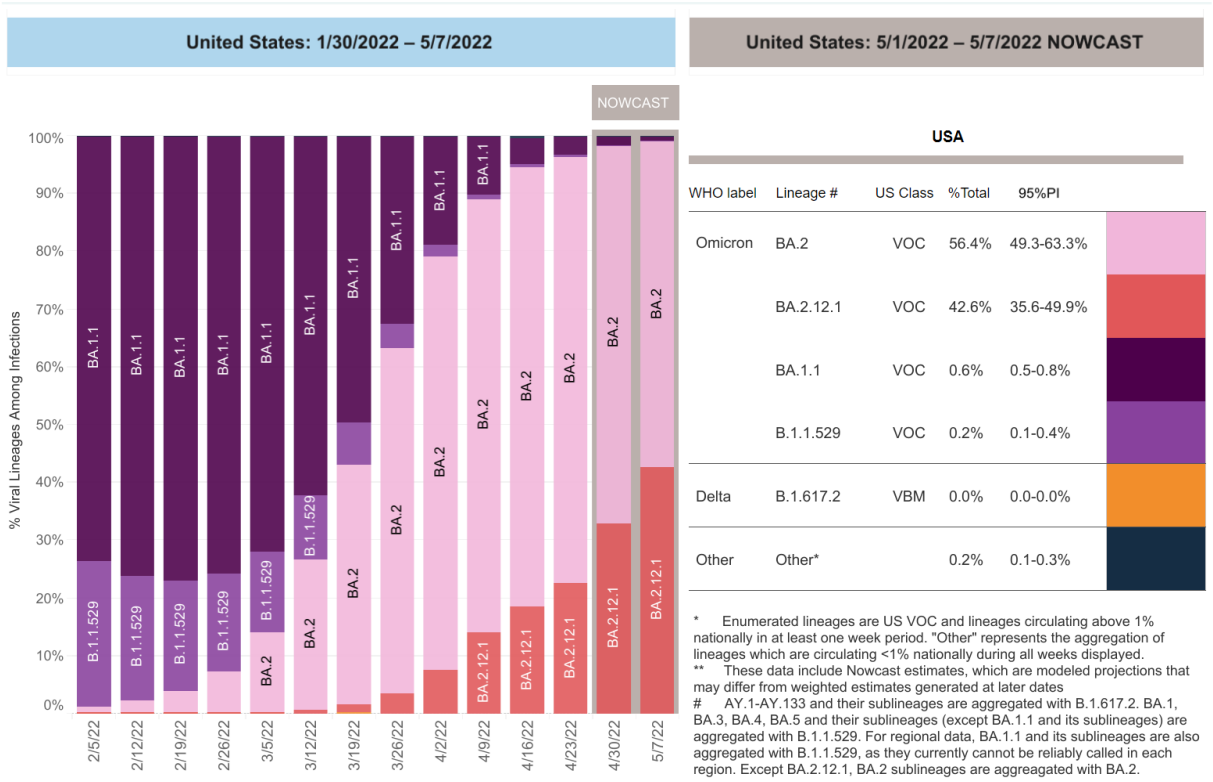
Comment: Public health officials are watching BA.4 and BA.5, which appear to have a growth advantage over BA.2. BA.4 and BA.5 can escape antibodies from previous infections caused by the original Omicron variant, BA.1. The newer subvariants also appear to escape antibodies in people who have been vaccinated and had breakthrough BA.1 infections. It is my hope that the combination of natural infection and vaccinations are reaching a level where Covid-19 is less dangerous for most people and its spread less disruptive. Stay tuned.

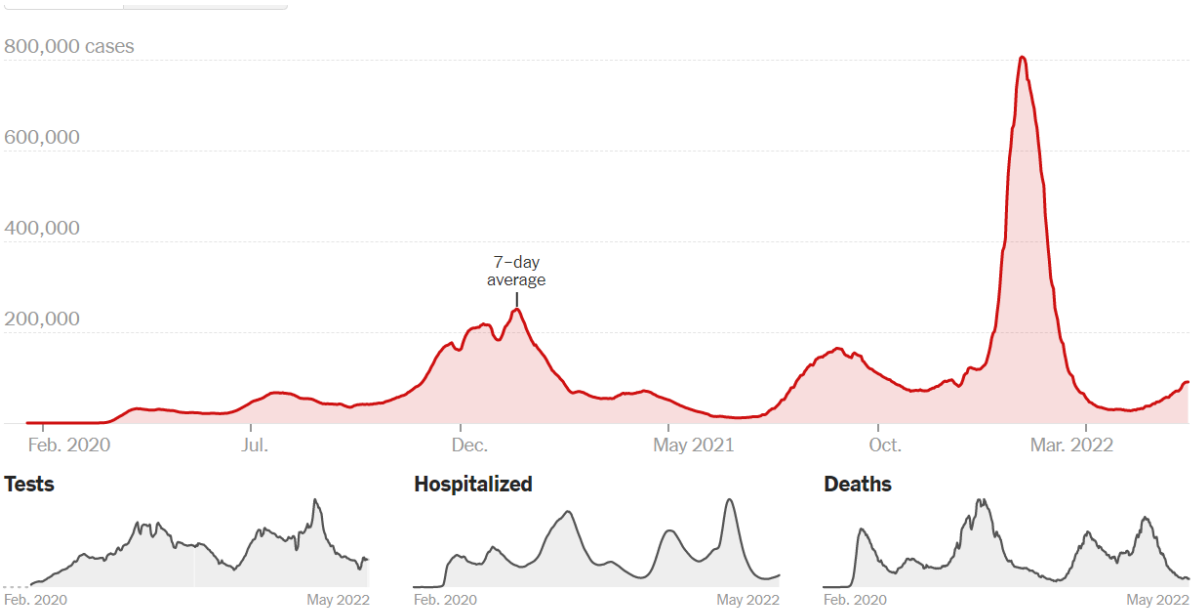
Other COVID-19 Updates

BA.2.12.1 accounted for nearly 43 percent of new cases for the week ending May 7, up from about 23 percent for the week ending April 23. Meantime, the prevalence of BA.2, which became dominant in March, has fallen from 74 percent of cases for the week ending April 23 to 56 percent as of May 7.

The daily average for new cases was 77,092 on May 15, up 60 percent over the last 14 days, according to federal data. Hospitalizations are up 24 percent nationwide over the last 14 days,

with a daily average of 19,270 people hospitalized May 15. Mortality continues to decline.**C** Modeling projects the nation's hospital admissions will increase over the next four weeks, with 600 to 8,700 new admissions likely reported May 27. Federal health officials are projecting a possible COVID-19 surge in the fall. The White House on May 6 projected 100 million infections could occur this fall and winter.





	DAILY AVG. ON MAY 15	14-DAY CHANGE	TOTAL REPORTED
Cases	90,423	+60%	82,414,028
Tests	806,152	+36%	—
Hospitalized	21,547	+24%	—
In I.C.U.s	2,302	+15%	—
Deaths	311	-3%	998,352

Comment: The projection for this fall and winter will be dependent on variants and vaccination strategies.

FDA Limits Use of Janssen COVID-19 Vaccine to Certain Individuals May 5, 2022

The FDA has further limited the authorized use of the J&J COVID-19 Vaccine to individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and to individuals 18 years of age and older who elect to receive the J&J COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine.

Key Points:

- After conducting an updated analysis, evaluation and investigation of reported cases, the FDA has determined that the risk of thrombosis with thrombocytopenia syndrome (TTS), a syndrome of rare and potentially life-threatening blood clots in combination with low levels of blood platelets with onset of symptoms approximately one to two weeks following administration of the J&J COVID-19 Vaccine, warrants limiting the authorized use of the vaccine.

