COVID-19 UPDATE: FOCUS ON VACCINES AND NEW THERAPEUTICS

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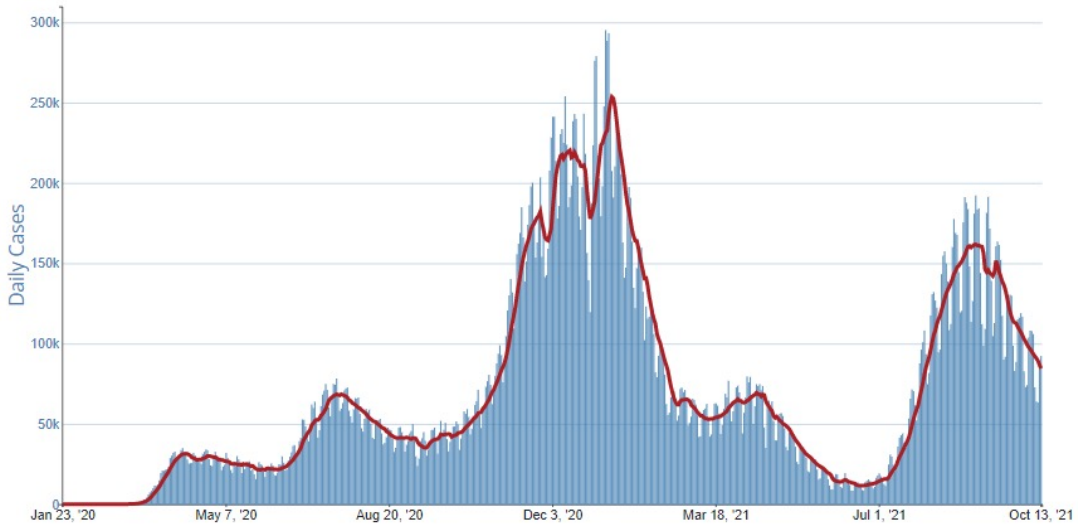
Disclosures: Consultancy; Pfizer, Sanofi, PDI, Germitec, Uvinnovators, Merck
All drugs/vaccines issues discussed consistent with FDA approvals or authorizations

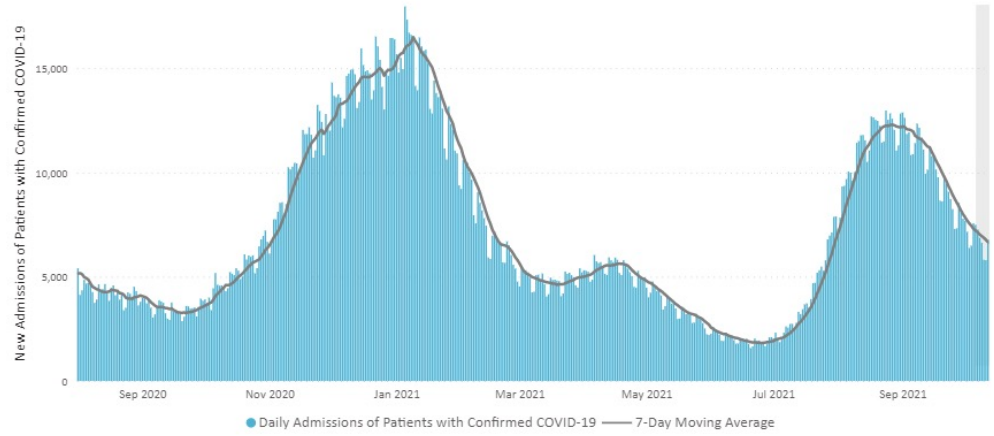
COVID-19 UPDATE

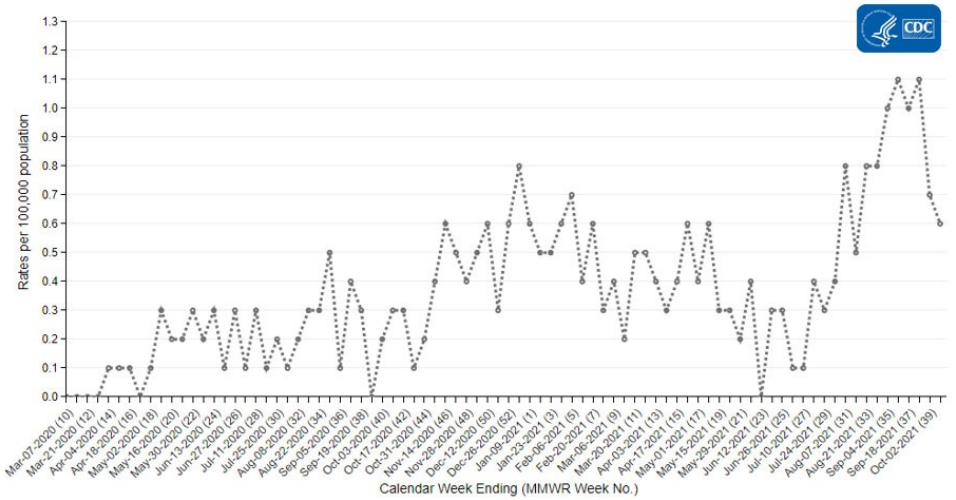
- Decreasing cases, (-12.5%, 7d ave) and hospitalizations (-8.8%, 7d ave) due to COVID-19 but continued high levels of transmission
- Deaths have surpassed, 700,000; estimated 787,834 deaths by 1 Jan 2022 (University of Washington)
- Delta variant continues to be the overwhelming most common variant (>98%)
- Booster doses of Moderna and J&J, recommended for authorization by FDA panel, 14 & 15, October; ACIP review 20-21 October
- COVID-19 vaccine (Pfizer), ages 5-11 years of age: FDA panel to meet October 26 to review
- CDC recommended urgent action to increase vaccination in pregnancy and announced data demonstrating safety of Pfizer boosters
- FDA EUA granted to new 'at-home' test; US planning to double testing capacity in the next few weeks (and invest $1 billion)
- Molnupiravir (ribonucleoside analog): Oral antiviral to treat COVID-19 (~50% reduction in hospitalizations or deaths)
  - For patients with mild-moderate disease; enrolled within 5 days of symptom onset
  - At interim analysis, 7.3% of patients who received molnupiravir were hospitalized through day 29, compared with 14.1% of placebo-treated patients who were hospitalized or died (Phase 3 MOVe-OUT trial): placebo, 8 deaths; treatment, 0 deaths
  - Consistent efficacy across viral variants Gamma, Delta and Mu; Similar side effects - Placebo, 40%; Mulnupiravair, 35%
- AZD7442 (long-acting antibody combination): Pre-exposure prophylaxis of symptomatic COVID-19; Risk reduction 77% (95% CI, 46, 90) in PROVENT trial; may provide up to 12 months protection with a single dose; data submitted to FDA for EUA

