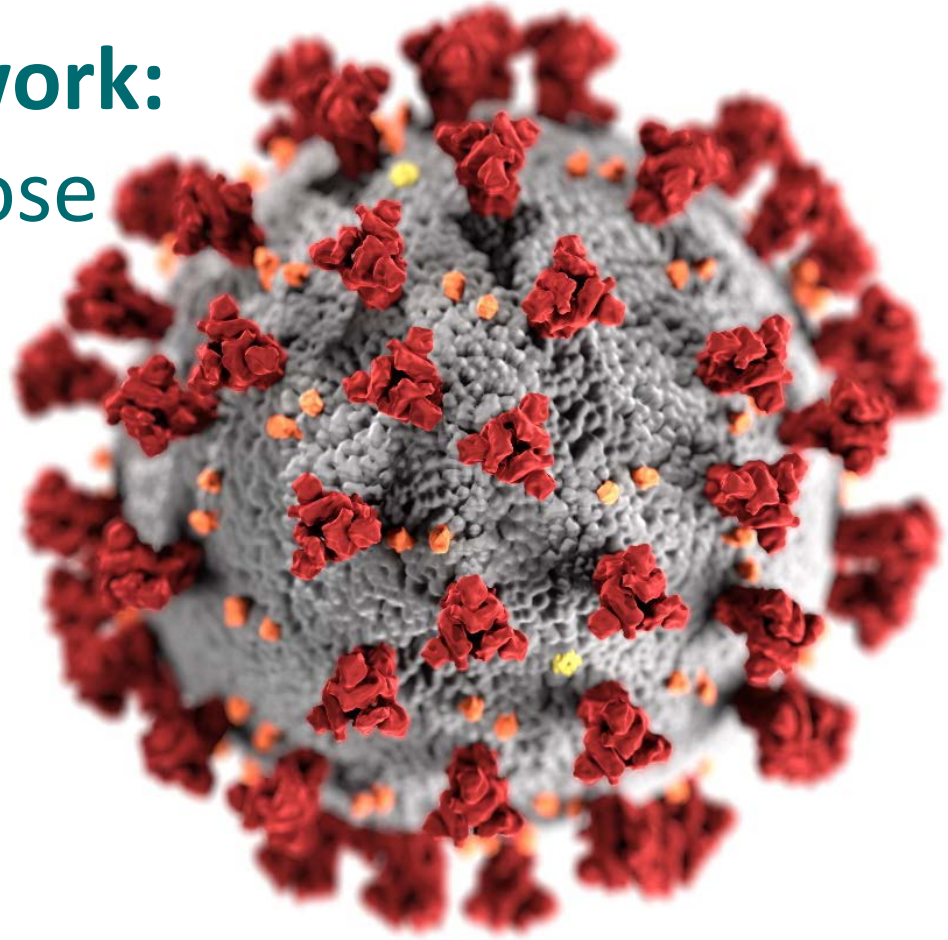
Evidence to Recommendation Framework:

Pfizer-BioNTech COVID-19 Booster Dose



Sara Oliver, MD, MSPH

ACIP Meeting

September 23, 2021

cdc.gov/coronavirus

Evidence to Recommendations (EtR) Framework

- Structure to describe information considered in moving from **evidence** to ACIP vaccine **recommendations**
- Provide **transparency** around the impact of additional factors on deliberations when considering a recommendation
- Questions around vaccine policy for booster doses are complex
  - Require some adaptation of our standard Evidence to Recommendation Framework

Evidence to Recommendations (EtR) Framework

Standard EtR Domains
Public Health Problem
Benefits and Harms
Values
Acceptability
Feasibility
Resource Use
Equity

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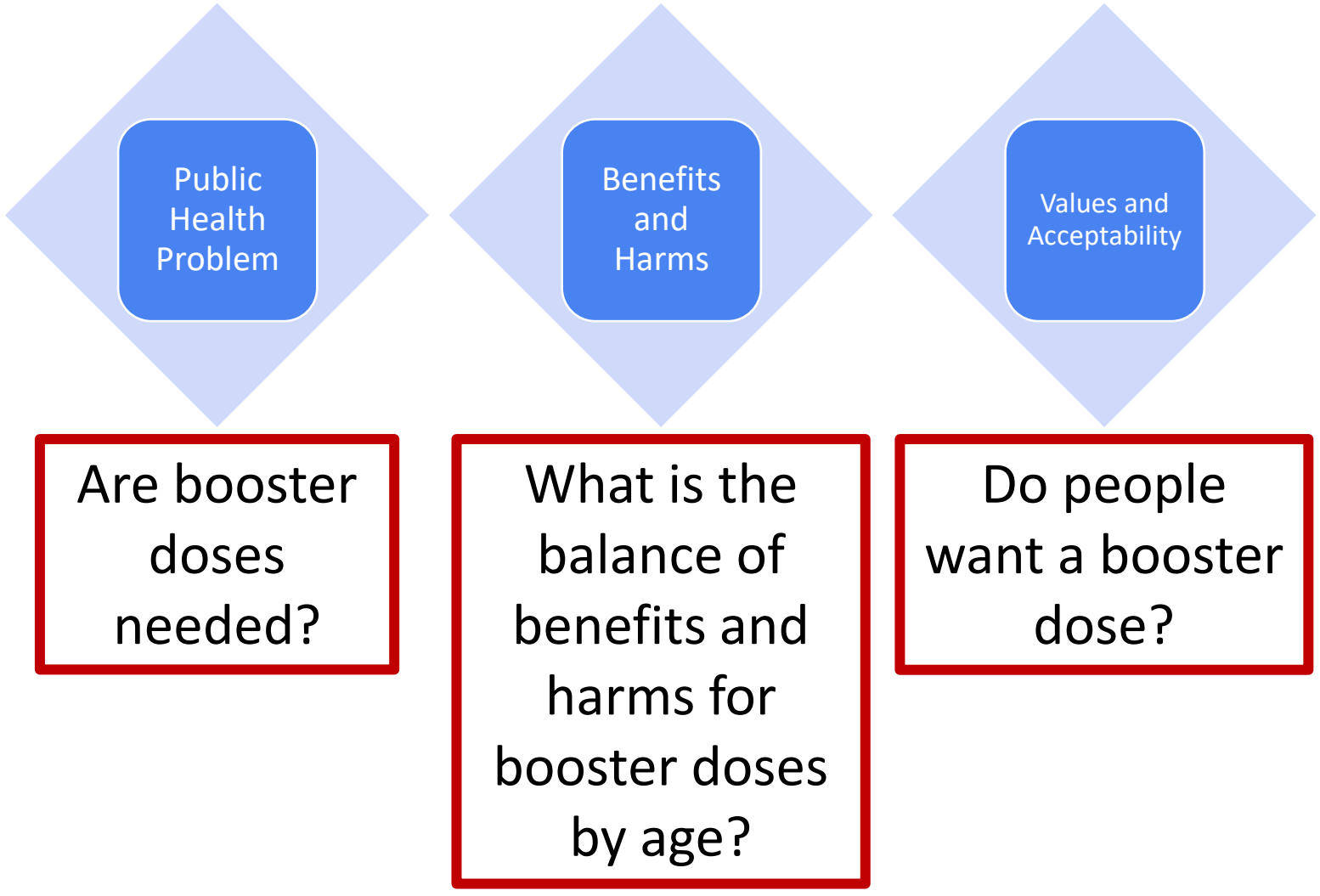

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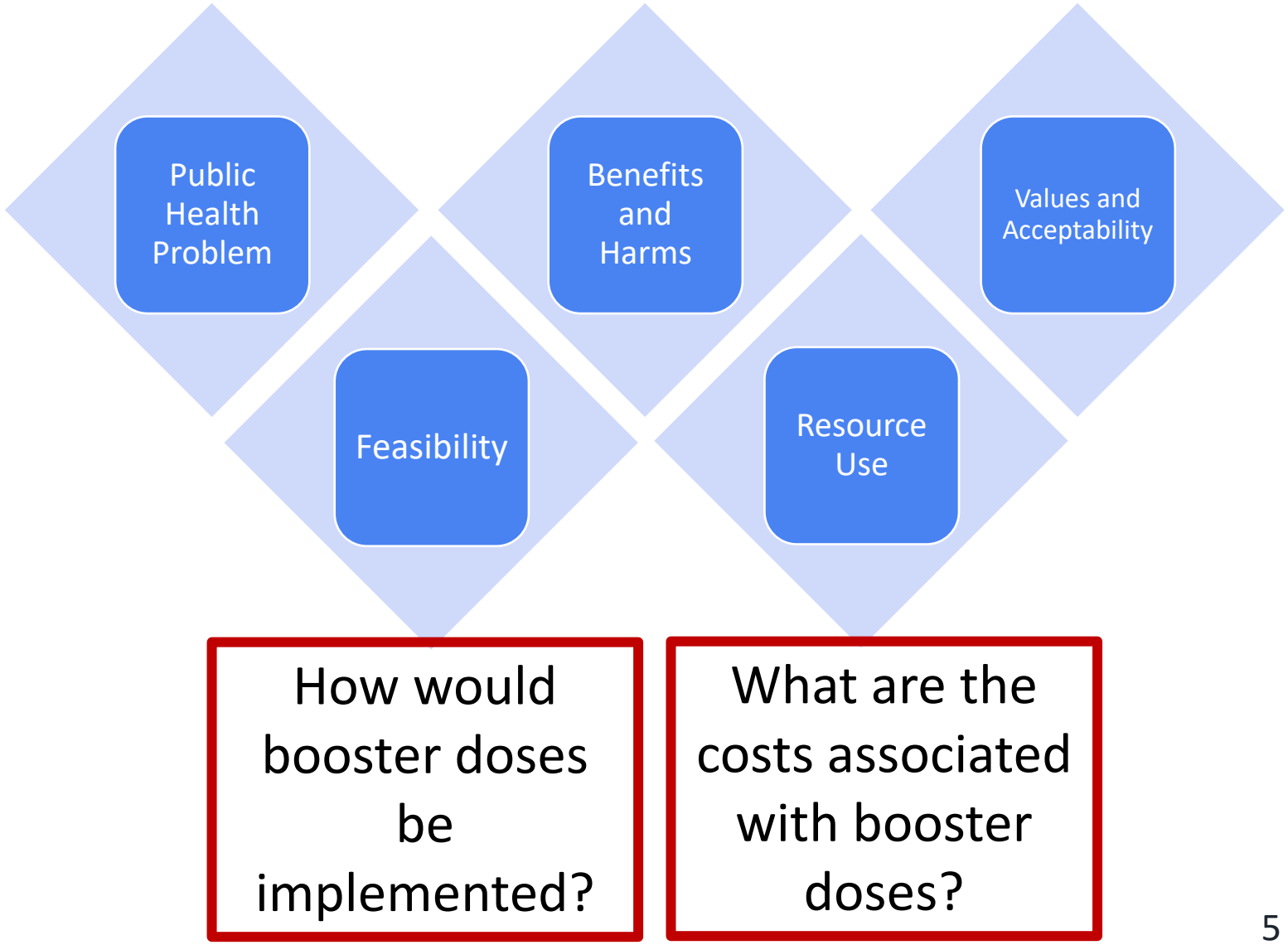

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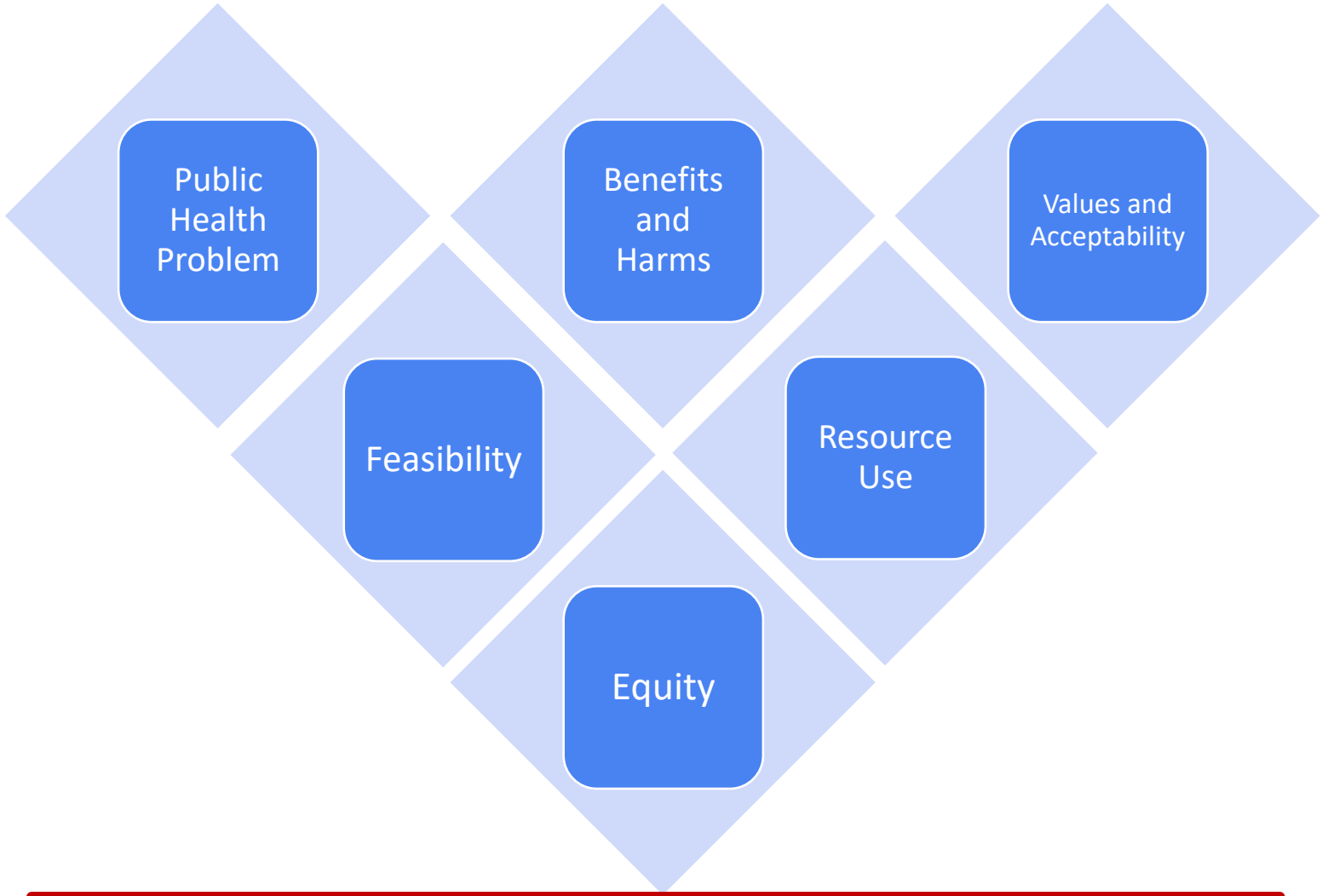


What are equity considerations for booster doses?

Booster doses of COVID-19 vaccines

- Policy on booster doses will be coordinated with **FDA** for regulatory allowance, and **ACIP** for recommendations for use

Evidence to Recommendations (EtR) Framework

Question

- Who should be recommended to receive a Pfizer-BioNTech COVID-19 booster dose under the current Emergency Use Authorization, based on the balance of benefits and risks?

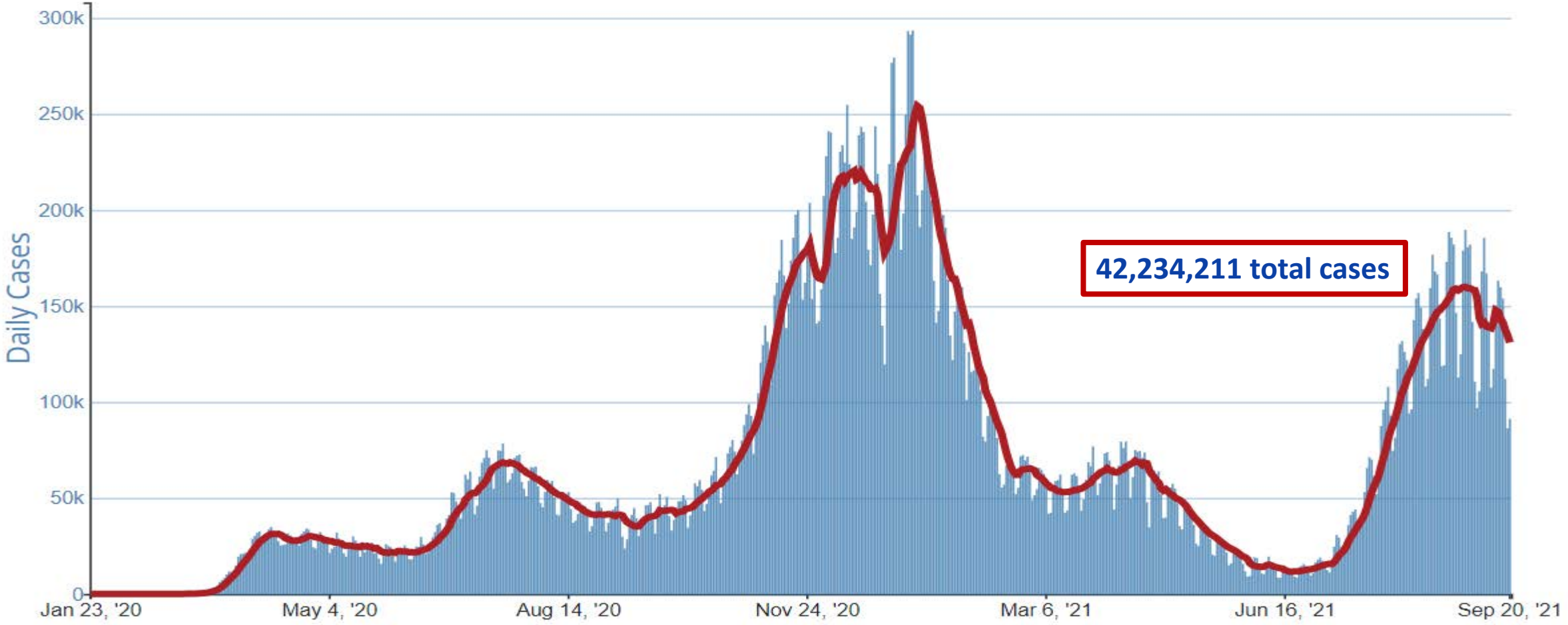
Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines

Are booster doses of COVID-19 vaccines needed?