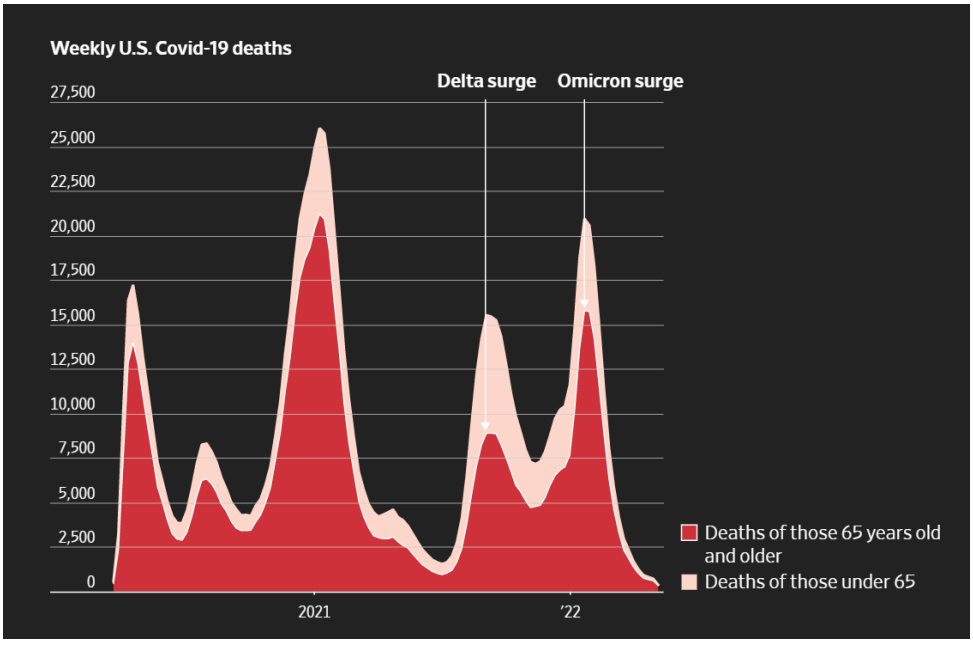
- The FDA has determined that the known and potential benefits of the vaccine for the prevention of COVID-19 outweigh the known and potential risks for individuals 18 years of age and older for whom other authorized or approved COVID-19 vaccines are not accessible or clinically appropriate, and for individuals 18 years of age and older who elect to receive the J&J COVID-19 Vaccine because they would otherwise not receive a COVID-19 vaccine.

- The Fact Sheet for Healthcare Providers Administering Vaccine now reflects the revision of the authorized use of the J&J COVID-19 Vaccine and includes a warning statement at the beginning of the fact sheet for prominence which summarizes information on the risk for TTS. Additionally, information on the revision to the authorized use of the vaccine and updated information on this risk of blood clots with low levels of blood platelets has been added to the Fact Sheet for Recipients and Caregivers.

Comment: In December 2021, after reviewing updated vaccine effectiveness and safety data, the ACIP made a preferential recommendation for the use of mRNA COVID-19 vaccines over the J&J COVID-19 Vaccine in all persons 18 years of age and older in the United States. The ACIP recommended and CDC endorsed that the J&J COVID-19 Vaccine may be considered in some situations: when a person has a contraindication to receipt of mRNA COVID-19 vaccines, when a person would otherwise remain unvaccinated for COVID-19 due to limited access to mRNA COVID-19 vaccines, and when a person wants to receive the J&J COVID-19 Vaccine despite the safety concerns identified. The FDA has determined that the reporting rate of TTS is 3.23 per million doses of vaccine administered and the reporting rate of TTS deaths is 0.48 per million doses of vaccine administered.

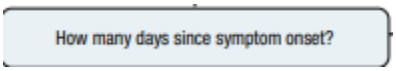
COVID-19 Death Toll May 5, 2022

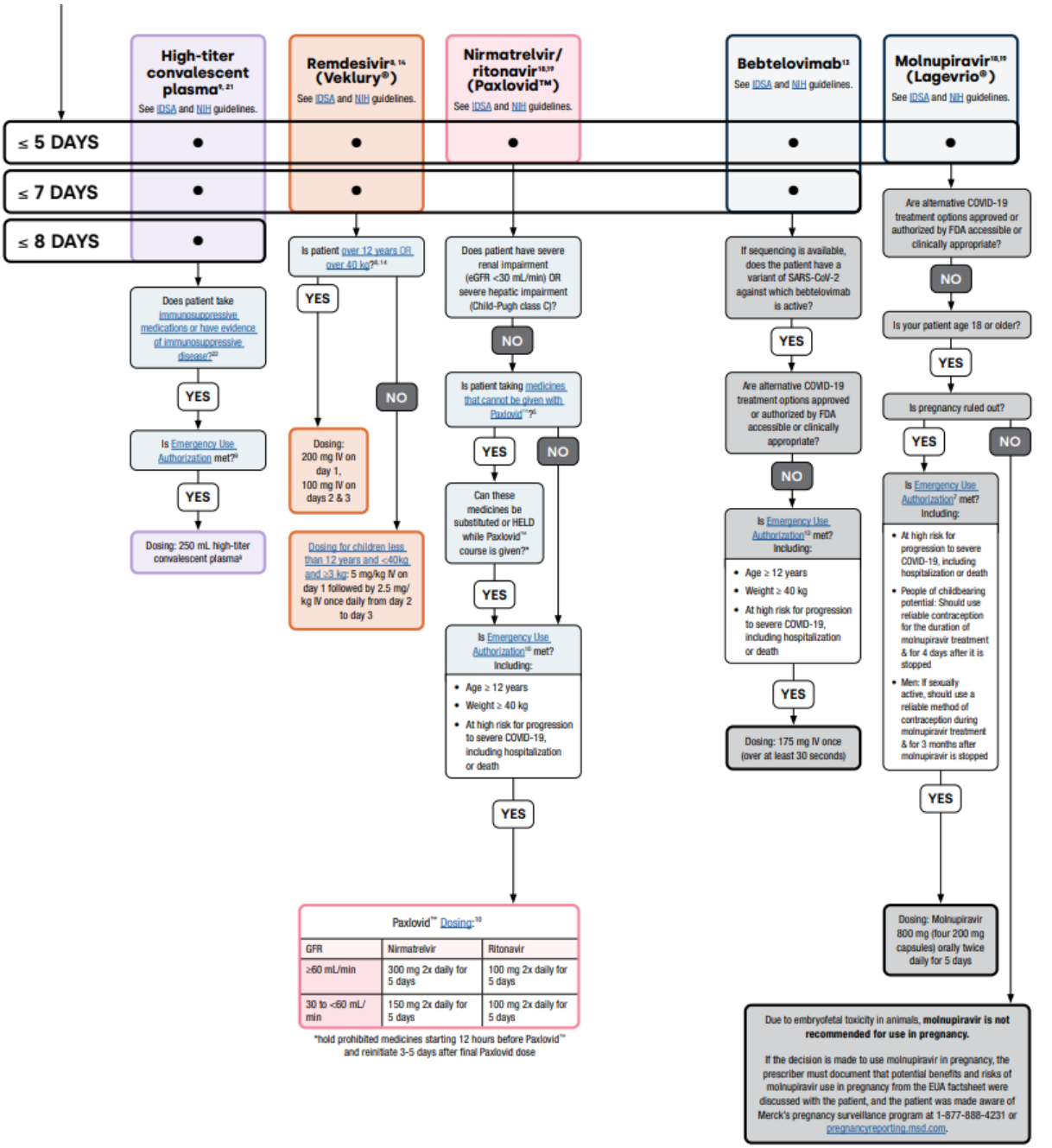
The WHO announced nearly 15 million more people died during the first two years of the pandemic than would have been expected during normal times. In the US we have passed the 1 million mark as of May 2022.



