Good morning

Today a brief mention that patients can now receive their COVID-19 vaccine and flu shot during the same visit.

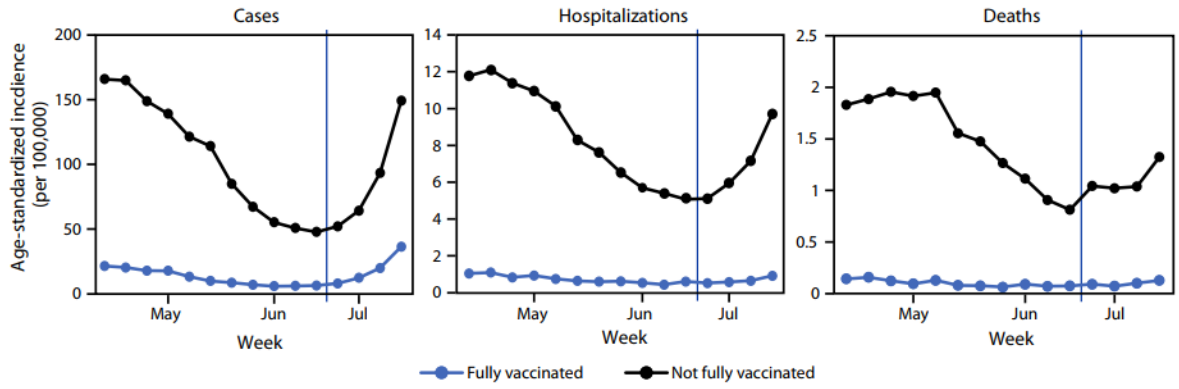
Under Journal Review several articles all published by CDC in MMWR on vaccine effectiveness. The next article is a very important article from Israel on natural immunity versus vaccine-induced immunity. The last article is an opinion piece in Lancet on evidence for boosters.

