Infectious Diseases Watch

April 4, 2022

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General Infectious Disease

Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

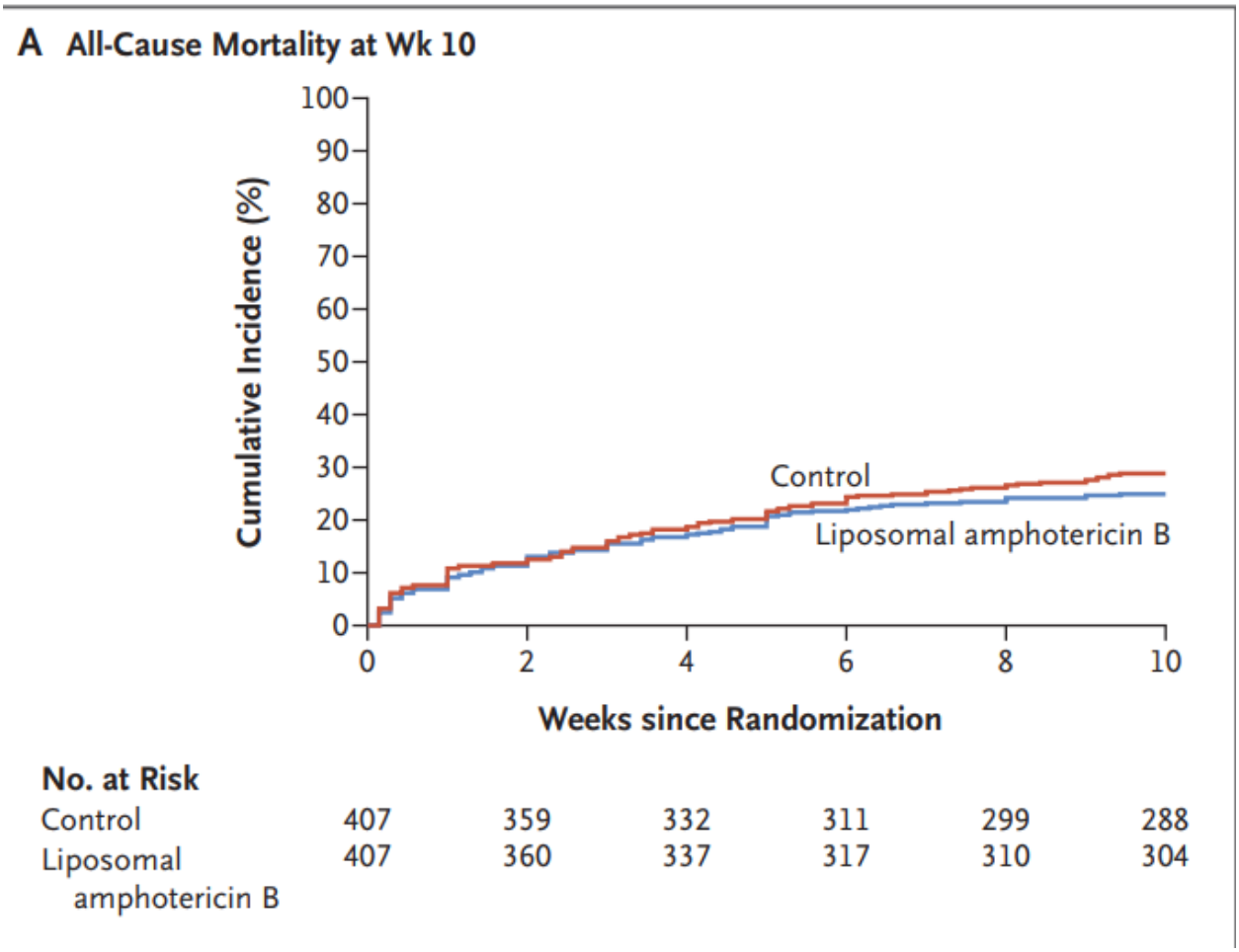
N Engl J Med 2022;386:1109-20

DOI: 10.1056/NEJMoa2111904

This is a phase 3 noninferiority RCT conducted in five African countries. They assigned HIV-positive adults with cryptococcal meningitis in a 1:1 ratio to receive either a single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1 plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or the current WHO–recommended treatment, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control). The primary end point was death from any cause at 10 weeks; the trial was powered to show noninferiority at a 10-percentage-point margin.

A total of 844 HIV-positive adults with a first episode of cryptococcal meningitis based on a positive India ink stain or cryptococcal antigen test were randomized; after 30 were excluded, the intention-to-treat population comprised 814 participants (407 in each treatment group). For the per-protocol analysis, 30 more individuals were excluded.

In the intention-to-treat and per-protocol analyses, 10-week mortality was 24.8% and 24.5%, respectively, in the liposomal amphotericin B group and 28.7% and 28.5% in the control group; both analyses fell within the prespecified noninferiority margin. Fungal clearance was similar in both groups, but fewer participants in the liposomal amphotericin B group had grade 3 or 4 adverse events.



Comment: In this trial, a single-dose liposomal amphotericin B combined with flucytosine, and fluconazole was noninferior to the WHO-recommended treatment for HIV-associated cryptococcal meningitis and was associated with fewer adverse events. This finding has clear benefit in resource-limited areas. However, some regions may not have access to liposomal amphotericin B. In addition, given success of the trial I do not see any reason that this regiment cannot be offered to patients everywhere as an alternative to the traditional 1- 2 weeks of receiving amphotericin B.

Antimicrobial Susceptibility Survey of Invasive Neisseria meningitidis, United States 2012–2016 J Infect Dis published March 10, 2022

doi.org/10.1093/infdis/jiac046

The incidence of invasive meningococcal disease (IMD) has declined in the U.S. but still carries a mortality of nearly 16%. Antibiotic management includes both treatment with empiric ceftriaxone or cefotaxime and prevention using rifampin, ciprofloxacin, or ceftriaxone. Although uncommon, multiple phenotypes characterized by reduced antibiotic susceptibility have been reported. To identify confirmed cases of IMD in the US, CDC investigators used two databases: The Active Bacterial Core Surveillance system (ABCs), consisting of information from 2012–

2016 on 44 million persons, and the Enhanced Meningococcal Diseases Surveillance (EMDS), including data from 2015–2016 on 98% of the population. Antimicrobial susceptibility testing was subsequently performed on the isolates.