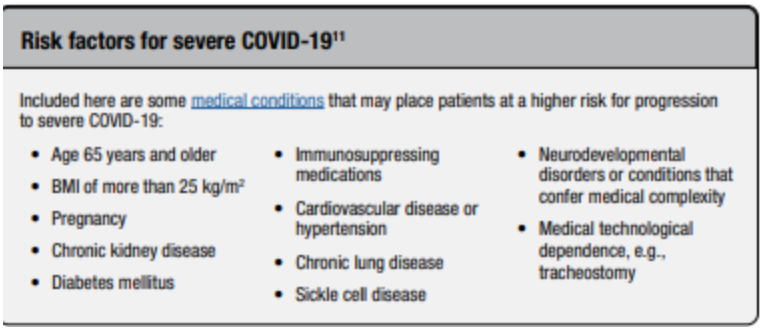
Comment: Much of the loss of life from the pandemic was concentrated in 2021, when more contagious variants emerged and just when vaccines were becoming widely available. In the US, the WHO estimated that roughly 930,000 more people than expected had died by the end of 2021, compared with the 820,000 Covid deaths that had been officially recorded over the same period. Why has US had so many deaths? Australia's Covid death rate sits at one-tenth of US per capita. When the pandemic began, 76 percent of Australians said they trusted the health care system (compared with around 34 percent of Americans), Australians were more likely than Americans to agree that "most people can be trusted" — a major factor, researchers found, in getting people to change their behavior for the common good to combat Covid, by reducing their movements, wearing masks and getting vaccinated. Vaccination uptake in Australia surged last year as soon as supplies arrived, rushing from roughly 10 percent of Australians over age 16 to 80 percent in six weeks. It was the fastest rate in the world at the time. Now, more than 95 percent of Australian adults are fully vaccinated — with 85 percent of the total population having received two doses. In the United States, that figure is only 66 percent. You be the judge!

IDSA Outpatient Covid-19 Treatment May 3, 2022





Comment: This is an excellent "Roadmap" when considering OP treatment. You need to also determine if your patient is at high risk for progression-see chart which is part of "Roadmap."



Risk factors for severe COVID-19[11]

Included here are some medical conditions that may place patients at a higher risk for progression to severe COVID-19:

- Age 65 years and older
- BMI of more than 25 kg/m²
- Pregnancy
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppressing medications
- Cardiovascular disease or hypertension
- Chronic lung disease
- Sickle cell disease
- Neurodevelopmental disorders or conditions that confer medical complexity
- Medical technological dependence, e.g., tracheostomy

FDA Authorized Pfizer booster for children 5-11

The FDA today amended the EUA for Pfizer vaccine allowing children ages 5-11 to get a single booster dose 5 months after completion of the primary series.

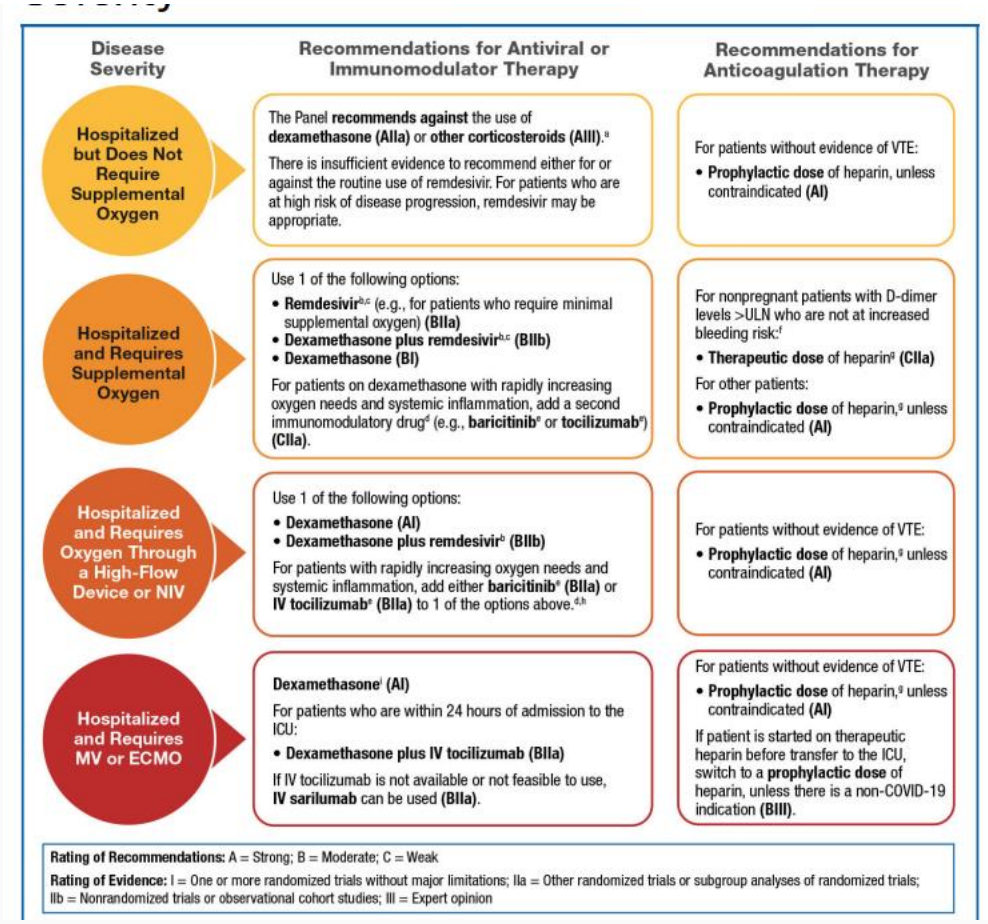
FDA Approves baricitinib for certain patients hospitalized with COVID-19 May 11, 2022

The FDA has approved a new indication for baricitinib as a treatment for adults hospitalized with COVID-19 who require supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation.

The FDA previously granted emergency use authorization (EUA) to baricitinib for use in combination with remdesivir as a treatment for adults and pediatric patients hospitalized with COVID-19. The EUA was later updated to authorize baricitinib as a standalone treatment. The drug remains under EUA status for hospitalized patients aged 2 to 17 years who require supplemental oxygen, mechanical ventilation or extracorporeal membrane oxygenation (ECMO).

The new indication of baricitinib is supported by findings from two randomized, double-blind, placebo-controlled phase 3 studies, ACTT-2 and COV-BARRIER, which demonstrated mortality benefits with baricitinib in patients hospitalized with COVID-19.

Comment: Baricitinib a Janus kinase inhibitor is the first immunomodulatory treatment to be approved by the FDA for COVID-19. I expect IL-6 inhibitors may be next. The FDA-approved labeling for baricitinib includes a boxed warning about an increased risk for serious infections, including tuberculosis, as well as mortality, malignancy, major adverse cardiovascular events and thrombosis. See most recent NIH guidelines below.



COVID-19 Journal Review

Association of SARS-CoV-2 Infection During Pregnancy With Maternal and Perinatal Outcomes JAMA published online May 2, 2022

doi:10.1001/jama.2022.5906

This analysis presents exploratory, population-level data from 6 Canadian provinces for the period of March 1, 2020, to October 31, 2021. A total of 6012 pregnant persons with a positive SARS-CoV-2 polymerase chain reaction test result at any time in pregnancy (primarily due to symptomatic presentation) were included and compared with 2 contemporaneous groups including age-matched female individuals with SARS-CoV-2 and unaffected pregnant persons from the pandemic time period. Main outcome: maternal and perinatal outcomes associated with SARS-CoV-2 infection as well as risk factors for severe disease (i.e., disease requiring hospitalization, admission to an intensive care unit/critical care unit, and/or oxygen therapy).