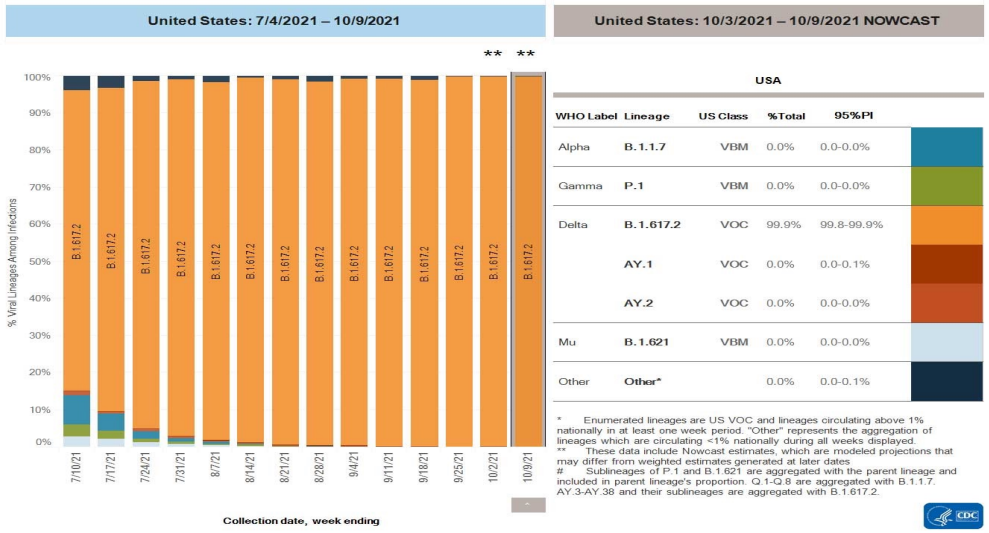
https://www.merck.com/news/merck-and-ridgebacks-investigational-oral-antiviral-molnupiravir-reduced-the-risk-of-hospitalization-or-death-by-approximately-50-percent-compared-to-placebo-for-patients-with-mild-or-moderat/

THE GOOD NEWS: CASES AND HOSPITALIZATIONS ARE DECREASING, CDC

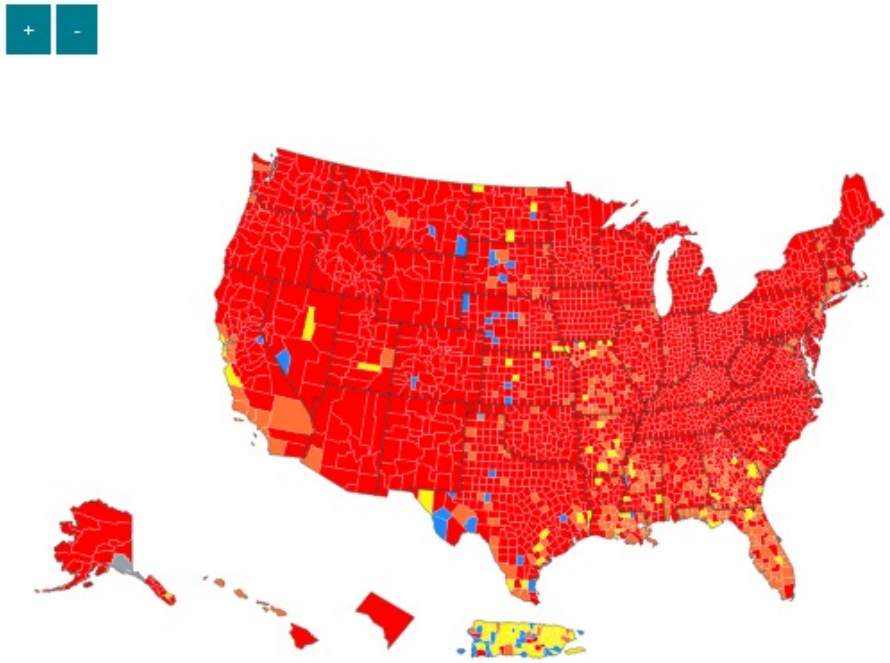








THE BAD NEWS: COVID-19 CASES REMAIN HIGH ACROSS THE US, CDC



Community Transmission in US by County

	Total	Percent	% Change
High	2826	87.71%	-3.35%
Substantial	249	7.73%	2.48%
Moderate	95	2.95%	0.53%
Low	46	1.43%	0.4%

How is community transmission calculated?

High Substantial Moderate Low No Data

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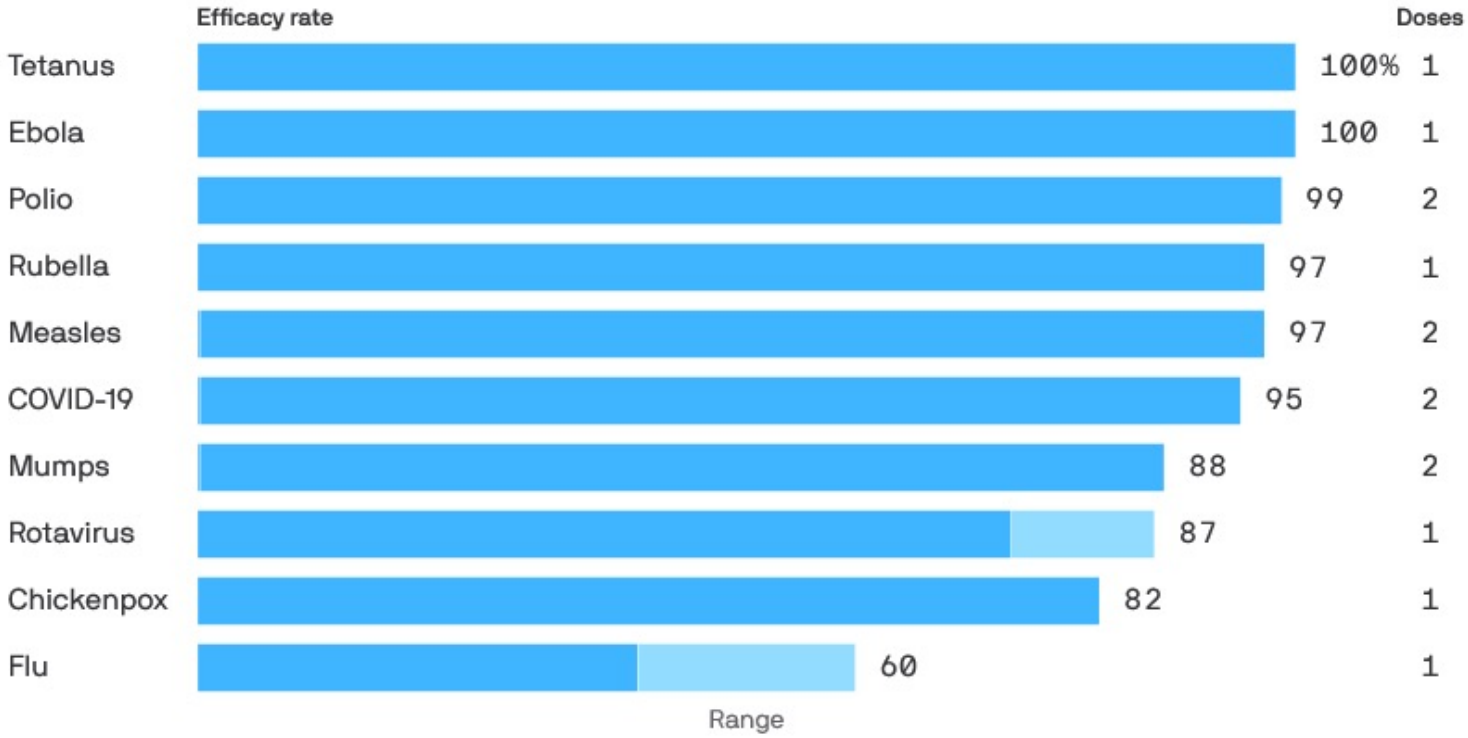
VACCINE EFFICACY