All *N. meningitidis* isolates were fully susceptible to cefotaxime, ceftriaxone, meropenem, rifampin, minocycline, and azithromycin. In the EMDS, reduced susceptibility to penicillin was seen in 31.5% of isolates, and 0.8% were fully resistant. For ciprofloxacin, 99.2% of isolates were fully susceptible; however, two were intermediate and two were fully resistant. Similar results were seen for the ABCs data.

Table 2. Antimicrobial susceptibility of isolates from invasive meningococcal disease cases, collected through Enhanced Meningococcal Disease Surveillance, United States, 2015–2016 (n=508[a])

	n (%)				MIC (µg/ml)		
	S	I	R	NS	MIC Range	MIC50	MIC90
Ampicillin	360 (70.9)	146 (28.7)	2 (0.4)	n/a	≤0.06 - >16	≤0.06	0.25
Penicillin	344 (67.7)	160 (31.5)	4 (0.8)	n/a	≤0.03 - >8	0.06	0.25
Cefotaxime	508 (100)	0 (0)	0 (0)	0 (0)	≤0.06 - 0.12	≤0.06	≤0.06
Ceftriaxone	508 (100)	0 (0)	0 (0)	0 (0)	≤0.06 - 0.12	≤0.06	≤0.06
Meropenem	508 (100)	0 (0)	0 (0)	0 (0)	≤0.12	≤0.12	≤0.12
Ciprofloxacin	504 (99.2)	2 (0.4)	2 (0.4)	n/a	≤0.015-4	≤0.015	≤0.015
Levofloxacin	504 (99.2)	2 (0.4)	2 (0.4)	n/a	≤0.015-4	≤0.015	≤0.015
Rifampin	508 (100)	0 (0)	0 (0)	n/a	≤0.25 - 0.5	≤0.25	≤0.25
Minocycline	508 (100)	0 (0)	0 (0)	n/a	≤0.25 - 1	≤0.25	0.5
Azithromycin	508 (100)	0 (0)	0 (0)	n/a	≤0.25 - 2	≤0.25	≤0.25
Trimethoprim-sulfamethoxazole	208 (40.9)	18 (3.5)	282 (55.5)	n/a	≤0.06/1.19 - >4/76	1/19	4/76

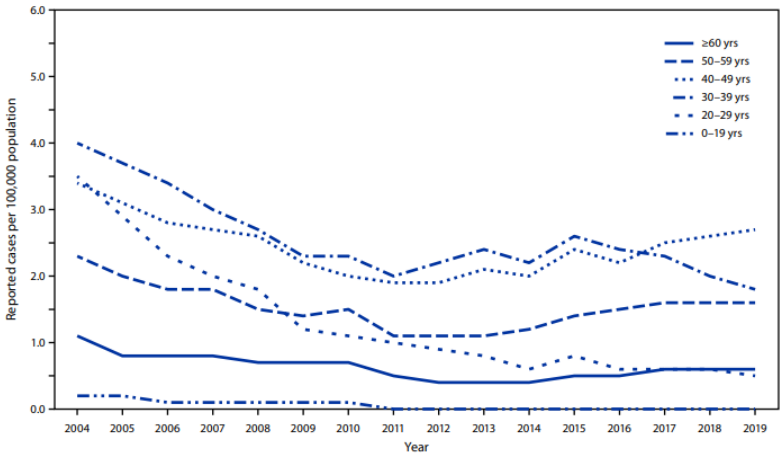
Comment: Although invasive meningococcal disease has been decreasing in US, this report highlights the concern for decreasing penicillin susceptible. The increasing penicillin-intermediate N. meningitidis population observed and the detection of the novel β-lactamase-producing, penicillin- and ciprofloxacin-resistant strain in 2019– 2020, (MMWR 2020; 69: 735-9) highlight the continued importance of N. meningitidis AMR surveillance in the United States. The good news is that 3rd GC and rifampin remain fully active.

Universal Hepatitis B Vaccination in Adults Aged 19–59 Years: Updated Recommendations of the Advisory Committee on Immunization Practices — United States, 2022 MMWR 2022; 71: 477-483

Approximately one half of acute hepatitis B cases reported in 2019 occurred among persons aged 30–49 years (see below). The number of cases of acute hepatitis B has increased among adults aged ≥40 years, particularly among those aged 40–49 years, for whom the rate of reported cases increased from 1.9 per 100,000 population in 2011 to 2.7 per 100,000 population in 2019. The rate among adults aged 50–59 years increased 45.5% during the same period (from 1.1 to 1.6 per 100,000 population) and accounted for 22.2% of reported cases in 2019. Acute HBV infections among adults leads to chronic hepatitis B disease in an estimated 2%–6% of cases. HepB vaccination coverage among adults aged ≥19 years is low. In 2018, self-reported HepB vaccination coverage (≥3 doses) among adults aged ≥19 years was 30.0% (MMWR 2021;70:1–26). HepB vaccination coverage (≥3 doses) was 40.3% for adults aged 19–49 years and only 19.1% for adults aged ≥50 years. In addition, only HepB vaccination coverage among adults with risk factors has been suboptimal. In 2018, self-reported coverage

(≥3 doses) was 33.0% among adults with chronic liver disease, 38.9% among travelers to countries where HBV infections have been endemic since 1995, 33.0% among adults with diabetes aged 19–59 years, and 67.2% among health care personnel.

Therefore, HepB vaccination is now recommended for adults aged 19–59 years and adults aged ≥60 years with risk factors for hepatitis B. Adults aged ≥60 years without known risk factors for hepatitis B may also receive HepB vaccines (Box). Infants and all other persons aged <19 years are already recommended to receive HepB vaccines.



