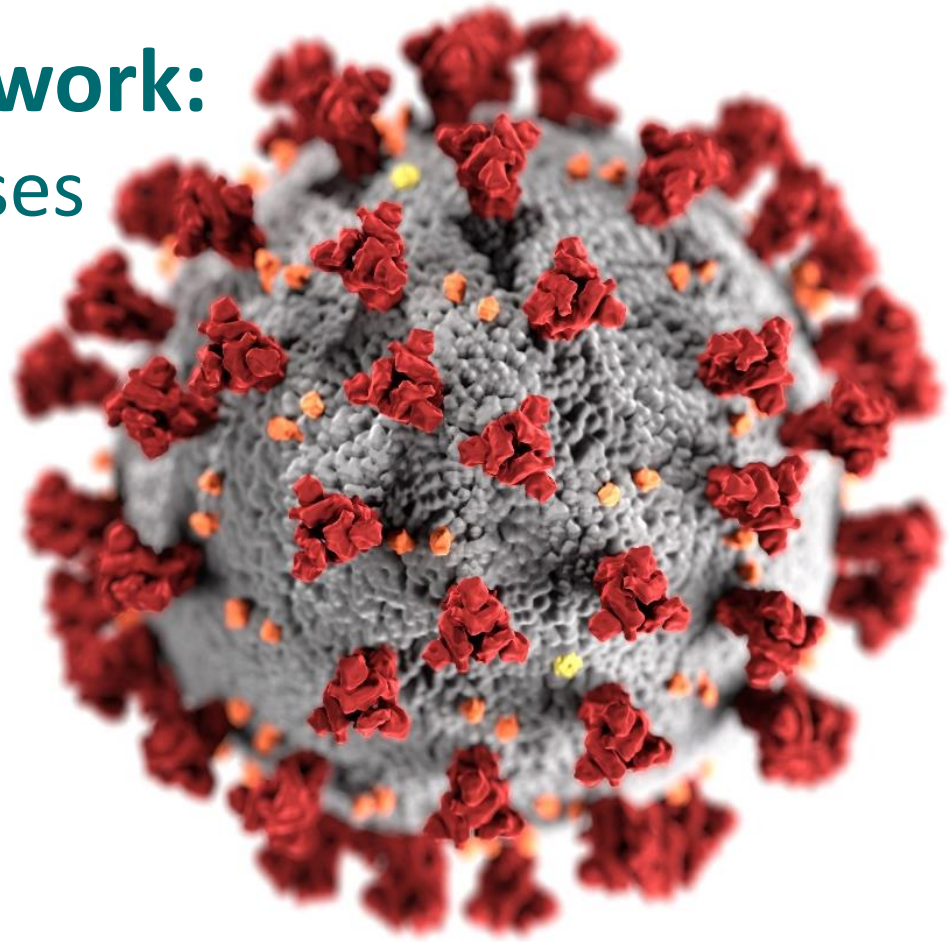
Evidence to Recommendations Framework:

Bivalent COVID-19 Vaccine Booster Doses



Sara Oliver, MD, MSPH
ACIP Meeting
September 1, 2022

cdc.gov/coronavirus

Evidence to Recommendations Framework

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

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

Soliciting feedback on the Equity Domain adjustment

- In April – August 2022, a subset of the COVID-19 ACIP Work Group engaged in a critical review of the Equity Domain and gathered extensive input and feedback on strategies to adjust the domain through the following mechanisms:
  - A thorough review of use of the Equity Domain (April 2022)
  - A one-time consultation with health equity experts (May 2022)
  - An iterative review of possible adjustment strategies with experts (June—August 2022)
  - Presentation to leadership and membership of the National Medical Association (August 2022)
  - Presentation to the Structural & Social Determinants of Health Workgroup of the Office of Minority Health and Health Equity (August 2022)
  - Throughout this process, it became clear that **consideration of equity is integral to every aspect** of production, study, authorization and recommendation of COVID-19 vaccines

Restructuring the Equity Domain of the Evidence to Recommendations (EtR) Framework

- The need for a **systematic**, **reliable**, and **action-oriented** review of evidence toward enhanced equity was made clear: **structural problems require structural solutions**
  - Adjustment of structure is required for meaningful change
  - Adjustment of the EtR Framework to enable systematic and reliable review of evidence toward actionable recommendations to enhance equity may facilitate meaningful change
- We recommend restructuring the Equity Domain as a consideration across each EtR Domain:

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)
Public Health Problem	• Is the problem of public health importance?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?
Values	• Does the target population feel the desirable effects are large relative to the undesirable effects? • Is there important variability in how patients value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?
Feasibility	• Is the intervention feasible to implement?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?
Equity	• What would be the impact of the intervention on health equity?

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)	Domain Equity Question(s)
Public Health Problem	• Is the problem of public health importance?	• Does the problem impact all populations equally?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?	• Are the desirable and undesirable anticipated effects demonstrated across all populations equally?
Values	• Does the population feel the desirable effects are large relative to the undesirable effects?	• Is there important variability in how patients or populations value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?	• Is the intervention equally acceptable across all populations?
Feasibility	• Is the intervention feasible to implement?	• Is the intervention equally feasible to implement across all populations?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	• Is the intervention a reasonable and efficient allocation of resources across all populations?

Evidence to Recommendations (EtR) Framework

EtR Domain	Question(s)	Domain Equity Question(s)
Public Health Problem	• Is the problem of public health importance?	• Does the problem impact all populations equally?
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?	• Are the desirable and undesirable anticipated effects demonstrated across all populations equally?
Values	• Does the population feel the desirable effects are large relative to the undesirable effects?	• Is there important variability in how patients or populations value the outcome?
Acceptability	• Is the intervention acceptable to key stakeholders?	• Is the intervention equally acceptable across all populations?
Feasibility	• Is the intervention feasible to implement?	• Is the intervention equally feasible to implement across all populations?
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	• Is the intervention a reasonable and efficient allocation of resources across all populations?

"The intervention" = Bivalent COVID-19 vaccine booster doses

"The problem" = COVID-19

Evidence to Recommendations (EtR) Framework

Question

- Does ACIP support the use of updated (bivalent) COVID-19 vaccine booster doses, for those individuals in age groups currently recommended to receive a COVID-19 vaccine booster?

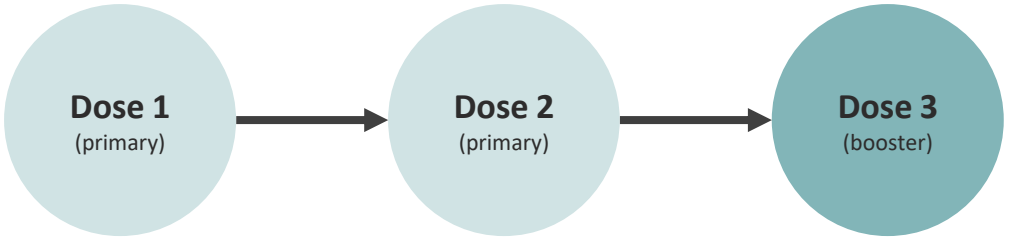
Evidence to Recommendations (EtR) Framework

Question

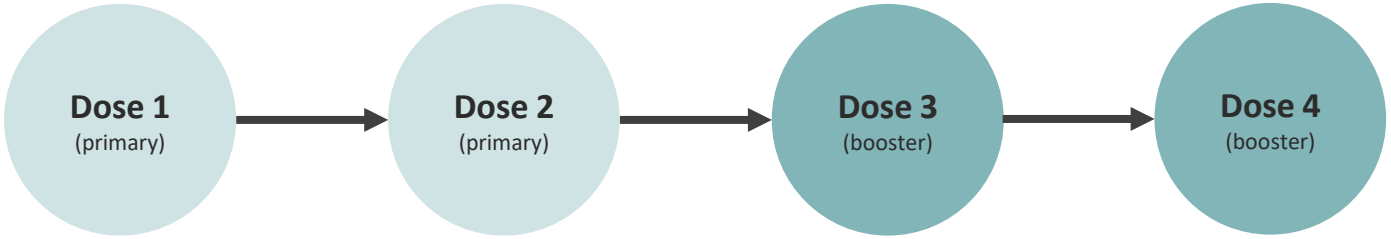
- Does ACIP support the use of updated (bivalent) COVID-19 vaccine booster doses, for those populations currently recommended to receive a COVID-19 vaccine booster?