Among 6012 pregnant individuals identified with SARS-CoV-2 in Canada (median age, 31 [IQR, 28-35] years), the greatest proportion of cases were diagnosed at 28 to 37 weeks' gestation

(35.7%). Non-White individuals were disproportionately represented. Being pregnant was associated with a significantly increased risk of SARS-CoV-2–related hospitalization compared with SARS-CoV-2 cases among all women aged 20 to 49 years in the general population of Canada (7.75% vs 2.93%; relative risk, 2.65 [95% CI, 2.41-2.88]) as well as an increased risk of intensive care unit/critical care unit admission (2.01% vs 0.37%; relative risk, 5.46 [95% CI, 4.50-6.53]). Increasing age, preexisting hypertension, and greater gestational age at diagnosis were significantly associated with worse maternal outcomes. The risk of preterm birth was significantly elevated among SARS-CoV-2–affected pregnancies (11.05% vs 6.76%; relative risk, 1.63 [95% CI, 1.52-1.76]), even in cases of milder disease not requiring hospitalization, compared with unaffected pregnancies during the same time period. They also observed increasing rates of adverse maternal outcomes concurrent with the emergence of the Delta variant.

Figure 2. Bivariable Log-Binomial Models of Relative Risks for Intensive Care Unit (ICU) Admission

Variables	No. (%) of patients		Absolute risk difference, % (95% CI)	Relative risk (95% CI)
	Not admitted to ICU	Admitted to ICU		
Age, y				
<30	2389 (98.76)	30 (1.24)	[Reference]	1 [Reference]
30-35	2327 (97.73)	54 (2.27)	1 (0.3 to 1.8)	1.71 (1.11-2.7)
≥36	1158 (97.07)	35 (2.93)	1.7 (0.6 to 2.7)	2.28 (1.41-3.72)
Body mass index				
<25	1267 (98.75)	16 (1.25)	[Reference]	1 [Reference]
25-29	746 (97.64)	18 (2.36)	1.1 (-0.1 to 2.3)	3.26 (1.79-6.15)
≥30	629 (95.88)	27 (4.12)	2.9 (1.2 to 4.5)	1.87 (0.96-3.69)
Preexisting hypertension				
No	5664 (98.16)	106 (1.84)	[Reference]	1 [Reference]
Yes	220 (94.02)	14 (5.98)	4.1 (1.1 to 7.2)	3.5 (1.72-6.34)
Type 1 or 2 diabetes				
No	5630 (98.12)	108 (1.88)	[Reference]	1 [Reference]
Yes	254 (95.49)	12 (4.51)	2.6 (0.1 to 5.1)	2.78 (0.99-6.05)
Asthma				
No	3908 (98.12)	75 (1.88)	[Reference]	1 [Reference]
Yes	140 (95.24)	7 (4.76)	2.9 (-0.6 to 6.3)	1.98 (0.84-3.95)
Gestational age at diagnosis, wk				
<14	1078 (99.81)	2 (0.19)	-1 (-1.5 to -0.4)	0.16 (0.03-0.55)
14-27	2060 (98.85)	24 (1.15)	[Reference]	1 [Reference]
≥28	2709 (96.65)	94 (3.35)	2.2 (1.4 to 3)	2.76 (1.79-4.41)
Race and ethnicity				
African, Black, or Caribbean	240 (97.96)	5 (2.04)	0.3 (-1.6 to 2.3)	1.12 (0.36-2.99)
East Asian or Southeast Asian	160 (94.67)	9 (5.33)	3.6 (0.1 to 7.1)	3.16 (1.32-7.24)
Hispanic or Latinx	90 (98.90)	1 (1.10)	-0.6 (-2.9 to 1.7)	0.62 (0.03-3.08)
Middle Eastern	139 (95.86)	6 (4.14)	2.4 (-0.9 to 5.8)	1.76 (0.69-4.22)
Other (including Indigenous)	232 (96.67)	8 (3.33)	1.6 (-0.8 to 4.1)	2.48 (0.88-6.16)
South Asian	370 (98.93)	4 (1.07)	-0.6 (-2 to 0.8)	0.63 (0.18-1.8)
White	754 (98.31)	13 (1.69)	[Reference]	1 [Reference]

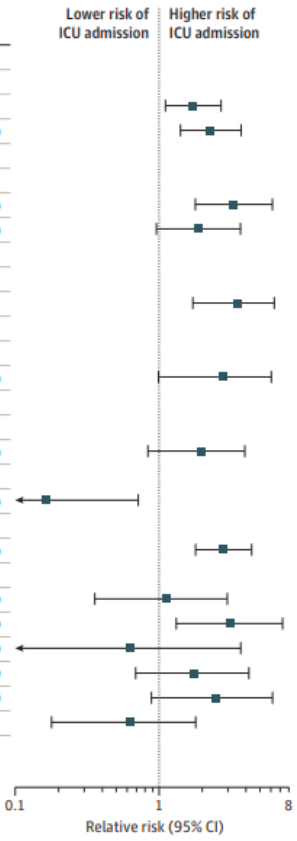
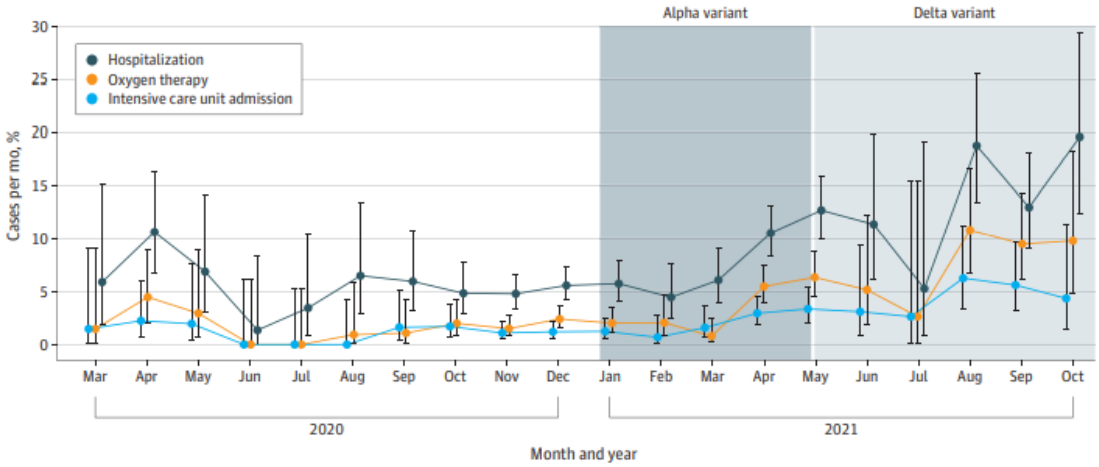


Figure 3. Adverse Maternal Outcomes Associated With SARS-CoV-2 Diagnosis in Pregnancy From March 1, 2020, to October 31, 2021 (N = 6012)



Total No. of SARS-CoV-2 cases by month	68	179	102	74	87	108	185	352	732	916	645	292	379	713	537	97	38	176	232	92

Comment: This article confirms prior studies that SARS-CoV-2 infection during pregnancy was significantly associated with increased risk of adverse maternal outcomes and preterm birth. Most analyses in this study used crude comparisons without adjustment because of a lack of detailed individual-level data. With the inability to perform multivariable analyses, significant associations could not be interpreted as representing independent risk factors. In addition, there was substantial missing date elements for both BMI and race and ethnicity.