All infants

Persons aged <19 years

Adults aged 19–59 years

Adults aged ≥60 years with risk factors for hepatitis B:

- Persons at risk for infection by sexual exposure
  - Sex partners of persons testing positive for HBsAg
  - Sexually active persons who are not in a long-term, mutually monogamous relationship (e.g., persons with more than one sex partner during the previous 6 months)
  - Persons seeking evaluation or treatment for a sexually transmitted infection
  - Men who have sex with men
- Persons at risk for infection by percutaneous or mucosal exposure to blood
  - Persons with current or recent injection drug use
  - Household contacts of persons testing positive for HBsAg
  - Residents and staff members of facilities for persons with developmental disabilities
  - Health care and public safety personnel with reasonably anticipated risk for exposure to blood or blood-contaminated body fluids
  - Persons on maintenance dialysis, including in-center or home hemodialysis and peritoneal dialysis, and persons who are predialysis
  - Persons with diabetes at the discretion of the treating clinician
- Others
  - International travelers to countries with high or intermediate levels of endemic hepatitis B virus infection (HBsAg prevalence of ≥2%)
  - Persons with hepatitis C virus infection
  - Persons with chronic liver disease (including, but not limited to, persons with cirrhosis, fatty liver disease, alcoholic liver disease, autoimmune hepatitis, and an alanine aminotransferase or aspartate aminotransferase level greater than twice the upper limit of normal)
  - Persons with HIV infection
  - Persons who are incarcerated

Adults aged ≥60 years without known risk factors for hepatitis B may receive hepatitis B vaccines

Abbreviation: HBsAg = hepatitis B surface antigen.

Comment: Universal adult HepB vaccination through age 59 years removes the need for risk factor screening and disclosure and could increase vaccination coverage and decrease hepatitis B cases. This appears to be a good revision based on recent infection rates. The challenge is execution.

COVID-19

COVID-19 News

FDA Authorized Second Booster

The FDA on March 29 amended emergency use authorizations to clear second booster doses of Pfizer and Moderna's COVID-19 vaccines for people 50 and older.

The agency said the additional shots are authorized to be administered at least four months after receiving the first booster among those in the designated age group, according to a news release. The FDA also authorized a second booster of Pfizer's vaccine for those 12 and older with certain immunocompromising conditions and a second booster of Moderna's vaccine among immunocompromised adults. This means some immunocompromised people would be able to get a fifth shot, as the primary series for this group includes three doses and one booster had already been approved.

Later on the CDC. updated its vaccine guidance to note that second boosters were now allowed. The CDC said the option of another dose was "especially important for those 65 and older and those 50 and older with underlying medical conditions that increase their risk for severe disease from Covid-19 as they are the most likely to benefit from receiving an additional booster dose at this time." About one-third of people aged 50 to 65 have significant medical conditions

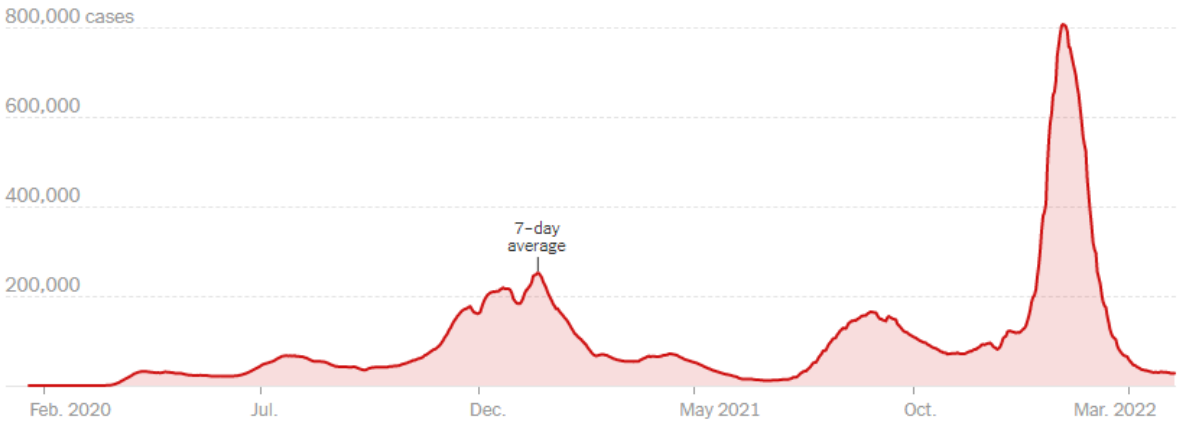
Comment: Neither the FDA nor the CDC convened its outside committee of experts to evaluate the new policy, sparking some criticism. The FDA made the decision with very limited data, largely from Israel. The strongest data in support of a second booster came from a newly released Israeli study that has not yet been peer reviewed. (See below Res Sq) Some experts believe this study is deeply flawed. (See comments after article review) Another study reviewed in ID Watch last month demonstrated that each additional dose only offers marginal value and short lived, but in a younger population. Therefore, a second booster dose in younger, healthy groups (<65 years) appears to have minimal effect in both boosted effectiveness against infection and reducing viral loads. This recommendation also assumes there are no unintended consequences of a second booster. [risk appears to be very low] Lastly, we need to clarify the goal of our vaccination program including boosters. Is it to continually boost neutralizing antibody protection against infection? Or is it to prevent severe illness, hospitalizations, and deaths and reduce the burden on our healthcare system?

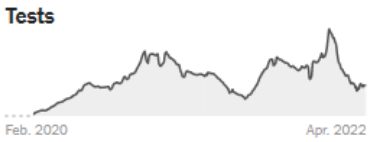
So, who should consider getting a second booster now? First only if 4-5 months since the first booster and… I have listed some recommendations to consider:

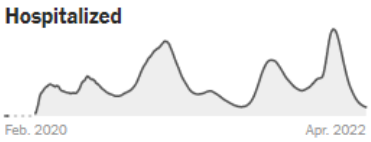
1. If you are over age 65
2. If you are over age 50 with several underlying high-risk medical conditions.
3. If you're in close contact with someone who is immunocompromised or elderly and want to avoid exposing them to Covid-19, you may want to get a second booster.
4. Your profession: If you work in a job where you are in constant close contact with large numbers of people and you're at higher risk of being exposed to Covid-19 especially healthcare.
5. Cases in your community
6. If you got your first booster it may make sense to time your second one to before a riskier time or event, such an international travel.
7. If I got my first booster and had a breakthrough Omicron case, there is no reason to get a second booster dose at this time since natural infection acts like a booster