Current recommendations

People ages 5-49 years

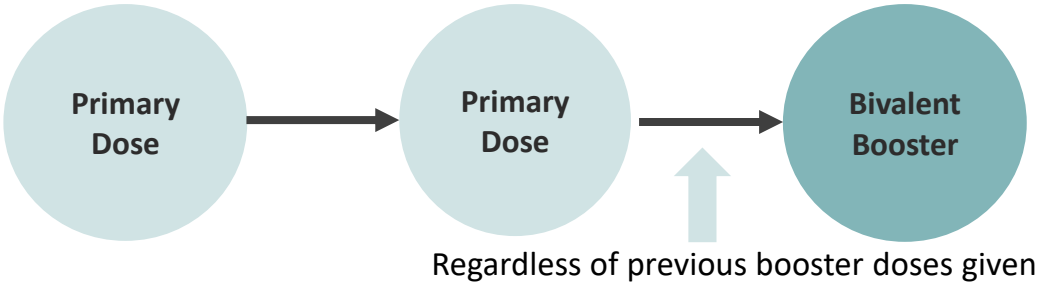


People ages 50 years and older



Future proposed recommendations

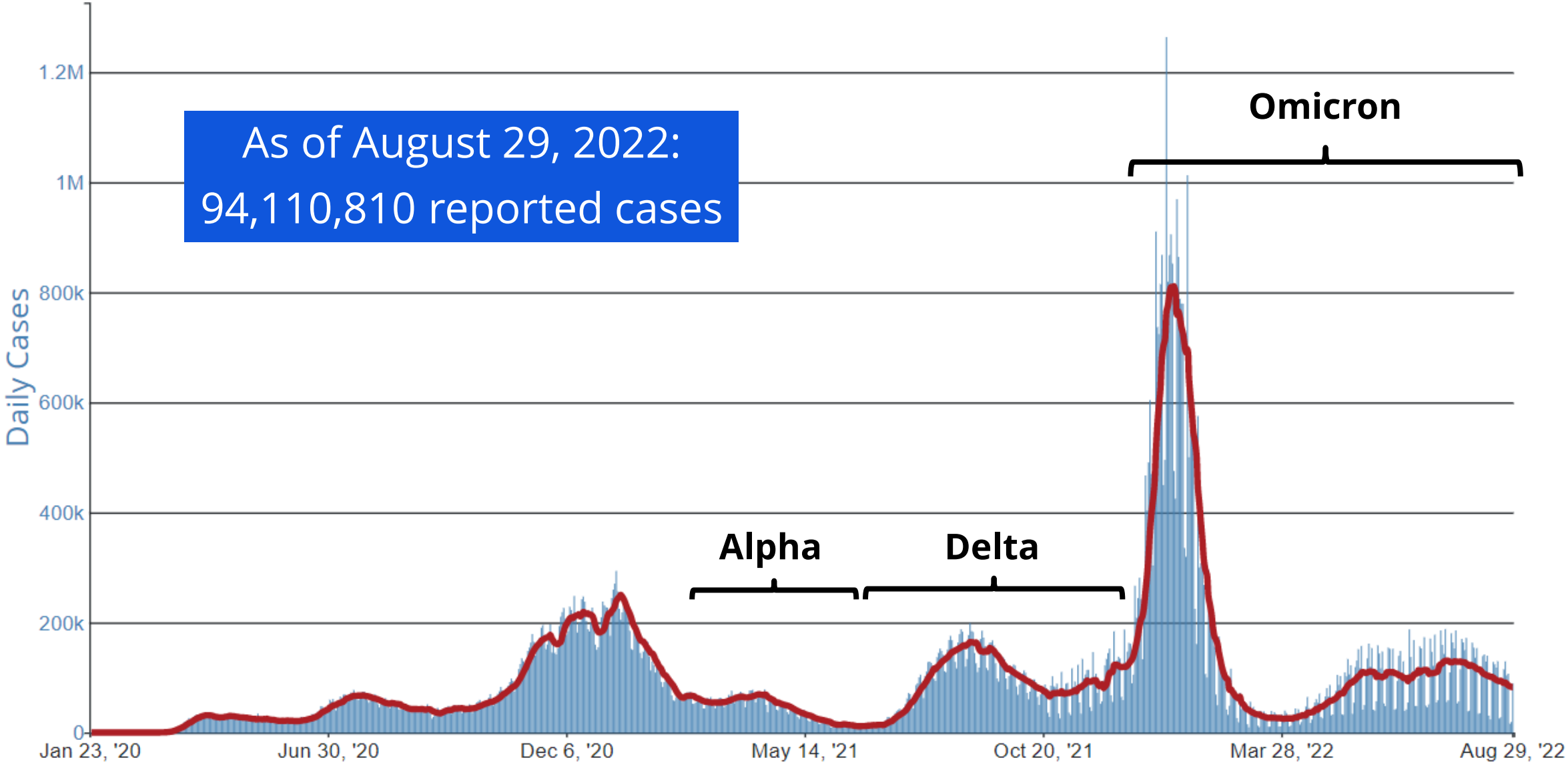
People ages 5 years and older*



***Ages** and **vaccines** as authorized by FDA and recommended by ACIP/CDC

EtR Domain: Public Health Problem

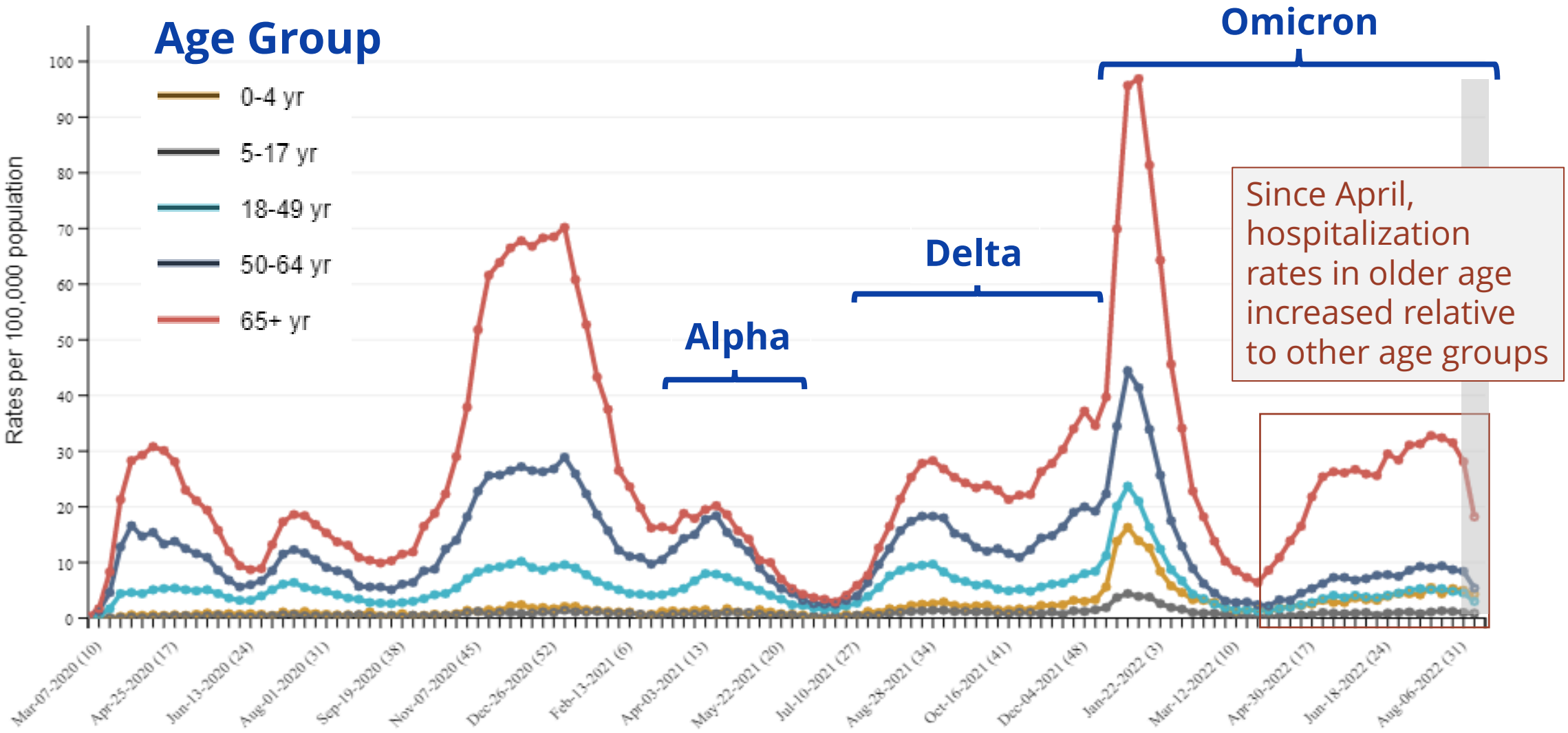
Daily Trends in Reported COVID-19 Cases, United States



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#trends_dailycases Accessed August 30, 2022

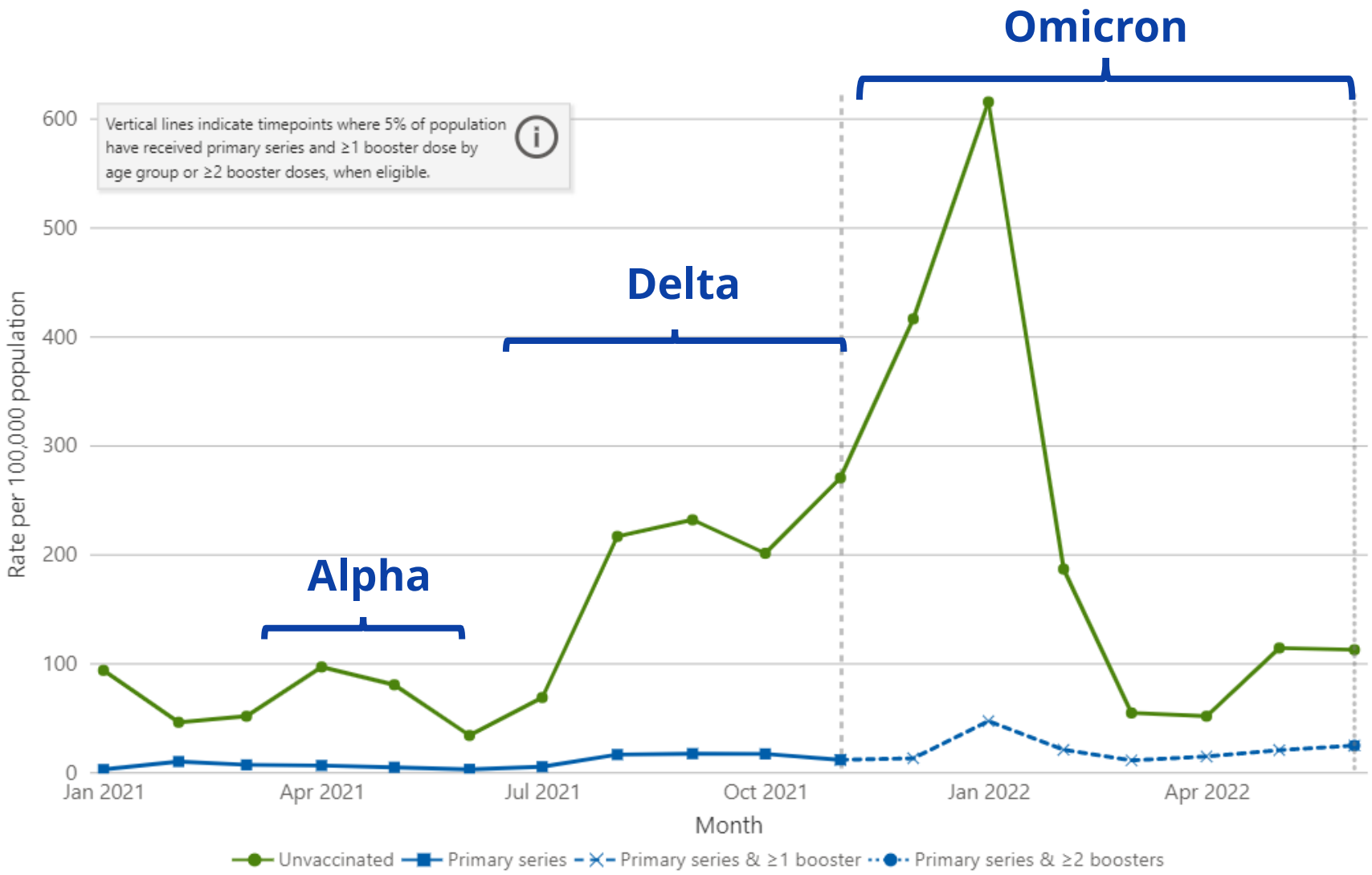
Weekly Trends in COVID-19-Associated Hospitalization Rates by Age Group

— COVID-NET, March 2020 – August 20, 2022



Source: COVID-NET; https://gis.cdc.gov/grasp/COVIDNet/COVID19_3.html Accessed August 26, 2022

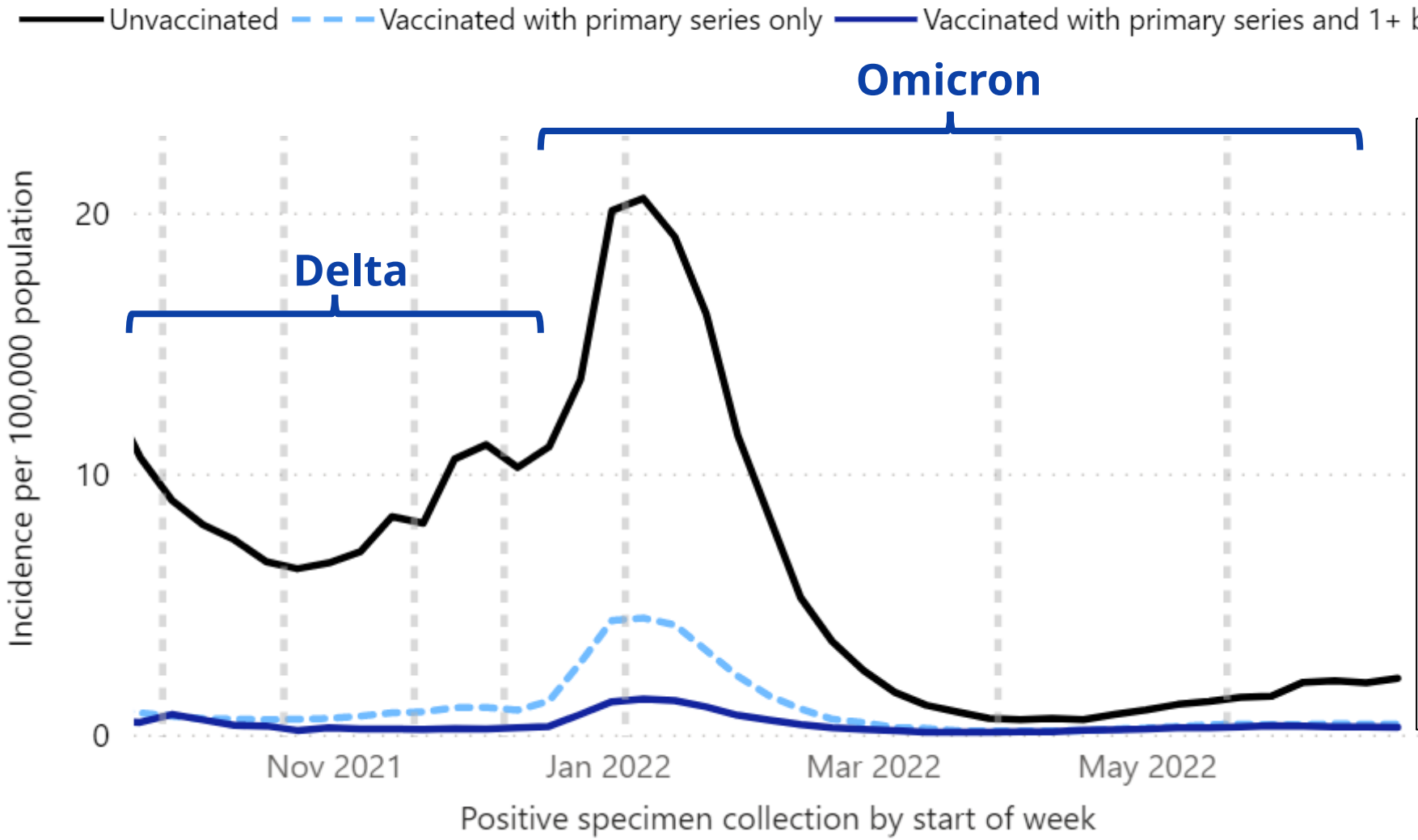
Age-Adjusted Rates of COVID-19-Associated Hospitalization by Vaccination Status and Receipt of Booster Dose in Adults Ages ≥18 Years, January 2021–June 2022



In June 2022, **unvaccinated** adults ages ≥18 years had **4.6X higher** COVID-19-associated hospitalization rates compared to those vaccinated with at least **one booster dose**

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalizations-vaccination Accessed August 3, 2022

Age-Adjusted Rates of COVID-19-Associated Deaths by Vaccination Status and Receipt of Booster Dose,* September 19, 2021 – July 2, 2022 (29 U.S. Jurisdictions)



In June 2022, **unvaccinated** people ages ≥5 years had **8X higher** COVID-19-associated death rates compared to those with at least **one booster dose**

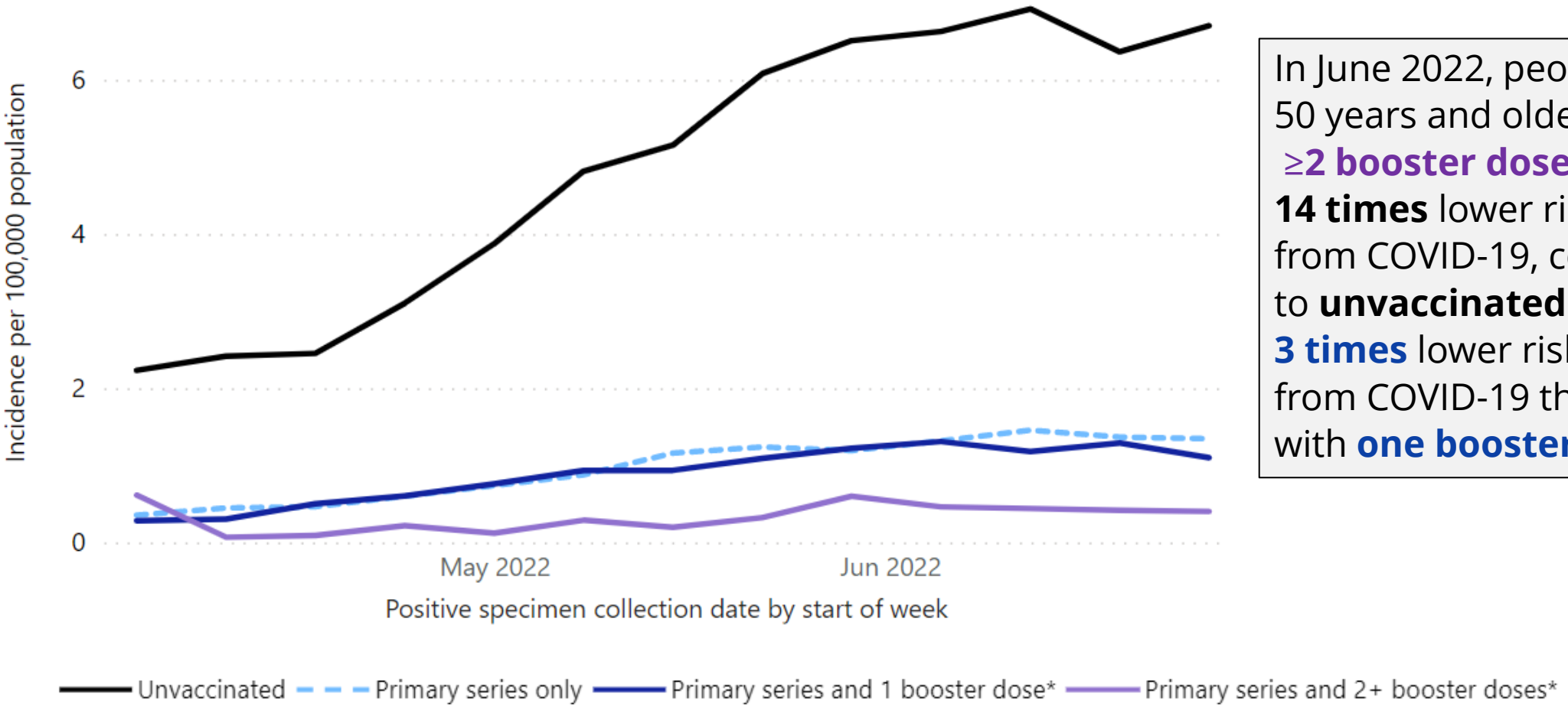
This was a decrease from ~**20X** during January-March 2022

*This includes people who received booster doses and people who received additional doses. Vertical lines denote changes in booster dose recommendations.

CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccine-status Accessed August 24, 2022

Death Rates by Vaccination Status and Receipt of 1st and 2nd Booster Doses Among People Ages 50+ Years

April 3–July 2, 2022 (25 U.S. Jurisdictions)

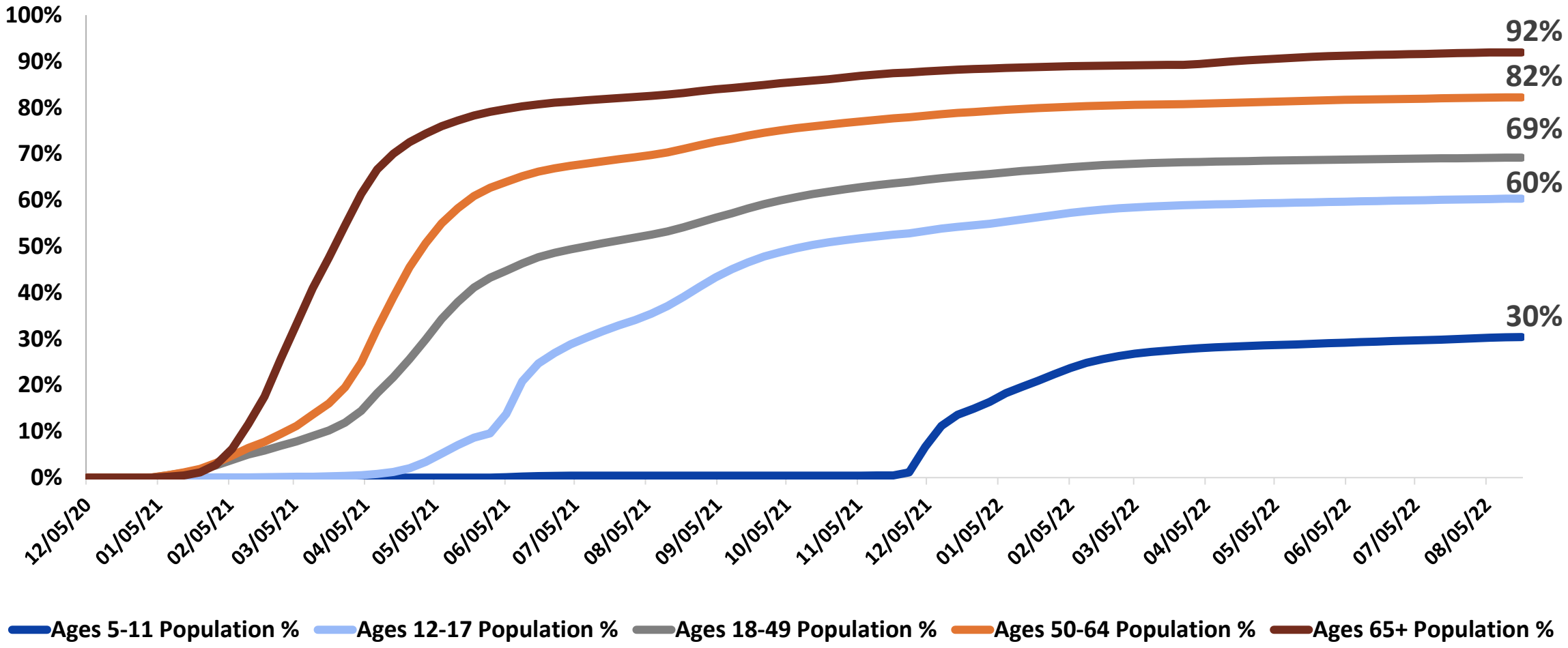


In June 2022, people ages 50 years and older with **≥2 booster doses** had **14 times** lower risk of dying from COVID-19, compared to **unvaccinated** people and **3 times** lower risk of dying from COVID-19 than people with **one booster dose**

*Includes either a booster or additional dose.

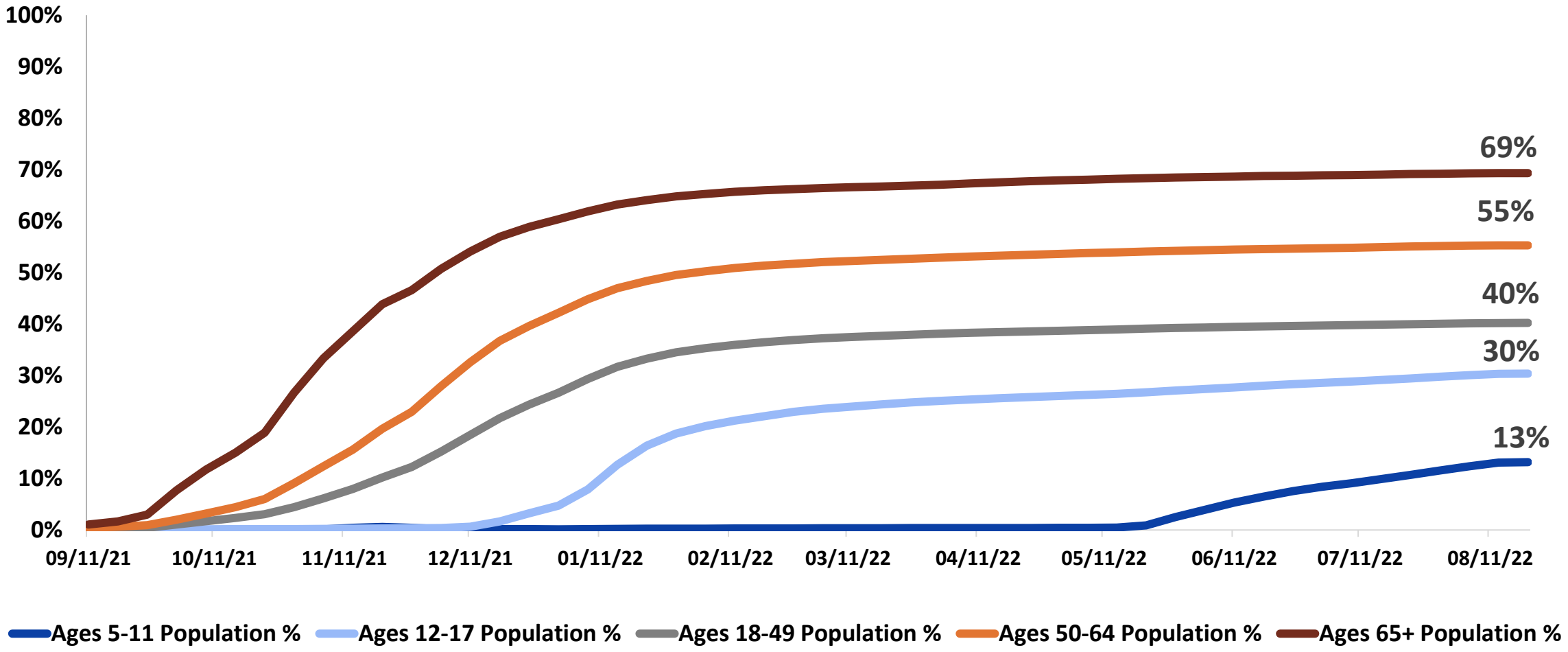
https://covid.cdc.gov/covid-data-tracker/#rates-by-vaccinbooine-status. Accessed August 24, 2022

Percent of population with a completed COVID-19 primary series – United States, January 2020 – August 2022



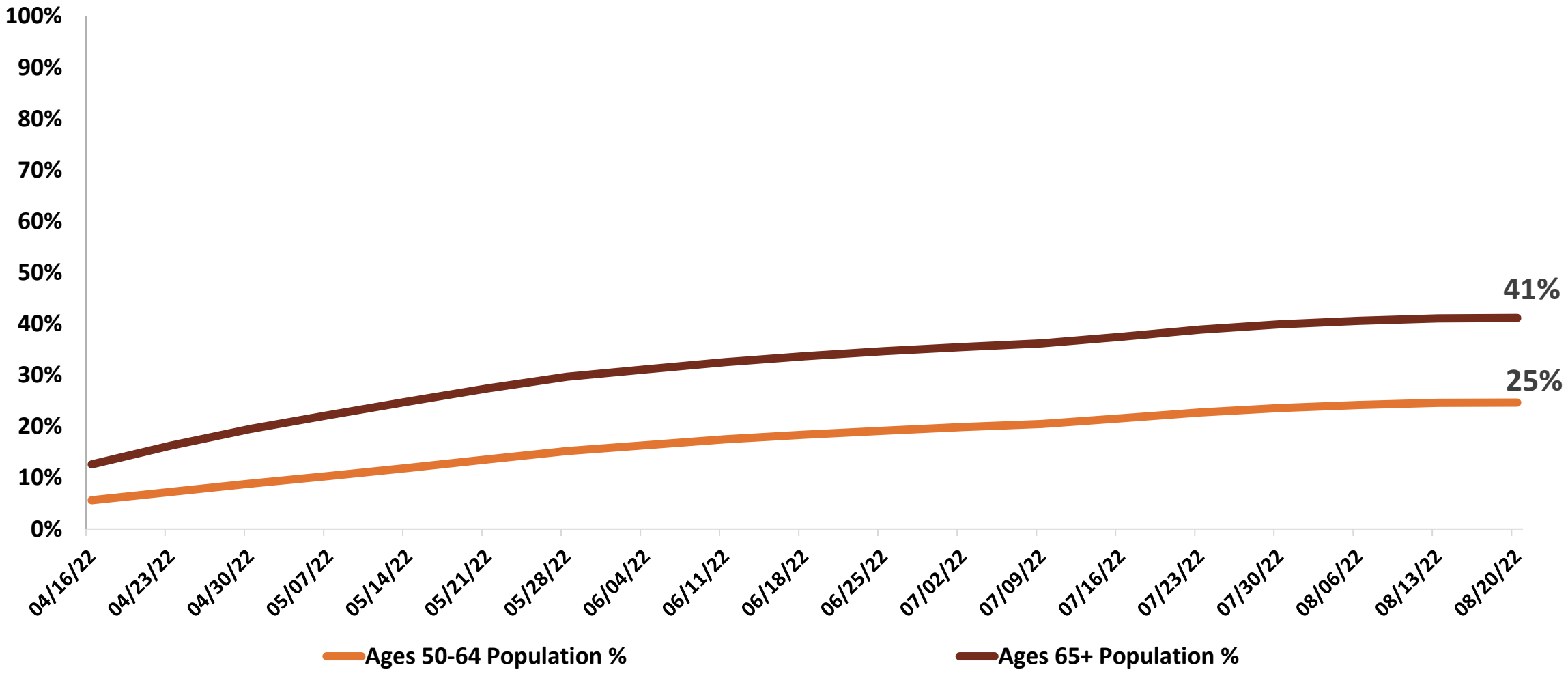
Source: CDC Immunization Data Lake. Accessed 8/22/22

Percent of population with a completed COVID-19 first booster – United States, September 2021 – August 2022



Source: CDC Immunization Data Lake. Accessed 8/22/22; First boosters does not include Texas for all ages or Idaho for ages <18

Percent of population with a completed COVID-19 second booster – United States, September 2021 – August 2022