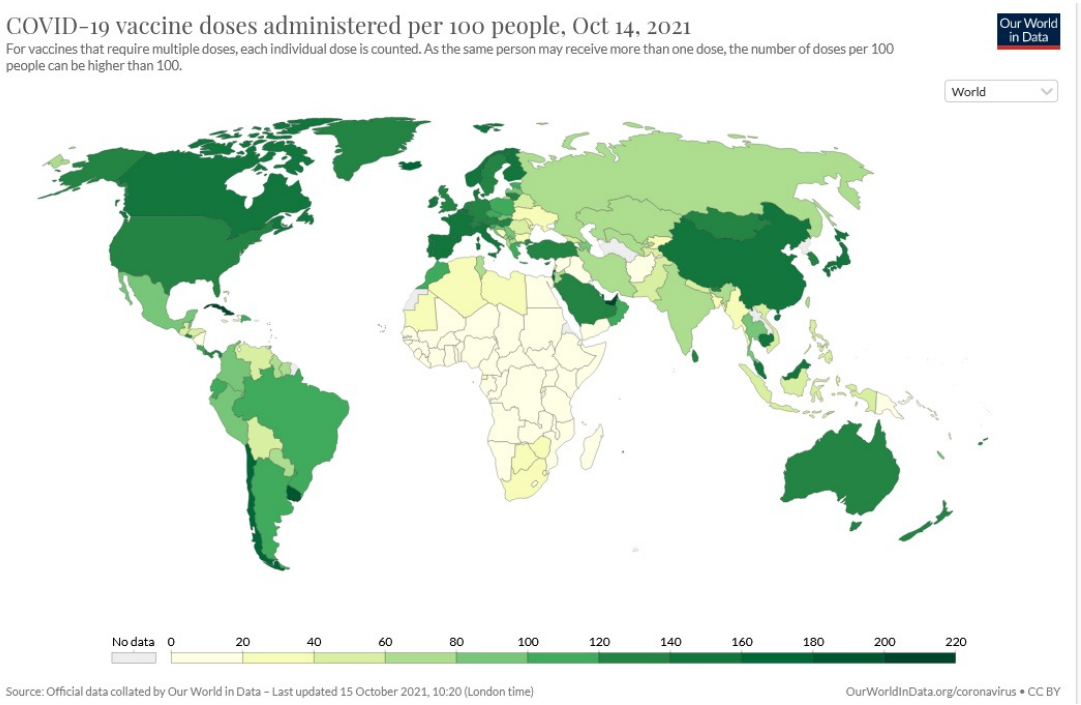


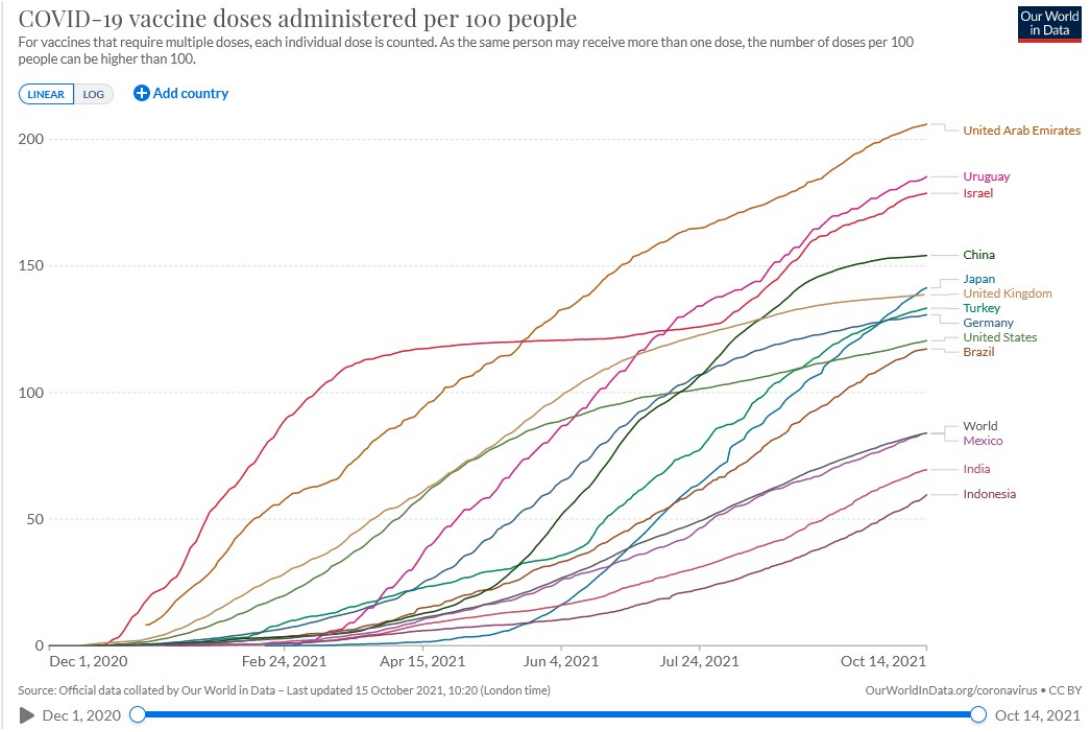
Data: CDC, Moderna and Pfizer; Note: Flu vaccine based on yearly average from 2009-2019. Moderna and Pfizer coronavirus vaccine efficacy based on early clinical trial data. Chart: Sara Wise/Axios

Fernandez M. https://www.axios.com/how-covid-19-vaccine-compares-fcf8073d-956d-4cef-a0a7-f9188445297e.html

WORLDWIDE COVID-19 VACCINE UPTAKE

47.3% of the world population has received at least one dose of a COVID-19 vaccine.
6.61 billion doses have been administered globally, and 22.4 million are now administered each day.