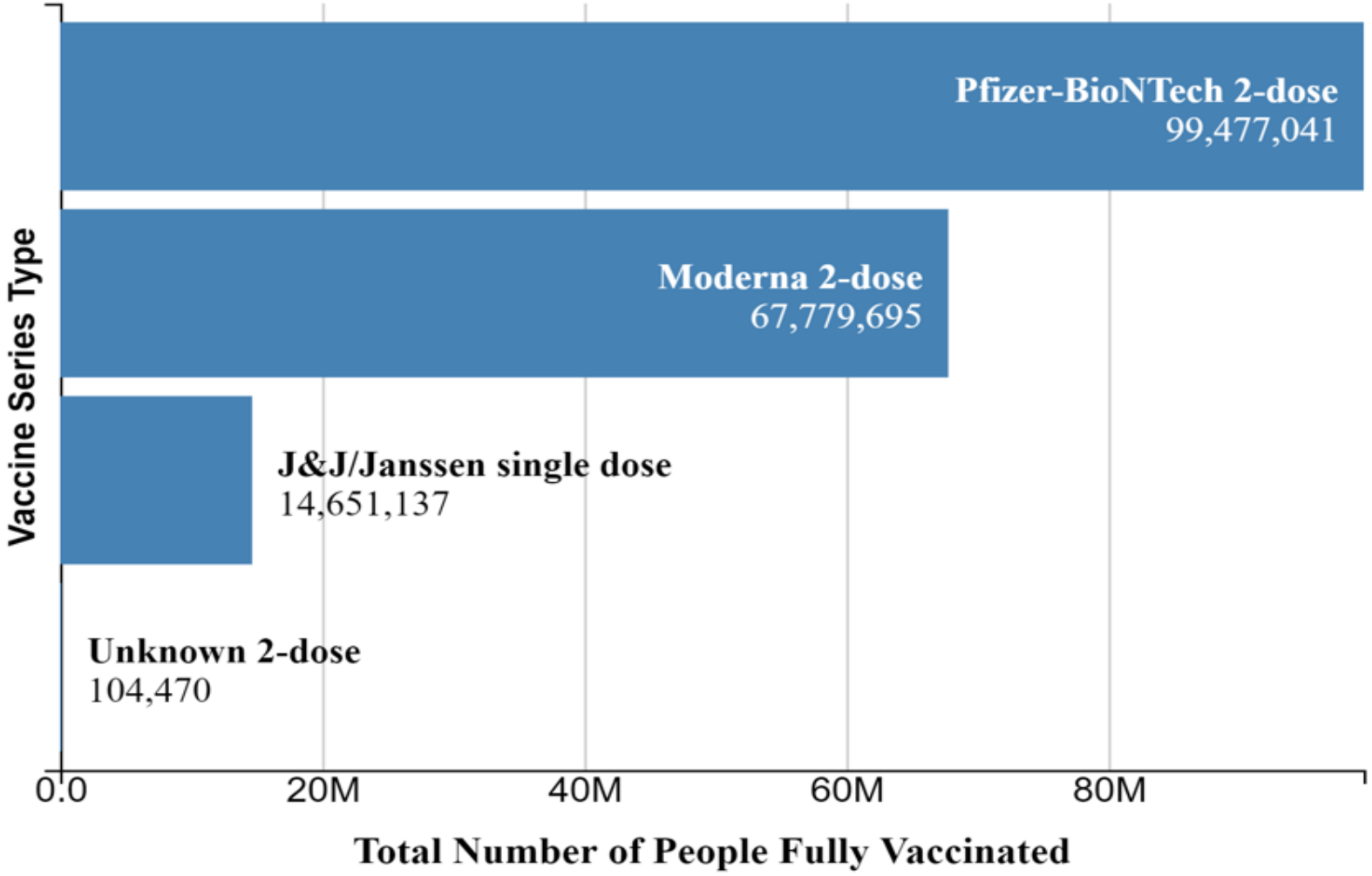
Daily trends in number of COVID-19 cases in the United States

January 23, 2020 – September 20, 2021



CDC. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases. Accessed September 22, 2021

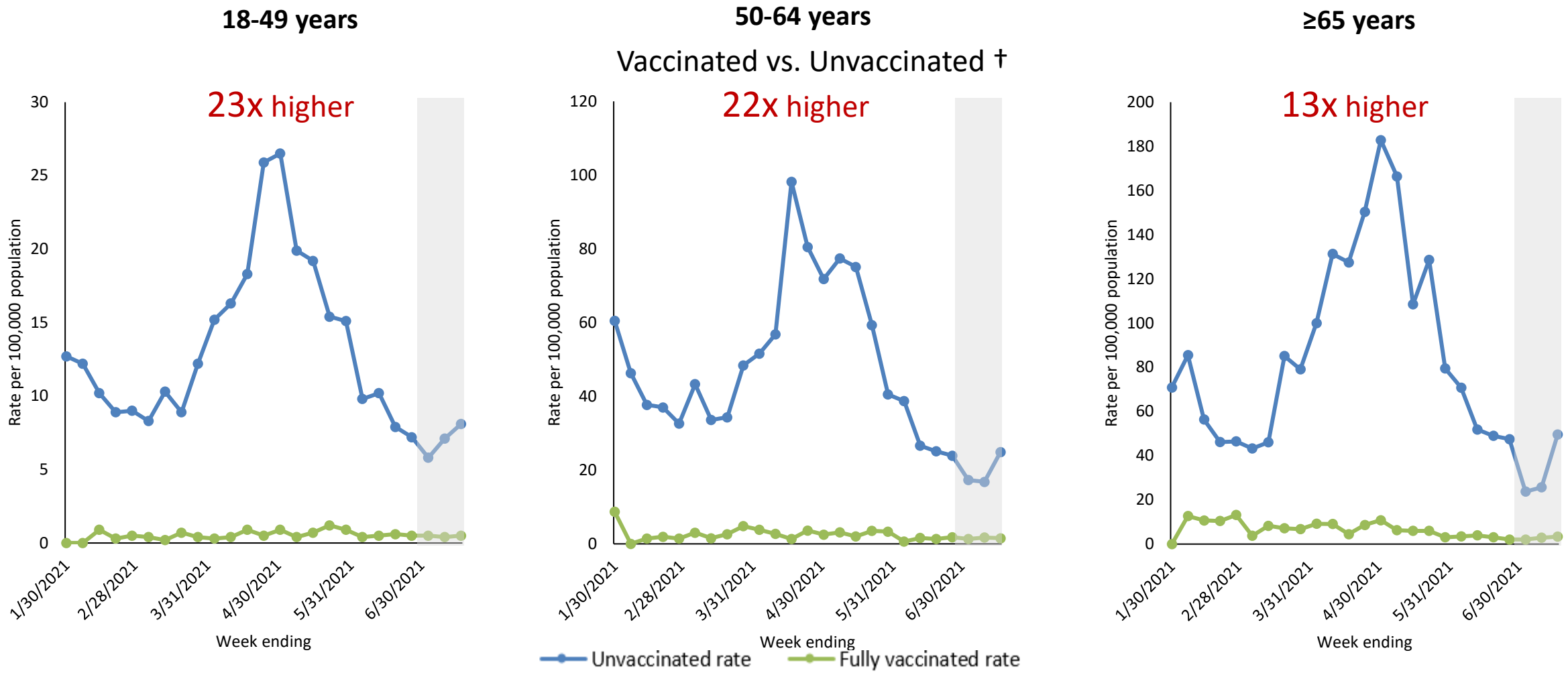
Number of people fully vaccinated in the U.S. by COVID-19 vaccine series type



182,012,343
Fully Vaccinated

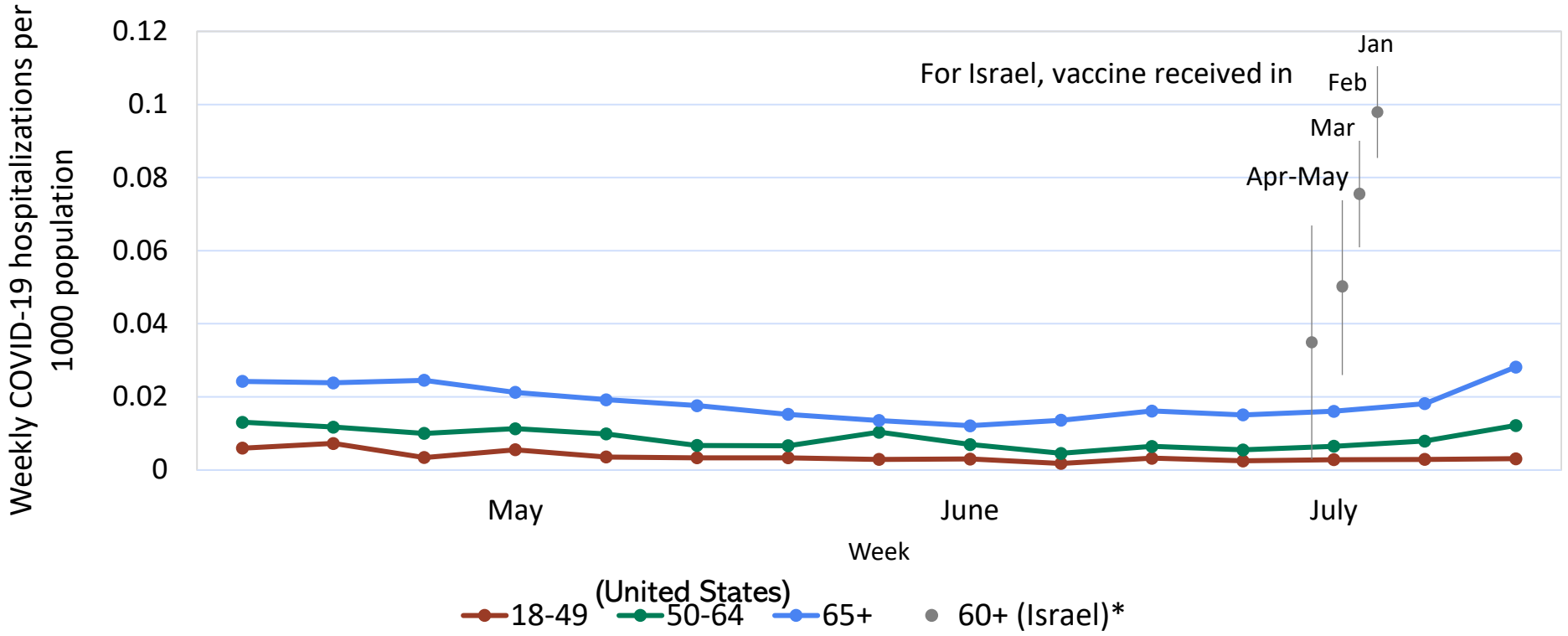
CDC. https://covid.cdc.gov/covid-data-tracker/#vaccinations_vacc-total-admin-rate-total. Accessed September 22, 2021

Age-adjusted weekly COVID-19-associated hospitalization rates among adults by week of admission and age group*—COVID-NET, January 24–July 17, 2021



*Data are preliminary and case counts and rates for recent hospital admissions are subject to lag. As data are received each week, prior case counts and rates are updated accordingly.
†Cumulative rate ratio from January 24 – July 17, 2021. Shaded area indicates preliminary July data that does not include one site.
Havers et al. https://medrxiv.org/cgi/content/short/2021.08.27.21262356v1. COVID-19-associated hospitalizations among vaccinated and unvaccinated adults ≥18 years - COVID-NET, 13 states, January 1-July 24, 2021

Incidence among vaccinated people, for hospitalization by month in United States and for severe disease by time since 2nd dose in Israel



*Israel estimates were derived from rate of severe COVID-19 (per 1,000 persons) from July 11, 2021 to July 31, 2021. Each data point represents all person stratified by when second dose of COVID-19 vaccine received.

Scobie HM, Johnson AG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status — 13 U.S. Jurisdictions, April 4–July 17, 2021. MMWR Morb Mortal Wkly Rep 2021;70:1284–1290.
Goldberg et al. Waning immunity of the BNT162b2 vaccine: A nationwide study from Israel. https://www.medrxiv.org/content/10.1101/2021.08.24.21262423v1.full-text

Public Health Problem:

Are booster doses of COVID-19 vaccines needed?

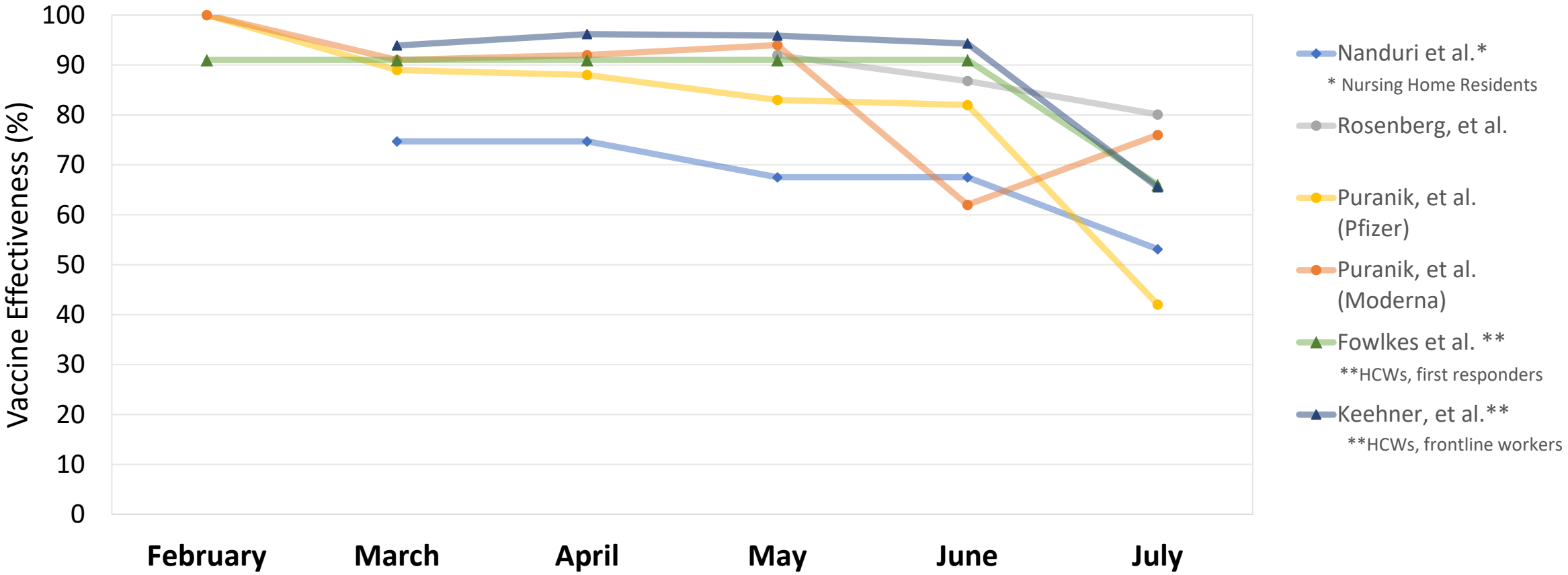
Is vaccine effectiveness (VE) waning by **age**?

Is VE waning for those with **underlying medical conditions**?

Is VE waning for those with **high-risk occupations**?

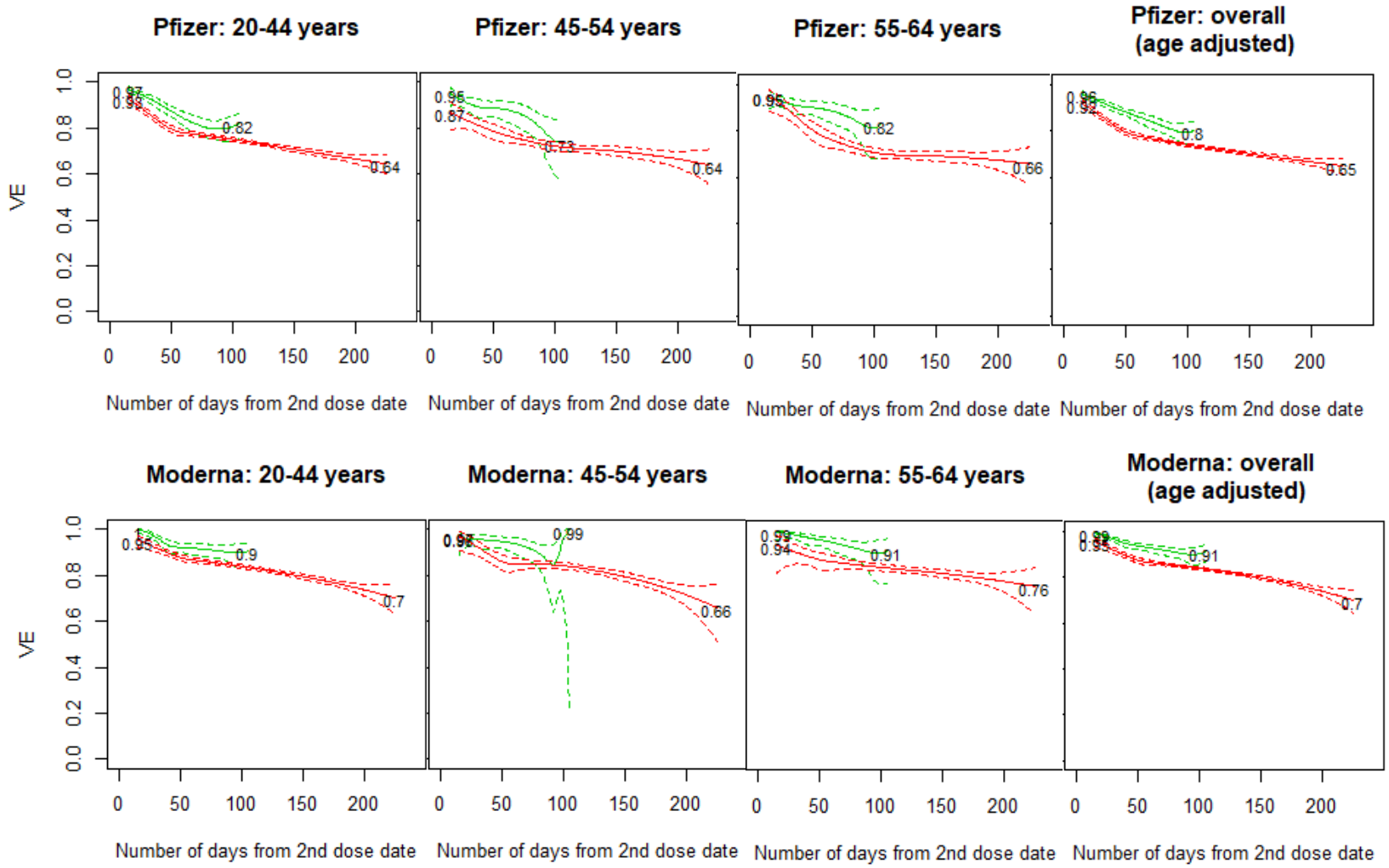
How do these data vary by **vaccine**?