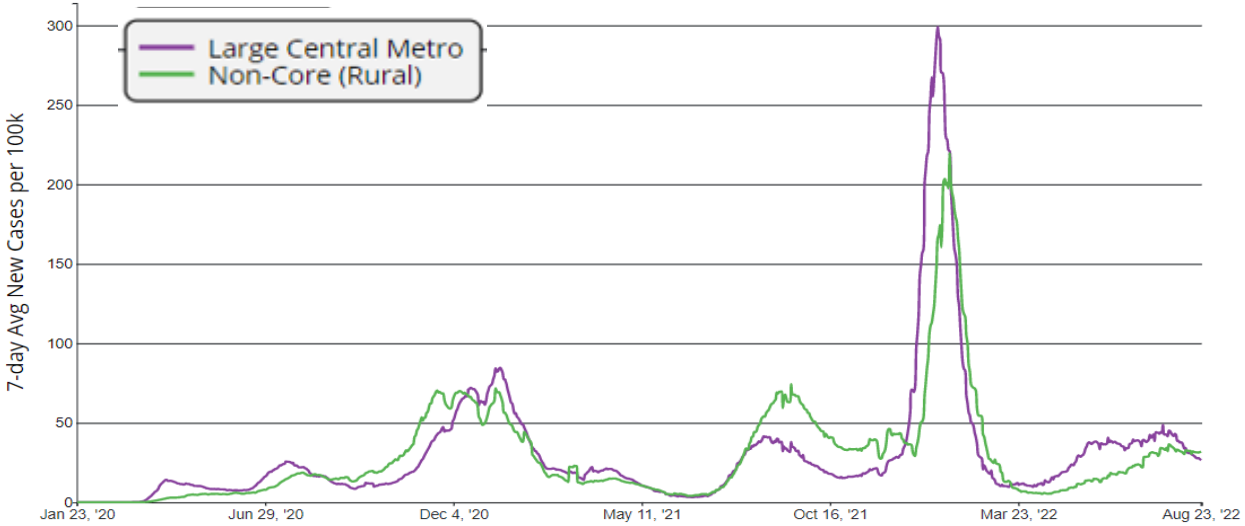
Source: CDC Immunization Data Lake. Accessed 8/22/22; Second boosters does not include Texas for all ages or Idaho for ages <18

Domain Equity Question:

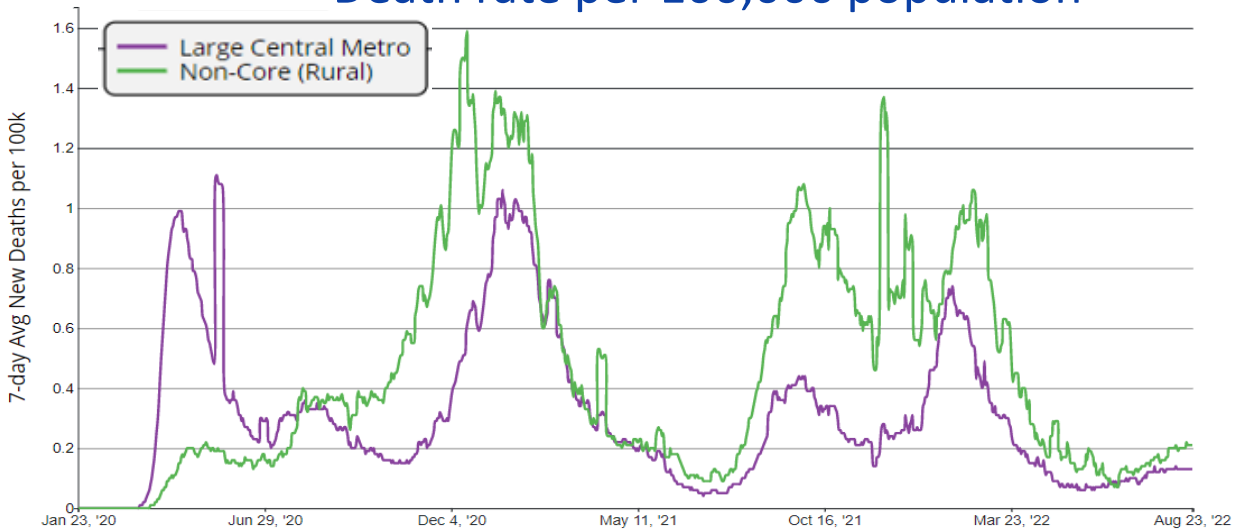
Does the problem impact all populations equally?

COVID-19 case and death rates in the United States, by county urban/rural classification

Case rate per 100,000 population



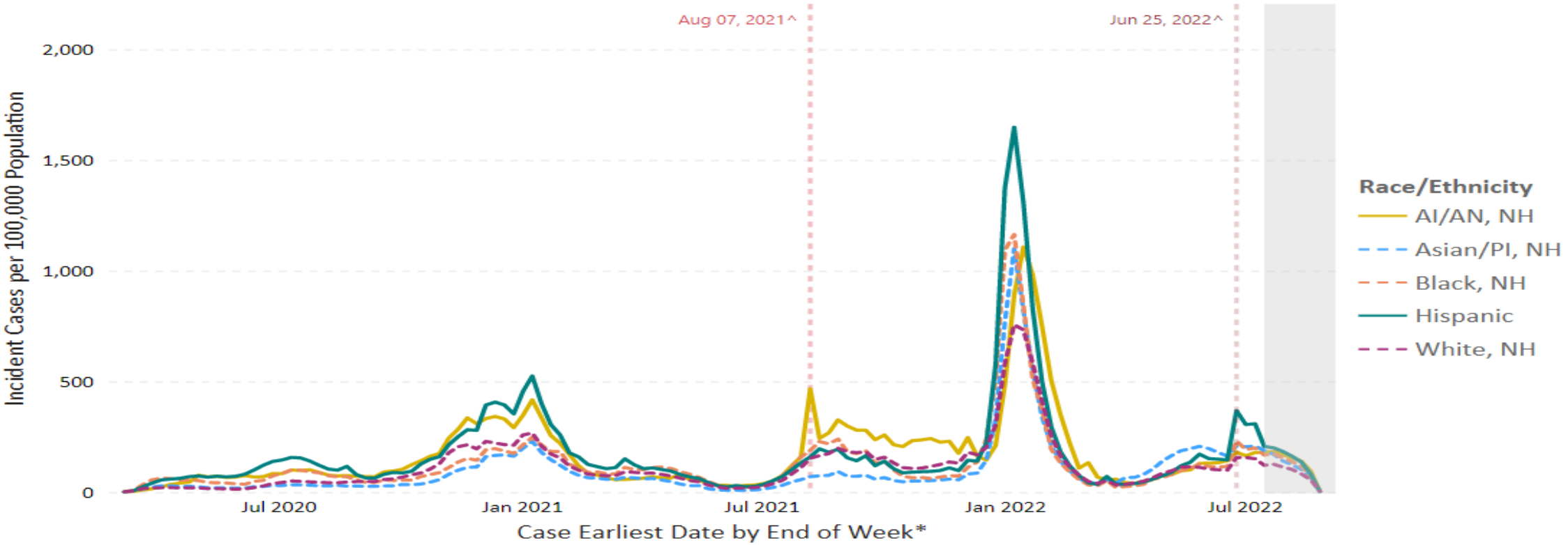
Death rate per 100,000 population



- In the recent Omicron surge, the case rate (left) was higher among a large metro classification, while death rate (right) was higher in rural populations

CDC COVID Data Tracker. Trends in COVID-19 Cases and Deaths in the United States, by County-level Population Factors. https://covid.cdc.gov/covid-data-tracker/#pop-factors_7daynewcases Accessed August 25, 2022

COVID-19 weekly cases per 100,000 population by race and ethnicity, United States, March 1, 2020 – August 27, 2022*



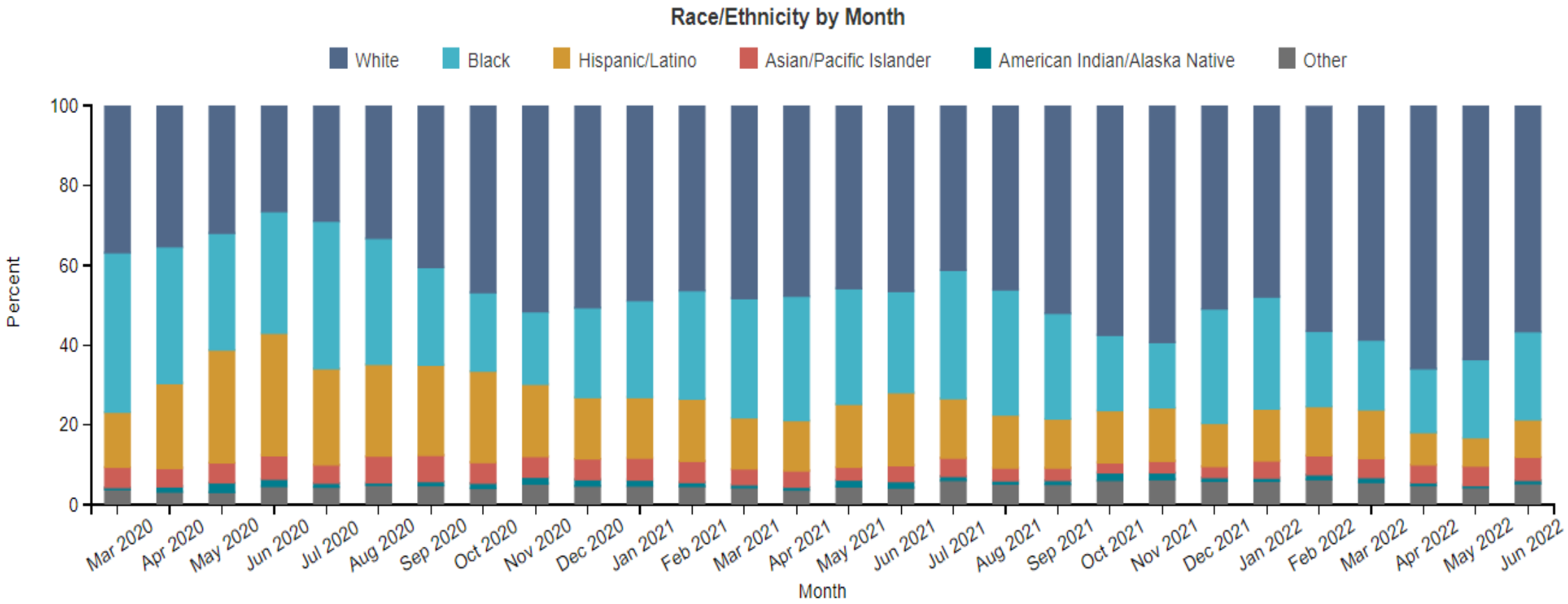
US: The most recent case record was reported during the week ending on Aug 27, 2022. Percentage of cases reporting race by date - 62.95%.

US territories are included in case and death counts but not in population counts. Potential six-week delay in case reporting to CDC denoted by gray bars. Weekly data with five or less cases have been suppressed. AI = American Indian, AN = Alaska Native, NH = Non-Hispanic, PI = Pacific Islander. Excludes cases with unknown or multiple races. *Case Earliest Date is the earliest of the clinical date (related to illness or specimen collection and chosen by a defined hierarchy) and the Date Received by CDC. The date for the current week extends through Saturday. ^Case rates for South Dakota during the week ending Aug 07, 2021, and Texas during the week ending Jun 25, 2022, are reflective of a data reporting artifact. Surveillance data are provisional, and as additional clinical date data becomes available, the case rates over time are subject to change.

Source: CDC COVID-19 Case Line-Level Data, 2019 US Census, HHS Protect; Visualization: Data, Analytics & Visualization Task Force and CDC CPR DEO Situational Awareness Public Health Science Team

CDC COVID Data Tracker. COVID-19 Weekly Cases and Deaths per 100,000 Population by Age, Race/Ethnicity, and Sex. https://covid.cdc.gov/covid-data-tracker/#demographicsovertime Accessed August 25, 2022

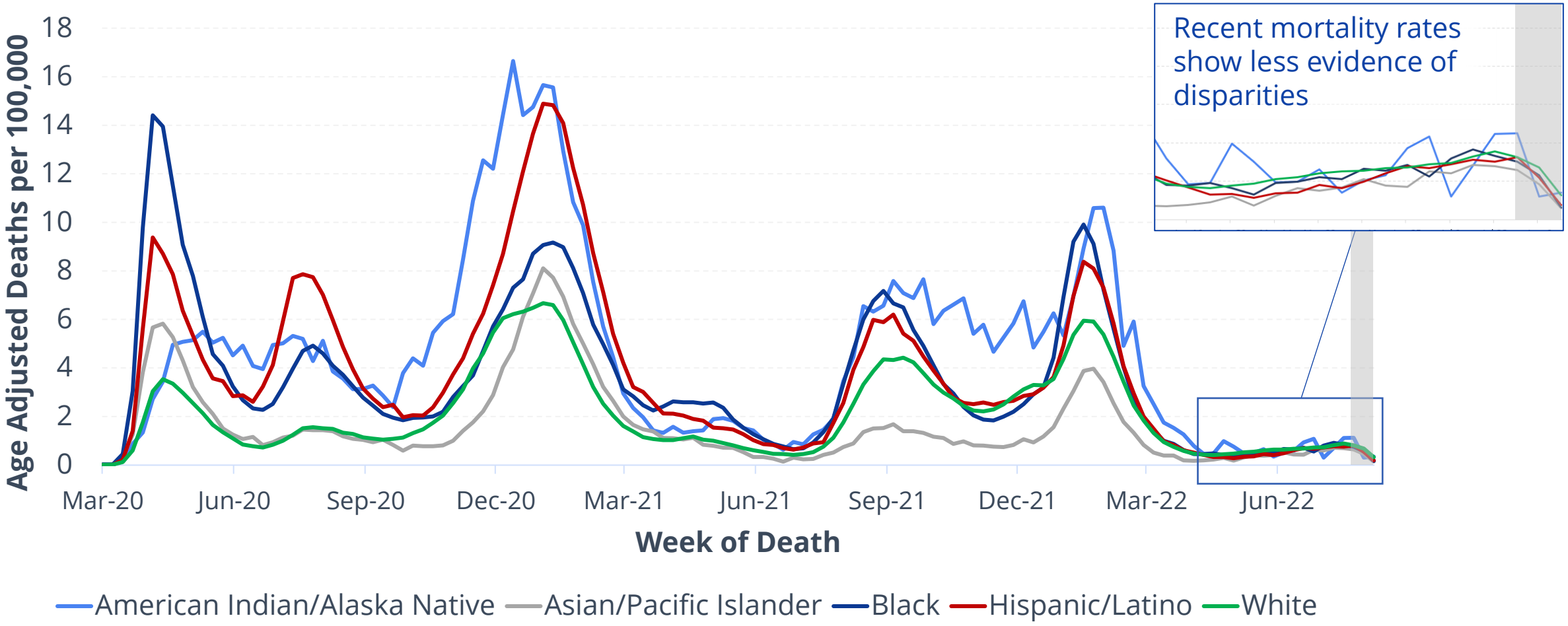
Characteristics of COVID-19-associated hospitalizations by race and ethnicity, March 1, 2020 – June 30, 2022