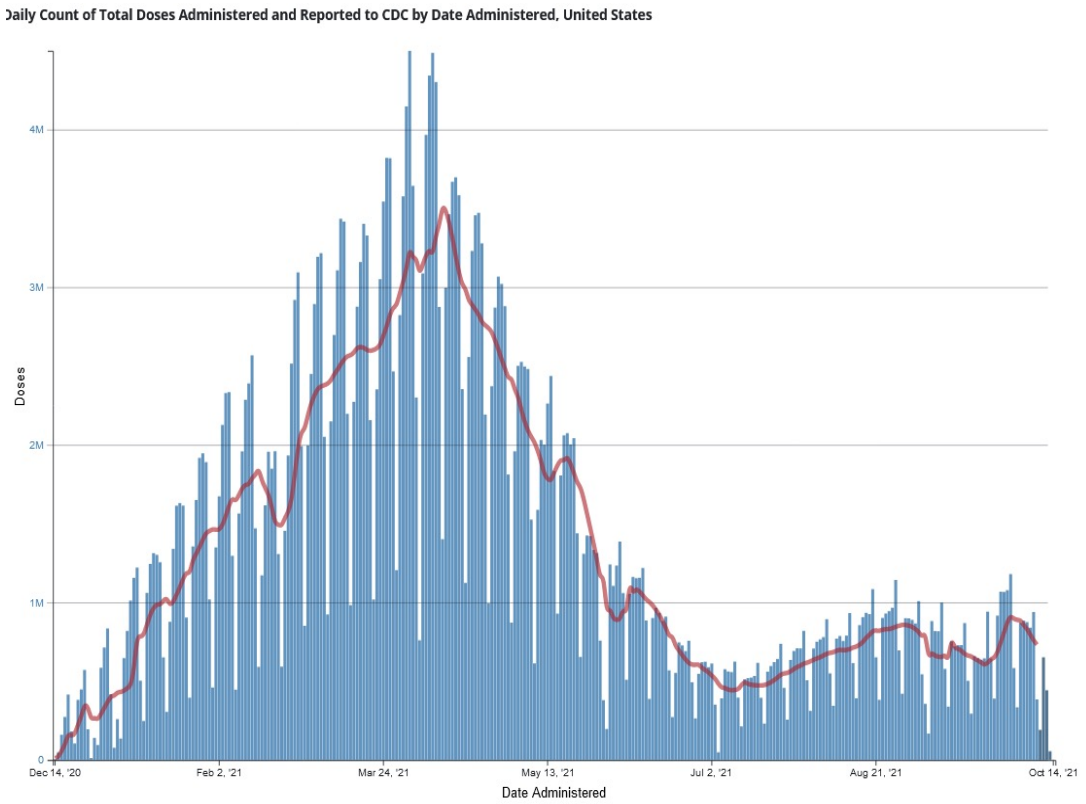




US rank among countries for percent vaccinated = 48

https://ourworldindata.org/grapher/covid-vaccination-doses-per-capita?tab=map

COVID-19 VACCINATION, US



Total Vaccine Doses

Delivered	490,951,045
Administered	405,444,558

Learn more about the distribution of vaccines.

188.3M
People fully vaccinated

9.32M
People received a booster dose**

At Least One Dose	Fully Vaccinated	Booster Dose
Vaccinated People	Count	Percent of US Population
Total	217,953,275	65.6%
Population ≥ 12 Years of Age	217,719,463	76.8%
Population ≥ 18 Years of Age	203,009,278	78.6%
Population ≥ 65 Years of Age	52,173,134	95.4%

***For surveillance purposes, COVID Data Tracker counts people as being "fully vaccinated" if they received two doses on different days (regardless of time interval) of the two-dose mRNA series or received one dose of a single-dose vaccine.**

****The count of people who received a booster dose includes anyone who is fully vaccinated and has received another dose of COVID-19 vaccine since August 13, 2021. This includes people who received booster doses and people who received additional doses.**

About these data

CDC | Data as of: October 14, 2021 6:00am ET. Posted: Thursday, October 14, 2021 7:30 PM ET

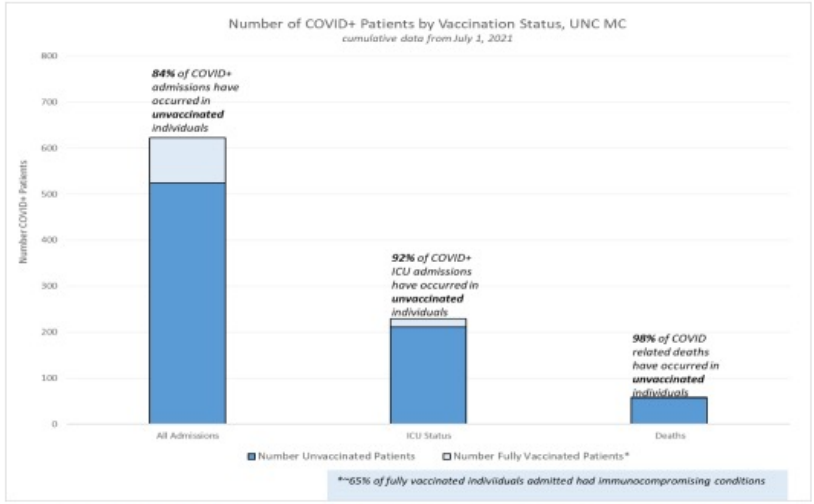
https://covid.cdc.gov/covid-data-tracker/#vaccination-trends