Vaccine effectiveness against **infection** over time
Adults ≥18 years of age



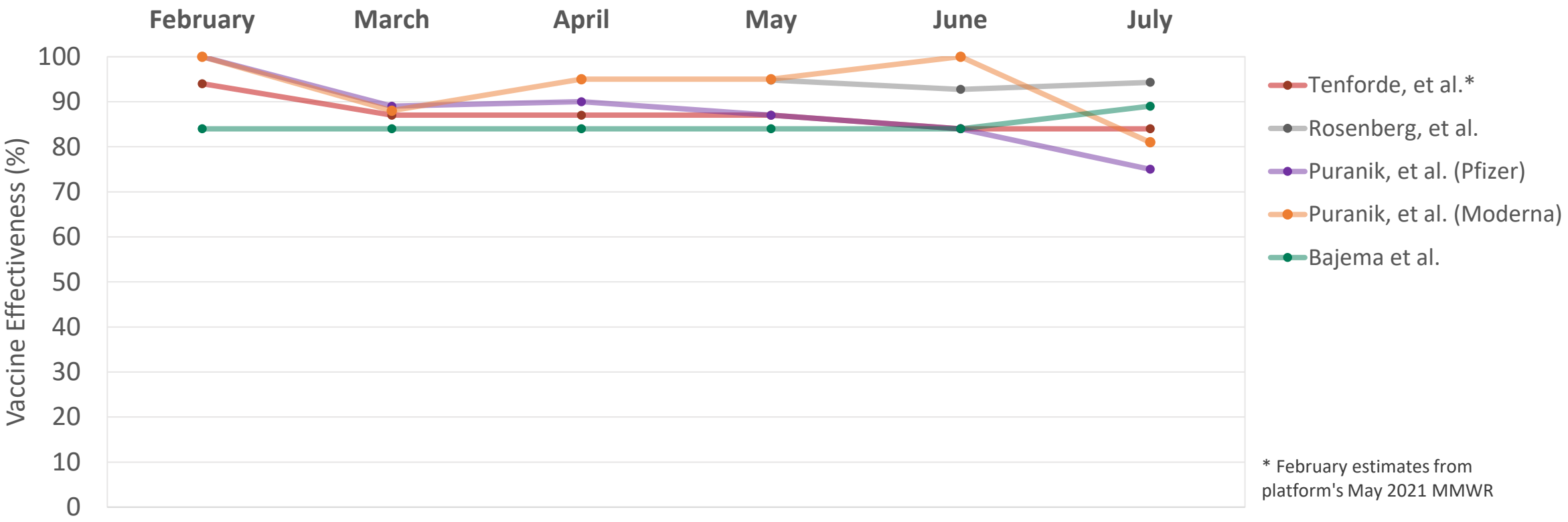
Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.
Nanduri S. Effectiveness of Pfizer-BioNTech and Moderna Vaccines in Preventing SARS-CoV-2 Infection Among Nursing Home Residents Before and During Widespread Circulation of the SARS-CoV-2 B.1.617.2 (Delta) Variant — National Healthcare Safety Network, March 1–August 1, 2021. MMWR Morbidity and Mortality Weekly Report. 2021 2021;70.
Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021.
Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707.
Keehner J, Horton LE, Binkin NJ et al. Resurgence of SARS-CoV-2 Infection in a Highly Vaccinated Health System Workforce. NEJM, September 1, 2021. DOI: 10.1056/NEJMc2112981

Vaccine effectiveness against **symptomatic infection**, by age and time since vaccination



Source: Unpublished ICATT data, 2021

Vaccine effectiveness against **hospitalization** by month
Adults ≥18 years of age

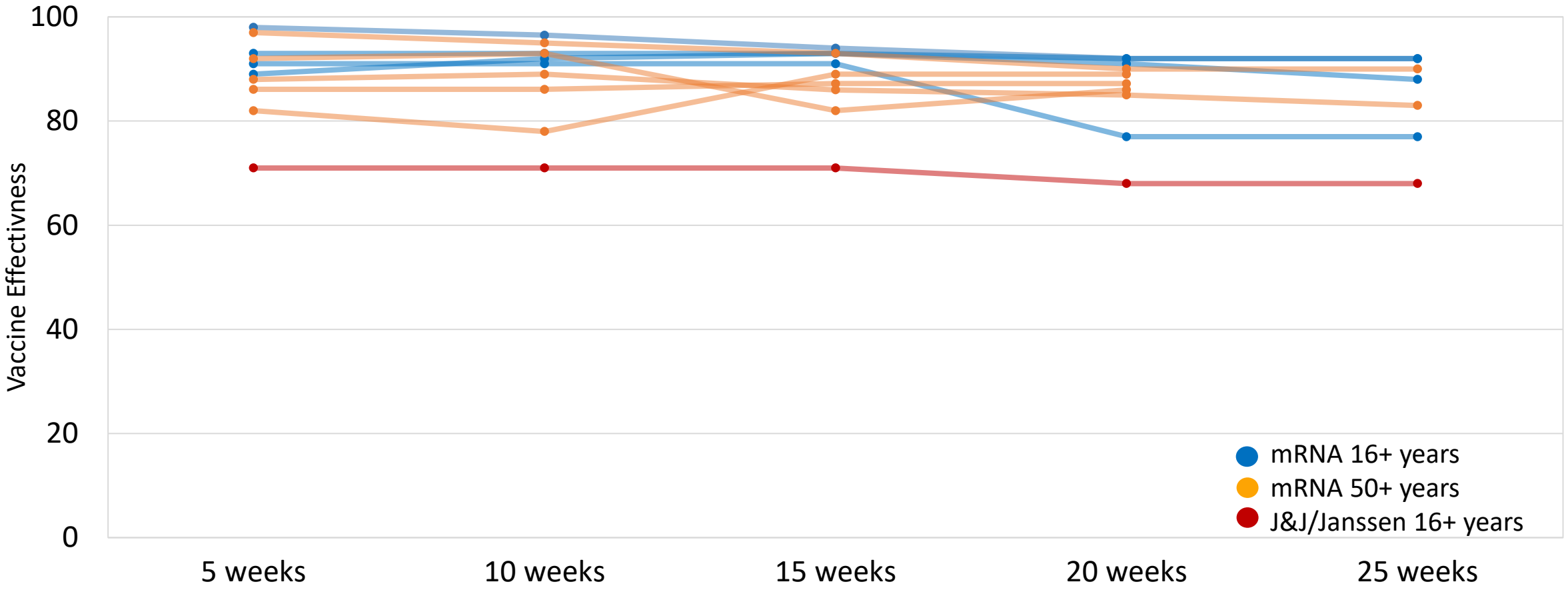


* February estimates from platform's May 2021 MMWR

Tenforde MW, Self WH, Naioti EA, et al. Sustained Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Associated Hospitalizations Among Adults — United States, March–July 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.
Tenforde MW, Olson SM, Self WH, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥65 Years — United States, January–March 2021. MMWR Morb Mortal Wkly Rep 2021;70:674–679.
Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status — New York, May 3–July 25, 2021. MMWR Morb Mortal Wkly Rep. ePub: 18 August 2021.
Puranik A, Lenehan PJ, Silvert E, et al. Comparison of two highly-effective mRNA vaccines for COVID-19 during periods of Alpha and Delta variant prevalence. medRxiv 2021.08.06.21261707.
Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep.

Vaccine effectiveness against **hospitalization** over time

Adults ≥16 years of age



Bajema KL, Dahl RM, Prill MM, et al. Effectiveness of COVID-19 mRNA Vaccines Against COVID-19–Associated Hospitalization — Five Veterans Affairs Medical Centers, United States, February 1–August 6, 2021. MMWR Morb Mortal Wkly Rep.

Thompson MG, Burgess JL, Naleway AL, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med 2021;385:320–9.

Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions — United States, March–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 17 September 2021.

Nunes et al. mRNA vaccines effectiveness against COVID-19 hospitalizations and deaths in older adults: a cohort study based on data-linkage of national health registries in Portugal. MedRXiv preprint.

Andrews et al. Vaccine effectiveness and duration of protection of Comirnaty, Vaxzevria and Spikevax against mild and severe COVID-19 in the UK. Preprint.

Tartof SY, Slezak JM, Fischer H, Hong V, Ackerson BK, Ranasinghe ON, et al. Six-month effectiveness of BNT162b2 mRNA COVID-19 vaccine in a large US integrated health system: a retrospective cohort study. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3909743

Summary

Vaccine effectiveness by age

- Significant declines in VE against **infection** in individuals ≥65 years of age for mRNA products in the Delta period
- Smaller declines in VE against **hospitalization** in individuals ≥65 years of age, but more substantial than younger populations
- Among adults <65 years of age: vaccines **remain effective** in preventing hospitalization and severe disease
- Vaccines may be less effective in preventing infection or symptomatic illness due to waning over time and the Delta variant

Public Health Problem:

Are booster doses of COVID-19 vaccines needed?

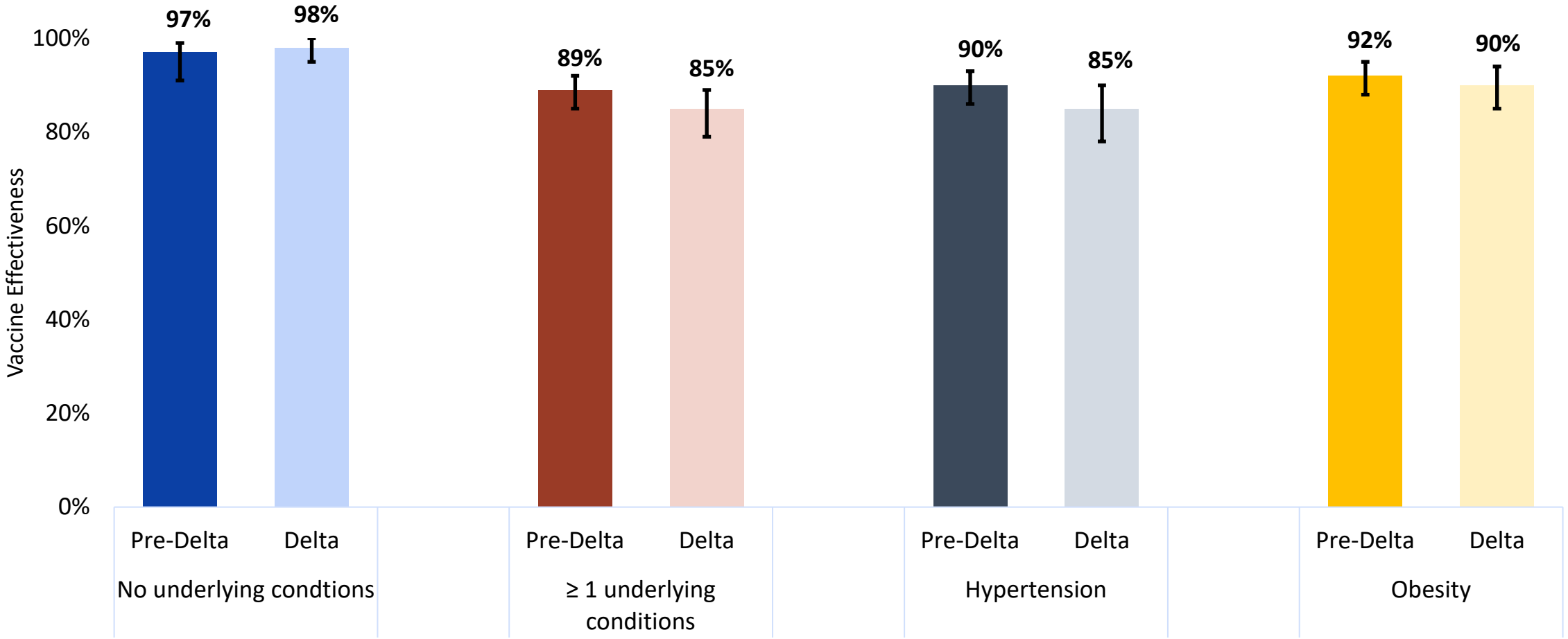
Is vaccine effectiveness (VE) waning by **age**?

Is VE waning for those with **underlying medical conditions**?

Is VE waning for those with **high-risk occupations**?

How do these data vary by **vaccine**?

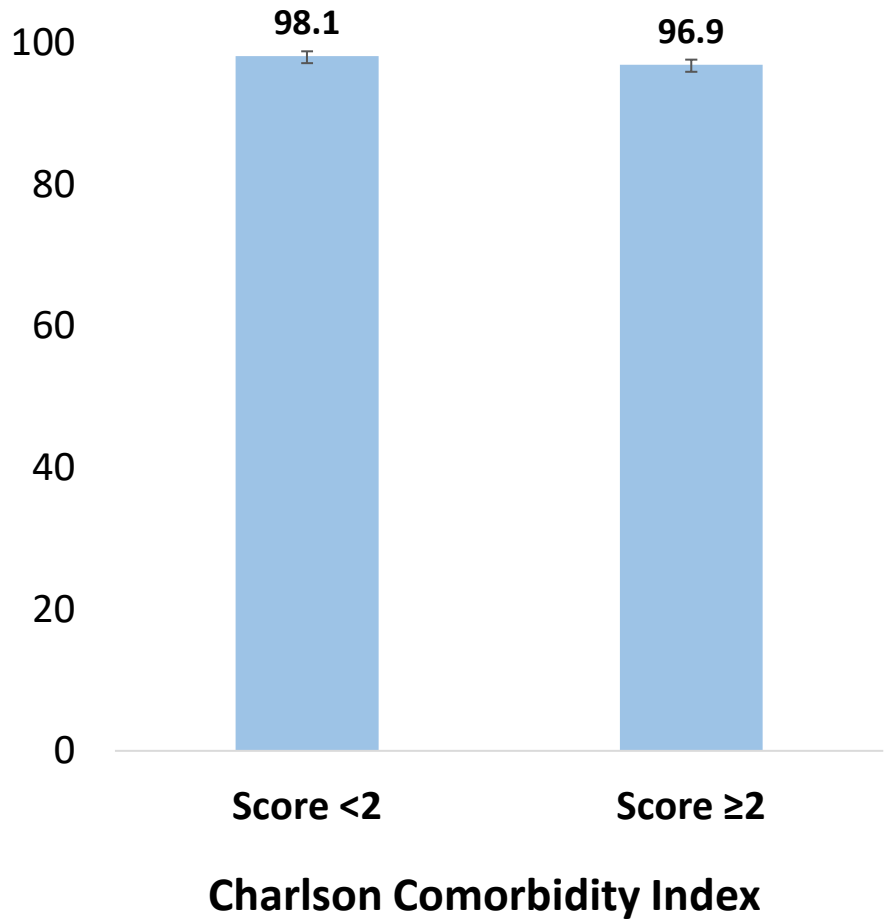
Vaccine effectiveness against **hospitalization** among adults with underlying medical conditions



Estimates controlled for age. Excludes individuals with immunocompromising conditions.

CDC unpublished, IVY Network

Vaccine effectiveness against **infection** among US veterans with underlying conditions, pre-Delta period



Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 Vaccine Effectiveness in a High-Risk National Population in a Real-World Setting. *Ann Intern Med*. 2021;M21-1577.

Summary

Vaccine effectiveness by underlying medical condition

- **Limited data** currently to evaluate VE by a variety of underlying medical conditions
  - Current data with limited waning in those with at least 1 underlying medical condition
- These estimates exclude immunocompromised individuals
- Estimates may not represent effectiveness across **all** underlying medical conditions
  - Cannot produce estimates for rare (and possibly more severe) underlying conditions
  - Spectrum of underlying medical conditions with a range of severity; may have varying impact in effectiveness

Public Health Problem:

Are booster doses of COVID-19 vaccines needed?

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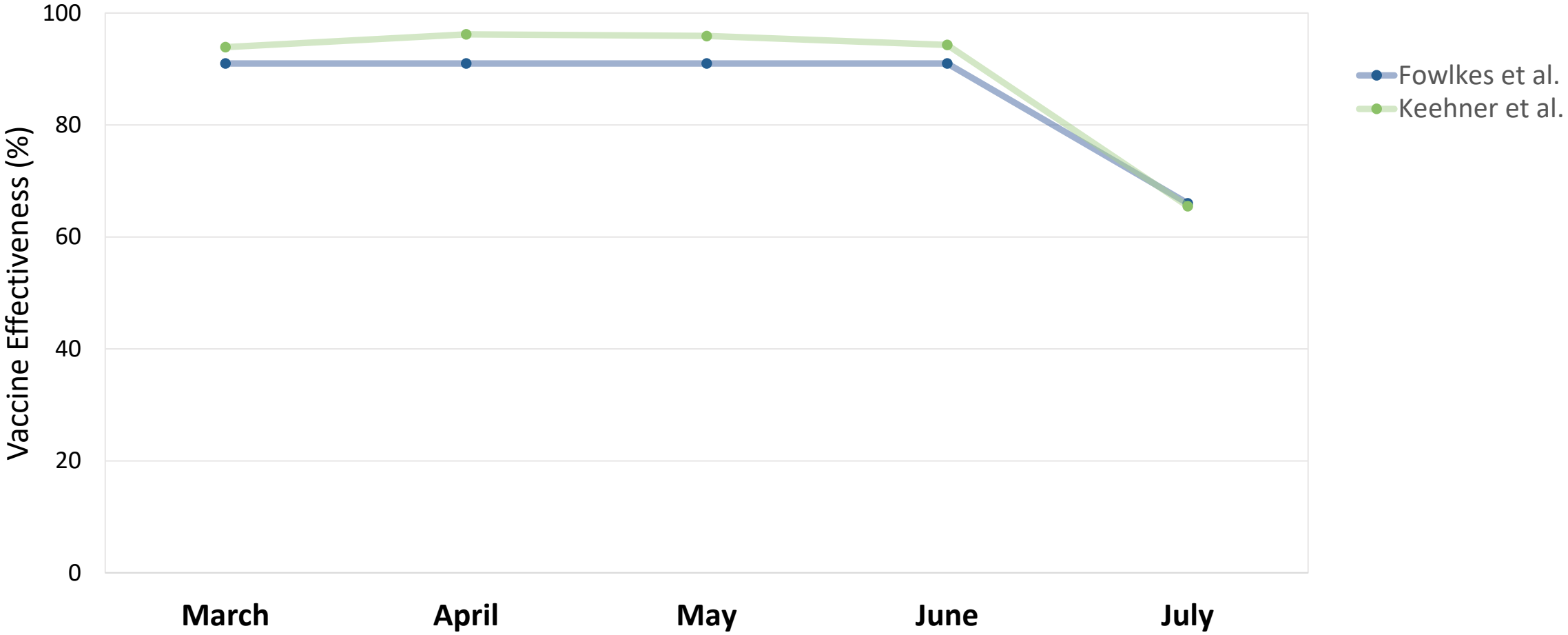
How do these data vary by **vaccine**?

Vaccine effectiveness against **infection** among healthcare providers, first responders and frontline workers



Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance — Eight U.S. Locations, December 2020–August 2021. MMWR Morb Mortal Wkly Rep. ePub: 24 August 2021.
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Summary

Vaccine effectiveness by high-risk occupation

- Effectiveness among healthcare and other frontline essential workers are similar to estimates for general population of the same age
- Severe disease among vaccinated essential workers is **rare**
- Vaccine effectiveness waning against **infections** in this population
  - Impact of lower VE against infections may be different among healthcare and other frontline essential workers
- Many prioritized for earlier doses of COVID-19 vaccines
  - Longer duration since primary series

Public Health Problem:
Are booster doses of COVID-19 vaccines needed?

Is vaccine effectiveness (VE) waning by **age**?