CDC COVID Data Tracker. COVID-NET Laboratory-confirmed COVID-19 hospitalizations. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network Accessed August 25, 2022

Weekly Trends in Age-Adjusted COVID-19 Mortality Rates by Race/Ethnicity, United States, March 1, 2020 – August 20, 2022

Provisional Death Certificate Data, National Vital Statistics System



Source: https://data.cdc.gov/NCHS/Provisional-Weekly-Deaths-by-Region-Race-Age/tpcp-uiv5 (National Vital Statistics System provisional death certificate data)

Summary

Public Health Problem

- As of August 2022, over **94 million** COVID-19 cases reported in the United States
- Since April 2022, hospitalization rates in older age groups increased relative to other age groups
  - Moreover, in June 2022, during Omicron predominance, unvaccinated adults ages 18 years and older had **4.6X** higher COVID-19-associated hospitalization rates compared to those vaccinated with at least one booster dose
- In June 2022, unvaccinated people ages ≥5 years had **8X** higher COVID-19-associated death rates compared to those with at least one booster dose
  - Additionally, people ages 50 years and older with ≥2 booster doses had **14X** lower risk of dying from COVID-19, compared to unvaccinated people and **3X** lower risk of dying from COVID-19 than people with one booster dose
- Vaccination rates are much higher among older adults relative to other age groups
- People of racial and ethnic minority groups have been disproportionately burdened by COVID-19 illness, hospitalization, and death

Public Health Problem

Work Group Interpretation

Is COVID-19 disease among populations currently recommended for a booster of public health importance?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

EtR Domain: Benefits and Harms

Summary of available data

- Clinical trial data from COVID-19 vaccine manufacturers
  - Moderna bivalent booster clinical trial
  - Pfizer-BioNTech bivalent booster clinical trial
- Other considerations
  - Myocarditis/pericarditis
  - Modeling data
  - Immune tolerance
  - Imprinting
  - Antigenic cartography
  - BA.1 and BA.4/BA.5
  - Prior SARS-CoV-2 infection
  - Non mRNA COVID-19 vaccines

Summary of available clinical trial data

- **Moderna** bivalent booster clinical trial with BA.1
  - mRNA-1273.214: 50 µg bivalent: 25 µg ancestral + 25 µg BA.1
- **Pfizer-BioNTech** bivalent booster clinical trial with BA.1
  - BNT162b2+BNT162b2 Omi: 30 µg bivalent: 15 µg ancestral + 15 µg BA.1
- No international data yet available for bivalent boosters
- No clinical trial data for bivalent boosters with BA.4/5 available to date

Evidence: Moderna

- Moderna Phase 2/3 trial, 50 µg bivalent vaccine (mRNA-1273.214)
- 25 µg each ancestral Wuhan-Hu-1 and Omicron B.1.1.529 spike as a second booster vaccine (P205 Part G) compared to 50 µg mRNA 1273 (ancestral) as a second booster vaccine (P205 Part F)
- Population: Adults aged ≥18 years (Study 205)
  - 437 participants received mRNA-1273.214 (bivalent)
  - 377 received mRNA-1273 booster (ancestral)
- Dosing interval from first booster to bivalent booster was 136 days and from first booster to second ancestral booster was 134 days
- Median follow up
  - Bivalent booster dose: 43 days
  - Ancestral booster dose: 57 days

Immunogenicity: Moderna bivalent booster

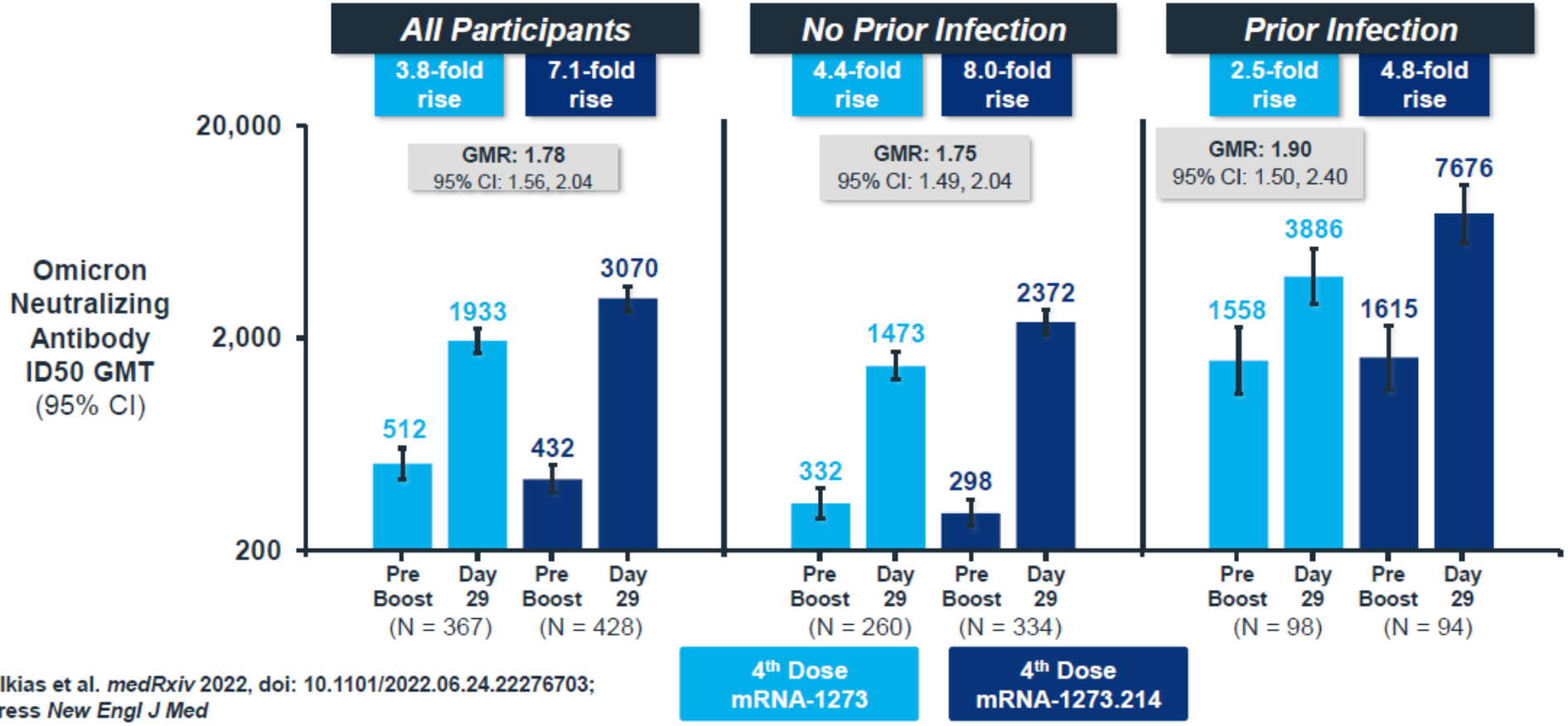
- Participants ≥18 years on **day 29** after the study vaccination
- Bivalent vaccine met superiority* criteria for both Omicron and ancestral SARS-CoV-2 antibodies

Assay	Timepoint	Bivalent mRNA-1273.214 GMT (95% CI)	mRNA-1273 GMT (95% CI)	Vaccine group/mRNA-1273 GMR
Without evidence of prior infection		N=334	N=260	
Omicron neutralizing antibody (ID_{50})	Day 29 post-dose	2372.4 (2070.6, 2718.2)	1473.5 (1270.8, 1708.4)	1.75 (1.49, 2.04)
Ancestral SARS-CoV-2 neutralizing antibody (ID_{50})		5977.3 (5321.9, 6713.3)	5649.3 (5056.8, 6311.2)	1.22 (1.08,1.37)
With or without evidence of prior infection		N=428	N=367	
Omicron neutralizing antibody (ID_{50})	Day 29 post-dose	3070.4 (2685.4, 3510.6)	1932.8 (1681.2, 2222.0)	1.78 (1.56, 2.04)
Ancestral SARS-CoV-2 neutralizing antibody (ID_{50})		6619.0 (5941.7, 7373.5)	6048.5 (5465.9, 6691.0)	1.24 (1.12, 3.36)

GMR= geometric mean ratio; GMT= geometric mean titer; ID_{50} = 50% inhibitory dilution
*Superiority criterion: the lower bound of the 95% CI for GMR is >1.0

https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf

Immunogenicity: Moderna bivalent booster



Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

- Met superiority criteria* in participants ≥18 years <u>with or without</u> evidence of infection on day 29

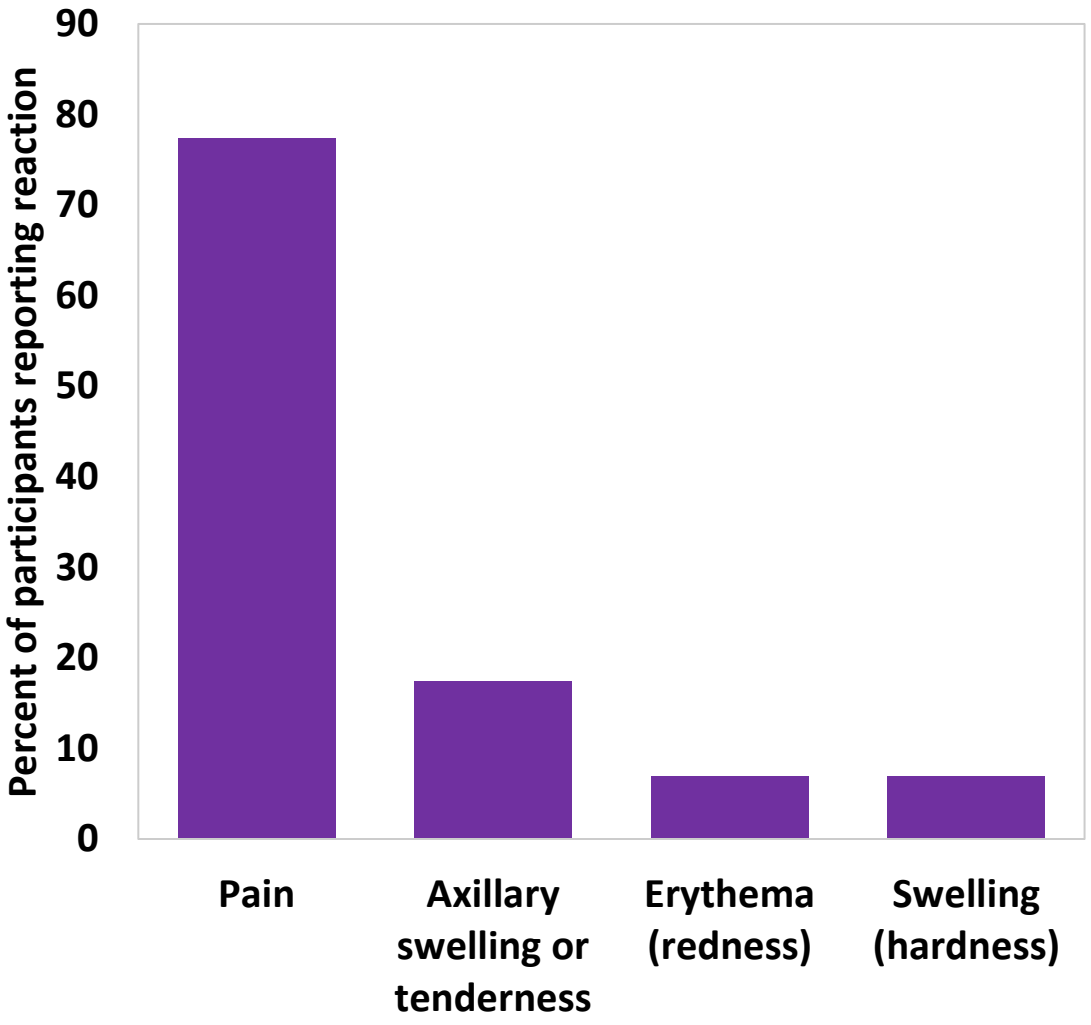
*Superiority criterion: the lower bound of the 95% CI for GMR is >1.0