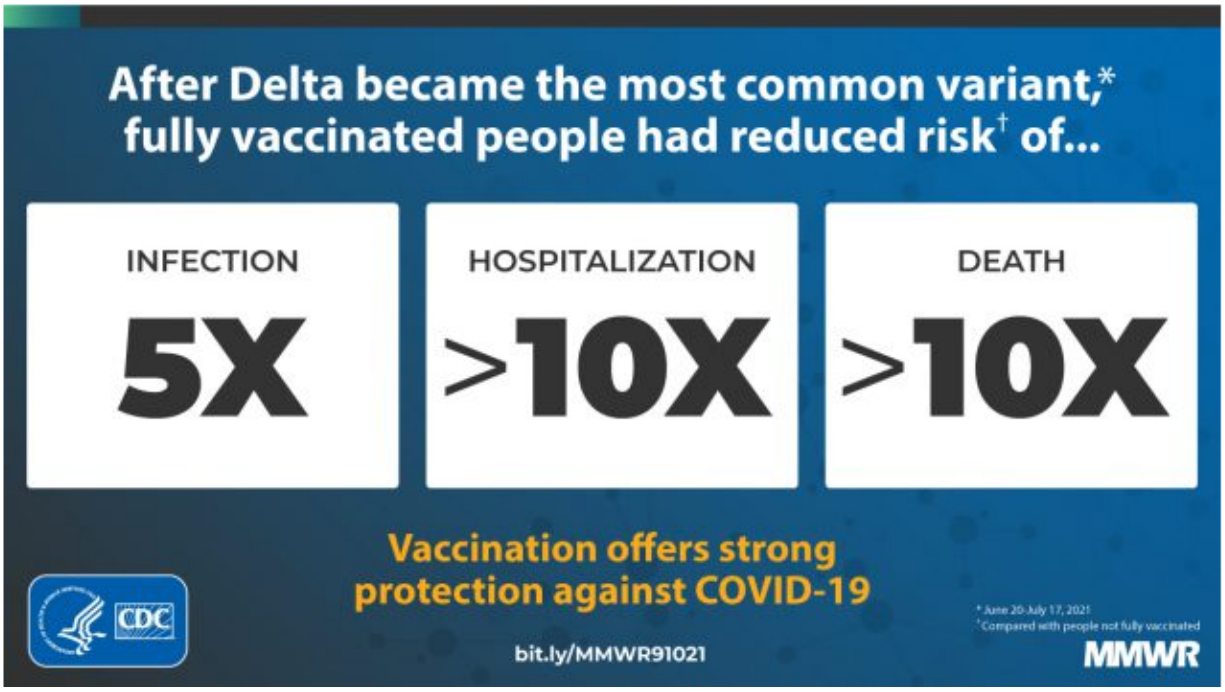
Have a great day

Ed

Flu and COVID-19 Vaccines Can Be Given on the Same Day: CDC and AAP
Patients can now receive their COVID-19 vaccine and flu shot during the same visit, according to updated recommendations by the CDC. Previously, the CDC recommended that people receive their COVID-19 vaccinations alone and schedule any other vaccinations at least 2 weeks before or after their COVID-19 immunization. However, sufficient data have now been collected regarding the safety of COVID-19 vaccines currently approved or authorized by FDA.

Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status — 13 U.S. Jurisdictions, April 4-July 17, 2021
MMWR September 10, 2021
Reported COVID-19 cases, hospitalizations, and deaths occurring among persons aged ≥18 years during April 4-July 17, 2021, were analyzed by vaccination status across 13 U.S. jurisdictions that routinely linked case surveillance and immunization registry data. Averaged weekly, age-standardized incidence rate ratios (IRRs) for cases among persons who were not fully vaccinated compared with those among fully vaccinated persons decreased from 11.1 (95% confidence interval [CI] = 7.8–15.8) to 4.6 (95% CI = 2.5–8.5) between two periods when prevalence of the Delta variant was lower (<50% of sequenced isolates; April 4–June 19) and higher (≥50%; June 20–July 17), and IRRs for hospitalizations and deaths decreased between the same two periods, from 13.3 (95% CI = 11.3–15.6) to 10.4 (95% CI = 8.1–13.3) and from 16.6 (95% CI = 13.5–20.4) to 11.3 (95% CI = 9.1–13.9).





Comment: Findings were consistent with a potential decline in vaccine protection against confirmed SARS-CoV-2 infection and continued strong protection against COVID-19-associated hospitalization and death. Bottom line vaccines work – getting vaccinated protects against severe illness from COVID-19, including the Delta variant. Since this is an ecological study, IRRs lacked multivariable adjustments and causality could not be assessed (i.e., possible differences in testing or behaviors in vaccinated and unvaccinated persons). Data assessed from 13 jurisdictions accounted ~ 25% of the US population, and therefore might not be generalizable.

Interim Estimates of COVID-19 Vaccine Effectiveness Against COVID-19-Associated Emergency Department or Urgent Care Clinic Encounters and Hospitalizations Among Adults During SARS-CoV-2 B.1.617.2 (Delta) Variant Predominance — Nine States, June-August 2021
MMWR September 10, 2021
Eligible medical encounters were defined as those among adults aged ≥18 years who had received SARS-CoV-2 molecular testing (primarily reverse transcription-polymerase chain reaction assay within 14 days before or 72 hours after the admission or encounter) and a COVID-19-like illness discharge diagnosis. Vaccination status was documented in electronic health records and immunization registries. Full vaccination was defined as receipt of the second dose of Pfizer or Moderna mRNA vaccines, or a single dose of J&J vaccine ≥14-days before the testing or encounter date. Patients who had received no COVID-19 vaccine doses were considered unvaccinated.

In this analysis of 32,867 patient visits in nine states, the investigators found that even as the Delta variant predominated, vaccines still had an overall effectiveness rate of 86% at preventing hospitalizations, though they were less protective for adults aged 75 and over.

Comment: These findings confirm the high protection of vaccines against moderate and severe COVID-19 resulting in ED, UC, and hospital visits and underscore the importance of full COVID-19 vaccination and continued benefits of COVID-19 vaccination even during Delta variant wave. Consistent with the Israel experience with Pfizer, vaccine efficacy may decline especially in the older population. VE by time

since vaccination was not examined; therefore, further evaluation of possible waning of vaccine protection is limited but currently underway. Second, VE for partial vaccination was not assessed. See next article.