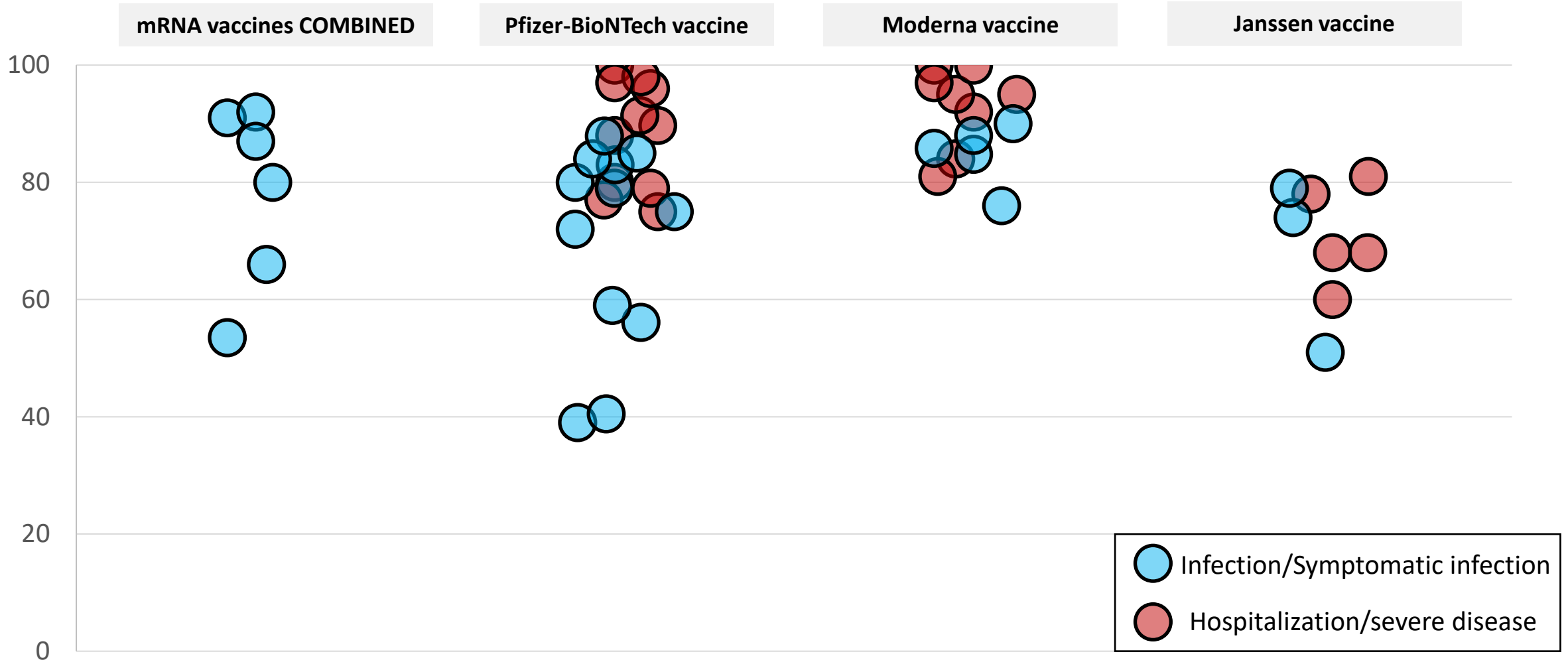
Is VE waning for those with **underlying medical conditions**?

Is VE waning for those with **high-risk occupations**?

How do these data vary by **vaccine**?

Summary of **VE estimates** since introduction of the Delta variant

Adults ≥18 years of age



See reference list in later slides

Summary

Vaccine effectiveness by vaccine

- Vaccine effectiveness varies by initial vaccine type
- Protection against **hospitalization** for mRNA vaccines **high**
- Protection against **infection** is lower for all vaccines

Summary

- Hospitalization rates are ~10X-22X higher in unvaccinated as compared to vaccinated adults
- Over 182 million people are fully vaccinated in the U.S.
- Although COVID-19 continues to be a public health problem, among persons who have received a primary series, data support continued protection against hospitalizations and deaths
  - Need to follow data around long-term outcomes among infections after vaccination

Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines

What is the balance of benefits and harms for booster doses by age?

Benefits and Harms:

What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine **safe** and **immunogenic** (GRADE)?

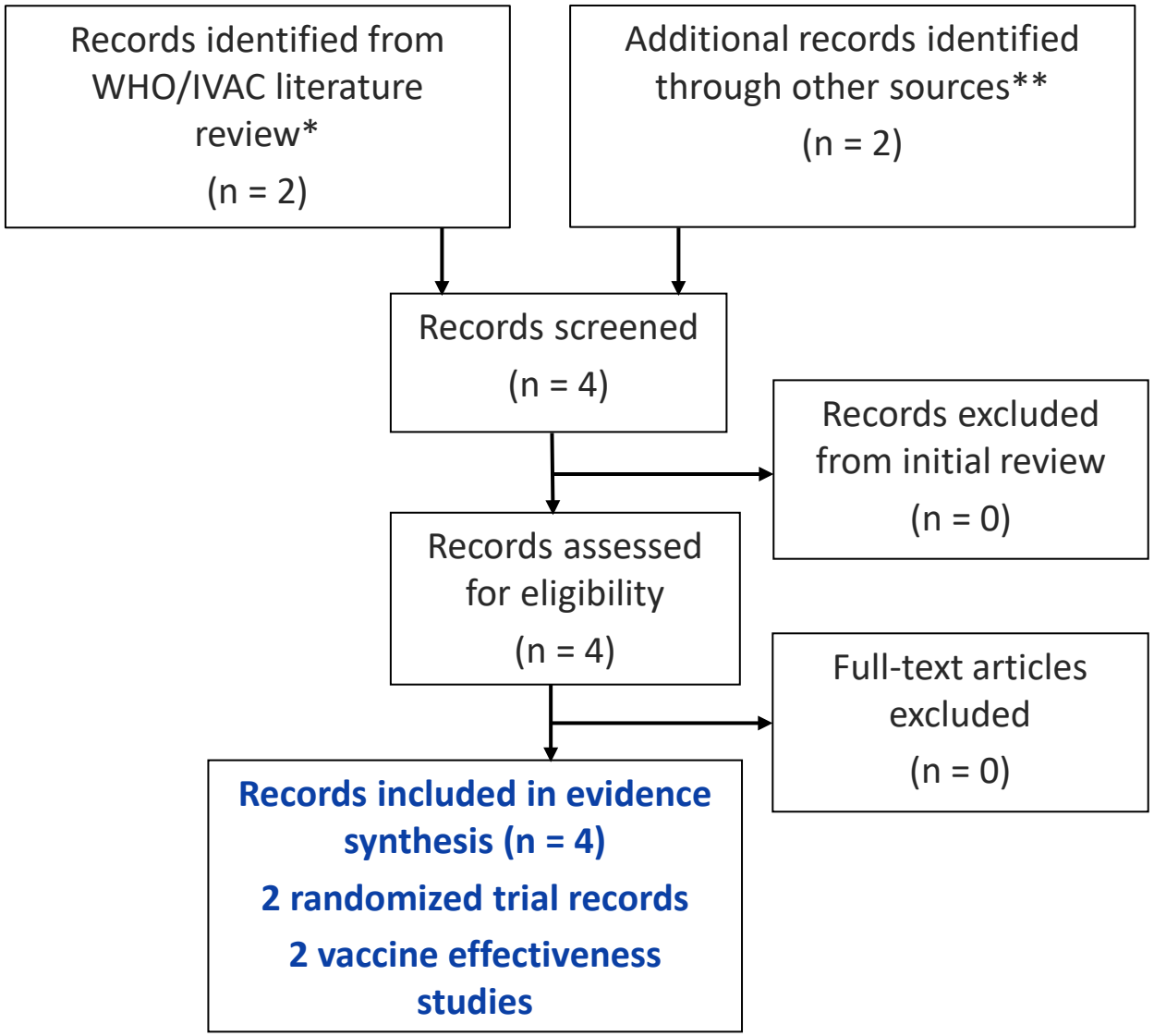
What is the **benefit/risk assessment** by age?

What is the summary of benefits and harms by **age** and **population**?

PICO Question

Population	Persons aged ≥18 years who completed a COVID-19 vaccine primary series ≥6 months ago
Intervention	Pfizer-BioNTech COVID-19 Vaccine BNT162b2 **booster dose** (30 µg, IM)
Comparison	No booster dose
Outcomes	Symptomatic laboratory-confirmed COVID-19 Hospitalization due to COVID-19 Death due to COVID-19 Transmission of SARS-CoV-2 infection Serious adverse events Reactogenicity

Evidence retrieval



Articles were eligible for inclusion if published or available on a pre-print server before 9/20/21.
-Criteria included in the ongoing systematic review conducted by the International Vaccine Access Center (IVAC) and the World Health Organization

*See https://view-hub.org/resources
** Phase 1 and Phase 2/3 Clinical Trail results from clinicaltrials.gov and other

Observational studies from Israel (n=2)

- Delta variant became dominant in Israel in mid-June
- Israel authorized a 3rd dose for immunocompromised residents on July 12, 2021, and for all residents ≥60 years on July 30, 2021
- Two studies have assessed the effectiveness of a 3rd dose:
  - Large studies: Data extracted from Ministry of Health national database or large health system database
  - Time since 2nd dose: ≥5 months
  - Control population: individuals that completed the 2 dose series

Cylus, J., Panteli, D. & van Ginneken, E. Who should be vaccinated first? Comparing vaccine prioritization strategies in Israel and European countries using the Covid-19 Health System Response Monitor. Isr J Health Policy Res 10, 16 (2021).
Bar-O et al. BNT162b2 vaccine booster dose protection: A nationwide study from Israel. medRxiv preprint Autust 31, 2021. doi: https://doi.org/10.1101/2021.08.27.21262679
Patalon et al. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. MedRxiv, August 31, 2021

Observational studies from Israel (n=2)

Documented Infection

Severe Disease

Bar-On et al.

July 25	26	27	28	29	30	31
Aug 1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	Sept 1	2	3	4

July 25	26	27	28	29	30	31
Aug 1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	Sept 1	2	3	4

exclusion window

follow up period

Patalon et al.

July 25	26	27	28	29	30	31
Aug 1	2	3	4	5	6	7
8	9	10	11	12	13	14
15	16	17	18	19	20	21
22	23	24	25	26	27	28
29	30	31	Sept 1	2	3	4

Both 3rd dose studies have short follow up periods, with a maximum of 21 days for documented infection and 16 days for severe disease

Bar-On YM, Goldberg Y, Mandel M, et al. Protection of BNT162b2 Vaccine Booster against Covid-19 in Israel [published online ahead of print, 2021 Sep 15]. *N Engl J Med*. 2021;10.1056/NEJMoa2114255.
Patalon et al. Short Term Reduction in the Odds of Testing Positive for SARS-CoV-2; a Comparison Between Two Doses and Three doses of the BNT162b2 Vaccine. MedRxiv, August 31, 2021

Outcome 1: Symptomatic laboratory-confirmed COVID-19 observational studies with dose 2 comparison group (n=2)

Location	Study	Population	Method[a]	Time period (dominant variant)	Days after booster dose	Control Group	Outcome	Booster vaccinees n/N (or person-time)	Dose 2 vaccinees n/N (or person-time)	Incremental VE (booster dose vs. dose 2)	95% CI
Israel[a]	Bar-On, September 2021	General population ≥60 years	Retrospective Cohort	7/30–8/31/21 (Delta)	≥12	Dose 2	Any infection	934 infections / 10,603,410 person-days	4,439 infections / 5,193,825 person-days	91.2%[b]	90.4–91.9%
Israel[a]	Patalon, August 2021 (preprint)	General population ≥40 years	Test Negative Design	8/1–8/21/21 (Delta)	14–20	Dose 2	Any infection	1,188 positive / 32,697 total tests	8.285 positive / 149,379 total tests	79%[c]	72–84%
			Matched case-Control					NR/30,295 booster vaccinees	NR/238,018 dose 2 vaccinees	70%[c]	62–76%

a. A minimum interval of 5 months after the 2nd dose is required to be eligible for the BNT162b2 booster dose in Israel. Israeli authorities approved a booster dose for "high risk-populations" on 7/12/21 and for persons aged ≥60 years on 7/30/21.
b. VE was calculated from the rate ratio reported in the manuscript. Rate ratio calculated using a Poisson regression model, adjusted for age (60–69, 70–79, ≥80), gender, demographic group (General Jewish, Arab, ultra-Orthodox Jewish), date of second vaccine dose (in half-month intervals), and calendar date.
c. VE calculated from odds ratios (and 95% CI) from logistic regression models, adjusted for 10-year age category, sex, time since vaccination category, comorbidities, and log number of positive tests.

NR: Not reported VE: vaccine effectiveness CI: confidence intervals

Evidence Table: Symptomatic laboratory-confirmed COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pfizer BioNTech COVID-19 Vaccine, 30 mcg, booster dose	Pfizer BioNTech COVID-19 Vaccine, 30 mcg, dose 2	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy against symptomatic COVID-19												
2	RCT	Very serious[a]	Not serious	Very serious[b]	Serious[c]	None	For Phase 2/3 trial participants aged 18-55, the ratio of geometric mean titers (GMT) of neutralizing antibodies at 1 month after booster dose (2,476.4 [2210.1, 2,774.9]) was noninferior to the GMT detected at 1 month after dose 2 (753.7 [95% CI 658.2, 863.1]). The geometric mean ratio was 3.29 (95% CI 2.76-3.91). Noninferiority was declared because the lower bound of the 2-sided 97.5% CI for the GMR is > 0.67 and the point estimate of the GMR is >=0.8.[d] For Phase 1 trial participants aged 65-85, the ratio of geometric mean titers (GMT) of neutralizing antibodies at 1 month after booster dose (1612.7 [875.5,2970]) was higher than the GMT detected at 1 month after dose 2 (195.8 [95% CI 114.7, 334.4]). The geometric mean ratio was 8.2 (95% CI for the point estimates do not overlap).[d]				**Type 4**	CRITICAL
1[e]	Obs	Not serious	Not serious	Very serious[f]	Not serious	None	934/1,137,804 (0.0%)[g]	4,439/1,137,804 (0.4%)[h]	**RR 0.09** (0.08 to 0.10)	277 fewer per 100,000 (from 290 to 275 fewer)	**Type 4**	CRITICAL

a. Concern for very serious risk of bias was present. Although a non-random subset of participants from the phase 3 trial were randomized to a booster dose or another investigational vaccine, none were randomized to a placebo, the only data available for GRADE were from a pre-post booster analysis.
b. Very serious concern for indirectness was noted because efficacy is inferred from immunobridging to the same participants after dose 2 of Pfizer-BioNTech COVID-19 vaccine, and because immunogenicity data were primarily for participants aged 18–55 years, which might not be representative of older participants.
c. Serious risk of imprecision was noted because number of study participants did not meet optimal information size.
d. Seroresponse was also assessed for noninferiority. 197/198 participants (99.5%) in the booster trial had a seroresponse at 1 month after booster dose, and 194/198 (98%) had a seroresponse at 1 month after dose 1, for a 1.5% difference (95% CI -0.7–3.7%). Noninferiority was declared because the lower bound of the 2-sided CI for the % difference is greater than -10. Seroresponse was not reported for Phase 1 trail participants.
e. The results of one study are shown. A second study (preprint) provided results for any SARS-C0V-2 infection, with a study population that overlapped with the included study, therefore results were not pooled. The additional study used test-negative design, and indicated a vaccine effectiveness of 79% (95% CI 72%-84%) for the booster dose compared to the primary series. This corresponds to a relative risk of 0.21 (95% CI 0.16–0.28).
f. Very serious concern for indirectness was noted. The outcome of the study was any SARS-CoV-2 infection, which was an indirect measure of the PICO outcome of symptomatic COVID-19. The short duration of follow-up likely limited assessment of VE.
g. The number of participants who received the booster dose was not known. The study population included 1,137,804 persons, who contributed 10,603,410 person-days to the booster cohort (≥12 days after booster; ≥ 5 months after dose 2).
h. The number of participants who did not receive the booster dose was not known. The study population included 1,137,804 persons, who contributed 5,193,825 person-days to the no booster cohort (2 vaccine doses).

CI: Confidence interval; **RR:** Risk ratio

Evidence Table: Hospitalization due to COVID-19

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pfizer BioNTech COVID-19 Vaccine, 30 mcg, booster dose	Pfizer BioNTech COVID-19 Vaccine, 30 mcg, dose 2	Relative (95% CI)	Absolute (95% CI)		
Vaccine efficacy against hospitalization due to COVID-19												
1	Obs	not serious	not serious	very serious[a]	not serious	none	29/1,137,804 (0.0%)[b]	294/1,137,804 (0.0%)[c]	**RR 0.05** (0.03 to 0.08)	26 fewer per 100,000 (from 27 to 25 fewer)	**Type 4**	CRITICAL

a. Very serious concern for indirectness was noted. The outcome of the study was severe COVID-19, which was an indirect measure of the PICO outcome of hospitalization for COVID-19. The short duration of follow-up likely limited an accurate assessment of VE.
b. The number of participants who received the booster dose was not known. The study population included 1,137,804 persons, who contributed 6,265,361 person-days to the booster cohort (≥12 days after booster; ≥ 5 months after dose 2).
c. The number of participants who did not receive the booster dose was not known. The study population included 1,137,804 persons, who contributed 4,574,439 person-days to the no booster cohort (2 vaccine doses).

CI: Confidence interval; **RR:** Risk ratio

Evidence Table: Harms

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pfizer BioNTech COVID-19 vaccine, 30 mcg, booster	no booster	Relative (95% CI)	Absolute (95% CI)		
Serious adverse events (follow up: median 2 months)												
1	randomized trials	very serious [a,b]	not serious	serious[c]	very serious[d]	none	1/306 (0.3%)[e]	43/10841 (0.4%)[b]	**RR 0.82** (0.11 to 5.96)	**71 fewer per 100,000** (from 353 fewer to 1,967 more)	**Type 4**	CRITICAL
Reactogenicity, grade >=3												
1	randomized trials	very serious [a,f]	not serious	serious[c]	serious[g]	none	19/289 (6.6%)	362/4108 (8.8%)[f]	**RR 0.62** (0.40 to 0.97)	**3,349 fewer per 100,000** (from 5,287 fewer to 264 fewer)	**Type 4**	IMPORTANT

a. Very serious risk of bias; although a non-random subset of participants from the phase 3 trial were randomized to a booster dose or another investigational vaccine, the only booster trial data available for GRADE were not according to randomization.
b. Comparison group is safety population, subgroup aged 16–55 years, with blinded follow-up from dose 1 to 1 month after dose 2, at the time of the data cut-off date for the Biologics Licensure Application to the FDA (March 13, 2021). Not all persons in the comparison group received two doses.
c. Serious concern for indirectness was noted because participants were restricted to persons aged 18–55 years and might not be representative of older participants.
d. Very serious concern for imprecision was present because the number of study participants did not meet optimal information size, and the 95% CIs for the relative and absolute risks include both benefits and harms. One event was observed among persons who received a booster dose.
e. One serious adverse event, a myocardial infarction, occurred 62 days after dose 3. This was judged by investigators to be unrelated to the intervention.
f. Comparison group based on any grade 3 reaction reported in all participants post dose 1 or 2, at the time of the data analysis prior to the Biologics Licensure Application to the FDA (March 13, 2021).
g. Serious risk of imprecision was noted because number of study participants did not meet optimal information size.