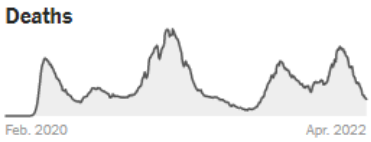
<u>While providing booster vaccine doses to high-risk groups may be beneficial, it is still critical to vaccinate those who have not yet been vaccinated to achieve sustainable control of Covid- 19 and prevent further morbidity and mortality.</u>

COVID-19 by the Numbers

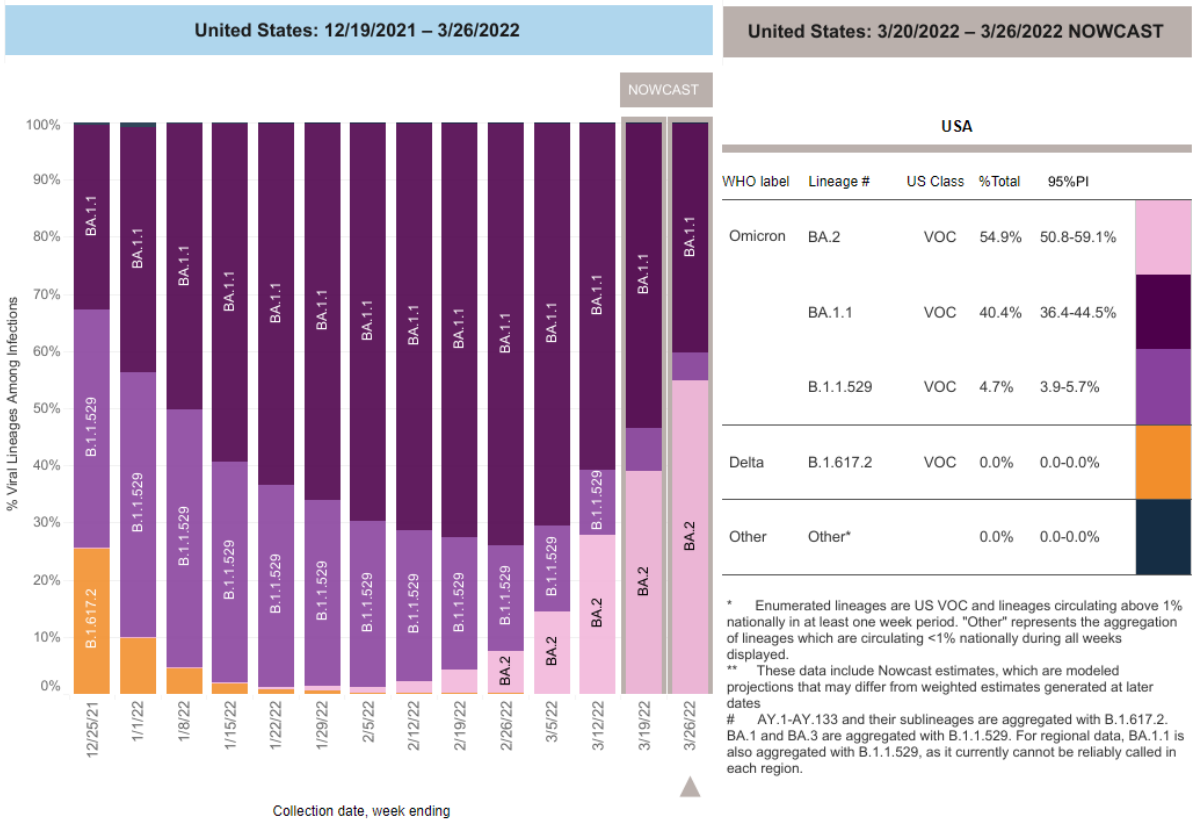








	DAILY AVG. ON APR. 2	14-DAY CHANGE	TOTAL REPORTED
Cases	27,431	-7%	80,051,976
Tests	910,522	+16%	—
Hospitalized	16,194	-29%	—
In I.C.U.s	2,491	-37%	—
Deaths	651	-42%	979,988



Comment: BA.2 is up to 55%. Reports of new cases in the US are still declining, though the decline has slowed. More than a dozen states have seen cases increase in cases over the past two weeks, including most of the Northeast. However, most states continue to see sustained declines, and cases remain at their lowest levels nationally since last July. Hospitalizations and deaths also continue to fall. In the past two weeks, hospitalizations have decreased by 33% and deaths decreased by over 40%.

COVID-19 Journal Review

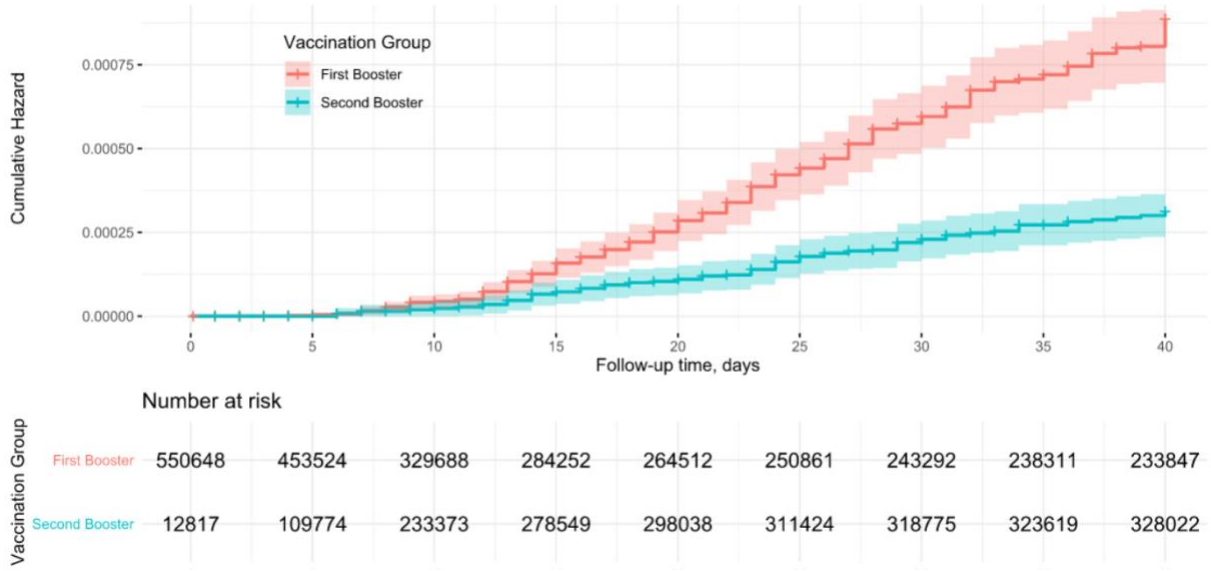
Second Booster Vaccine and Covid-19 Mortality in Adults 60 to 100 Years Old