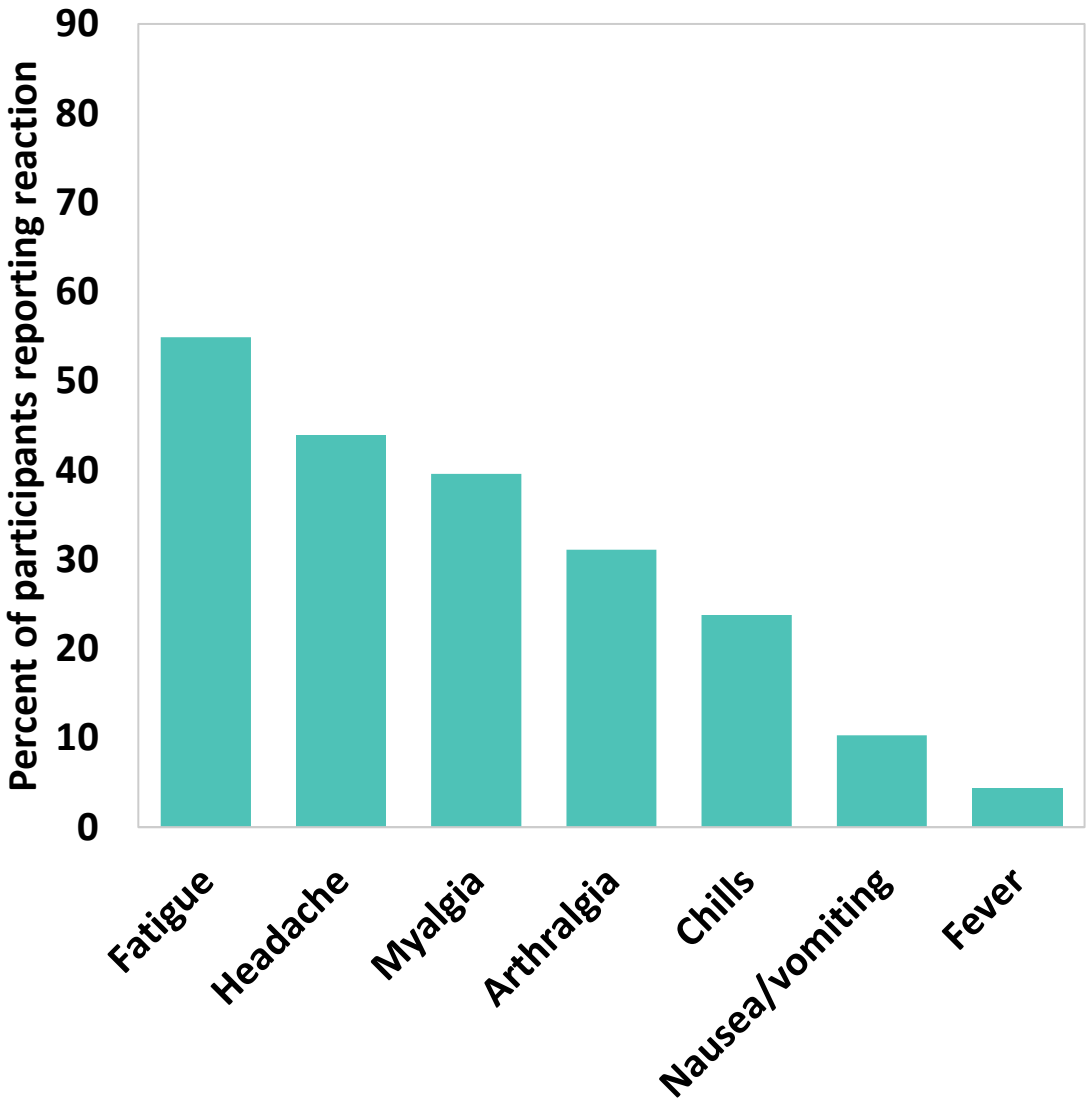
https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf

Reactogenicity: Moderna bivalent booster

- Local reactogenicity from Moderna bivalent booster (mRNA-1273.214) as a 4th dose **similar** to reactogenicity from 2nd dose of primary series and 3rd dose of mRNA-1273
- Systemic adverse reactions from Moderna bivalent booster (mRNA-1273.214) as a 4th dose **lower than** systemic reactions from 2nd dose of primary series and 3rd dose of mRNA-1273
- Fifteen participants (3.4%) had a Grade 3 local reaction and the most commonly reported was redness (2.1%)
- Twenty-four participants (5.5%) had a Grade 3 systemic reaction and the most commonly reported was fatigue (3.4%)
- No Grade 4 solicited systemic reactions were reported

Local and systemic reactogenicity: Moderna bivalent booster





Serious adverse events: Moderna bivalent booster

- No severe adverse events were assessed as related to vaccine
- 2 participants each experienced two serious adverse events: prostate cancer diagnosis and traumatic fracture within 28 days of the booster dose
- There were no deaths or adverse events of special interest, including myocarditis or pericarditis
- In the bivalent booster group, all severe events included reactogenicity events (fatigue, chills, arthralgia, headache); one participant reported lymphadenopathy (axillary/cervical)

Evidence: Pfizer

- **Pfizer-BioNTech** bivalent booster clinical trial with BA.1 (C4591031)
  - Forth dose of 30 µg bivalent [BNT162b2 (ancestral)+BNT162b2 Omi (BA.1)] compared with fourth dose of 30 µg BNT162b2 (monovalent)
    - Substudy E evaluated safety and immunogenicity among participants ages >55 years
      - Population: 305 participants received bivalent BNT162b2 Omi (BA.1) and 305 received monovalent BNT162b2
      - Dosing interval from first booster to second booster was 6.3 months
      - Median follow-up after second booster 1.7 to 1.8 months

Immunogenicity: Pfizer bivalent booster, ages >55 years

- Superiority* criterion met against Omicron BA.1 and non-inferiority criterion met against reference strain

Assay	Timepoint	Bivalent Vaccine OMI 30µg GMT (95% CI)	BNT162b2 30µg GMT (95%)	Vaccine group/BNT162b2 30µg GMR (95% CI)
		N=178	N=163	
SARS-CoV-2 neutralization assay—Omicron BA.1—NT50 (titer)	1 month post-dose	711.0 (588.3, 859.2)	455.8 (365.9, 567.6)	1.56 (1.17, 2.08)
		N=186	N=182	
SARS-CoV-2 neutralization assay—Reference strain—NT50 (titer)	1 month post-dose	5933.2 (5188.2, 6785.2)	5998.1 (5223.6, 6887.4)	0.99 (0.82, 1.20)

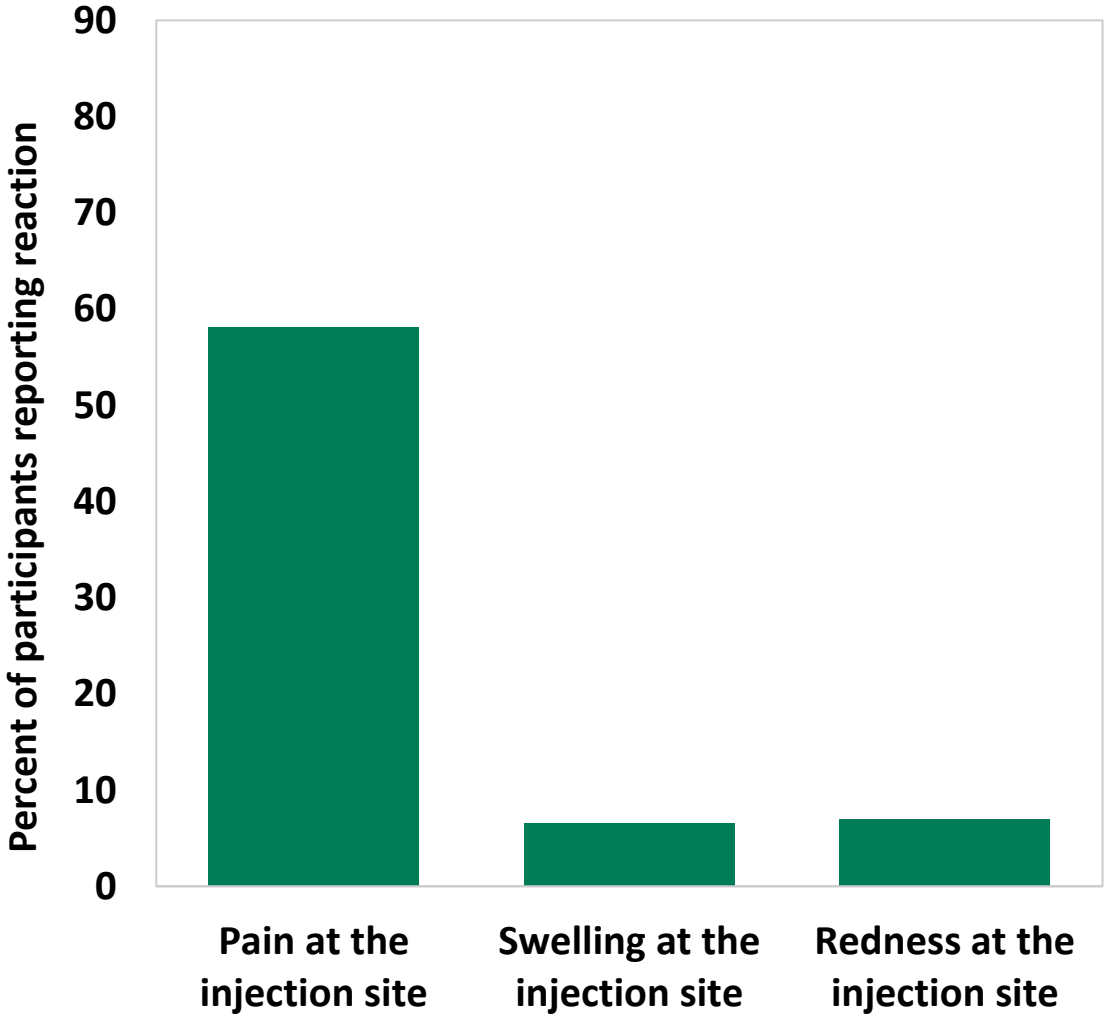
*simple superiority criterion: the lower bound of the 95% CI for GMR is >1.0; non-inferiority criterion: the lower bound of the 95% CI for GMR is >0.67

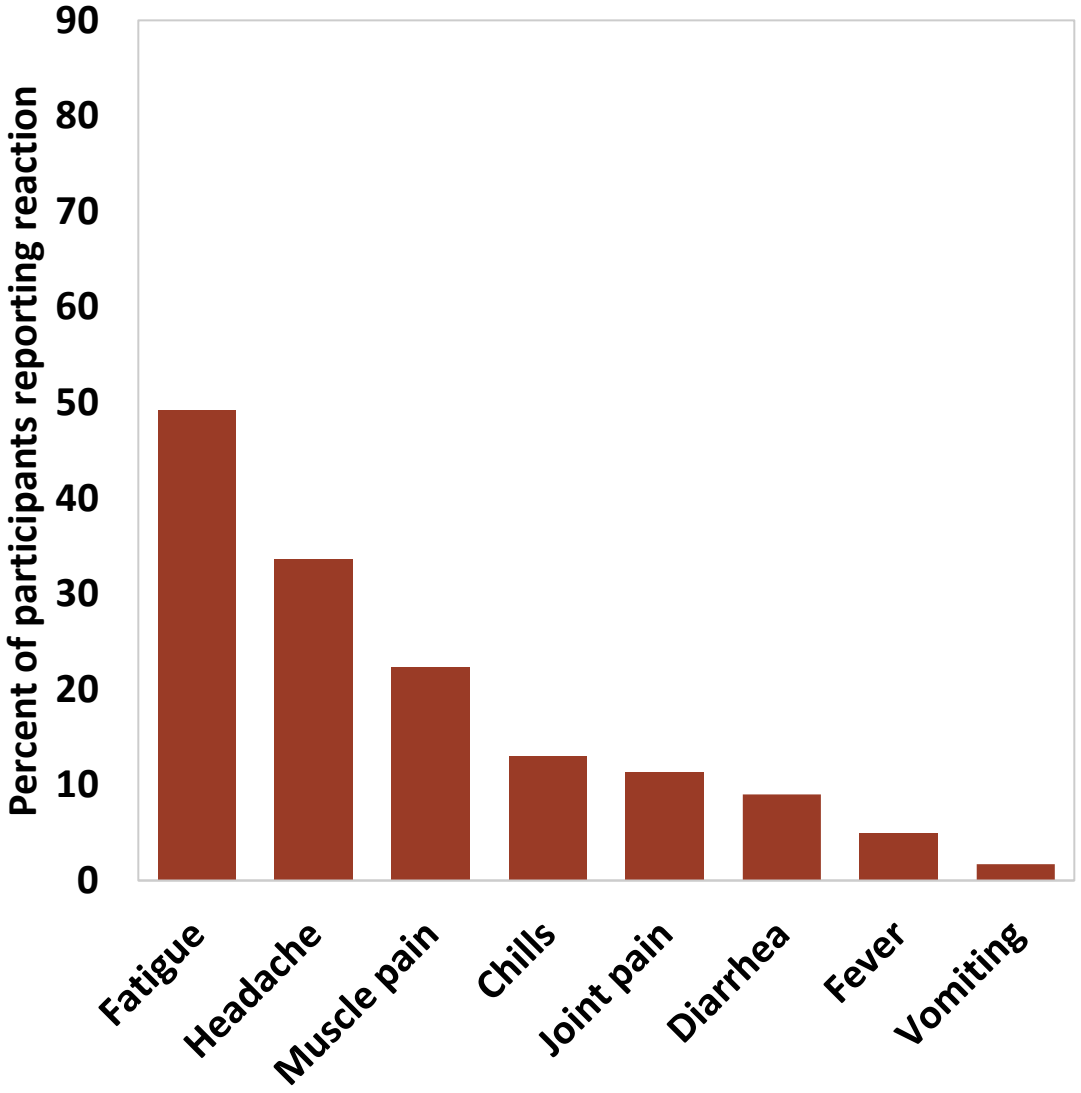
Vaccines and Related Biological Products Advisory Committee June 28, 2022 Meeting Presentation- Pfizer/BioNTech COVID-19 Omicron-Modified Vaccine Options (fda.gov)

Reactogenicity: Pfizer bivalent booster

- Safety population Study D, n=640
- Bivalent Omicron-modified vaccine (30-µg) showed similar local and systemic event profile as the prototype vaccine among participants age >55 years
  - Fever >38.9 °C to 40.0 °C was reported by 4 participants in the vaccine group. No fevers >40.0 °C were reported.
- For 18–55-year-olds, monovalent Omicron-modified vaccine (30 µg dose) showed similar reaction as prototype vaccine. No bivalent reactogenicity data available in this age group.