CI: Confidence interval; **RR:** Risk ratio

Lymphadenopathy was more common after the 3rd dose than after the 2nd dose

- 16/306 participants (5.2%) in the Phase 3 trial (adults 18–55 years) reported lymphadenopathy
  - All 16 subjects had axillary lymphadenopathy
  - One subject also had lymphadenopathy reported in the neck
  - One severe event of lymphadenopathy was reported by 1 participant (onset of 2 days post-booster), recovered/resolved 5 days from onset
- Lymphadenopathy was observed more frequently following the booster dose than after primary series doses (**5.2**% compared to **0.4**%)

Clinical trial data requested by CDC.

Safety data regarding 3rd dose Pfizer-BioNTech COVID-19 vaccination, Israel

- 3rd doses became authorized for all adults ≥60 years on July 30, 2021
  - Expanded to ≥12 years at the end of August
- ~2.8 M 3rd doses administered to persons ≥12 years (through September 13)
  - Most to persons **≥60 years**
- Rates of reported systemic, local, neurologic, allergic, and other reactions were substantially lower after dose 3 than after dose 1 or 2. Suspected under-reporting
- 1 case of myocarditis in individual ≥30 years of age
  - Due to limited follow up time, unable to determine rates of myocarditis in younger adults from Israeli data available to date

https://www.fda.gov/media/152205/download

Summary of GRADE

Outcome	Importance	Design (# of studies)	Findings	Evidence type
Benefits				
Symptomatic laboratory-confirmed COVID-19	Critical	RCT (2) OBS (1)	Pfizer-BioNTech COVID-19 booster dose induced immune responses (GMR, seroresponse) noninferior to those following dose 2. Observational data suggest increased protective effect against any SARS-CoV-2 infection.	**4**
Hospitalization due to COVID-19	Critical	RCT (0) OBS (1)	Observational data suggest increased protective effect against severe COVID-19.	**4**
Death due to COVID-19	Important	RCT (0) OBS (0)	No data available.	**ND**
Transmission of SARS-CoV-2 infection	Important	OBS (0)	No data available.	**ND**
Harms				
Serious adverse events	Critical	RCT (1)	No SAEs were attributed to booster dose.	**4**
Reactogenicity	Important	RCT (1)	Grade ≥3 reactogenicity was reported by 6.6% of booster dose recipients.	**4**

Evidence type: 1=high; 2=moderate; 3=low; 4=very low; ND, no data

Benefits and Harms:

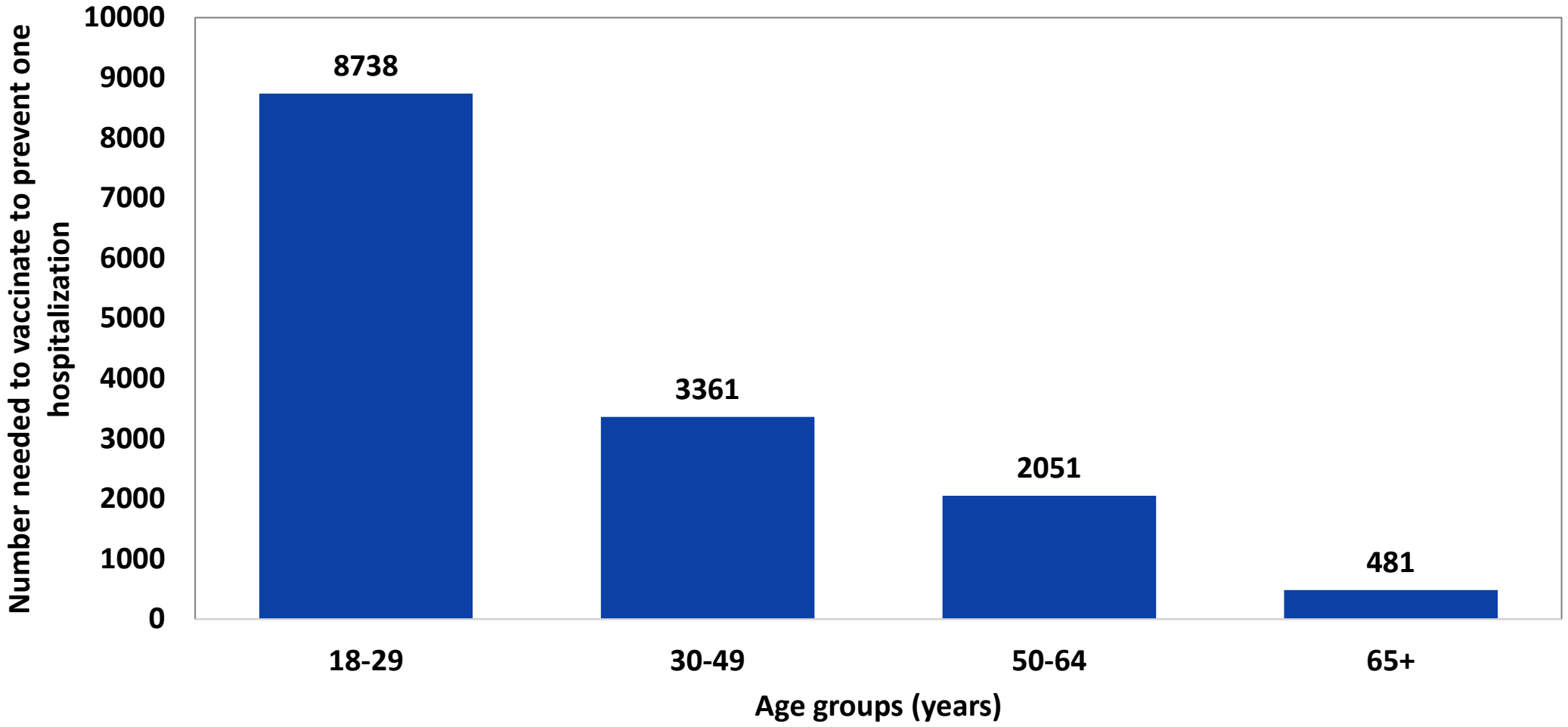
What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine **safe** and **immunogenic** (GRADE)?

What is the **benefit/risk assessment** by age?

What is the summary of benefits and harms by **age** and **population**?

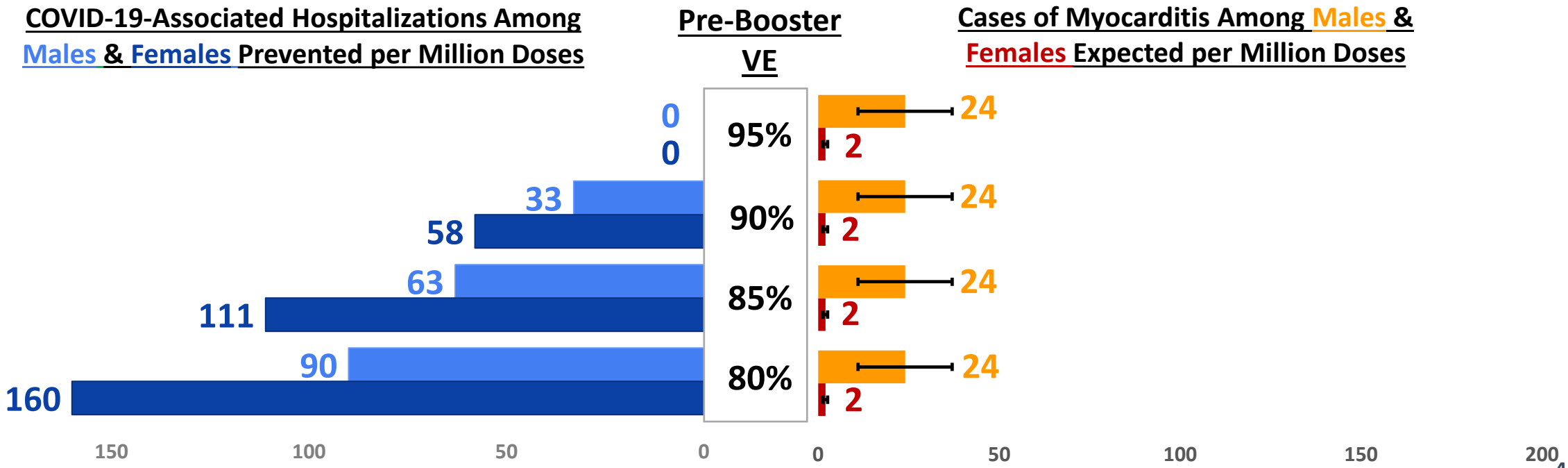
Number needed to vaccinate with booster dose to prevent one hospitalization over 6 months



Benefits and risks after Pfizer-BioNTech COVID-19 vaccination for persons aged 18 – 29 years, by sex

For every million doses of vaccine given

Benefit/risk balance among younger population varies by sex, VE after booster dose, rates of myocarditis, and incidence.
As incidence declines, **more uncertainty** around the balance of benefits and risks



[1]https://www.cdc.gov/mmwr/volumes/70/wr/mm7037e1.htm?s_cid=mm7037e1_w.

Summary

Benefit/risk assessment

- Risks of myocarditis after a 3rd dose of mRNA vaccines is **unknown**
  - After 2nd dose, risk varies by **age** and **sex**
- Benefit/risk balance is the most favorable for **adults ≥65 years of age** using current estimates of vaccine effectiveness
- Benefit/risk balance among younger population **varies** by sex, VE after booster dose, rates of myocarditis, and incidence. As incidence declines, more **uncertainty** around the balance of benefits and risks

Benefits and Harms:

What is the balance of benefits and harms for booster doses by age?

Are booster doses of the COVID-19 vaccine **safe** and **immunogenic** (GRADE)?

What is the **benefit/risk assessment** by age?

What is the summary of benefits and harms by **age** and **population**?

Summary-balance of benefits and harms for booster doses

- Data from clinical trial limited in size (n~300) and age (primarily 18-55 years)
- Booster dose of Pfizer-BioNTech COVID-19 vaccine **increases immune response** in those who have completed a primary series approximately 6 months previously
- Individual benefit/risk balance **varies by age**
  - Largest benefit from vaccination of individuals ≥65 years of age
  - Benefit to other ages incrementally smaller, given higher VE maintained from primary series
  - Even within age categories, likely variation within balance of benefits and risks given risk of exposure, medical condition and sex
- Unable to account for other benefits
  - Possible impact on rates of community transmission

Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines

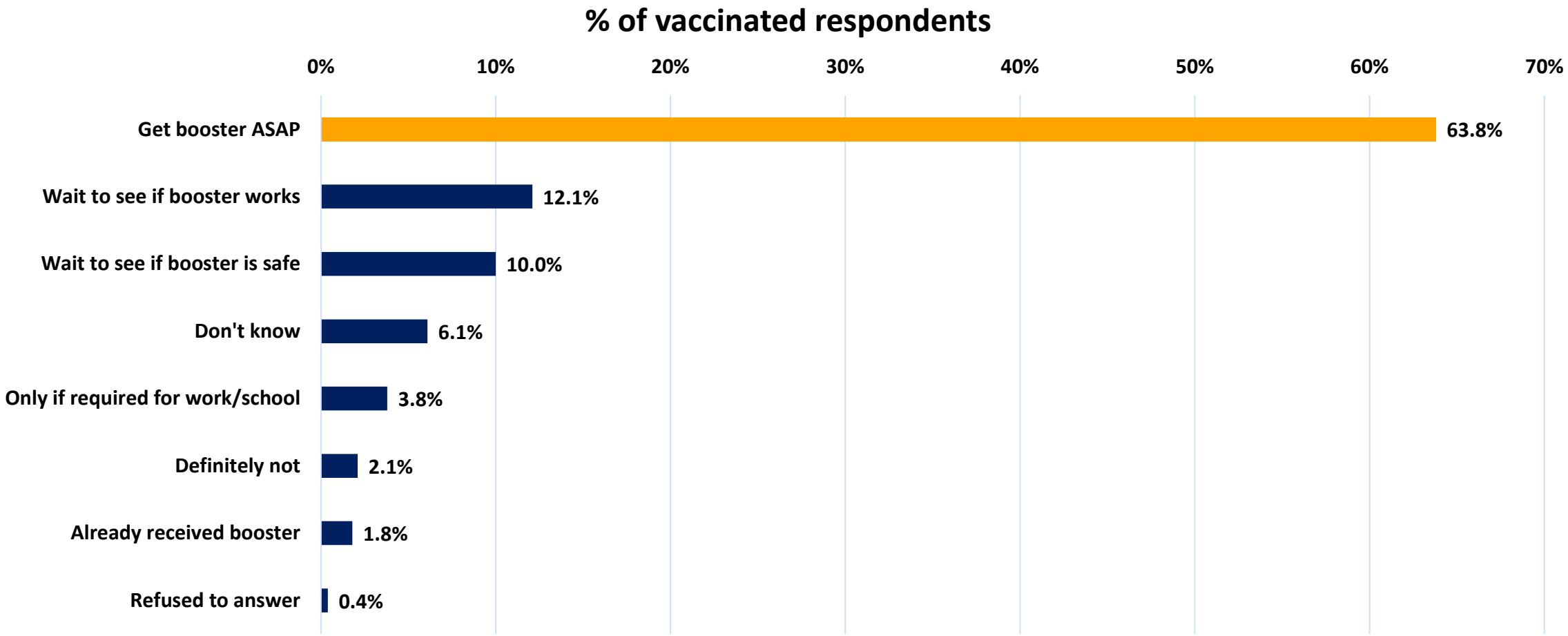
Do people want a booster dose?

Values and Acceptability

- In published surveys completed in August (n=5), **76%-87%** of vaccinated adults reported they would get a booster dose, if available[1-5]
  - In one survey, this increased to 93% of surveyed adults if it was recommended by their primary care provider

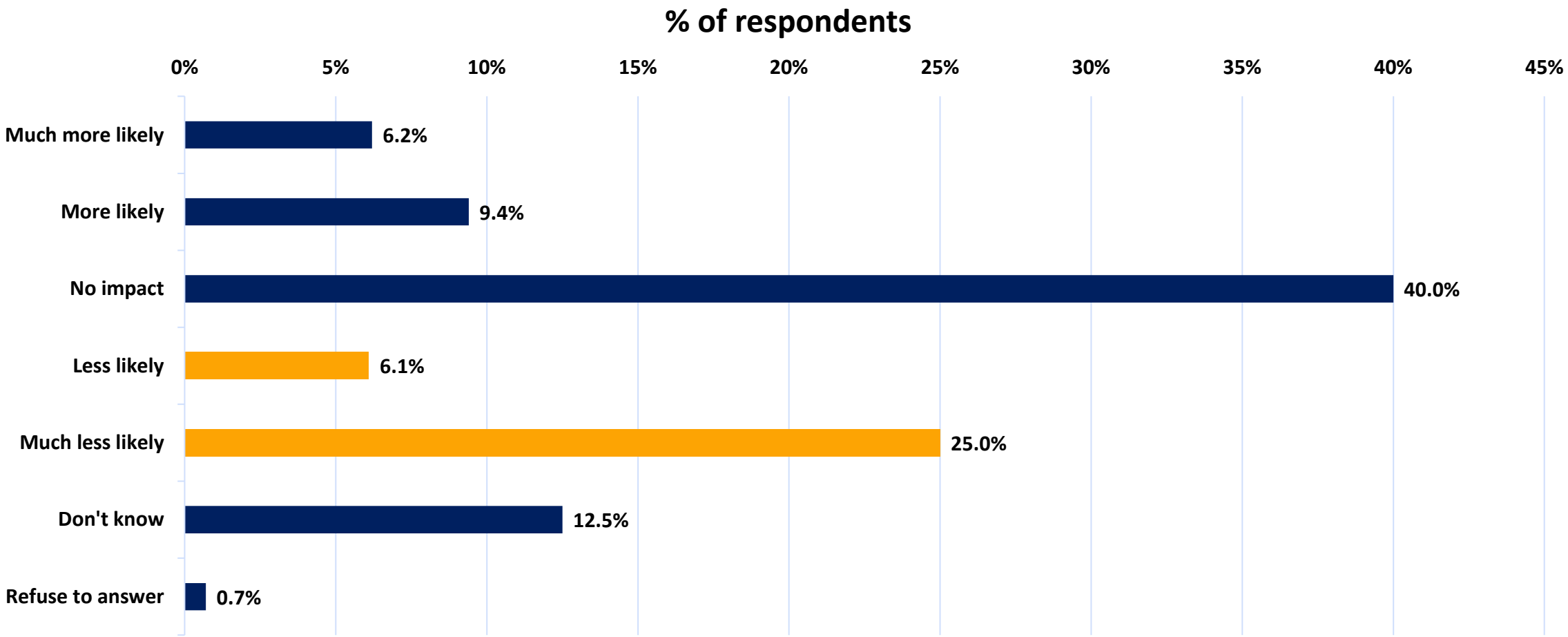
1. Axios Ipsos Poll. August 2, 2021.
2. Axios Ipsos Poll. August 30, 2021.
3. Marist Poll. September 3, 2021. https://maristpoll.marist.edu/polls/npr-pbs-newshour-marist-national-poll-covid-september-3-2021/
4. Morning Consult Poll. August 25, 2021. https://morningconsult.com/2021/08/25/covid-booster-shot-poll/
5. Reuters/Ipsos Poll. September 1, 2021. https://www.reuters.com/business/healthcare-pharmaceuticals/most-vaccinated-americans-want-covid-19-booster-shots-reutersipsos-poll-2021-09-01/

Around 2/3 of vaccinated respondents said they would get a COVID-19 booster vaccine