Research Square posted online March24, 2022

This is a retrospective cohort study which included all members of Clalit Health Services, aged 60 to 100, eligible for the second booster. Mortality due to Covid-19 among participants who received the second booster was compared with participants who received one booster dose. A Cox proportional-hazards regression model with time-dependent covariates was used to estimate the association between the second booster and death due to Covid-19 while adjusting for demographic factors and coexisting illnesses. For each participant in the study, the following

sociodemographic data were extracted: age, sex, demographic group (general Jewish population, ultra-Orthodox Jewish population, or Arab population and socioeconomic status.

A total of 563,465 participants met the eligibility criteria. Of those, 328,597 (58%) received a second-booster dose during the 40-day study period. Death due to Covid-19 occurred in 92 second-booster recipients and in 232 participants who received one booster dose (adjusted hazard ratio 0.22; 95% CI 0.17 to 0.28). Among participants aged 60 to 69, death from Covid-19 occurred in 5 of 111,776 participants in the second-booster group and 32 of 123,786 participants in the first-booster group (adjusted hazard ratio, 0.16; 95% CI, 0.06 to 0.41; P<0.001). Among participants aged 70 to 79, death from Covid-19 occurred in 22 of 134,656 participants in the second-booster group and 51 of 74,717 participants in the first-booster group (adjusted hazard ratio, 0.28; 95% CI, 0.17 to 0.46; P<0.001)



Comment: This study demonstrates a reduction in Covid-19 mortality by the second booster in eligible subjects. The observed effect of a 78% reduction in mortality rates was somewhat lower than the observed effect of the first booster dose on mortality in the elderly population in Israel (90%). (N Engl J Med. 2021; 385:2413-2420) In the study in Res Sq fewer than 1 in 200 people over 60 who got Omicron ended up with severe disease after three doses. A fourth dose further reduced that likelihood, but the effect was driven by those with major risk factors. One of the limitations of the study is a relatively short period (40 days) of follow-up. In addition, during this time, the infection rate in Israel from the omicron variant rose to be the highest in the world. Moreover, during this period, almost no social-distancing restrictions were imposed on the public in Israel. Therefore, exposure to SARS-CoV-2 was substantial, and accordingly, the number of Covid-19 severe events was sufficient to demonstrate significant associations between the second booster dose and reduced Covid-19 mortality rates. Participants were all volunteers which may introduce a bias since the subjects who volunteered are more likely to be more careful about their health. The main demographic groups in Israel – the general population, the Ultra-Orthodox Jewish population, and the Arab population, also manifest different health-related behavioral patterns. An example, the investigators observed significantly lower uptake of the second booster in minority population sectors. They used regression

analysis adjusted for these subpopulations to try and overcome possible bias. During the study time period medical centers tested every patient for SARS-CoV-2 on admission. Therefore, it is possible that participants in this study died from other causes and incidentally tested positive for Covid-19. In the US during the Omicron wave only ~ 50% of admissions were actually due to Covid-19. Since this was a retrospective cohort study, confounding clinical and sociodemographic characteristics may have biased the observed effectiveness. Lastly, an important drawback of this study is the absence of safety data, as it was out of the scope of the study.

BNT162b2 Protection against the Omicron Variant in Children and Adolescents N Engl J Med published online March 30, 2022

DOI: 10.1056/NEJMoa2202826

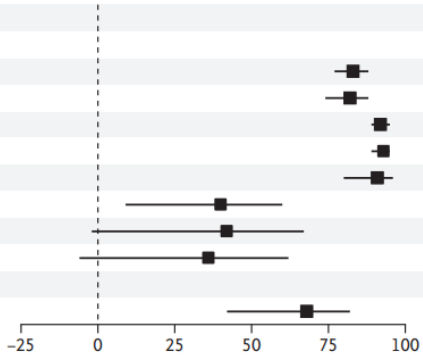
This study involved 1,185 COVID-19 patients admitted to 31 US pediatric hospitals and 1,627 controls aged 5 to 18 years admitted for other indications. The 918 adolescents were enrolled from July 1 to December 18, 2021 (Delta variant era) and from Dec 19, 2021, to Feb 17, 2022 (Omicron era).

The 267 children aged 5 to 11 were enrolled only during the Omicron period because the Pfizer vaccine wasn't authorized for that age-group until October 2021. Owing to insufficient numbers of severely ill patients in this age-group, VE against critical illness—defined as those who required life support, such as mechanical ventilation—could not be evaluated.

Among the 1,185 total hospitalized patients, 1,043 (88%) were unvaccinated, 291 (25%) required life support, and 14 (1.2%) died. Of 12- to 18-year-olds, 87% were unvaccinated, 27% were critically ill, of whom 2% needed extracorporeal membrane oxygenation (ECMO) (93% of them were unvaccinated), and 13 died. Among children 5 to 11 years, 92% were unvaccinated and 16% needed life support (90% unvaccinated), including 2 who required ECMO and 1 who died. VE) of two doses of the Pfizer vaccine given at least 14 days earlier against COVID-19 hospitalization among 12- to 18-year-olds in the Delta-dominant period was 93% (95% confidence interval [CI], 89% to 95%) 2 to 22 weeks after vaccination and 92% (95% CI, 80% to 97%) at 23 to 44 weeks.

In the Omicron-dominant period, VE was 40% (95% CI, 9% to 60%) against hospitalization, 79% (95% CI, 51% to 91%) against critical COVID-19, and 20% (95% CI, −25% to 49%) against noncritical illness among 12- to 18-year-olds after a median interval of 162 days since vaccination. Among patients aged 5 to 11, VE against Omicron hospitalization was 68% (95% CI, 42% to 82%) at a median of 34 days after vaccination.