https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total

UNC Medical Center & CDC Surveillance

UNCH Infection Prevention COVID-19 and Respiratory Virus Weekly Data Report

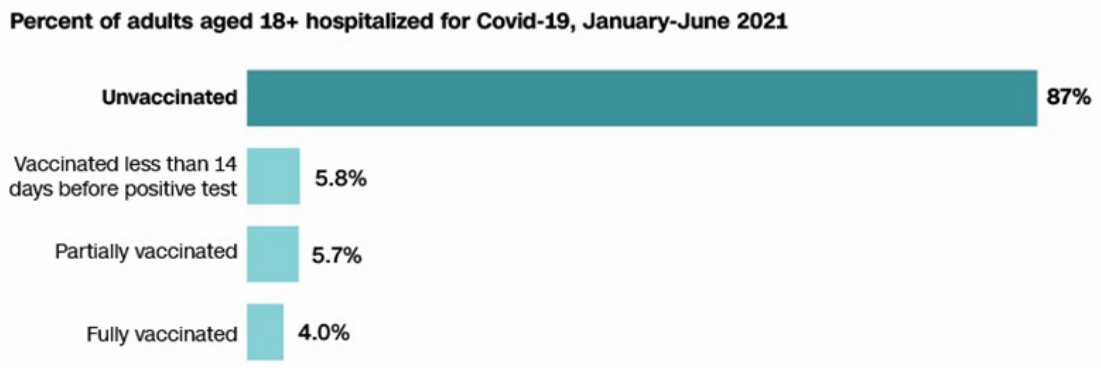
Reporting for week ending: 10/9/2021



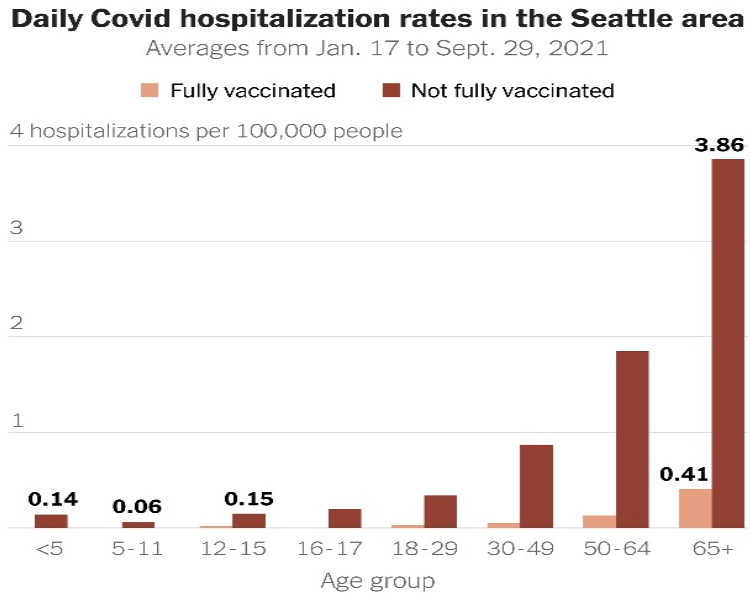
COVID-19 positive admissions to UNC Hospitals and deaths broken down by vaccination status. Vaccination status is captured in Epic and may be an underrepresentation of the true number of vaccinated patients. Patients are considered fully vaccinated 14 days after their second dose or 14 days after receipt of J&J vaccine.

Among vaccinated persons, 66% were on cancer chemotherapy, had an solid organ transplant, or were on high dose steroids