Local and systemic reactogenicity: Pfizer bivalent booster, ages >55 years





Serious adverse events: Pfizer bivalent booster

- No severe adverse events were assessed as related to vaccine
- No life-threatening (Grade 4) adverse events, or deaths were reported by participants
- No cases of anaphylaxis, hypersensitivity, myocarditis, pericarditis, appendicitis, Bell's palsy or rash were reported
- In the bivalent booster group, all severe events included reactogenicity events; fatigue, chills, arthralgia, headache.
- Mild to moderate events of lymphadenopathy

Summary

Clinical trial data

- Bivalent booster doses of both Moderna & Pfizer-BioNTech COVID-19 vaccines **increase immune response** in those who have completed a primary series and a previous booster
  - Compared with ancestral booster dose
    - Demonstrated superior response to Omicron
    - Demonstrated non-inferior response to ancestral strain
- Similar reactogenicity profile to primary series (and ancestral booster dose)
- Data from clinical trial limited in size, age, and bivalent booster type

Potential myocarditis risk following bivalent booster dose

- Myocarditis risk following bivalent COVID-19 vaccine booster dose is unknown
- Limited data on 2nd booster dose of current COVID-19 vaccine (only adults ages ≥50 years), but will review risk of myocarditis following **2nd dose** in **primary series** and **1st booster dose** by age group/sex

VAERS reporting rates of verified myocarditis per 1 million mRNA COVID-19 vaccinations (Pfizer-BioNTech and Moderna combined), days 0–7 post-vaccination*,†

	Dose 2 (primary series)		1st booster dose	
Age group	Male	Female	Male	Female
5–11 years	2.5	0.7	0.0	0.0
12–15 years	47.1	4.2	12.9	0.7
16–17 years	78.7	7.4	21.6	0.0
18–24 years	39.3	3.9	13.1	0.6
25–29 years	15.3	3.5	4.4	2.2
30–39 years	7.8	1.0	1.9	0.9
40–49 years	3.3	1.6	0.2	0.6
50–64 years	0.7	0.5	0.4	0.1
65+ years	0.3	0.5	0.7	0.2

CDC + FDA

VAERS

* As of August 18, 2022. Reports verified to meet case definition by provider interview or medical record review.

† An estimated 1–10 cases of myocarditis per 100,000 person years occurs among people in the United States, regardless of vaccination status; adjusted for days 0–7 risk interval, this estimated background is **0.2 to 2.2 per 1 million person-day 0–7 risk interval** (peach shaded cells indicate that reporting rate exceeded estimated background incidence for the period)

VSD incidence rates of verified myocarditis/pericarditis in the 0–7 days after Pfizer-BioNTech vaccination in people ages 12–39 years, dose 2 and 1st booster*

	Dose 2 primary series Pfizer-BioNTech			1st booster dose Pfizer-BioNTech		
	Cases	Dose 2 admin	Incidence rate/ million doses (95% CI)	Cases	1st boosters admin	Incidence rate/ million doses (95% CI)
12–15 years						
Males	31	205,955	150.5 (102.3 – 213.6)	5	81,613	61.3 (19.9 – 143.0)
Females	5	204,074	24.5 (8.0 – 57.2)	0	84,114	0.0 (0.0 – 35.6)
16–17 years						
Males	14	102,091	137.1 (75.0 – 230.1)	9	47,874	188.0 (86.0 – 356.9)
Females	1	107,173	9.3 (0.2 – 52.0)	2	55,004	36.4 (4.4 – 131.3)
18–29 years						
Males	27	331,889	81.4 (53.6 – 118.4)	7	166,973	41.9 (16.9 – 86.4)
Females	2	400,321	5.0 (0.6 – 18.0)	1	240,226	4.2 (0.1 – 23.2)
30–39 years						
Males	5	341,527	14.6 (4.8 – 34.2)	3	197,554	15.2 (3.1 – 44.4)
Females	3	410,713	7.3 (1.5 – 21.3)	1	268,412	3.7 (0.1 – 20.8)

VSD vaccine safety datalink

*Primary series surveillance for 18+ ended May 21, 2022, all other data through August 20, 2022.

VSD incidence rates of verified myocarditis/pericarditis in the 0–7 days after Moderna vaccination in people ages 12–39 years, dose 2 and 1st booster*

	Dose 2 primary series Moderna			1st booster dose Moderna		
	Cases	Dose 2 admin	Incidence rate/ million doses (95% CI)	Cases	1st boosters admin	Incidence rate/ million doses (95% CI)
12–15 years						
Males	N/A	N/A	N/A	N/A	N/A	N/A
Females	N/A	N/A	N/A	N/A	N/A	N/A
16–17 years						
Males	N/A	N/A	N/A	N/A	N/A	N/A
Females	N/A	N/A	N/A	N/A	N/A	N/A
18–29 years						
Males	19	195,809	97.0 (58.4 – 151.5)	7	109,337	64.0 (25.7 – 131.9)
Females	0	243,560	0.0 (0.0 – 12.3)	1	156,707	6.4 (0.2 – 35.6)
30–39 years						
Males	8	216,583	36.9 (15.9 – 72.8)	1	149,468	6.7 (0.2 – 37.3)
Females	1	259,780	3.9 (0.1–21.4)	2	191,765	10.4 (1.3 – 37.7)

***Primary series surveillance for 18+ ended May 21, 2022, all other data through August 20, 2022.
** Monitoring ongoing, no data provided if less than 2,500 doses given in a subgroup

VSD vaccine safety datalink

Myocarditis/pericarditis crude reporting rates per million doses administered following COVID-19 mRNA vaccines:

Ontario, December 13, 2020 to August 14, 2022

Age group (years)	Females: Dose 1	Females: Dose 2	Females: Dose 3	Males: Dose 1	Males: Dose 2	Males: Dose 3
5-11*	3.2**	12.8	0	3.1**	8.2	0
12-17	36.8	33.1	0	75.4	164.4	60.0
18-24	29.5	46.8	0	56.1	202.4	35.7
25-29	15.2	31.4	8.1	58.5	77.7	14.5

Note: Includes all reports of myocarditis or pericarditis identified through case-level review (n=782), regardless of the reports meeting the Brighton Collaboration case definition for myocarditis or pericarditis. There are no myocarditis/pericarditis AEFIs reported in age group 0-4 years.

*The reporting rate for the 5-11 year age group only includes reports of myocarditis/pericarditis following Pfizer-BioNTech Comirnaty pediatric COVID-19 vaccine (10 mcg) authorized for this age group and doses administered of the Pfizer-BioNTech Comirnaty pediatric COVID-19 vaccine (10 mcg) product. There were four reports among those 11-year-olds (i.e., who turned 12 years of age by the end of 2021) who received the Pfizer-BioNTech Comirnaty COVID-19 vaccine (30 mcg) indicated for 12+ years of age as per the provincial program. These reports are excluded from age group-specific reporting rate calculations but included in the total reporting rate calculation.

**Interpret with caution as this reporting rate is based on one report.

https://www.publichealthontario.ca/-/media/Documents/nCoV/epi/covid-19-aefi-report.pdf?sc_lang=en

CDC enhanced surveillance for myocarditis outcomes following mRNA COVID-19 vaccination in VAERS case reports:

Individuals ages 5–29 years

Key findings

- At least 90 days after myocarditis diagnosis, most patients who were reached reported **no impact** on their quality of life, and most did not report missing school or work
- 226 patients received a follow-up assessment: **Most** (80.1%) healthcare providers who completed surveys indicated the patient was **fully recovered** or **probably fully recovered**
  - There was substantial heterogeneity in initial and follow-up treatment and testing
  - There did not appear to be a single test that was indicative of recovery

As previously presented to ACIP:
https://www.cdc.gov/vaccines/acip/meetings/downloads/slides-2022-06-22-23/03-COVID-Shimabukuro-508.pdf

Other considerations for COVID-19 vaccine boosters:
Myocarditis and pericarditis

- Risk of myocarditis/pericarditis has been identified after COVID-19 vaccines
  - Risk is rare and primarily observed in adolescent and young adult males
  - Among VAERS data, reporting rates of myocarditis are **lower** after booster dose, compared to dose 2 of primary series
  - Among VSD data, incidence following dose 2 of primary series and booster dose are **similar**, but case counts are **small**
  - Among surveillance data from Canada indicate that the risk of myocarditis and/or pericarditis following a first booster dose appear **lower** than the risk following second dose of a primary series
    - Observed for both Pfizer-BioNTech and Moderna vaccine products and across all age groups[1]
- Most individuals with myocarditis/pericarditis have **fully recovered** at follow-up
- The risk of adverse cardiac outcomes were **1.8 – 5.6 times higher** after SARS-CoV-2 infection than after mRNA COVID-19 vaccination among males ages 12 – 17 years[2]
- Interval of **8 weeks** between vaccine doses may further lower myocarditis risk

1. Public Health Agency of Canada. NACI: Recommendations on the use of bivalent Omicron-containing mRNA COVID-19 vaccines. Sept 1, 2022 2. DOI: http://dx.doi.org/10.15585/mmwr.mm7114e1

COVID-19 Vaccine Safety Technical (VaST) Work Group Assessment – Booster Doses

VaST reviews data from U.S. safety monitoring systems* as well as from other sources; through August 2022, VaST had held 64 teleconference meetings

- COVID-19 mRNA vaccine booster doses:

  v-safe: reactions and health impacts not higher after a booster dose than after primary series dose 2

  VAERS: no additional concerns; myocarditis reporting rates lower after booster dose than after primary series dose 2

  VSD: few myocarditis/pericarditis cases after booster doses and risk estimates imprecise; risk after booster doses appears similar to risk after primary series dose 2

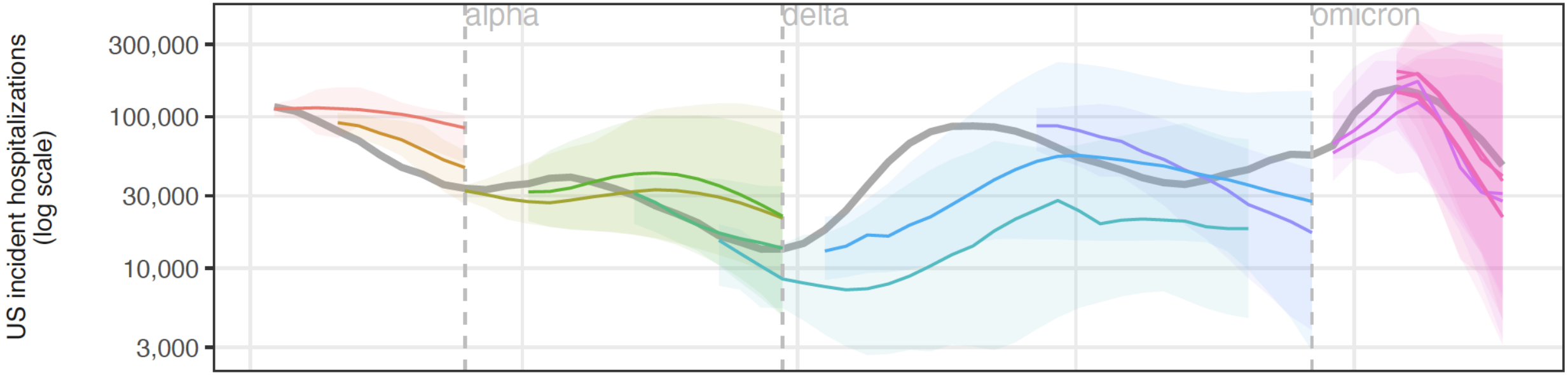
- Vaccination in pregnancy: no safety concerns from any of the systems that have data on primary series and first booster dose

- VaST will continue to review safety data, including data after bivalent vaccine booster

*Vaccine Adverse Event Reporting System (VAERS), v-safe, Vaccine Safety Datalink (VSD), Clinical Immunization Safety Assessment (CISA) project

COVID-19 Scenario Modeling Hub

- A multi-team effort aimed at creating and modeling planning scenarios for the mid- to long-term COVID-19 situation
- 5 – 10 submissions per scenario round at the national level
- Results are ensembled and summarized by the hub (as summarized by figure below)
- Round 14 and 15 were planning scenarios projecting COVID-19 burden through mid-2023 under different booster policies



Scenarios: Boosters and Variants

- **Round 14**
  - VE of bivalent boosters assumed to be 80% against symptomatic disease with non-immune escape strains
  - Targeted booster campaign ages ≥ 50 years vs. flu like uptake* in ages ≥ 18 years
  - No variant vs. a fall "variant X" with 40% immune escape and 20% increased severity
  - Data cutoff June 4, release July 19
- **Round 15**
  - Rapid round aimed to update round 14 and consider booster timing
  - Same VE and variant assumptions as round 14
  - Scenario assumed booster recommendations with flu-like uptake* starting in September 2022 vs. November 2022
  - Data cutoff July 30, release August 12