Effectiveness of Covid-19 Vaccines in Ambulatory and Inpatient Care Settings
N Engl J Med published online September 8, 2021
DOI: 10.1056/NEJMoa2110362
The investigators conducted a study involving adults (≥50 years of age) with Covid-19-like illness who underwent molecular testing for SARS-CoV-2. They assessed 41,552 admissions to 187 hospitals and 21,522 visits to 221 emergency departments or urgent care clinics during the period from January 1 through June 22, 2021, in multiple states. The patients' vaccination status was documented in electronic health records and immunization registries. They used a test-negative design to estimate vaccine effectiveness by comparing the odds of a positive test for SARS-CoV-2 infection among vaccinated patients with those among unvaccinated patients. Vaccine effectiveness (VE) was adjusted with weights based on propensity – for vaccination scores and according to age, geographic region, calendar time (days from January 1, 2021, to the index date for each medical visit), and local virus circulation.

The effectiveness of mRNA vaccination (≥14 days after the second dose) was 89% (95% confidence interval [CI], 87 to 91) against laboratory confirmed SARS-CoV-2 infection leading to hospitalization, 90% (95% CI, 85 to 93) against infection leading to an ICU admission, and 91% (95% CI, 89 to 93) against infection leading to an emergency department or urgent care clinic visit. The effectiveness of full vaccination with respect to a Covid-19-associated hospitalization or emergency department or urgent care clinic visit was similar with the Pfizer and Moderna vaccines and ranged from 81% to 95% among adults 85 years of age or older, persons with chronic medical conditions, and Black or Hispanic adults. The effectiveness of the J&J vaccine was 68% (95% CI, 50 to 79) against laboratory confirmed SARS-CoV-2 infection leading to hospitalization and 73% (95% CI, 59 to 82) against infection leading to an emergency department or urgent care clinic visit. mRNA-based vaccines were highly effective among adults who were 85 years of age or older and persons with chronic medical conditions. mRNA-based vaccines were similarly effective with respect to Covid-19-associated hospitalization and an emergency department or urgent care clinic visit for Black and Hispanic subjects. In addition, the effectiveness of full mRNA-based vaccination remained consistently high at least until 112 days after the second dose, which was the longest interval since vaccination during our study period.

Comment: In this publication Covid-19 vaccines in the US were shown to be highly effective against SARS-CoV-2 infection requiring hospitalization, ICU admission, or an emergency department or urgent care clinic visit. This vaccine effectiveness extended to populations that are disproportionately affected by SARS-CoV-2 infection. The percentage of patients who were clinically tested for SARS-CoV-2 by molecular assay differed across network partners and clinical settings, and VE estimates may be biased if clinicians make testing decisions based on vaccination status. The circulation of SARS-CoV-2 variants of concern increased during the study period, and we were unable to evaluate whether vaccine effectiveness differed according to SARS-CoV-2 lineages. Most of the observations were done during the alpha wave before delta. The VE only went out to 4 months.

Effectiveness of COVID-19 mRNA Vaccines Against COVID-19-Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1-August 6, 2021
MMWR September 10, 2011 Article provided by Maria C. Rodriguez-Barradas
During February 1-August 6, 2021, adults aged ≥18 years hospitalized at five VAMCs (in Atlanta, Georgia; Bronx, New York; Houston, Texas; Los Angeles, California; and Palo Alto, California) were screened for

inclusion in this test-negative case-control assessment. Patients were eligible for inclusion if they had COVID-19-like illness (i.e., fever, new or worsened cough or shortness of breath, loss of taste or smell, oxygen saturation on room air <94%, requirement for noninvasive ventilation or endotracheal intubation with mechanical ventilation, or chest radiograph or computed tomography pulmonary findings consistent with pneumonia) and a molecular test PCR or isothermal nucleic acid amplification test for SARS-CoV-2 performed within 14 days before admission or during the first 72 hours of hospitalization. The first SARS-CoV-2 test within this eligibility period was considered the qualifying test. Patients with COVID-19-like illness who received a positive SARS-CoV-2 test result were included as case-patients, and those with COVID-19-like illness with negative SARS-CoV-2 test results were included as controls.