Subgroup	Vaccinated Case Patients	Vaccinated Control Patients	Vaccine Effectiveness (95% CI)
	no. of patients/total no. (%)		%
Adolescents 12–18 yr of age			
Age group			
12–15 yr	63/543 (12)	313/828 (38)	83 (77 to 88)
16–18 yr	59/375 (16)	229/529 (43)	82 (74 to 88)
Delta-predominant period	33/684 (5)	442/1161 (38)	92 (89 to 95)
2–22 wk since vaccination	25/676 (4)	372/1091 (34)	93 (89 to 95)
23–44 wk since vaccination	6/657 (1)	60/779 (8)	92 (80 to 97)
Omicron-predominant period	89/234 (38)	100/196 (51)	40 (9 to 60)
2–22 wk since vaccination	35/180 (19)	39/135 (29)	43 (–1 to 68)
23–44 wk since vaccination	52/197 (26)	59/155 (38)	38 (–3 to 62)
Children 5–11 yr of age			
Omicron-predominant period	20/267 (7)	50/270 (19)	68 (42 to 82)



Comment: The evidence in this study clearly shows that vaccination reduces this risk substantially in 5- to 11-year-olds. While vaccination provided adolescents with lower protection against hospitalization with omicron versus delta, it still prevented severe disease from both variants. They could not evaluate vaccine effectiveness after a booster dose because eligibility for booster doses was not expanded to include adolescents 12 to 15 years of age until January 2022, and only a small number of patients received a booster dose during the surveillance period in this analysis. As of March 16, 2022, only 57% of 12- to 18-year-olds and 27% of those aged 5 to 11 had received two Pfizer doses.

Effect of Early Treatment with Ivermectin among Patients with Covid-19 N Engl J Med published online March 30, 2022

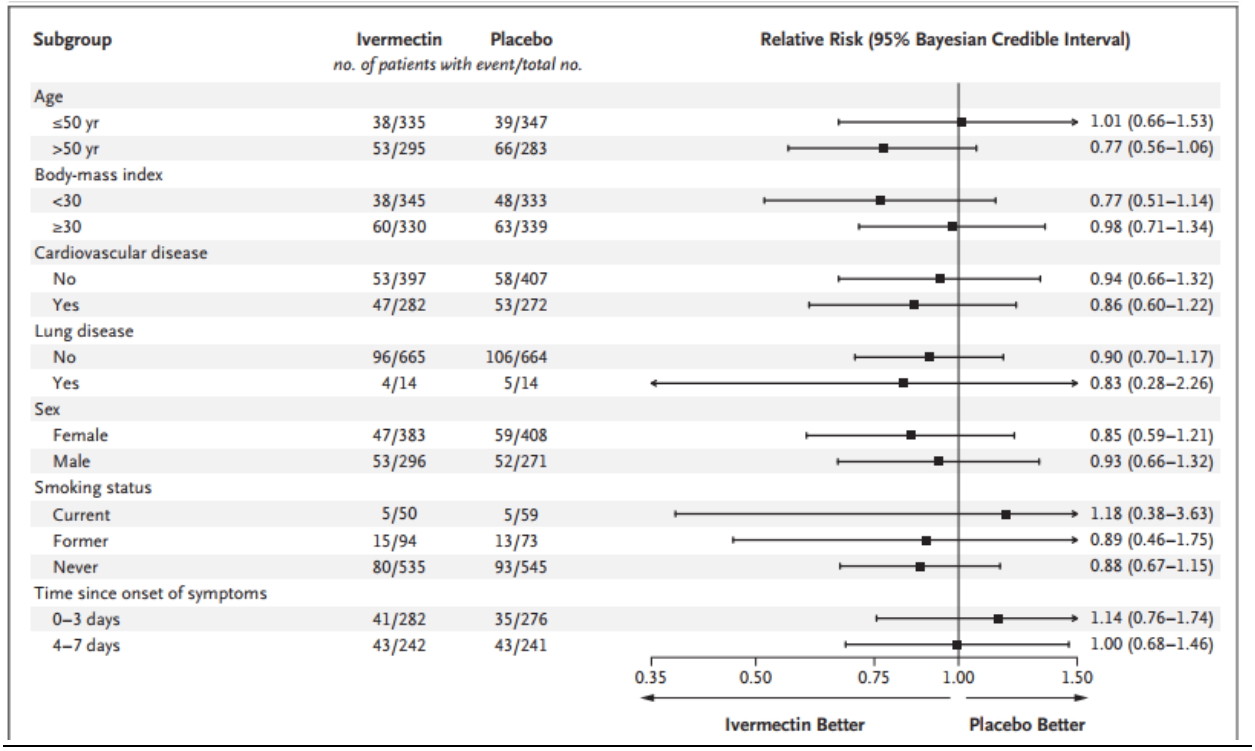
DOI: 10.1056/NEJMoa2115869

The investigators conducted a double-blind, randomized, placebo-controlled, adaptive platform trial involving symptomatic SARS-CoV-2–positive adults recruited from 12 public health clinics in Brazil. Patients who had had symptoms of Covid-19 for up to 7 days and had at least one risk factor for disease progression were randomly assigned to receive ivermectin (400 μg per kilogram of body weight) once daily for 3 days or placebo. The primary composite outcome was hospitalization due to Covid-19 within 28 days after randomization or an emergency department visit due to clinical worsening of Covid-19 within 28 days after randomization.

A total of 3515 patients were randomly assigned to receive ivermectin (679 patients), placebo (679), or another intervention (2157). Overall, 100 patients (14.7%) in the ivermectin group had a primary-outcome event, as compared with 111 (16.3%) in the placebo group (relative risk, 0.90; 95% Bayesian credible interval, 0.70 to 1.16).