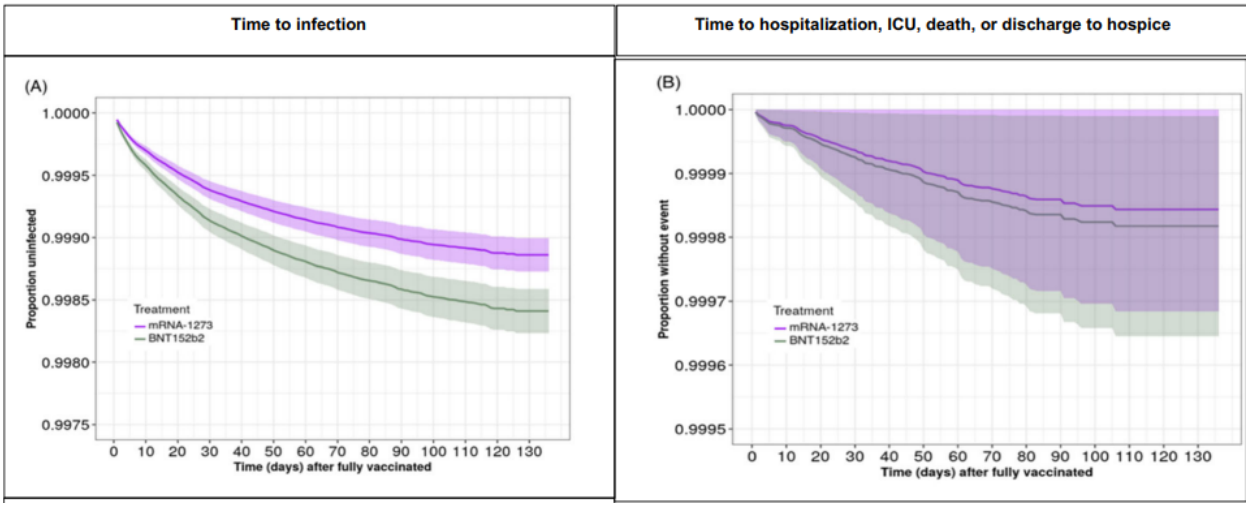
Comparative effectiveness over time of the mRNA-1273 (Moderna) vaccine and the BNT162b2 (Pfizer-BioNTech) vaccine Nat Comm published online May 2, 2022

doi.org/10.1038/s41467-022-30059-3

Optum Labs scientists in Minnesota compared the effectiveness of the Moderna and Pfizer COVID-19 vaccines by analyzing healthcare claims from fully vaccinated Americans insured by a single US insurer (Medicare Advantage and commercial insurance). Among 8,848 infected participants, 35% had received the Moderna vaccine, and 65% had received Pfizer. Follow-up was 14 to 151 days after the second vaccine dose. The researchers also analyzed data from those younger and older than 65 years who had never been infected. The primary outcome was the rate of Covid-19 infection occurring at 30, 60, and 90 days at least 14 days after the second dose of either the Moderna vaccine or the Pfizer vaccine. Vaccinated individuals aged ≥ 18 and enrolled at least 1 month in 2020 with complete vaccination date (last dose + 2 weeks) on or before May 31, 2021 were included.

Moderna was slightly more effective against COVID-19 infection starting shortly after the second dose and improved over time, with the need to vaccinate 1,047 people to prevent 1 infection at 30 days (aOR, 0.67; 95% CI, 0.63 to 0.71), decreasing to 290 at 90 days (aOR, 0.66; 95% CI, 0.60 to 0.73). However, the vaccines didn't differ in terms of protection against hospitalization, ICU admission, or death/transfer to hospice (aOR, 1.23; 95% confidence interval [CI], 0.67 to 2.25). A time-to-event analysis showed similar results, including for infection (adjusted hazard ratio [aHR], 0.69; 95% CI, 0.66 to 0.72) and composite ICU admission or death/hospice (aHR, 0.76; 95% CI, 0.50 to 1.16) and composite hospitalization, ICU admission, or death/hospice

(aHR, 0.67; 95% CI, 0.51 to 0.89). Stratified analyses were similar when including only never-infected patients, only those aged 65 and older, and only younger participants. Among participants, congestive heart failure (aHR, 1.52; 95% CI, 1.03 to 2.26), high blood pressure (aHR, 2.17; 95% CI, 1.30 to 3.62), and lymphoma (aHR, 7.03; 95% CI, 4.31 to 11.47) increased the odds of composite hospitalization, ICU admission, or death/hospice.



Comments: Delta infection was of very low prevalence when the data was collected, and therefore unlikely affected our comparative effectiveness results. However, as new VOCs emerge such as Omicron, VE will be impacted by their ability to evade vaccine-induced immunity. This analysis is restricted to commercially insured and Medicare Advantage beneficiaries from a single U.S. insurer. They were unable to measure SARS-CoV-2 infection that is not apparent in medical claims or via laboratory testing, which likely results in an overestimate of the vaccines' protective effects. This also includes the fact that the "time-to-infection" represents date of infection from their data (positive PCR test, or ICD-10 code of U07.1 in claims), rather than the date on which SARS-CoV-2 was contracted. Nonetheless both vaccines were very effective in preventing severe Covid-19. This evaluation needs to be updated for the Omicron wave.

Remdesivir and three other drugs for hospitalised patients with COVID-19: final results of the WHO Solidarity randomised trial and updated meta-analyses