The adjusted effectiveness of full vaccination in preventing COVID-19-associated hospitalization during the entire evaluation period (February 1-August 6, 2021) was 86.8% (95% CI = 80.4%–91.1%). The adjusted vaccine effectiveness among persons admitted to the hospital before Delta variant predominance (February 1-June 30) (84.1%; 95% CI = 74.1%–90.2%) was similar to vaccine effectiveness during Delta variant predominance (July 1-August 6) (89.3%; 95% CI = 80.1%–94.3%). The estimated vaccine effectiveness among persons aged ≥65 years (79.8%; 95% CI = 67.7%–87.4%) was lower than among persons aged 18-64 years (95.1%; 95% CI = 89.1%–97.8%), and no difference was found between persons who had completed the full vaccination series <90 days (86.1%; 95% CI = 76.5%–91.8%) versus ≥90 days (87.2%; 95% CI = 78.2%–92.5%) before their SARS-CoV-2 test date. Adjusted vaccine effectiveness estimates were also similar for Black (86.9%; 95% CI = 76.9%–92.6%) and White persons (88.1%; 95% CI = 77.4%–93.8%), as well as for Pfizer (83.4%; 95% CI = 74.0%–89.4%) and Moderna vaccines (89.3%; 95% CI = 80.1%–94.3%).

Characteristic	Case-patients vaccinated/total	Controls vaccinated/total	Adjusted vaccine effectiveness % (95% CI)
Overall	**54/388 (13.9)**	**378/787 (48.0)**	**86.8 (80.4–91.1)**
Age group, yrs			
18–64	10/199 (5.0)	93/275 (33.8)	95.1 (89.1–97.8)
≥65	44/189 (23.3)	285/512 (55.7)	79.8 (67.7–87.4)
Race/Ethnicity¶			
Black, non-Hispanic	24/195 (12.3)	169/379 (44.6)	86.9 (76.9–92.6)
White, non-Hispanic	21/141 (14.9)	171/334 (51.2)	88.1 (77.4–93.8)
COVID-19 vaccine product among fully vaccinated			
BNT162b2 (Pfizer-BioNTech)	43/388 (11.1)	242/787 (30.7)	83.4 (74.0–89.4)
mRNA-1273 (Moderna)	11/388 (2.8)	136/787 (17.3)	91.6 (83.5–95.7)
Date of hospital admission			
February 1–June 30	22/270 (8.1)	249/618 (40.3)	84.1 (74.1–90.2)
July 1–August 6	32/118 (27.1)	129/169 (76.3)	89.3 (80.1–94.3)
No. of days since fully vaccinated			
<90 days	19/388 (4.9)	215/787 (27.3)	86.1 (76.5–91.8)
≥90 days	35/388 (9.0)	163/787 (20.7)	87.2 (78.2–92.5)

Comment: COVID-19 vaccine protection against hospitalization before Delta variant predominance was similar to vaccine effectiveness during Delta variant predominance. There was a decline with age, to 80% for those aged 65 and older, down from 95% for adults aged 18 to 64. This is consistent with the article above. These articles taken together provide evidence that a third dose may be indicated in persons over age 65.

Comparing SARS-CoV-2 Natural Immunity to Vaccine-Induced Immunity: Reinfections Versus Breakthrough Infections

medRxiv published online August 24, 2021
doi.org/10.1101/2021.08.24.21262415;
The investigators conducted a retrospective observational study comparing three groups: (1) SARS-CoV-2-naïve individuals who received a two-dose regimen of the Pfizer vaccine, (2) previously infected individuals who have not been vaccinated, and (3) previously infected *and* single dose vaccinated individuals. Three multivariate logistic regression models were applied. In all models they evaluated 4 outcomes: SARS-CoV-2 infection, symptomatic disease, COVID-19-related hospitalization and death. The follow-up period was June 1 to August 14, 2021, when the Delta variant was dominant in Israel.