Of the 211 primary-outcome events, 171 (81.0%) were hospital admissions. Findings were similar to the primary analysis in a modified intention-to-treat analysis that included only patients who received at least one dose of ivermectin or placebo (relative risk, 0.89; 95% Bayesian credible interval, 0.69 to 1.15) and in a per-protocol analysis that included only patients who reported 100% adherence to the assigned regimen (relative risk, 0.94; 95% Bayesian credible

interval, 0.67 to 1.35). There were no significant effects of ivermectin use on secondary outcomes or adverse events.



Comment: The results of this study was reviewed in the WSJ several weeks ago before publication and reported in ID Watch March 21, 2022. The evidence supporting the role of ivermectin in the treatment of Covid-19 has been inconsistent at best. The WHO has concluded, on the basis of results obtained before this trial, that there existed only very-low-certainty evidence regarding ivermectin and thus recommended against the use of ivermectin for the treatment of patients with Covid-19 outside the clinical trial setting. The NIH stated there is insufficient evidence for the COVID-19 Treatment Guidelines Panel to recommend either for or against the use of ivermectin for the treatment of COVID-19. The IDSA Guidelines state**:** In hospitalized or outpatient patients with COVID-19, the IDSA panel suggests against ivermectin outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence) The findings in this trial are consistent with these guidelines. This study goes a long way in demonstrating the lack of efficacy of ivermectin in a properly conducted trial.

Early Outpatient Treatment for Covid-19 with Convalescent Plasma N Engl J Med published online March 30, 2022

DOI: 10.1056/NEJMoa2119657

This is a multicenter, double-blind, RCT. They evaluated the efficacy and safety of Covid-19 convalescent plasma, as compared with control plasma, in symptomatic adults (≥18 years of age) who had tested positive for SARS-CoV-2, regardless of their risk factors for disease progression or vaccination status. Participants had to be enrolled within 8 days after symptom onset and received a transfusion within 1 day after randomization. The primary outcome was

Covid-19–related hospitalization within 28 days after transfusion. Transfusion of Covid-19 convalescent plasma had to contain >1:320 SARS-CoV-2 anti–spike protein antibody levels.

Participants were enrolled from June 3, 2020, through October 1, 2021. [pre-Omicron] A total of 1225 participants underwent randomization, and 1181 received a transfusion. 44% of these participants received a transfusion within 5 days. In the prespecified modified intention-to-treat analysis that included only participants who received a transfusion, the primary outcome occurred in 17 of 592 participants (2.9%) who received convalescent plasma and 37 of 589 participants (6.3%) who received control plasma (absolute risk reduction, 3.4 percentage points; 95% confidence interval, 1.0 to 5.8; P=0.005), which corresponded to a relative risk reduction of 54%. 53 of the 54 participants with Covid-19 who were hospitalized were unvaccinated and 1 participant was partially vaccinated.

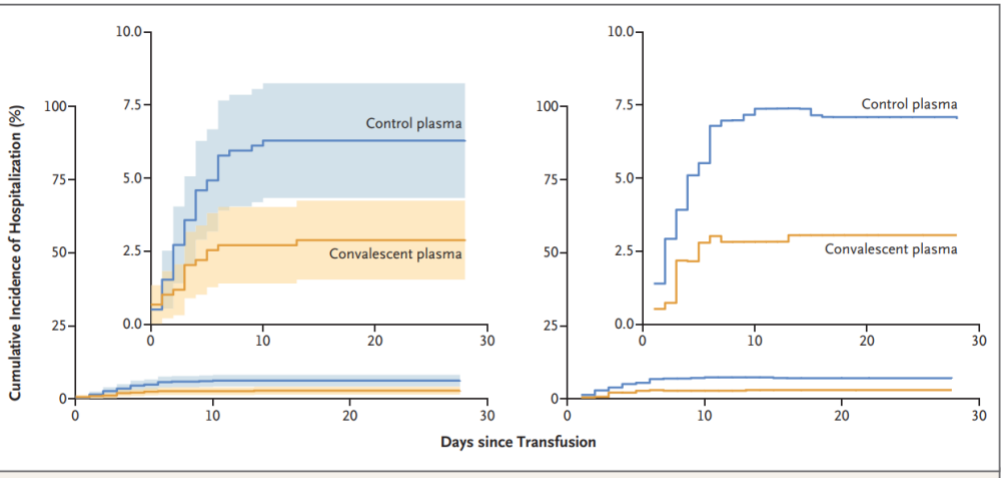


Figure 2. Cumulative Incidence of Coronavirus Disease 2019–Related Hospitalization.
On the left, the results of the unadjusted analysis are shown. Shading indicates the 95% confidence interval. On the right, estimates according to the adjusted targeted minimum loss–based estimation model are shown. The insets show the same data on an expanded y axis.

Comment: The findings in this study are similar to the efficacy of monoclonal antibodies[regeneron] against SARS-CoV-2.(N Engl J Med 2021;384:238-51) The population in this study included participants who had had symptoms for up to 8 days, whereas the recent trial of sotrovimab included participants who had had symptoms for 5 days or less,(N Engl J Med 2021;385:1941-50) and a trial of bamanivimab plus etesevimab was limited to infusion within 3 days after a diagnosis of SARS-CoV-2 infection. (N Engl J Med 2021; 385:1382-92) In a subgroup analysis in this trial, early transfusion (administration ≤5 days after symptom onset) appeared to be associated with a greater reduction in the risk of hospitalization. The investigators point out although monoclonal antibodies are available in high-income countries, they are expensive to produce, require time for new drug approval, and may not be widely available during Covid-19 surge conditions. In contrast, Covid-19 convalescent plasma is available in low-income and middle-income countries, and relatively inexpensive to produce. A few points to consider. First the incidence of hospitalization in the control-plasma group was 6.3%, which is lower than the incidence of hospitalization among persons with Covid-19 in the US (approximately 8%). Second, only 35% of the participants who received a transfusion were 50 years of age or older. Last, the trial was not large enough for definitive subgroup analyses according to medical coexisting conditions or pregnancy.