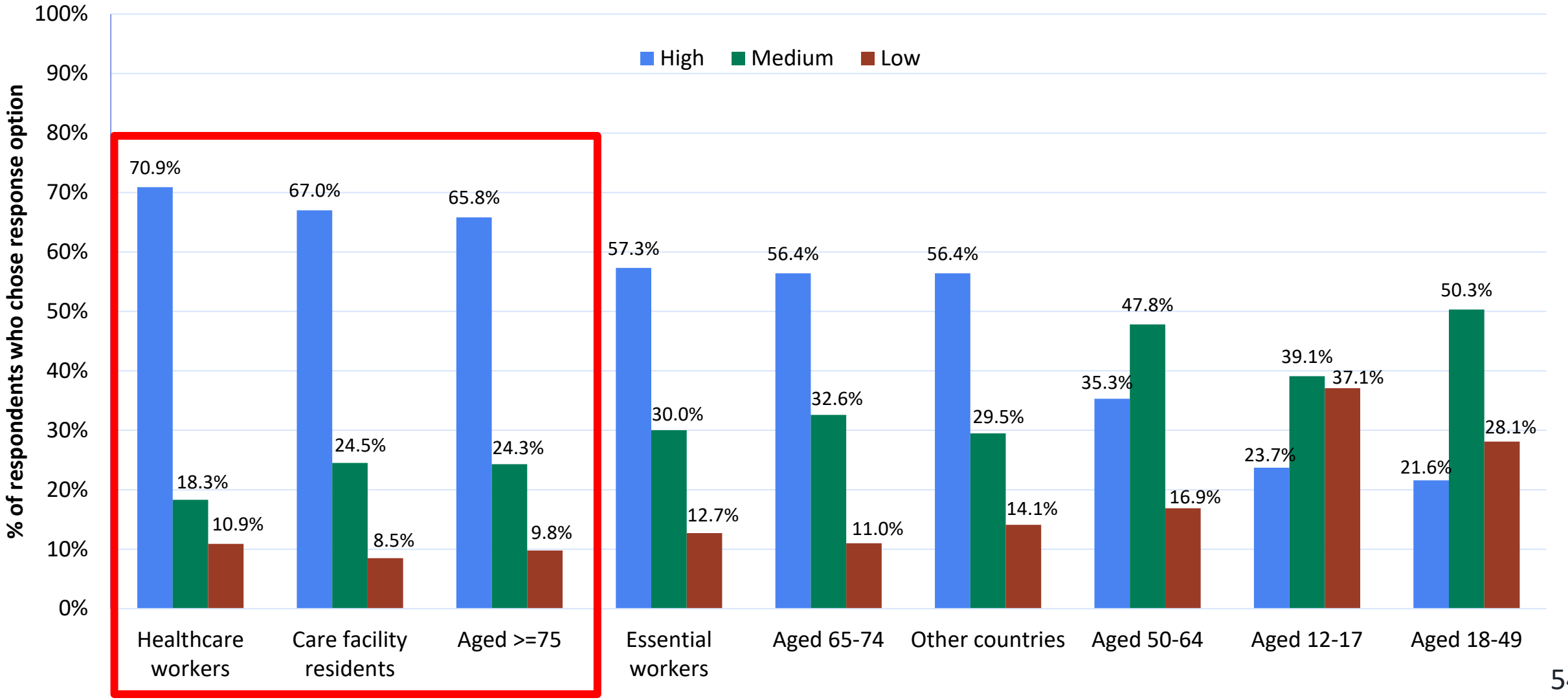
CDC/University of Iowa unpublished data, August 2021

Around 1/3 of unvaccinated respondents said that COVID-19 booster vaccines would make them less likely to get vaccinated at all



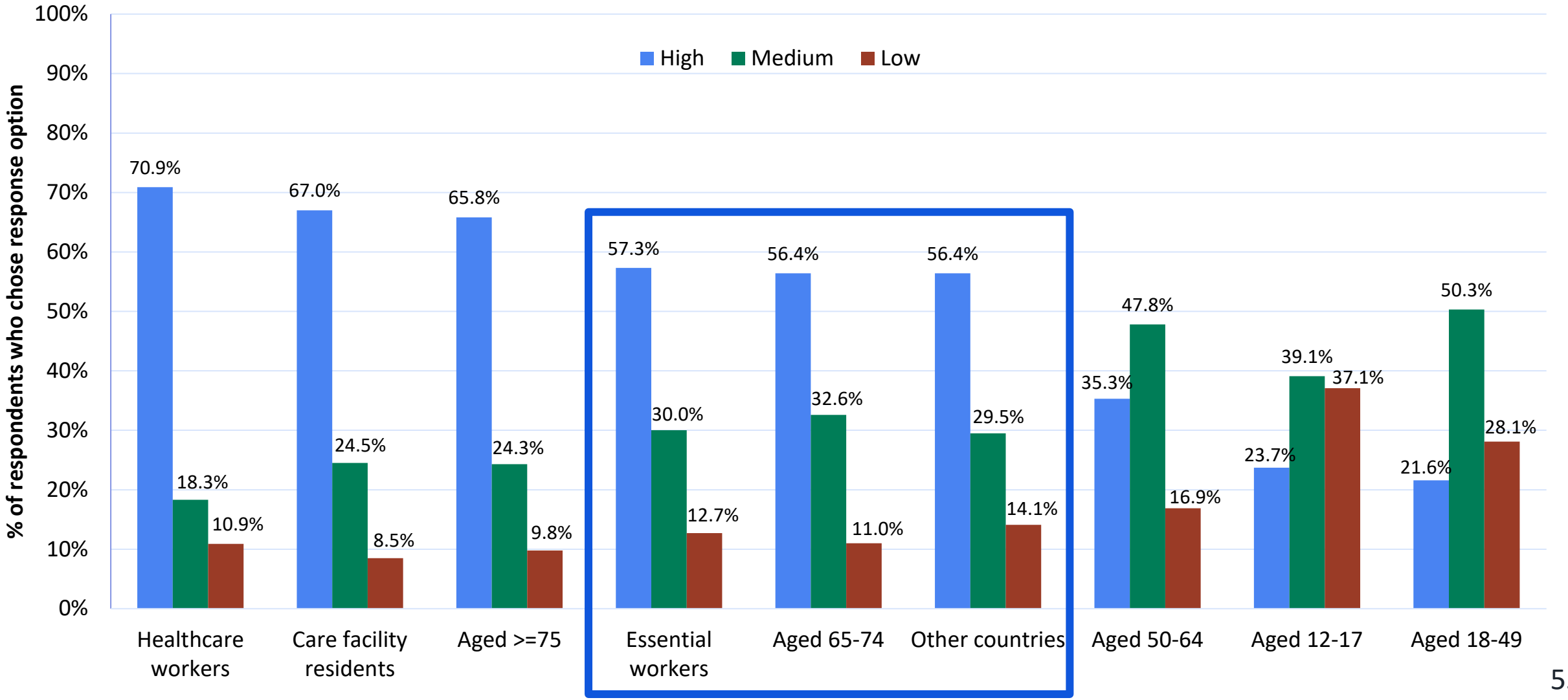
CDC/University of Iowa unpublished data, August 2021

At least 2/3 of respondents believed that healthcare workers, LTCF residents and adults ≥75 should be prioritized for booster doses



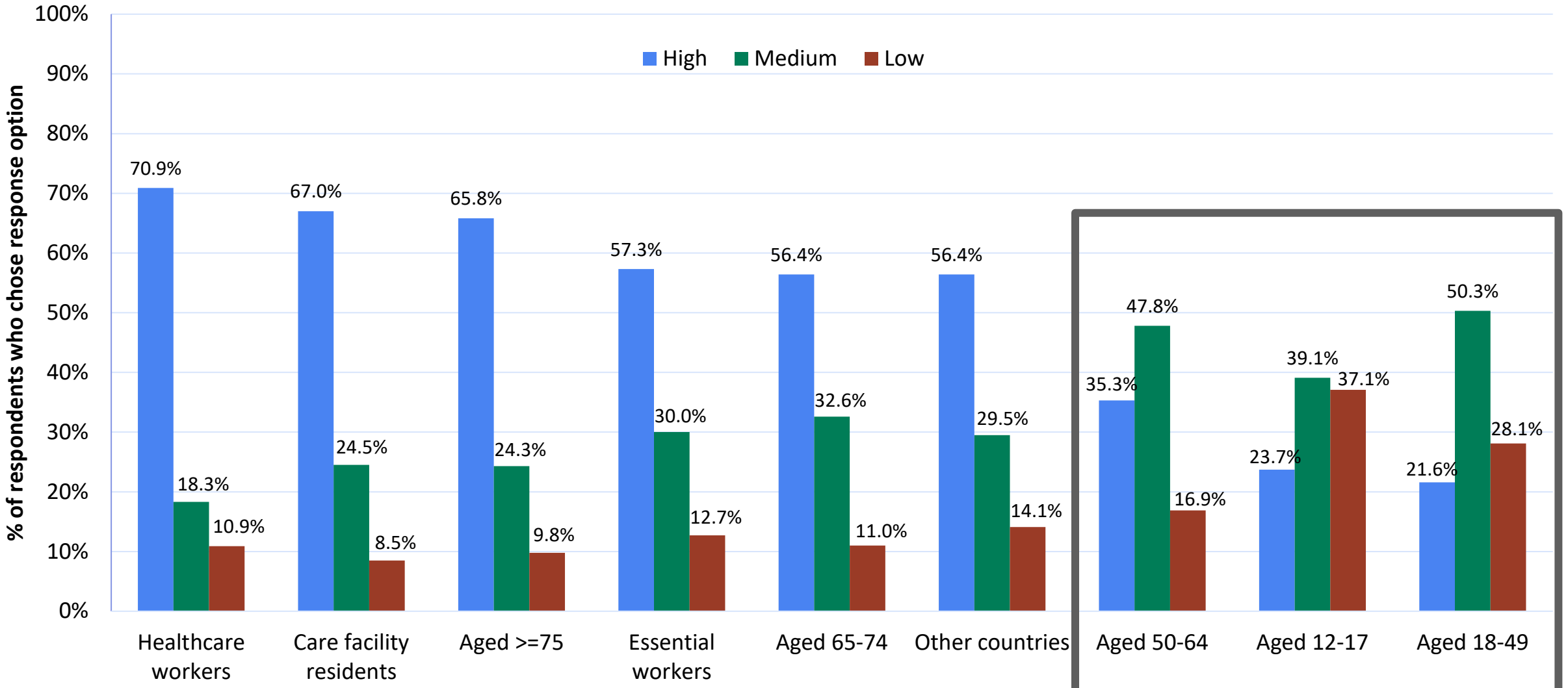
CDC/University of Iowa unpublished data, August 2021

Over half felt that essential workers, adults aged 65–74 years of age and other countries should be recommended for booster doses



CDC/University of Iowa unpublished data, August 2021

Adults ≤64 years were the least prioritized groups for booster doses



CDC/University of Iowa unpublished data, August 2021

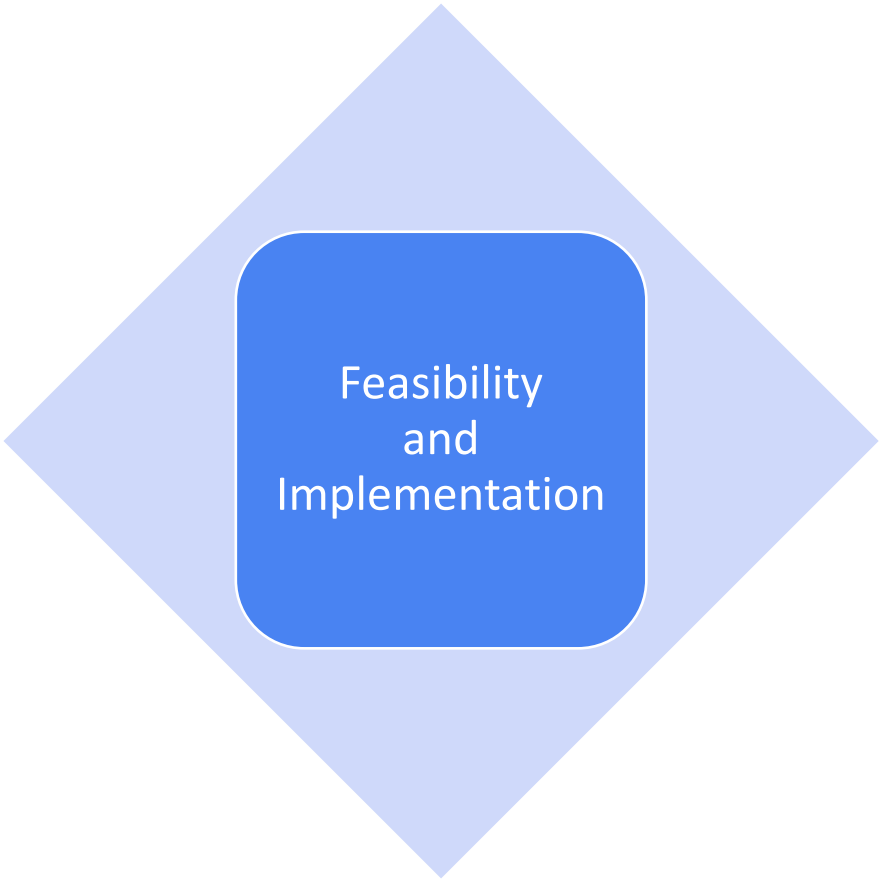
Summary

Values and Acceptability

- At least **2/3** of vaccinated adults willing to receive a booster dose
- Survey respondents prioritized older adults and healthcare workers for booster doses; younger adults less prioritized

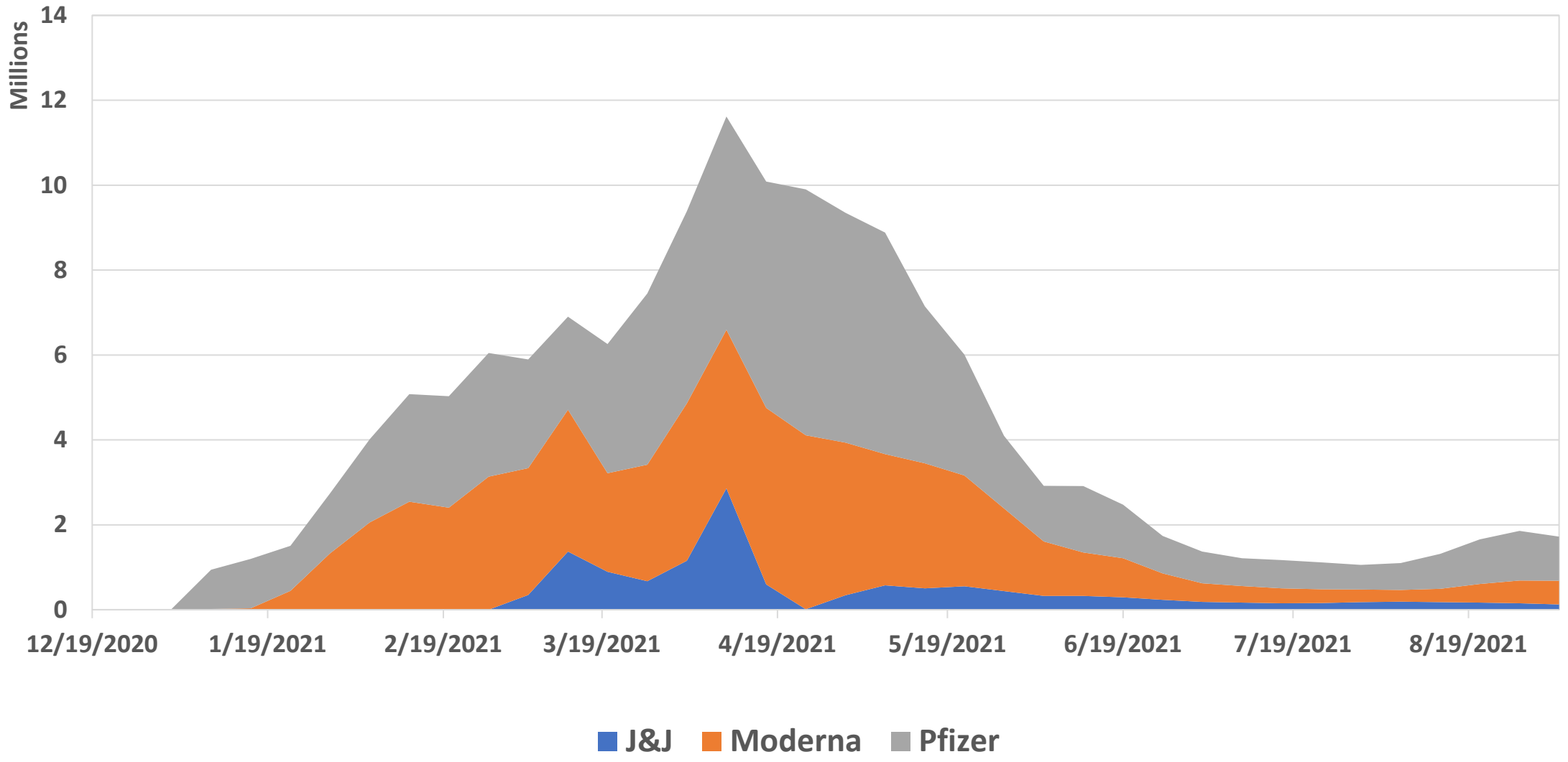
Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines



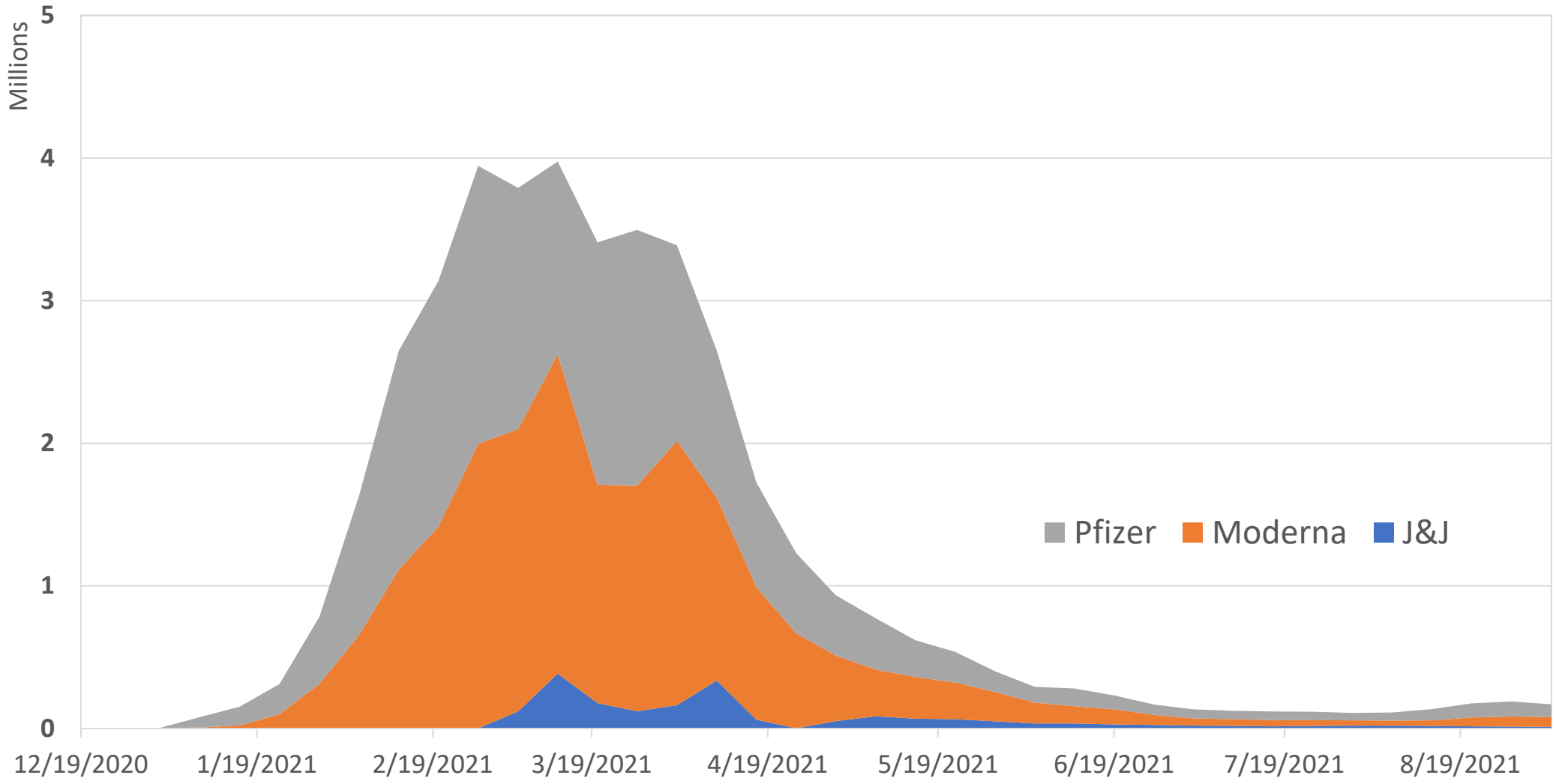
How would booster doses be implemented?