SARS-CoV-2-naïve vaccinees had a 13.06-fold (95% CI, 8.08 to 21.11) increased risk for breakthrough infection with the Delta variant compared to those previously infected, when the first event (infection or vaccination) occurred during January and February of 2021. The increased risk was significant (P<0.001) for symptomatic disease as well. When allowing the infection to occur at any time before vaccination (from March 2020 to February 2021), evidence of waning natural immunity was demonstrated, though SARS-CoV-2 naïve vaccinees had a 5.96-fold (95% CI, 4.85 to 7.33) increased risk for breakthrough infection and a 7.13-fold (95% CI, 5.51 to 9.21) increased risk for symptomatic disease. SARS-CoV-2-naïve vaccinees were also at a greater risk for COVID-19-related-hospitalizations compared to those that were previously infected. Individuals who were both previously infected with SARS-CoV-2 and given a single dose of the vaccine gained additional protection against the Delta variant.

Comment: This study demonstrated that natural immunity confers longer lasting and stronger protection against infection, symptomatic disease and hospitalization caused by the Delta variant of SARS-CoV-2, compared to the Pfizer two-dose vaccine-induced immunity. This analysis addressed protection afforded solely by Pfizer vaccine, and therefore does not address other vaccines or long-term protection following a third dose, of which is underway in Israel. Additionally, this is an observational real-world study, where PCR screening was not performed by protocol, therefore might be underestimating asymptomatic infections, as these individuals may not get tested. If this study is correct, we need to be thinking about immunity passports which honors natural immunity rather than vaccine passports. In addition, one dose is probably adequate after natural infection. See next article.

Considerations in Boosting COVID-19 Vaccine Immune Responses
Lancet published online September 13, 2021 highlights
doi.org/10.1016/ S0140-6736(21)02046-8

- Boosting could be appropriate for some individuals in whom the primary vaccination, defined here as the original one-dose or two-dose series of each vaccine, might not have induced adequate protection—e.g., recipients of vaccines with low efficacy or those who are immunocompromised.
- Boosting might ultimately be needed in the general population because of waning immunity to the primary vaccination or because variants expressing new antigens have evolved to the point at which immune responses to the original vaccine antigens no longer protect adequately against currently circulating viruses
- Although the benefits of primary COVID-19 vaccination clearly outweigh the risks, there could be risks if boosters are widely introduced too soon, or too frequently, especially with vaccines that can have immune-mediated side-effects (such as myocarditis, which is more common after the second dose of some mRNA vaccines, or Guillain-Barre syndrome, which has been associated with adenovirus-vectored COVID-19 vaccines.)

- Current evidence does not, therefore, appear to show a need for boosting in the general population, in which efficacy against severe disease remains high. Even if humoral immunity appears to wane, reductions in neutralizing antibody titer do not necessarily predict reductions in vaccine efficacy over time, and reductions in vaccine efficacy against mild disease do not necessarily predict reductions in the (typically higher) efficacy against severe disease.
- Although vaccines are less effective against asymptomatic disease or against transmission than against severe disease, even in populations with fairly high vaccination rates the unvaccinated are still the major drivers of transmission and are themselves at the highest risk of serious disease.
- Thus, any decisions about the need for boosting or timing of boosting should be based on careful analyses of adequately controlled clinical or epidemiological data, or both, indicating a persistent and meaningful reduction in severe disease, with a benefit–risk evaluation that considers the number of severe cases that boosting would be expected to prevent, along with evidence about whether a specific boosting regimen is likely to be safe and effective against currently circulating variants.
- They conclude that none of the data on vaccines so far provides credible evidence in support of boosters for the general population.