Lancet published online May 2, 2022

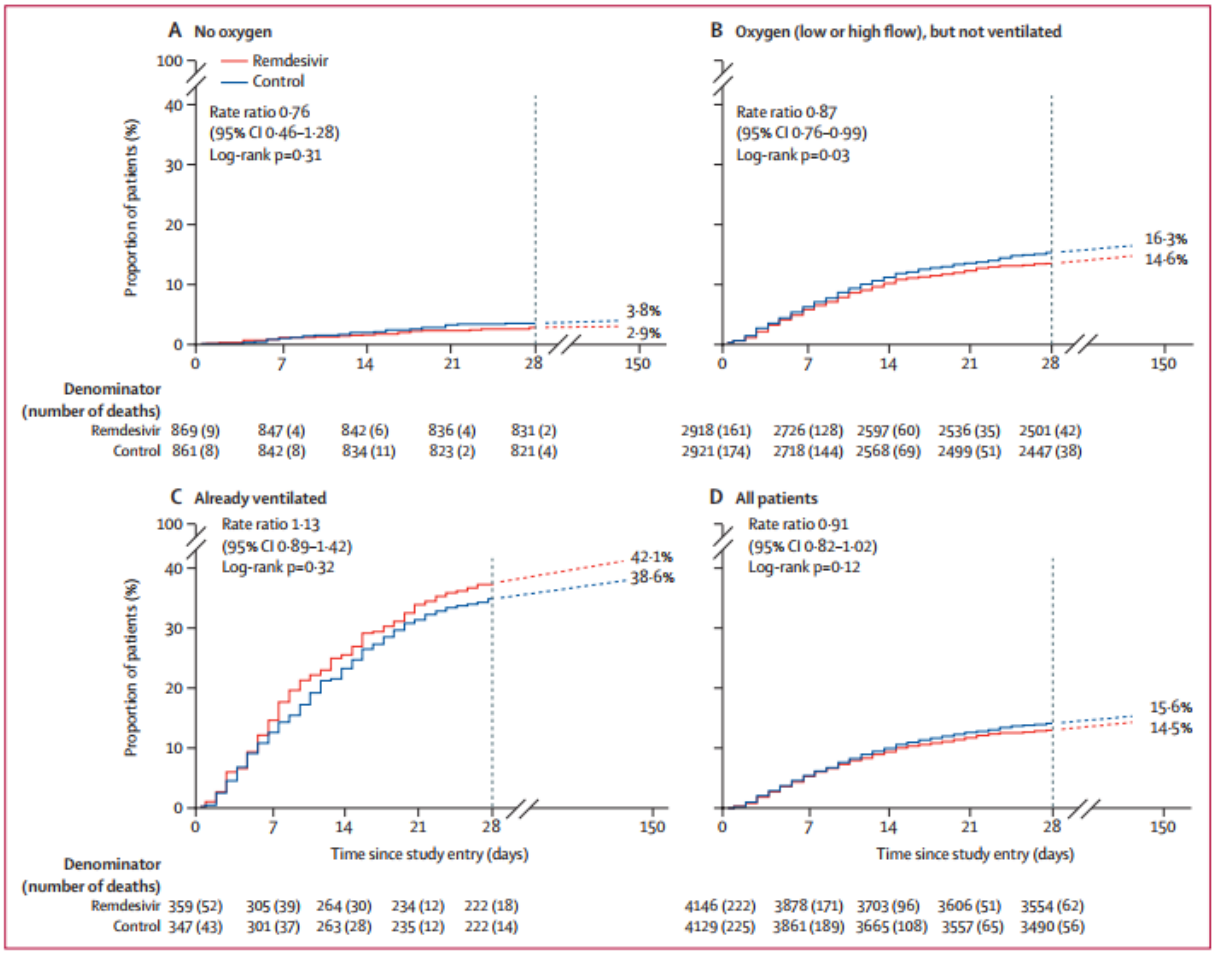
doi.org/10.1016/ S0140-6736(22)00519-0

The Solidarity trial among COVID-19 inpatients has previously reported interim mortality analyses for four repurposed antiviral drugs. Lopinavir, hydroxychloroquine, and interferon (IFN)-β1a were discontinued for futility but randomization to remdesivir continued. This publication reports the final results of Solidarity and meta-analyses of mortality in all relevant trials to date.

Solidarity enrolled consenting adults (aged ≥18 years) recently. Participants were randomly allocated, in equal proportions between the locally available options, to receive whichever of the four study drugs (lopinavir, hydroxychloroquine, IFN-β1a, or remdesivir) were locally available at that time or no study drug (controls). All patients also received the local standard of care. No placebos were given. The protocol specified primary endpoint was in-hospital mortality,

subdivided by disease severity. Secondary endpoints were progression to ventilation if not already ventilated, and time-to-discharge from hospital. Final log-rank and Kaplan Meier analyses are presented for remdesivir and are appended for all four study drugs. Meta-analyses give weighted averages of the mortality findings in this and all other randomized trials of these drugs among hospital inpatients.

Between March 22, 2020, and Jan 29, 2021, 14304 potentially eligible patients were recruited from 454 hospitals in 35 countries in all six WHO regions. Solidarity enrolled 14221 patients, including 8275 randomly allocated (1:1) either to remdesivir (ten daily infusions, unless discharged earlier) or to control. Overall, 602 (14·5%) of 4146 patients assigned to remdesivir died versus 643 (15·6%) of 4129 assigned to control (mortality rate ratio [RR] 0·91 [95% CI 0·82–1·02], p=0·12). Of those already ventilated, 151 (42·1%) of 359 assigned to remdesivir died versus 134 (38·6%) of 347 assigned to control (RR 1·13 [0·89–1·42], p=0·32). Of those not ventilated but on oxygen, 14·6% assigned to remdesivir died versus 16·3% assigned to control (RR 0·87 [0·76–0·99], p=0·03). Of 1730 not on oxygen initially, 2·9% assigned to remdesivir died versus 3·8% assigned to control (RR 0·76 [0·46–1·28], p=0·30). Combining all those not ventilated initially, 11·9% assigned to remdesivir died versus 13·5% assigned to control (RR 0·86 [0·76–0·98], p=0·02) and 14·1% versus 15·7% progressed to ventilation (RR 0·88 [0·77–1·00], p=0·04). The non-prespecified composite outcome of death or progression to ventilation occurred in 19·6% assigned to remdesivir versus 22·5% assigned to control (RR 0·84 [0·75–0·93], p=0·001). Allocation to daily remdesivir infusions (*vs* open-label control) delayed discharge by about 1 day during the 10-day treatment period. A meta-analysis of mortality in all randomized trials of remdesivir versus no remdesivir yielded similar findings.



Comment: Solidarity alone, or meta-analyses of all trials, suggest no mortality reduction in already-ventilated patients, but some mortality reduction (with a wide confidence interval) in patients who are receiving oxygen but are not ventilated. Unfortunately, high-flow versus low-flow oxygen were not recorded separately at enrolment into Solidarity, therefore, it was not known whether any protective effect in non-ventilated patients extends to those on high-flow oxygen. In the NIH trial (ACTT-1), subgroup analysis did not find benefit for patients on high-flow oxygen. In Solidarity and in the meta-analyses, there was low mortality (3%) in hospitalized patients with COVID-19 who were not receiving oxygen. This study was limited by not including data on days from illness onset to RDV administration, viral loads measured by cycle threshold values, viral antigen levels, and other factors. A recent trial has shown benefit in giving RDV for 3 days in the outpatient setting to prevent progression for high-risk patients who has symptoms for <7 days. See next article

Unravelling the Treatment Effect of Baricitinib on Clinical Progression and Resource Utilization in Hospitalized COVID-19 Patients: Secondary Analysis of the Adaptive COVID-19 Treatment Randomized Trial-2 OFID published April 22, 2022

The ACTT-2 trial randomized COVID-19 patients at 67 trial sites across 8 countries to treatment with BCT or RMT. This analysis was restricted to the 891 ACTT-2 participants who required any level of supplemental oxygen therapy at baseline. Participants in ACTT-2 were assessed daily

throughout hospitalization using an 8-category ordinal score (OS) scale. A participant's score for a given day represented the worst clinical status for that participant during the preceding 24 hours.

Overall, BCT resulted in more linear improvement and lower incidence of clinical deterioration compared with RMT (hazard ratio [HR], 0.74; 95% confidence interval [CI], 0.58–0.95). The benefit was pronounced among participants enrolled on high-flow oxygen or non-invasive positive pressure ventilation (OS 6; n = 216). In this group, BCT sped clinical improvement (HR, 1.21; 95% CI, 0.99–1.51) while slowing clinical deterioration (HR, 0.71; 95% CI, 0.48–1.02), which reduced the expected days in OS 6 per 100 patients by 74 days (95% CI, -8–154) and the expected days in OS 7 per 100 patients by 161 days (95% CI, 46–291) compared with RMT.

Among participants receiving low-flow oxygen therapy at enrollment (OS 5; n = 564), the clinical courses were consistent with a more direct path to recovery and lower total clinical burden among patients treated with BCT than those treated with RMT. Incidence of clinical deterioration was lower among patients given BCT (BCT, 22.9% vs RMT, 30.1%; HR, 0.75; 95% CI, 0.54-1.02). Though the majority of participants in baseline OS 5 eventually recovered in both arms (505 of 564), the initial change in clinical status was more often in a positive direction in the BCT arm. More patients receiving BCT exhibited linear improvement (75.0% vs 67.4%) and fewer patients transiently worsened prior to recovery.

On the contrary, BCT did not benefit participants who were mechanically ventilated at enrollment. The proportion of patients who recovered or required non-intensive care unit (ICU) level therapies at the end of follow-up was only modestly better compared with patients receiving RMT (BCT, 56% [30/54] vs RMT, 42% [24/57]). Accordingly, BCT was not shown to speed clinical improvement (HR, 1.05; 95% CI, 0.76-1.49) or slow clinical deterioration (HR, 0.89; 95% CI, 0.46-1.66) among participants in baseline OS 7.

Comment: The ACTT-2 Trial found that BCT sped recovery in hospitalized COVID-19 patients versus RMT. They examined how BCT affected progression throughout hospitalization and utilization of intensive respiratory therapies. Baseline OS 6 patients experienced the greatest benefit from BCT, and multistate models revealed that BCT had a multifaceted benefit in both speeding clinical improvement and impeding clinical deterioration in this group. Baseline OS 6 participants treated with BCT had a lower total clinical burden and significantly lower expected use of critical care-level respiratory therapy. They conclude that BCT use in OS 5 and OS 6 patients has the potential to reduce utilization of ICU-level support. Most participants in ACTT-2 were not treated with dexamethasone, as this was not part of the standard of care until the final weeks of study.