94% of patients who died had a comorbidity

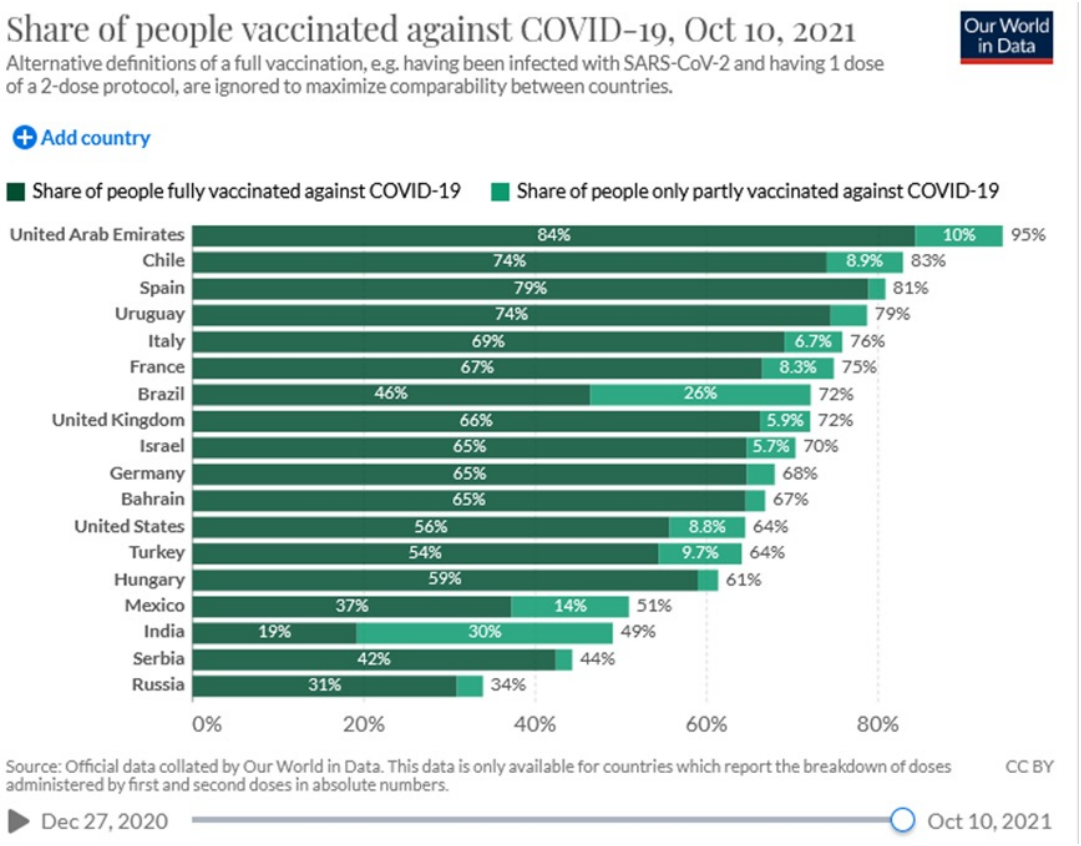


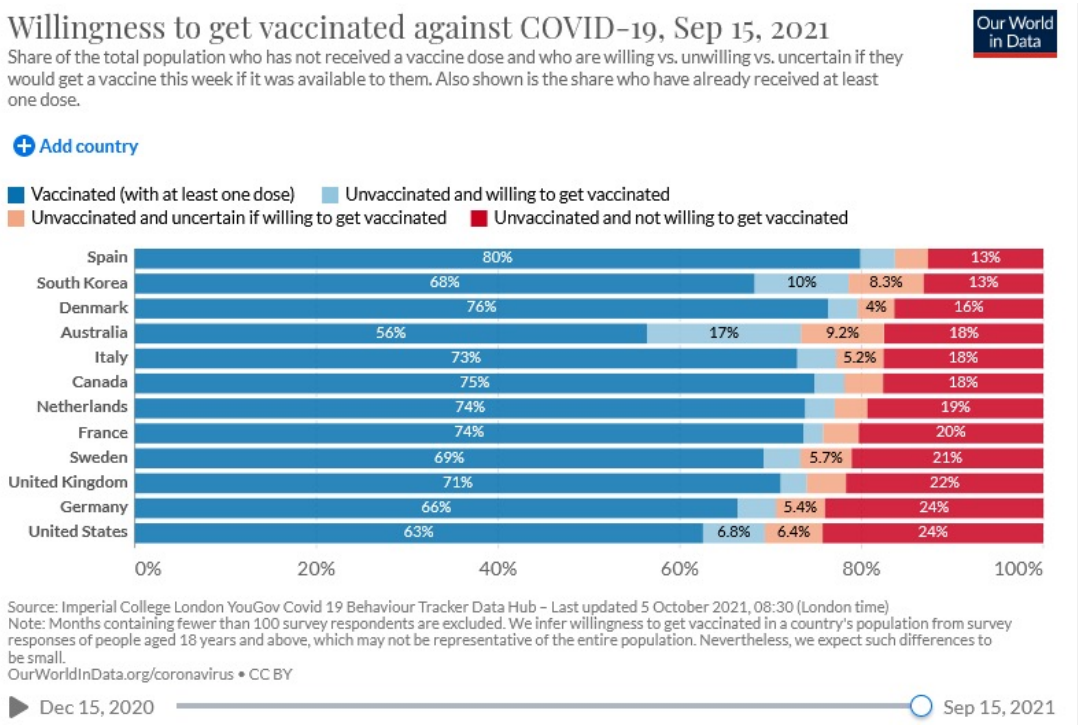
Havers FP, et al. https://www.medrxiv.org/content/10.1101/2021.08.27.21262356v1.full#T3



https://www.nytimes.com/2021/10/12/briefing/covid-age-risk-infection-vaccine.html