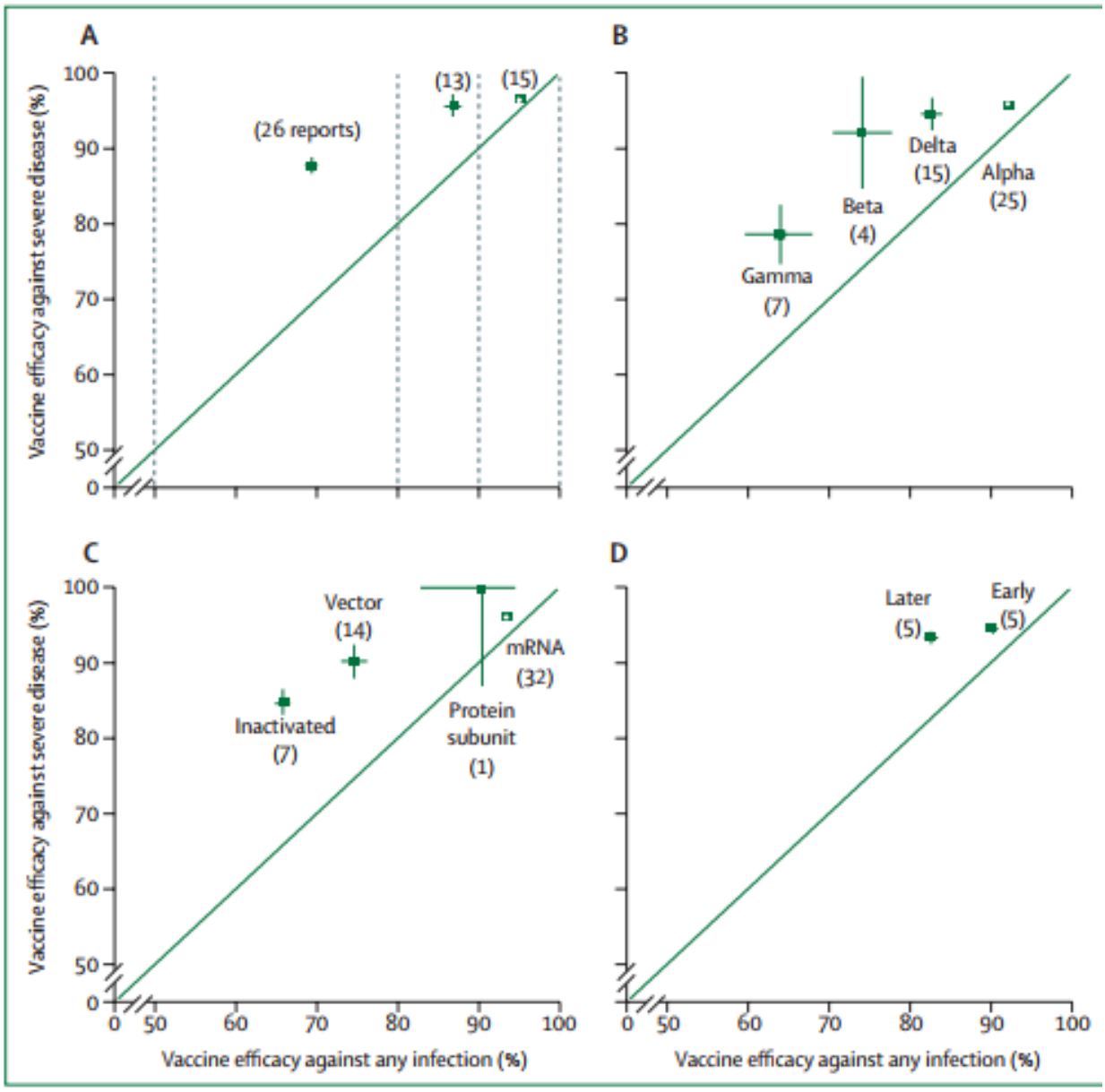


Figure: **Vaccine efficacy against severe disease versus vaccine efficacy against any infection**

Comment: I do not have all the answers, but I have whiplash. The US spends a lot on healthcare yet we cannot answer basic questions about Covid-19. Some of the best research has come from Israel and the UK. American public health agencies should be producing more data on breakthrough infections, boosters, and natural immunity, but they are catching up. But messaging from the CDC and Washington has failed to provide the information needed and to communicate in a way that engenders public trust on a sound Covid-19 strategy.