See NIH guidelines above

IDSA just updated their guidelines:

- Among hospitalized adults with severe* COVID-19, the IDSA panel suggests baricitinib with corticosteroids rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence)
- Among hospitalized patients with severe* COVID-19 who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone. (Conditional recommendation, Low certainty of evidence)

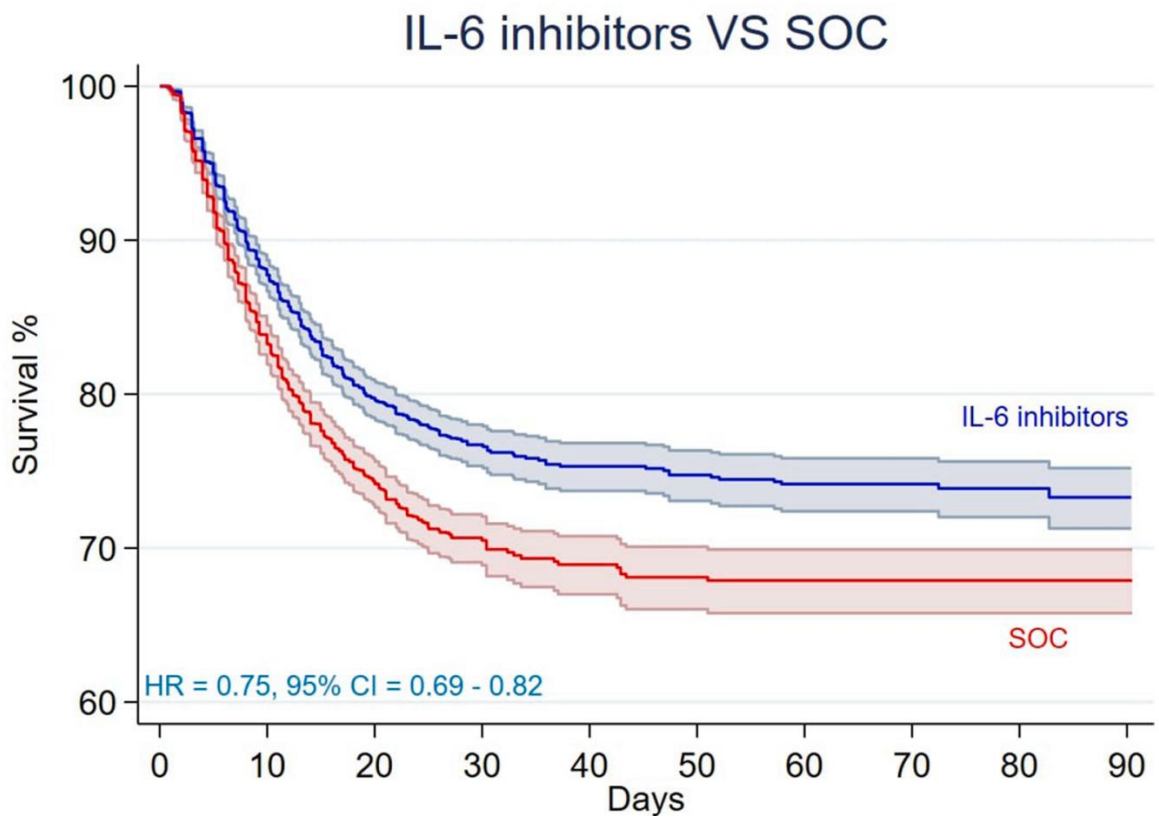
*Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation

See next article

Interleukin-6 inhibitors reduce mortality in coronavirus disease-2019: An individual patient data meta-analysis from randomized controlled trials Eur J Intern Med published online April 6, 2022

Randomized control trials (RCTs) comparing IL-6 inhibitors to SOC in hospitalized COVID-19 patients were deemed eligible

Eleven studies were identified, incorporating 7467 patients (IL-6 inhibitors: 4103, SOC: 3364). IL-6 inhibitors were associated with decreased risk for death compared to SOC at the one-stage meta-analysis (Hazard Ratio [HR]: 0.75, 95% Confidence interval [CI]: 0.69–0.82, p<0.0001) and the two-stage meta-analysis (HR: 0.85, 95%CI: 0.77–0.93, p<0.001, I2 = 0.0%). Meta-regression analysis revealed that the difference in OS between the two groups was not influenced by the mean age of patients. At secondary meta-analyses, IL-6 inhibitors were associated with decreased odds for intubation OR:0.74, 95%CI:0.65–0.85, p<0.001, $I2$=0.0%). IL-6 inhibitors were associated with increased odds for discharge compared to SOC (OR:1.28, 95% CI:1.15–1.42, p<0.001, $I2$=0.0%).



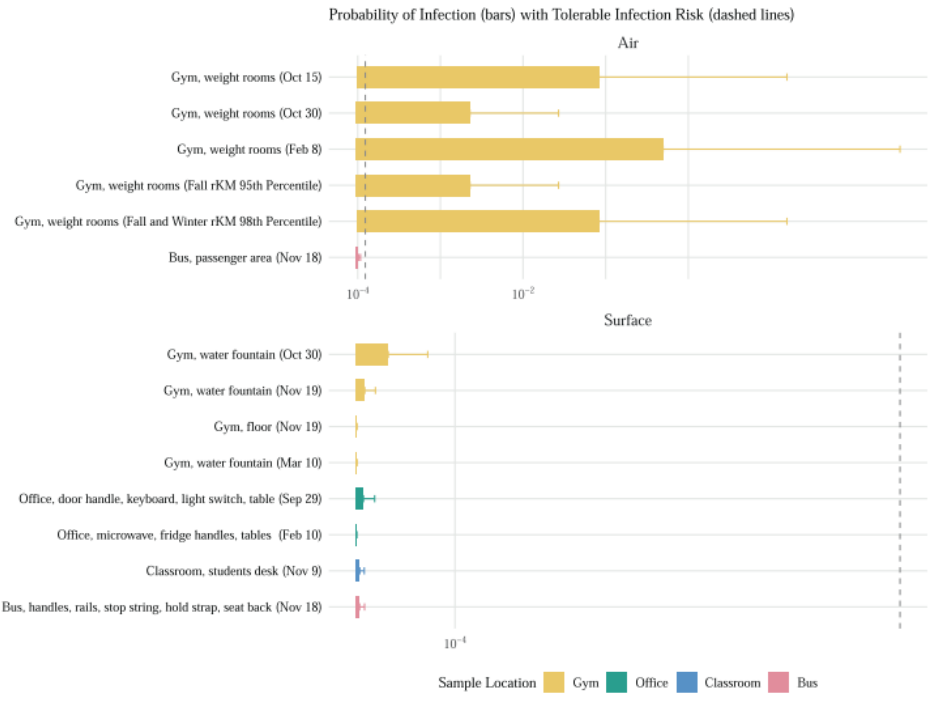
Comment: This meta-analysis of individual patient data from randomized trials shows that IL-6 inhibitors significantly reduce the risk of death compared to SOC. IL-6 inhibitors are also

associated with better outcomes in terms of intubation and discharge rates compared to SOC. There are several limitations in this study. Firstly, whereas their methodology allowed us to reconstruct IPD in terms of survival time and censoring status, it did not provide the authors with patient level prognostic covariates. Therefore, they were unable to examine the effect of the differences in SOC between the included studies in their findings. Lastly, they were unable to examine the notion that differences in each country-level COVID-19 peak incidence during the trial window might have confounded our finding. See NIH and IDSA guidance above

Monitoring SARS-CoV-2 in air and on surfaces and estimating infection risk in buildings and buses on a university campus J Exposure Science & Environmental Epidemiol published online April 27, 2022

Air and surface samples were collected using wetted wall cyclone bioaerosol samplers and swab kits, respectively, in a longitudinal environmental surveillance program from August 2020 until April 2021 on the University of Michigan. Quantitative RT-PCR with primers and probes targeting gene N1 were used for SARS-CoV-2 RNA quantification. The RNA concentrations were used to estimate the probability of infection by quantitative microbial risk assessment modeling and Monte-Carlo simulation.