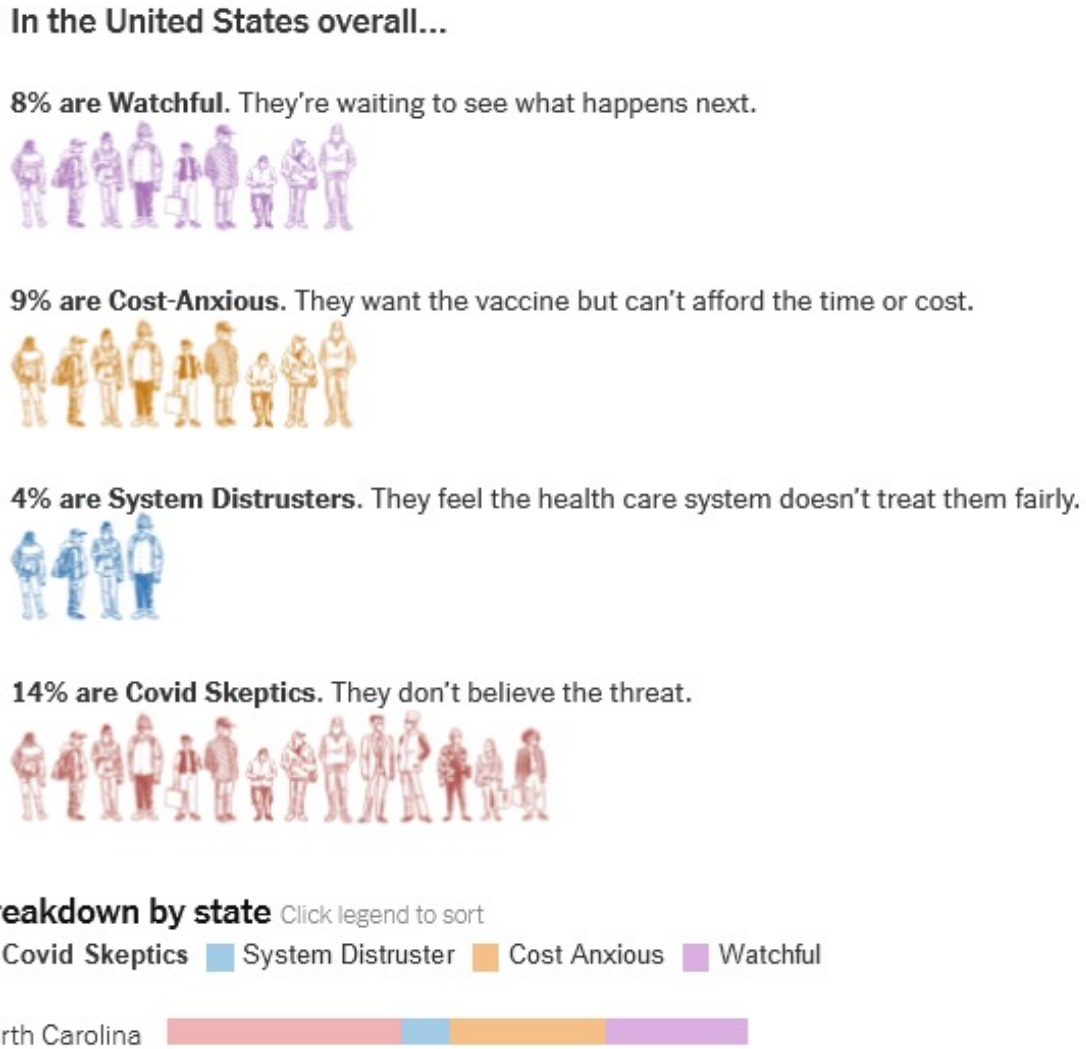
COVID-19 VACCINATIONS, US





https://ourworldindata.org/covid-vaccinations

Reasons for vaccine hesitancy



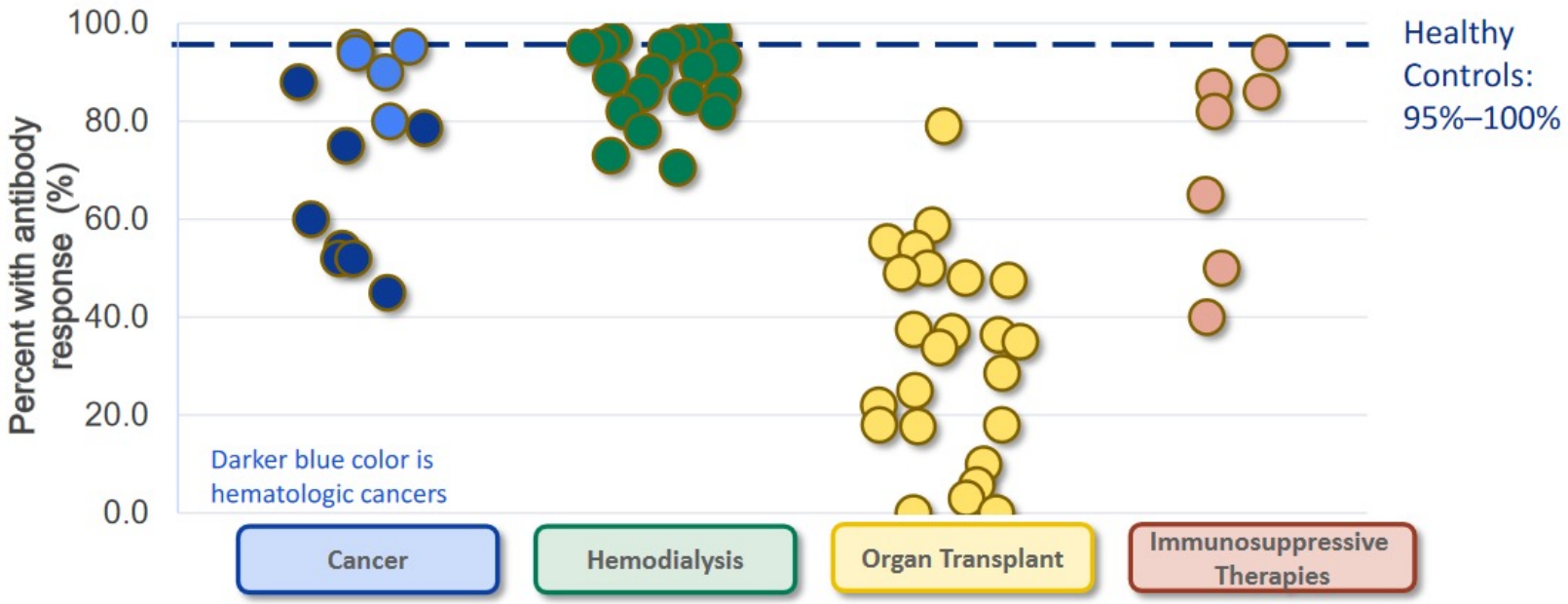
- The **Watchful** are holding out to see what kind of experience their friends or neighbors have with the vaccine before committing themselves. Solution=Allow for a "vaccinate later" option
- The **Cost-Anxious** worry about the time and potential expense of getting vaccinated (even if it is actually free). Solution=stress that vaccine is free and encourage businesses to provide paid time off for both vaccines
- The **System Distrusters** believe that the health care system doesn't treat them fairly. Most, but not all, members of this group are people of color. Solution=engage trusted member of their own communities to air concerns and be transparent
- **Covid Skeptics** are at the far end of the spectrum as the least likely to get vaccinated. The primary barrier for people in this group are their specific, deeply held beliefs about Covid-19. Everyone in this group believes at least one conspiracy theory related to the pandemic. Solution=avoid trying to debunk person's beliefs; listen to concerns and emphasize that vaccination is their own personal choice – and it protects friends and family members

https://www.nytimes.com/interactive/2021/05/18/opinion/covid-19-vaccine-hesitancy.html

THE ABC SCIENCE COLLABORATIVE

RATIONALE FOR 3RD DOSE OF AN mRNA VACCINE IN IMMUNOCOMPROMISED PERSONS

Percent of subjects with antibody response after two mRNA COVID-19 vaccine doses by immunocompromising condition and study (n=63)



- Studies that compared response after 1st and 2nd dose demonstrated less robust response after dose 1
- Antibody measurement and threshold levels vary by study protocol

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BENEFITS OF 3RD DOSE OF AN mRNA VACCINE IN IMMUNOCOMPROMISED PERSONS

Study	Patient Population	2nd Dose			3rd Dose Seronegative after 2 nd dose		
		Sample Size	Seronegative N (%)	Seropositive N (%)	Sample Size	Seronegative N (%)	Seropositive N (%)
Kamar et al.	Recipients of solid-organ transplant	99	59 (60)	40 (40)	59	33 (56)	**26 (44)**
Werbel et al.	Recipients of solid-organ transplant	30	24 (80)	6 (20)	24	16 (67)	**8 (33)**
Longlune et al.	Patients on hemodialysis	82	13 (16)	69 (84)	12	7 (58)	**5 (42)**
Epsiet al.	Patients on hemodialysis	106	66 (62)	40 (38)	12	6 (50)	**6 (50)**
Ducloux et al.	Patients on hemodialysis	45	5 (11)	40 (89)	5	3 (60)	**2 (40)**

- Among those who had **no detectable antibody** response to an initial mRNA vaccine series,

33-50% developed an antibody response to an additional dose

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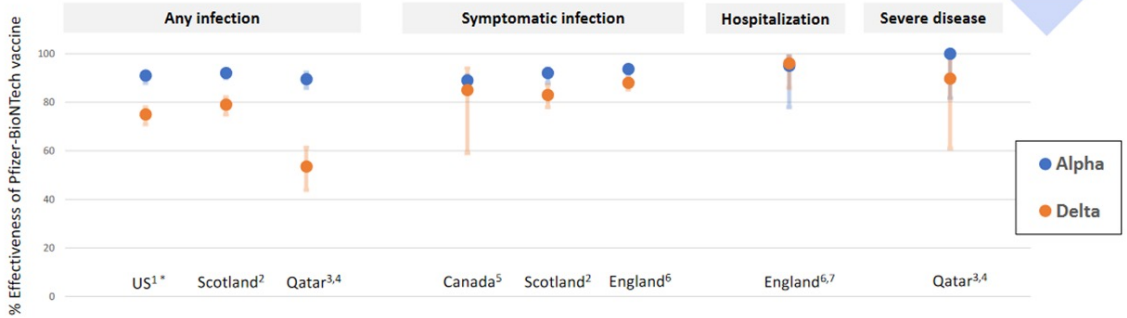
VACCINE EFFECTIVENESS, WORLDWIDE

Booster doses of COVID-19 vaccines:
Is effectiveness reduced because of the Delta variant?