Completed primary vaccination series by week



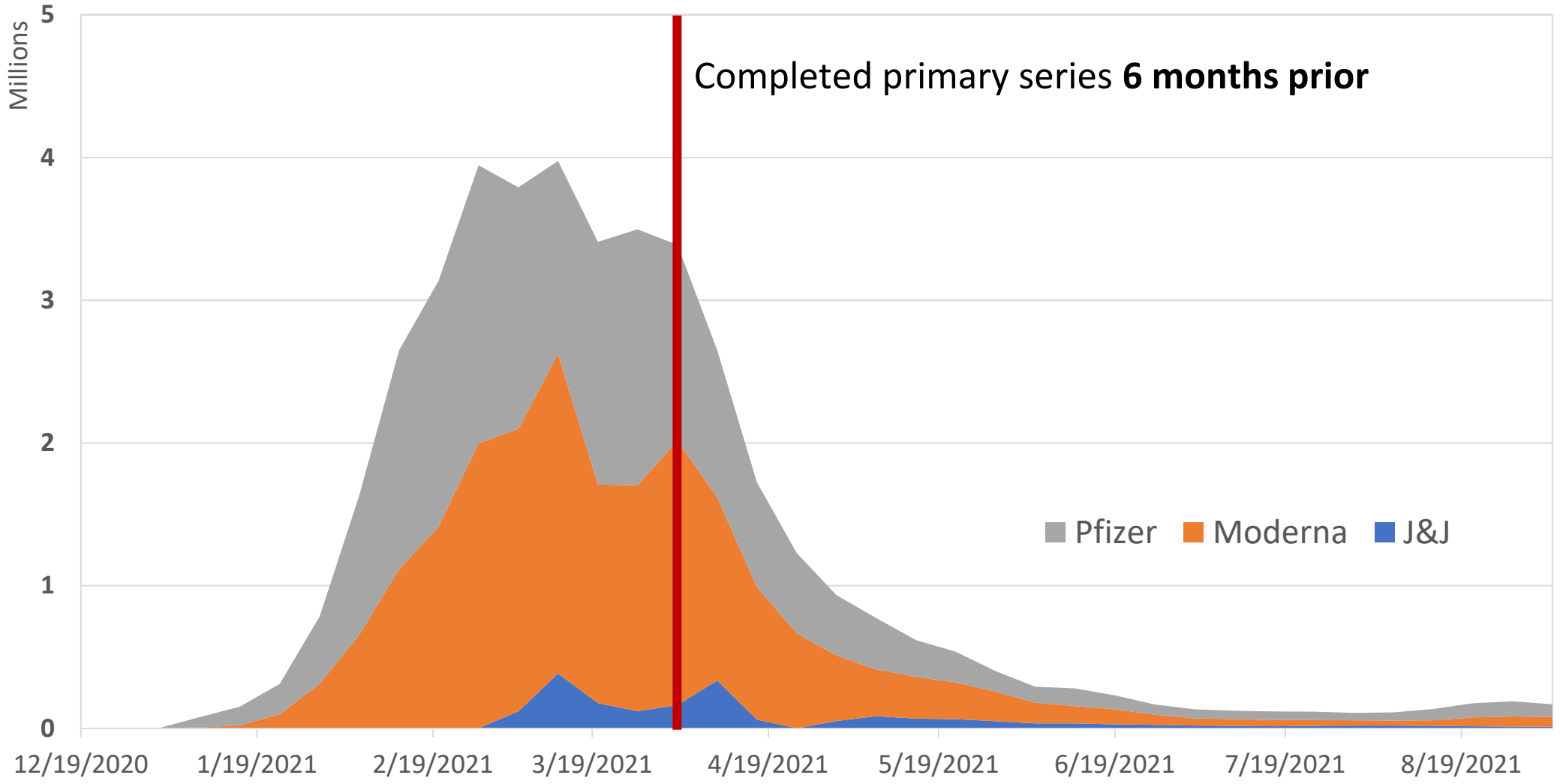
Completed primary vaccination series by week:

Adults ≥65 years of age

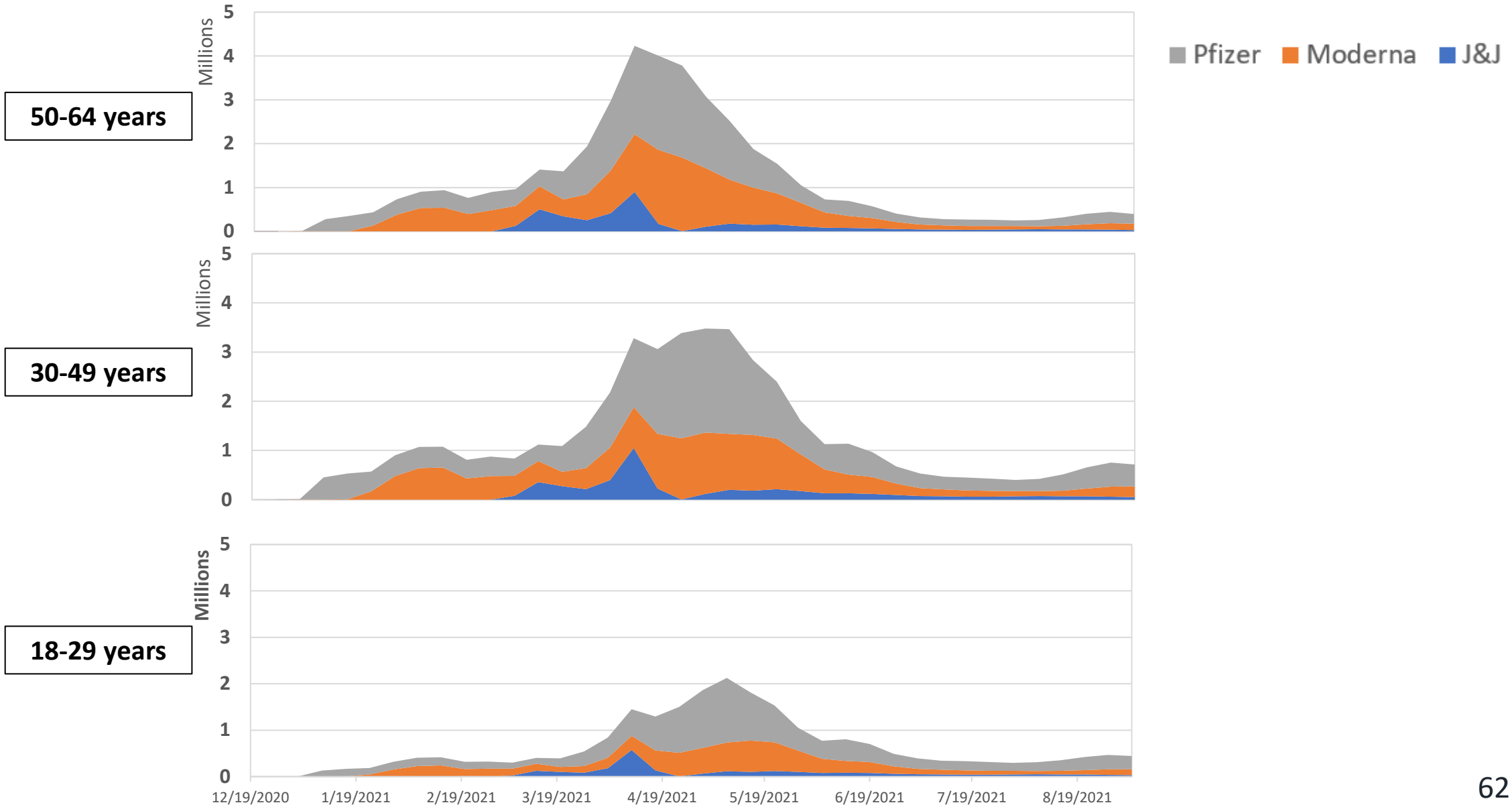


Completed primary vaccination series by week:

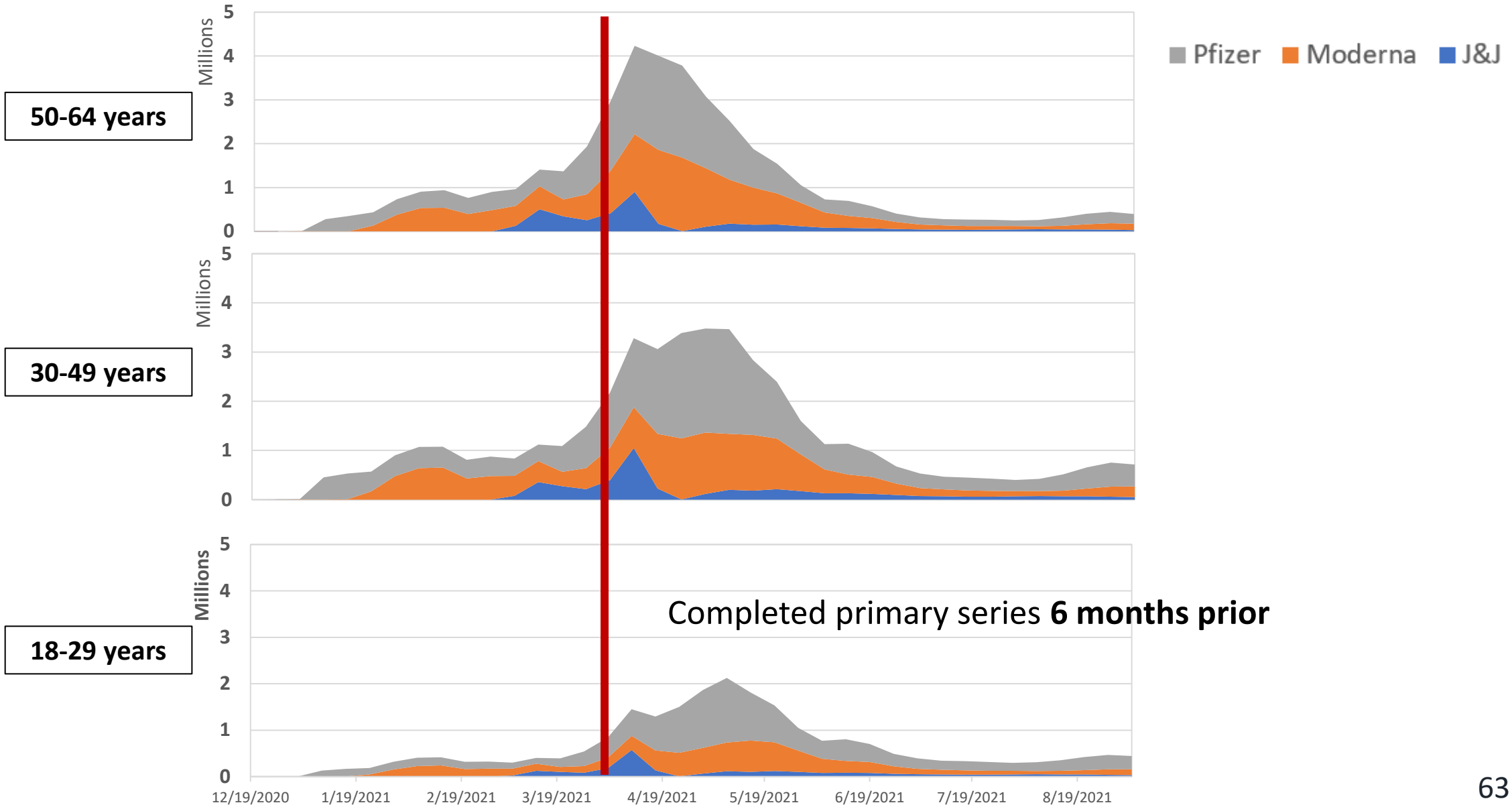
Adults ≥65 years of age



Completed primary vaccination series by week and age



Completed primary vaccination series by week and age



Number of persons eligible (in millions) for a booster dose on September 27th, 2021

	≥6 months after primary series			
Age group	**Pfizer-BioNTech**	**Moderna**	**Janssen/J&J**	**Total**
18-29 years old	2.0	1.5	0.3	**3.9**
30-49 years old	5.5	4.4	0.9	**10.8**
50-64 years old	5.3	4.4	1.2	**11.0**
65+ years old	13.6	12.9	0.8	**27.4**
Total	**26.4**	**23.4**	**3.3**	**53.0**

Jurisdictional preparations

- Jurisdictions have begun preparing for implementation of booster doses
- Booster doses likely given in a variety of settings: pharmacies, providers offices, health departments, occupational clinics and federal programs (e.g., LTCF program)
  - Over 70% of current COVID-19 vaccine administration occurring in **pharmacies**
- Many jurisdictions experiencing surge in cases of COVID-19, outreach for unvaccinated individuals to receive primary series, fall/winter influenza campaigns

Implementation

Variation in primary series receipt

- 3 vaccines are currently being administered in the United States
- For **additional doses** of **mRNA vaccines** in immunocompromised persons, the current recommendations state that the additional dose should be the same product as the primary series.
  - If the product given for the first 2 doses is not available, the other vaccine product may be administered
- Evidence reviewed by FDA only evaluated a booster dose of Pfizer-BioNTech vaccine after completion of a Pfizer-BioNTech primary series

Implementation

Long-term care facility (LTCF) residents

- LTCFs can arrange for an on-site vaccination clinic or help residents access vaccine in local community
  - Federal LTCF program can help implement vaccination in long-term care settings
- 8.1 million doses administered during original LTCF program (December 2020-March 2021): 6.2M (**76**%) were Pfizer-BioNTech, 1.9M (**24**%) were Moderna
- LTCFs can have substantial turnover over time:
  - 30% per month for residents
  - 100% per year for staff

Implications for public health recommendations

Definition of ‘fully vaccinated’

- Current CDC clinical considerations state:

“For public health purposes, immunocompromised people who have completed a primary vaccine series (i.e. 2-dose mRNA vaccine series or a single dose of the Janssen vaccine) are considered fully vaccinated ≥2 weeks after completion of the primary series”

- Based on current data, the definition of ‘**fully vaccinated**’ would remain the same after recommendations for booster dose
  - Fully vaccinated ≥2 weeks after completion of the primary series

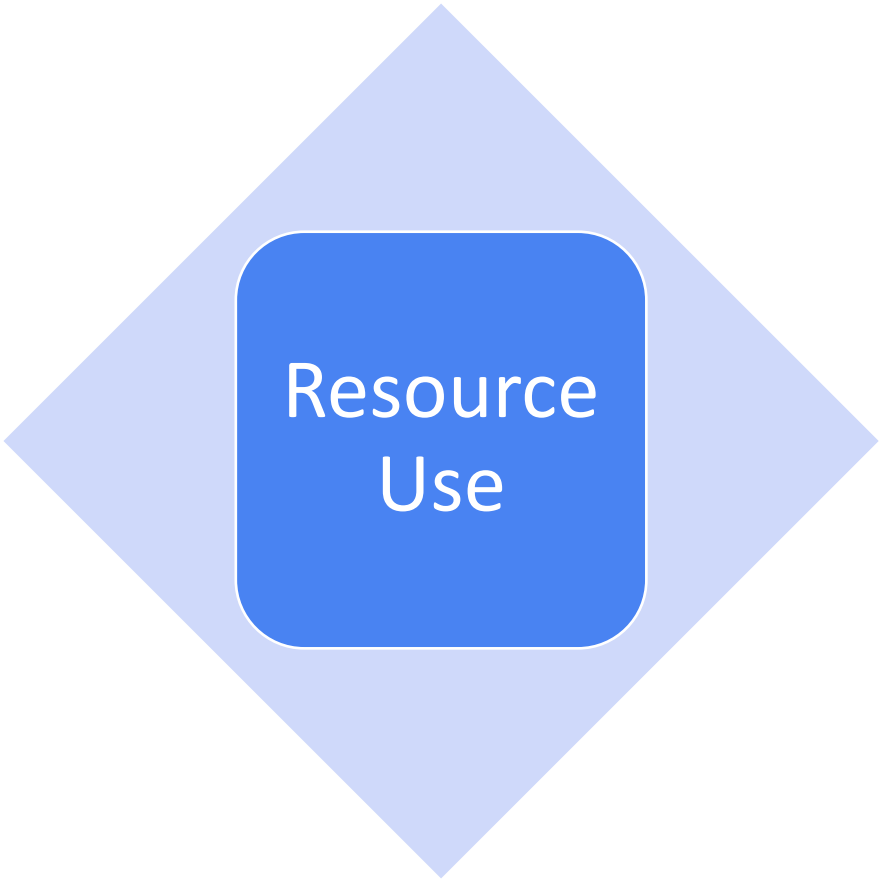
https://www.cdc.gov/vaccines/covid-19/clinical-considerations/covid-19-vaccines-us.html

Summary - Feasibility and Implementation

- To date, >220 million doses of Pfizer-BioNTech Covid-19 vaccine have been administered in the U.S., demonstrating that the vaccine is feasible to implement
  - ~2.24 million individuals have received an additional dose
- Over **27 million** adults ≥65 years of age completed their primary series ≥6 months ago
  - Over **50 million** adults ≥18 years of age completed their primary series ≥6 months ago
- Pharmacies delivering majority of COVID-19 vaccines currently
- Recommendations that are **clear** and **simple** will facilitate implementation

Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines



What is the cost associated with booster doses?