With the continued evolving SARS-CoV-2 variants with the potential resistance to currently available monoclonal antibodies, the potential usefulness of developing capacity for the

availability and distribution of Covid-19 convalescent plasma, especially locally sourced, which should include antibodies to circulating strains may be worth considering. The NIH Covid-19 Guidelines state there is insufficient evidence for the Panel to recommend either for or against the use of COVID-19 convalescent plasma for the treatment of COVID-19 in nonhospitalized patients infected with SARS-CoV-2. The IDSA Covid-19 Guidelines state that among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)

Utility of Follow-up COVID-19 Antigen Tests After Acute SARS-CoV-2 Infection Among Healthcare Personnel Clin Infect Dis published online March 30, 2022

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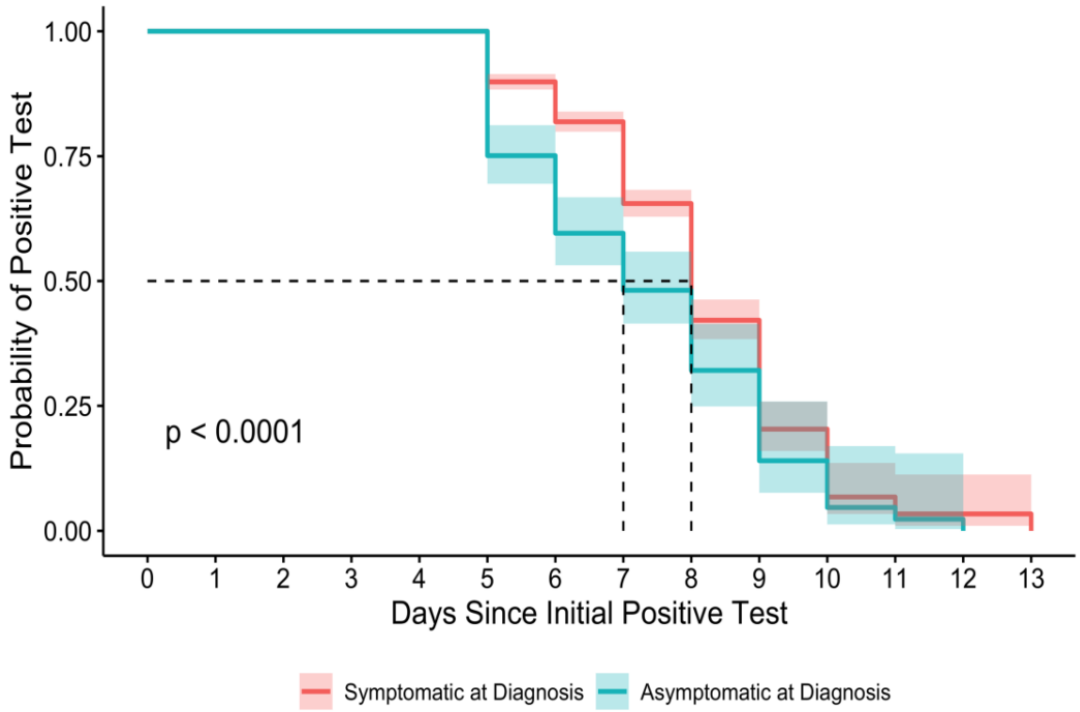
This is a retrospective cohort study involving all Mayo Clinic sites who were diagnosed with Covid-19 between January 3, 2022, and January 22, 2022. All HCWs underwent a rapid Ag test for return-to-work purposes.

Employee demographics and exposures of interest including age, sex, prior SARS-CoV-2 infection, vaccination status, presence of symptoms at diagnosis, source of infection (if known), and healthcare worker category (job with or without patient contact) were included. Vaccination timing and status was determined from Mayo Clinic occupational health records. Vaccine status at the time of infection was categorized as “Up to date” when initial vaccination was completed at least 2 weeks prior to diagnosis and a booster dose has been received or is not, “booster overdue” when initial vaccination was completed at least 2 weeks prior to diagnosis, and a booster dose is overdue; “Partially vaccinated” when at least one dose of vaccine was received but initial vaccination series was not complete or was completed less than 2 weeks prior to diagnosis; and “Unvaccinated” when no vaccine doses have been received. The primary outcome was the timing of the first negative Ag test after the initial positive molecular test. Employees were offered a rapid Ag test if they met certain criteria: 1) ≥5 days since symptom onset, or from an initial positive COVID-19 molecular test if asymptomatic at the time of diagnosis, 2) no fever for at least 24 hours without fever-reducing medications, 3) no current symptoms or mild residual symptoms that were improving, 4) not moderately or severely immunosuppressed or severe/critical SARS-CoV-2 infection, and 5) anticipated to work on campus. If the employee tested positive by rapid Ag test at day ≥5 were not allowed to return to work and instructed to repeat the rapid Ag 24-72 hours later.

There were 1661 employees with a new positive SARS-CoV-2 diagnostic test between January 3 and January 22, 2022, who subsequently underwent rapid Ag a median of six days after the initial positive test. The initial rapid Ag was positive in 1076 (64.8%) individuals. Among those individuals, a second rapid Ag was performed in 585 (54.4%) individuals at a median of 7 days after their initial diagnostic SARS-CoV-2 test. Sixty- four HCW completed >2 rapid Ag between day 5 and 9 after initial positive test. Compared to employees with a negative rapid Ag, those with a positive rapid Ag were significantly more likely to have reported symptoms at the time of diagnosis ($p<0.01$) HCW with a positive rapid Ag were more likely to have direct patient contact and be up to date on Covid-19 vaccination. Compared to standard 10-day isolation,

rapid Ag reduced time by 2 days on average. Return-to-work test on day 5 was negative for only 199 (11.9%) of HCWs



Comment: These findings have significant implications for management of infected HCW. There are prior studies [reported in ID Watch over the last few months] that correlate positive rapid Ag with positive viral culture and the potential for transmission of SARS-CoV-2 infection. Based on this study, a significant percentage of infected HCW may continue to shed high concentrations of SARS-CoV-2 during days 5 to 10 after their initial diagnosis. This study demonstrates that rapid Ag can be used to guide return-to- work decisions safely for HCWs. These findings do not support a time-based return to work strategy shorter than 10 days. Given the increased transmissibility of the Omicron variant as well as the at-risk populations cared for by HCWs I support the addition of rapid Ag as a condition to return to work. I raised this concern when the CDC reduced isolation to 5 days and then later added testing if possible at day 5. It is critical to decrease the possibility of nosocomial transmission to patients by HCWs.