Public Health Problem



- Globally, among studies assessing infections with Alpha vs Delta: mild decrease in Delta VE[1-7]
- Other factors may include study methods, **interval** between doses, and **timing** with vaccination and variant increases

References: 1. Tartof et al. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3909743 2. Sheikh A, et al. https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)01358-1/fulltext 3. Tang et al. https://www.medrxiv.org/content/10.1101/2021.08.11.21261885v1 4. Abu-Raddad et al. https://www.nejm.org/doi/full/10.1056/NEJMc2104974 5. Nasreen S, et al. https://www.medrxiv.org/content/10.1101/2021.06.28.21259420v2 6. Bernal Lopez et al. https://www.medrxiv.org/content/10.1101/2021.05.22.21257658v1 7. Stowe et al. https://khub.net/web/phe-national/public-library/-/document_library/v2WsRK3ZlEig/view/479607266 *Included other variants

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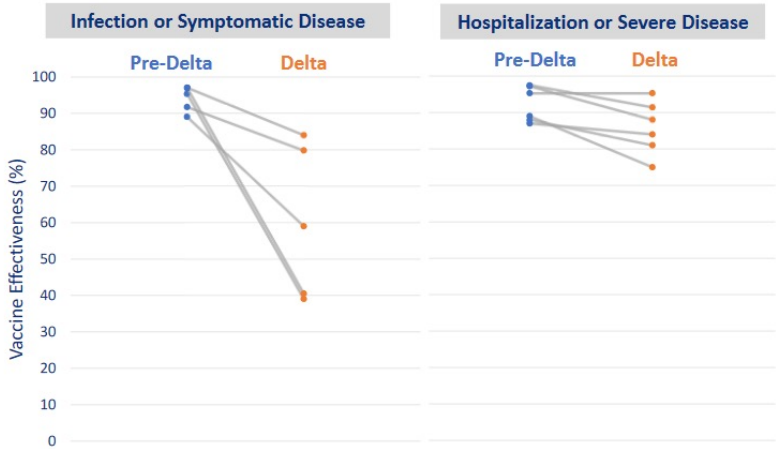
Vaccine effectiveness in the Pre-Delta and Delta Periods



In studies comparing the 'Pre-Delta' and 'Delta' periods:

- Pre-Delta vaccine effectiveness estimates high (**87% or higher**)
- Since the introduction of the Delta variant (varies by region)
  - VE against **infection** ranges from **39–84%**
  - VE against **hospitalization** ranges from **75–95%**

References: 1. Israel Ministry of Health (committee/he/files_publications_corona_two-dose-vaccination-data.pdf) 2. Haas et al. (Israel) https://doi.org/10.1016/S0140-6736(21)00947-8 3. Pouwels et al. (UK) survey/finalfinalcombinedve20210816.pdf 4. Puranik https://www.medrxiv.org/content/10.1101/2021.08.06.21261707v2 5. Rosenberg (US) https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e1.htm 6. Tenforde (US) https://www.cdc.gov/mmwr/volumes/70/wr/mm7034e2.htm

ACIP, 30 August 2021, Sara Oliver

BNT162b2 vaccine booster dose protection: A nationwide study from Israel

- Goal: Estimate the reduction in RR for confirmed infection and severe COVID-19 provided by the booster dose (booster dose initiated 67/30/21)
- Methods: 1,144,690 individuals aged 60y and older who were eligible for a booster dose were followed between July 30 and August 22, 2021. Outcomes per person-days at risk were compared between the cohorts using Poisson regression, adjusting for possible confounding factors.
- Results: Twelve days or more after the booster dose we found an 11.4-fold (95% CI: [10.0, 12.9]) decrease in the relative risk of confirmed infection, and a >10-fold decrease in the relative risk of severe illness. Under a conservative sensitivity analysis, we find ≈5-fold protection against confirmed infection.

Table 2. Summary of the results of the Poisson regression analysis for different cohorts: people who received only two vaccine doses and people for whom 12 days or more have passed since their booster dose. For each group, we provide the total number of person-days at risk for each cohort, the number of confirmed infections and severe COVID-19 in each cohort, and the estimated protection of the booster against confirmed infection and severe illness, given as a fold change in relative risk.

Cohort	Person-days at risk	Confirmed infections	Severe COVID-19	Estimated booster protection (95% CI)	
				Against confirmed infection	Against severe illness
2 doses only ("no-booster" cohort)	4,018,929	3,473	330	1	1
12+ days from 3rd dose ("booster" cohort)	3,351,598	313	32	11.4 [10, 12.9]	15.5 [10.5, 22.8]

Bar-On YM, et al. https://doi.org/10.1101/2021.08.27.21262679

SHORT-TERM REDUCTION IN ODDS OF TESTING POSITIVE FOR SARS-CoV-2: 2 vs 3 DOSES, PFIZER VACCINE

- Goal: Retrospective study of short-term effectiveness of 3 vs 2 doses against Delta variant, test-negative design/matched case-contro
- Results: Booster shot demonstrated that 7-13 days after booster there is a 48-68% reduction in the odds of testing positive for SARS-CoV-2 infection and that 14-20 days after the booster the marginal effectiveness increases to 70-84% (95% CI, 79%, 88%)

Figure 1. Reduction in the odds of testing positive to SARS-CoV-2 in third-dose vaccinees (marginal effectiveness of the booster).

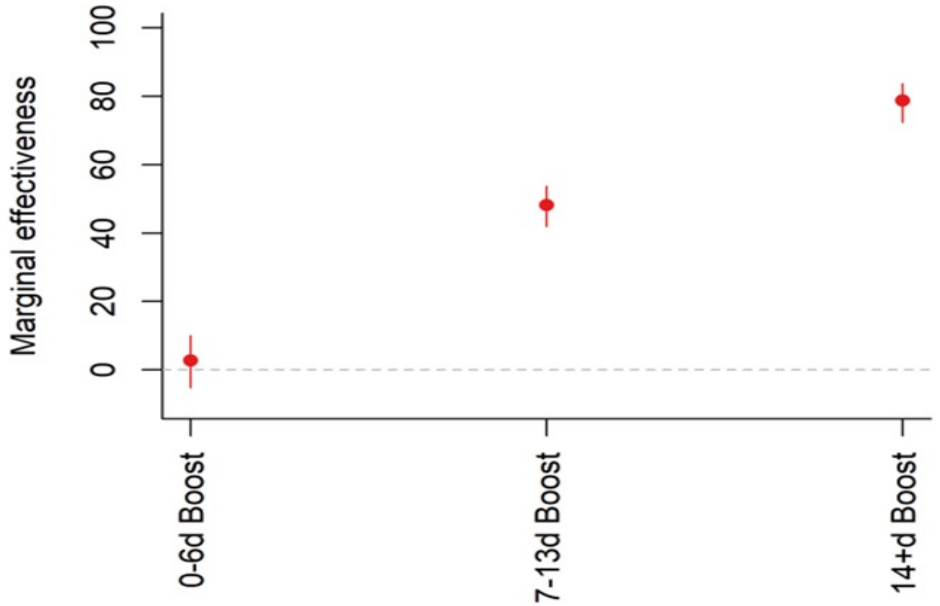


Table 1 - Testing results among those with those with at least two doses of the vaccine at different time points, August 1- August 21, 2021

Time after booster receipt	Test positive (N)	Total Tests (N)	Percent Positive
No booster	8695	154,279	5.6%
0-6 days	770	15,166	5.1%
7-13 days	378	12,461	3.0%
14-20 days	72	5489	1.3%

Patalon T, et al. https://doi.org/10.1101/2021.08.29.21262792

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