Summary - Resource Use

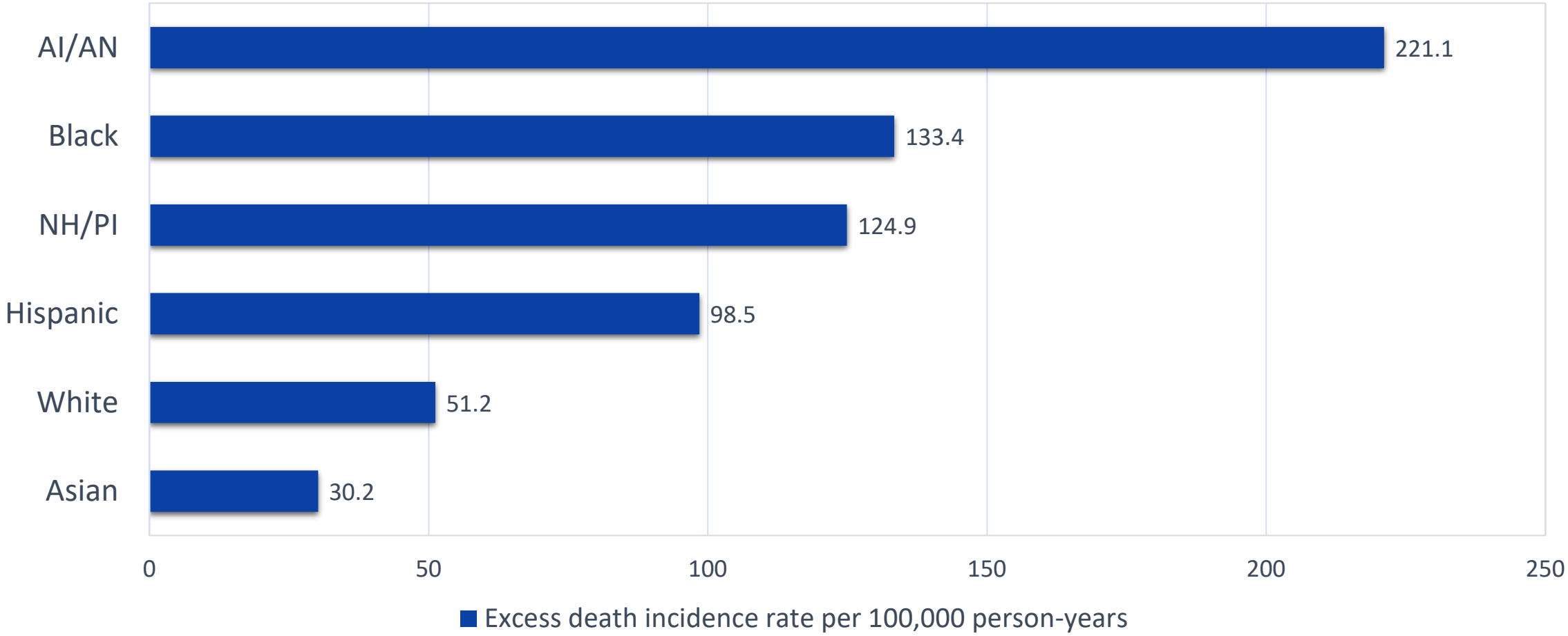
- All COVID-19 vaccines, including booster doses, will be provided **free of charge** to the U.S. population. However, health systems or health departments could incur costs for vaccination program planning and implementation
- Fees for administration of COVID-19 vaccines recommended by ACIP are reimbursable by insurance or other federal programs
- Cost effectiveness analyses will be important in the future, when vaccine not purchased and distributed by the federal government

Evidence to Recommendations Framework

Booster doses of COVID-19 vaccines

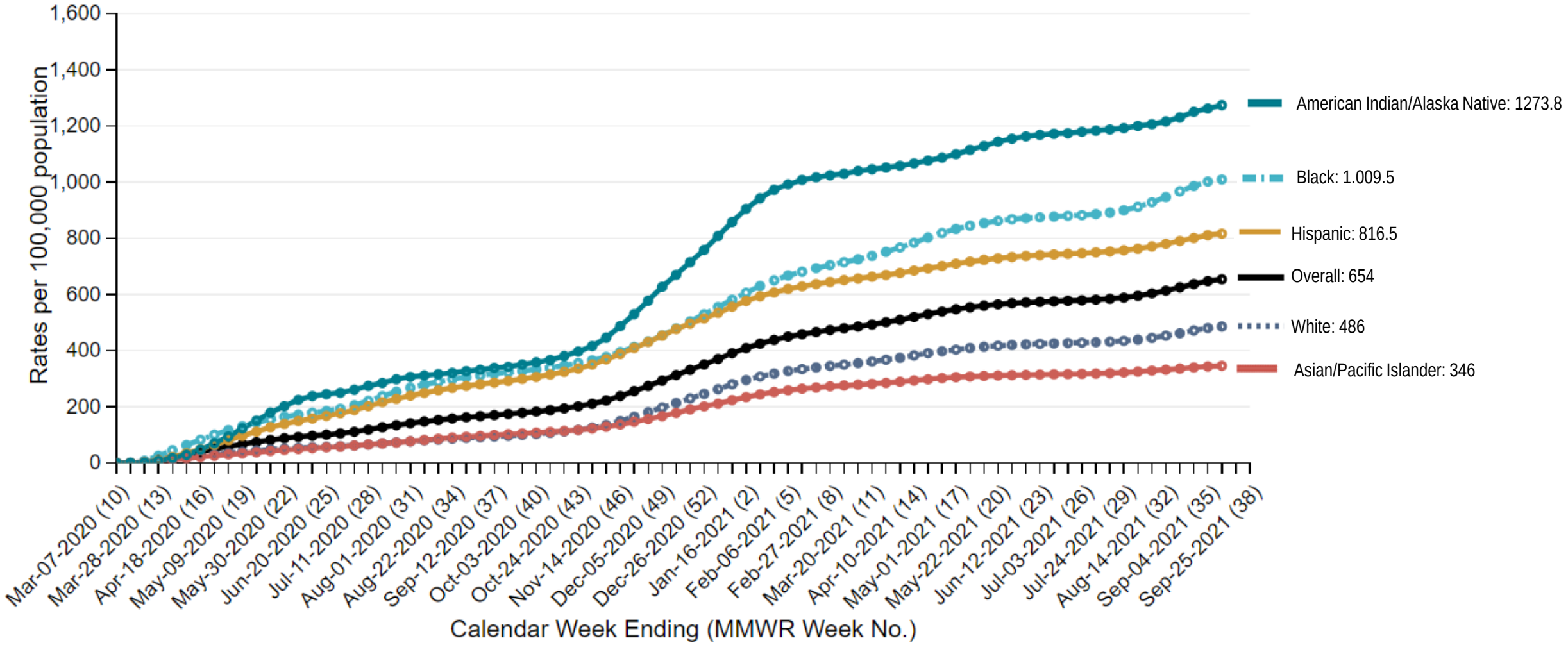
What are the equity considerations with booster doses?

Annual excess death incidence rates for persons aged 25-64 years by race/ethnicity – United States, 2020



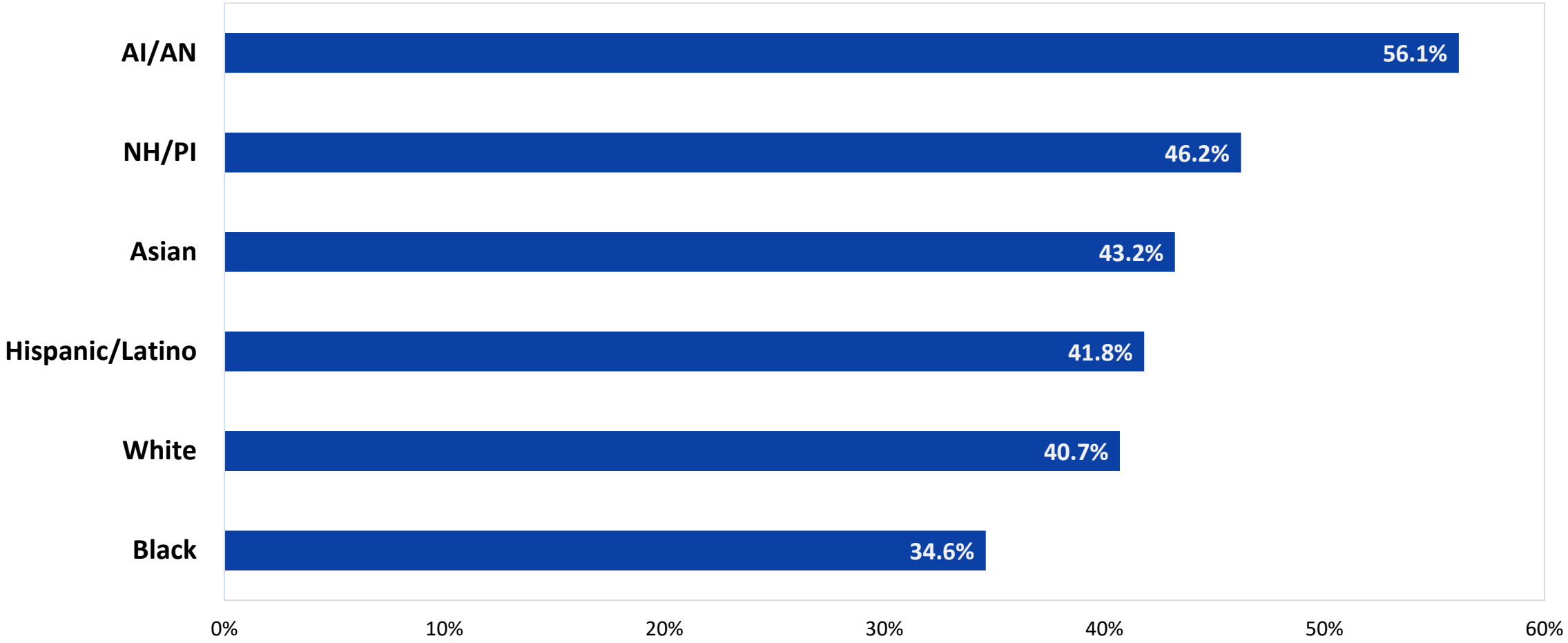
Rossen LM, Ahmad FB, Anderson RN, et al. Disparities in Excess Mortality Associated with COVID-19 — United States, 2020. MMWR Morb Mortal Wkly Rep 2021;70:1114–1119. DOI: http://dx.doi.org/10.15585/mmwr.mm7033a2

Cumulative COVID-19 associated hospitalizations in the United States by race/ethnicity, March 7, 2020 – September 11, 2021



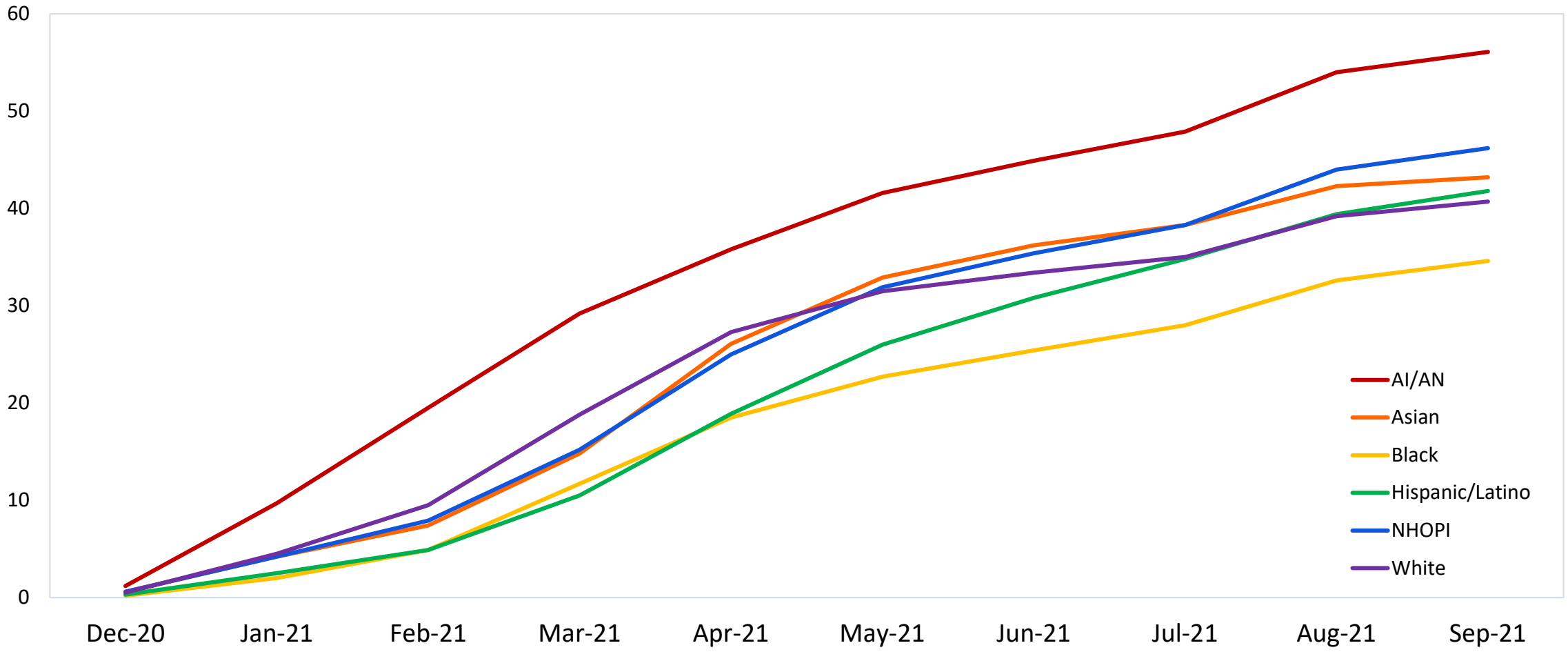
CDC. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed September 21, 2021

What percentage of people in each race or ethnic group received at least one dose of COVID-19 vaccine?



CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends. Accessed September 21, 2021

Percentage of people who have received at least one dose of the COVID-19 vaccine by race/ethnicity over time



CDC. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends as of September 20, 2021, and US Census Bureau National Population Estimates

Vaccine effectiveness by race and ethnicity

- Among VE platforms able to provide specific estimates for vaccine effectiveness by race or ethnicity, **no differences** noted
- VE against hospitalization among adults ≥50 years of age:
  - Overall: 89% (95% CI: 87-91%)
  - Black individuals: 86% (95% CI: 75-92%)
  - Hispanic individuals: 90% (95% CI: 85-93%)
- VE against hospitalization among VA centers:
  - Black individuals: 86% (95% CI: 77-93%)
  - White individuals: 88% (95% CI: 77-94%)

M Thompson et al. NEJM https://www.nejm.org/doi/pdf/10.1056/NEJMoa2110362?articleTools=true

Summary - Equity

- COVID-19 disease and COVID-19 vaccination varies by socioeconomic and sociodemographic groups
  - However, vaccine effectiveness does not vary by race and ethnicity
- Equity gap in vaccines administered by race is closing
  - Disparities were more pronounced this spring (individuals who would be 6 months after 2nd dose)

Summary

Work Group Interpretation

- **Top priority** should be **continued vaccination** of **unvaccinated individuals**
- Jurisdictions have a variety of vaccination and disease control priorities
  - E.g. COVID-19 cases, delivery of primary COVID-19 vaccines series and influenza vaccines
- Balance of benefits and risks **varies by age**
  - Adults ≥65 years have the clearest benefit/risk
  - Benefit to other age groups incrementally smaller, given high effectiveness maintained from primary series

Goals of booster program:

- Prevention of **severe disease**
- Other considerations are important, such as maintaining workforce and healthcare capacity, prevention of transmission, individual benefit/risk balance

Clinical Considerations

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Type of recommendation	We do not recommend the intervention	We recommend the intervention for individuals based on assessment of **benefits** and **risks**	We recommend the intervention

Used when the **risks** clearly outweigh the **benefits** in a population

Used when there is <u>diversity</u> of the **benefits** and **risks** in a population

Can allow <u>flexibility</u> across a population

Used when the **benefits** clearly outweigh the **risks** in a population

Policy Options

Policy question #1:

Should adults **≥65 years of age** and **LTCF residents** receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

Policy Options

Policy question #1:

Should adults **≥65 years of age** and **LTCF residents** receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

Policy question #2:

Should adults **18–64 years of age** at risk for severe COVID-19 due to **underlying medical conditions** or at risk of SARS-CoV-2 exposure due to **occupation/setting** receive a Pfizer-BioNTech COVID-19 vaccine booster dose?

Policy Question #1

Adults ≥65 years of age and LTCF residents

PROS	CONS
• Highest risk of severe disease • Largest impact in waning VE against severe disease • Prioritized for early doses of COVID-19 vaccines (longer duration since primary series)	Age cut-off may not represent continuum of risk

Policy Question #2

Adults 18–64 years of age at risk for severe COVID-19 due to **underlying medical conditions** or at risk of SARS-CoV-2 exposure due to **occupation/setting**

Type of recommendation	PROS	CONS
Standard recommendation	• Simple • Reduces barriers for individuals who may have increased risk of disease • Reduction in infection could reduce work absenteeism	• Not strong evidence of increased risk of hospitalization or death in all individuals • Balance of benefits and risks likely varies • Large number of people initially eligible (>50 million)
Recommended for individuals based on assessment of benefits and risks	• Reduces barriers for individuals who may have increased risk of disease • Reduction in infection could reduce work absenteeism • Reflects uncertainty in current balance of benefits and risks in this population	• Large number of people initially eligible (>50 million) • More complicated to implement

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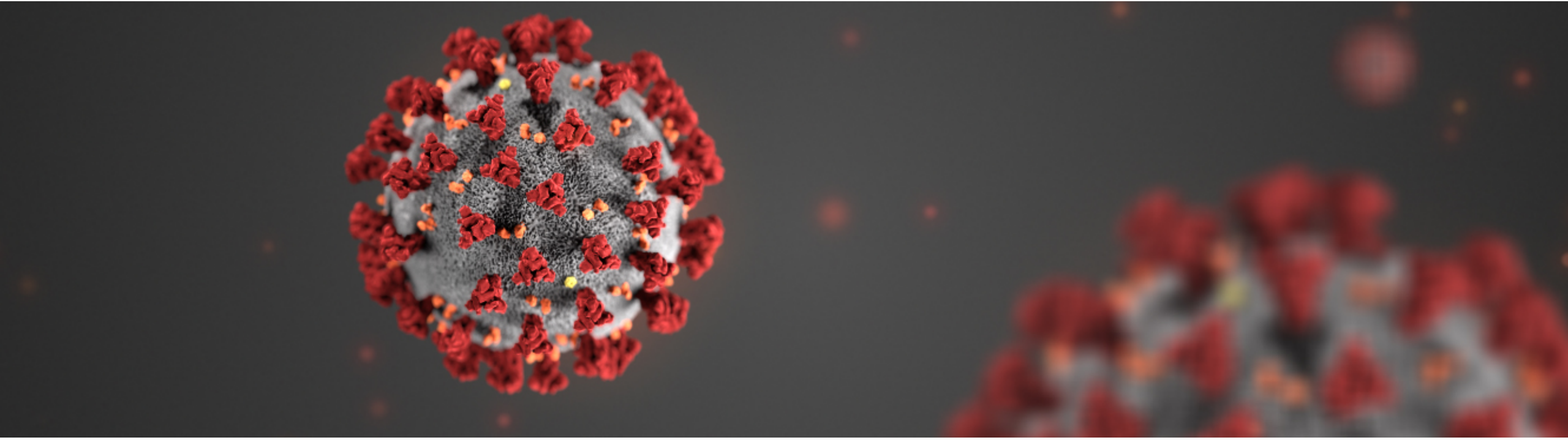
- Heather Scobie
- Ian Plumb
- Amy Blain
- Neela Goswami
- Mary Chamberland
- CDC/University of Iowa
- VTF ACIP WG Team
- ACIP COVID-19 Vaccines Work Group
- Vaccine Task Force
- Epi Task Force
- Respiratory Viruses Branch



For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Thank you

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.