In total, 256 air samples and 517 surface samples were collected during the study period, among which positive rates were 1.6% and 1.4%, respectively. Point-biserial correlation showed that the total case number on campus was significantly higher in weeks with positive environmental samples than in non-positive weeks ($p = 0.001$). The estimated probability of infection was about 1 per 100 exposures to SARS-CoV-2-laden aerosols through inhalation and as high as 1 per 100,000 exposures from contacting contaminated surfaces in simulated scenarios. The riskiest setting was the gym, with positive indications found for 75% of air samples and 50% of all surface samples. Most of the contaminated gym surfaces involved drinking fountain buttons; no samples taken from gym equipment turned up positive.



Comment: In this study, SARS-CoV-2 transmission was 1,000 times more likely from air versus surfaces. This matches clinical studies early on which indicated that surfaces were a minor contribution to transmission compared to aerosols. Given the lockdowns and policies in place to mitigate the spread of COVID-19 during the study, no samples were collected among a large aggregation of people, and some samples were collected when only a few people were present, so the negative results need to be interpreted with caution especially as the indoor activities are gradually back to prepandemic levels. The study was conducted on a university campus, so generalizable to the general population or other non-healthcare settings may not be applicable.

Efficacy and Safety of a Recombinant Plant-Based Adjuvanted Covid-19 Vaccine

N Engl J Med published online May 4, 2022

DOI: 10.1056/NEJMoa2201300

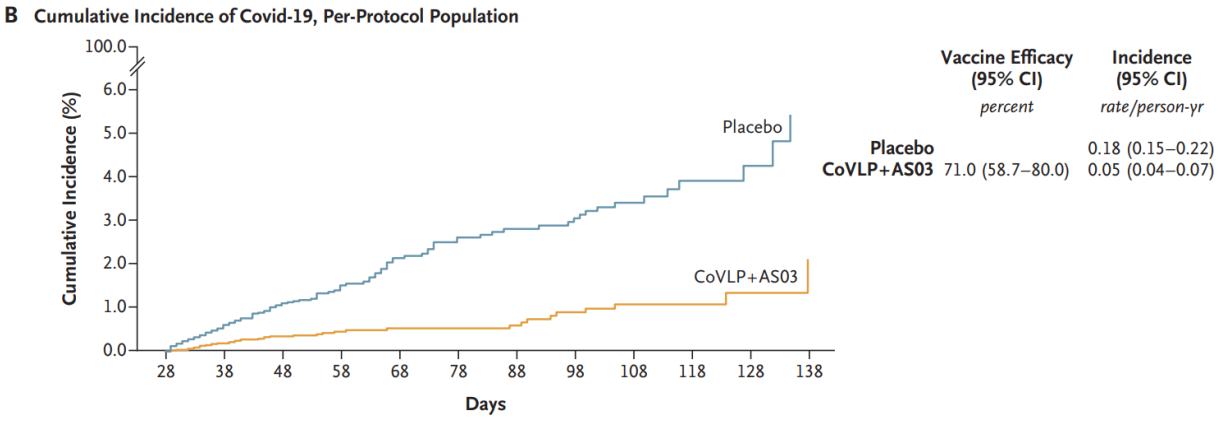
Efficacy and Safety of the RBD-Dimer–Based Covid-19 Vaccine ZF2001 in Adults

N Engl J Med published online May 4, 2022

DOI: 10.1056/NEJMoa2202261

The first vaccine is a plant-based particle vaccine, developed by Medicago/GSK, and was tested on participants in Argentina, Brazil, Canada, Mexico, the United Kingdom, and the United States from Mar 15 to Sep 2, 2021. The vaccine, CoVLP, was administered in two shots 21 days apart, and results were compared to placebo. The study continued until at least 160 COVID-19 cases were detected in participants at least 7 days following the second dose of vaccine.

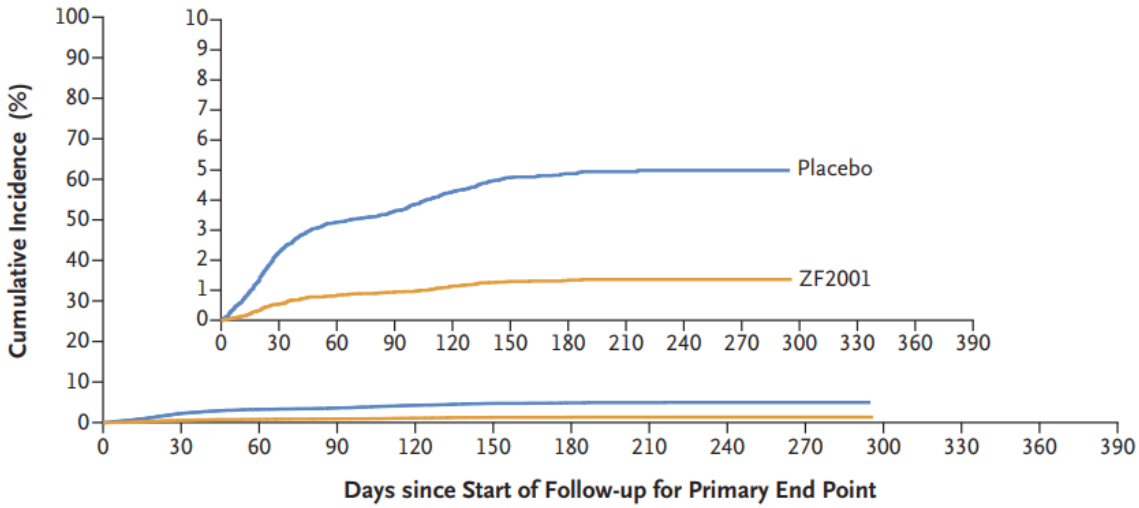
A total of 24,141 volunteers participated in the trial. Vaccine efficacy was 69.5% (95% confidence interval [CI], 56.7% to 78.8%) against any symptomatic COVID-19 caused by five variants that were identified by sequencing, the authors found. Results were even stronger for efficacy against moderate-to-severe disease, at 78.8% (95% CI, 55.8% to 90.8%). No severe cases or deaths were recorded in the vaccine group. The vaccine group had more adverse effects, but none were severe.



The second vaccine, ZF2001, was tested at 31 clinic sites in Uzbekistan, Indonesia, Pakistan, and Ecuador, and later in China. The vaccine is made by Anhui Zhifei Longcom of China.

Participants were randomized to receive placebo or three injections of vaccine administered 30 days apart. The trial took place from Dec 12, 2020, to Dec 15, 2021.

Only 158 of 12,625 participants in the ZF2001 group contracted COVID-19 during the trial, compared with 580 of 12,568 participants in the placebo group. Vaccine efficacy against infection was 75.7% (95% CI, 71.0% to 79.8%) and 87.6% (95% CI, 70.6% to 95.7%) against severe to critical disease. Two participants in the vaccine group, and 12 in the placebo group, died of COVID-19, resulting in an 86.5% (95% CI, 38.9% to 98.5%) efficacy rate against death. Genotype sampling from COVID-19 cases in the study showed primarily Delta, Alpha, and B.1.617.3 variants. The authors said vaccine efficacy was 76.1% (95% CI, 70.0% to 81.2%) against Delta, 88.3% (95% CI, 66.8% to 97.0%) against Alpha, and 75.2% (95% CI, 55.3% to 87.0%) against Kappa



Comment: Neither trial assessed how well the vaccines performed against asymptomatic infections, and both had very few participants over the age of 60. Bottom line, these new vaccines need further testing.