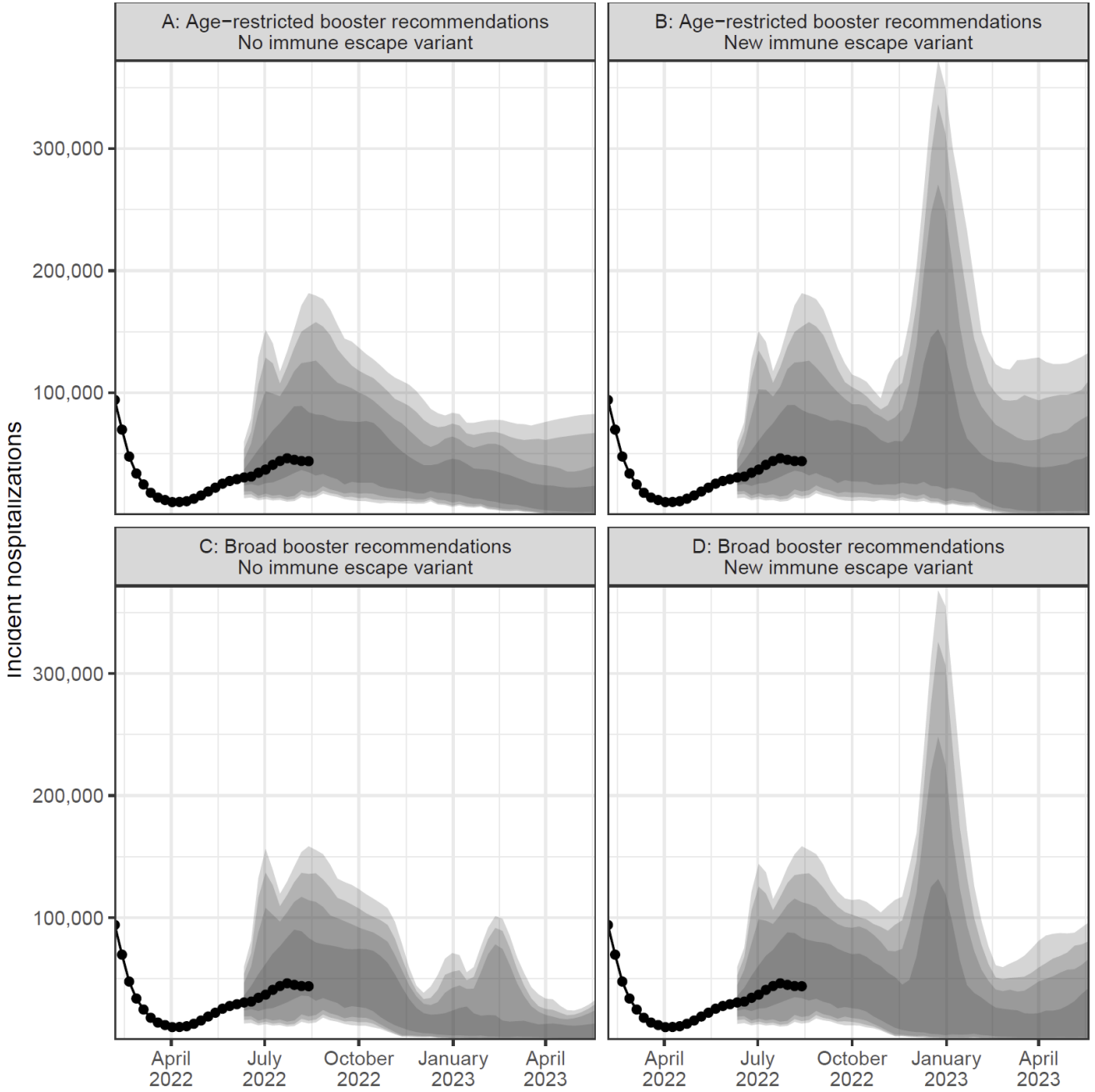
*Assumed 10% reduction of influenza uptake in 2020–2021 season
~**34**% for adults ages 18–49 years
~**50**% for adults ages 50–64 years
~**68**% for adults ages ≥65 years

https://data.cdc.gov/Flu-Vaccinations/Influenza-Vaccination-Coverage-for-All-Ages-6-Mont/vh55-3he6

Round 14: National ensemble projection intervals - Hospitalizations

Round 14

Regardless of presence of a new variant, flu-like vaccine uptake in individuals ages ≥18 years would lead to a >**20%** reduction in **hospitalizations** and **>15%** reduction in **deaths** versus a recommendation for individuals ages ≥50 years only



https://covid19scenariomodelinghub.org/

Round 15: National ensemble projection intervals - Hospitalizations

Round 15

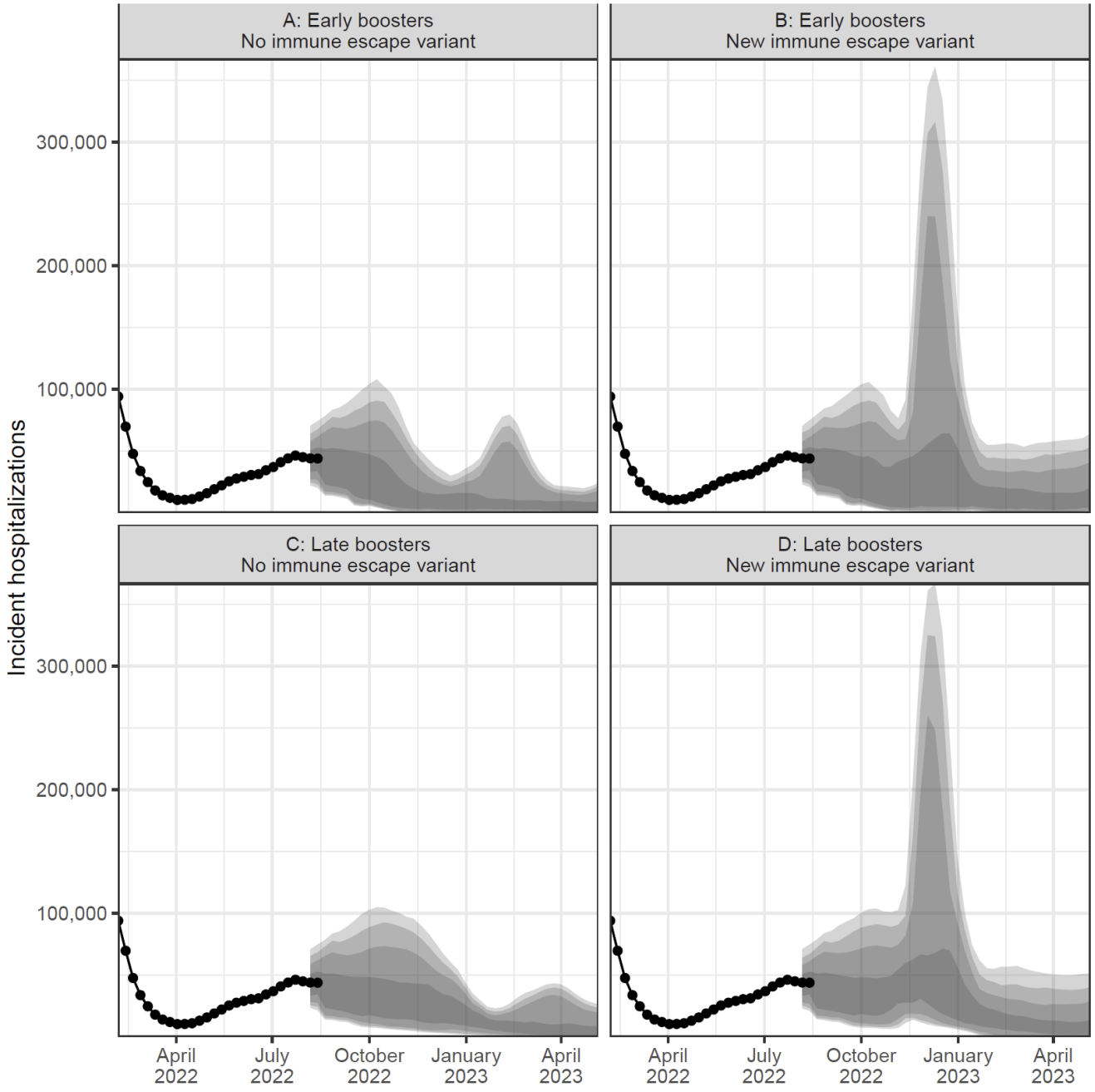
Absent a new variant, boosters to individuals ages ≥18 years in **September** could prevent

137,000 <u>more</u> hospitalizations[1]

and

9,700 <u>more</u> deaths[2]

compared to boosters in **November**



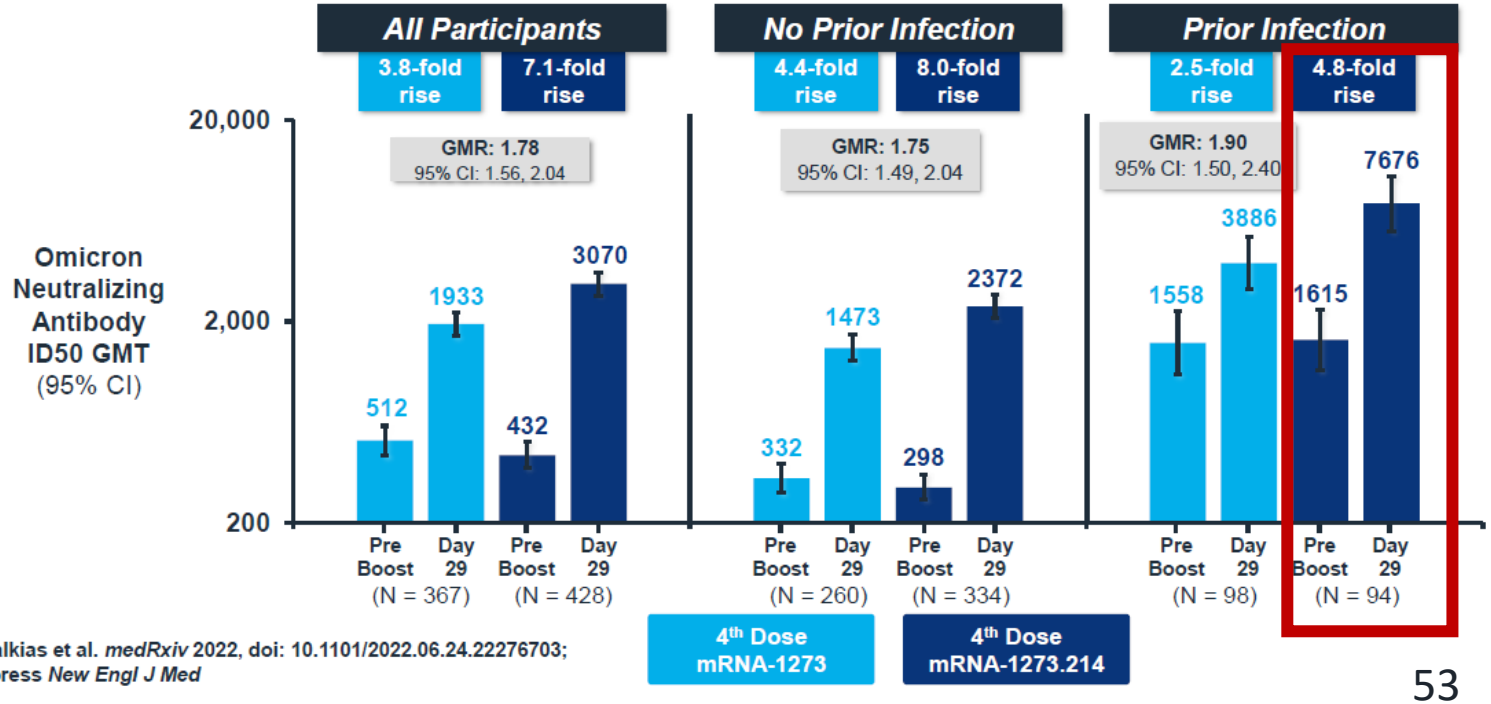
[1]95% Confidence Interval: 21,000-251,000

[2]95% Confidence Interval: 500-19,000

https://covid19scenariomodelinghub.org/

Other considerations: Immune tolerance

- Concern that giving additional doses of COVID-19 vaccine would lead to lower antibody levels (failure to restore antibody levels to what was seen after a previous dose) or T-cell exhaustion
- Bivalent vaccine able to improve vaccine titers in individuals <u>without</u> prior SARS-CoV-2 infection and provided a robust boost in antibody titers for individuals <u>with</u> prior infection
- High antibody titers for a bivalent vaccine and prior SARS-CoV-2 infection may lead to **slower waning** and **prolonged protection** against COVID-19 and severe disease

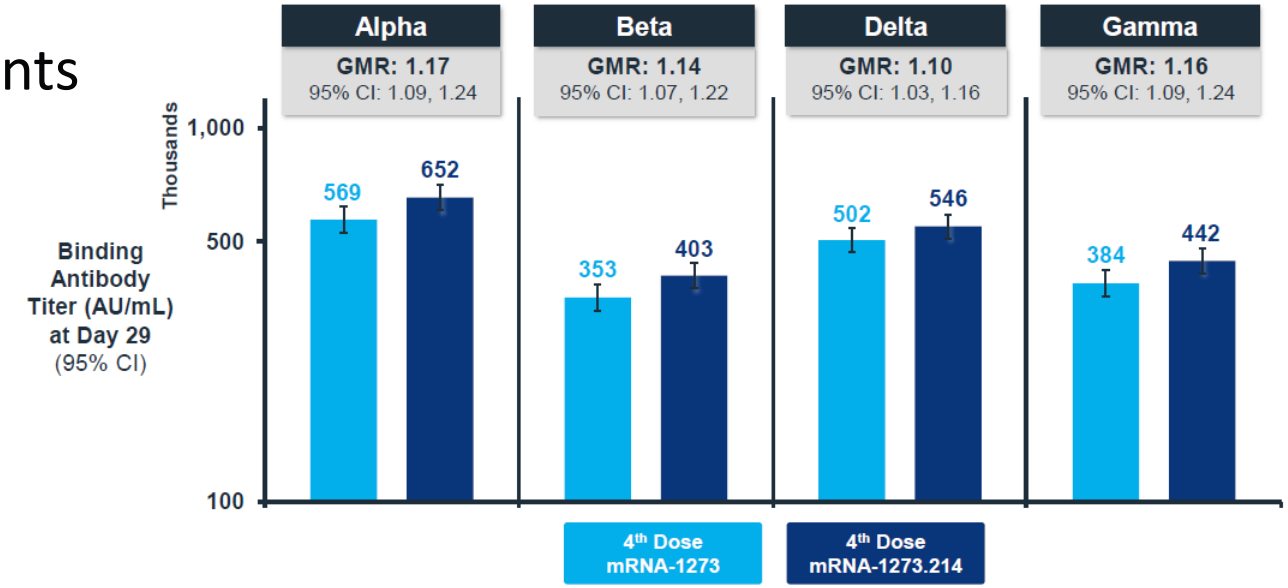


Chalkias et al. *medRxiv* 2022, doi: 10.1101/2022.06.24.22276703; in press *New Engl J Med*

Other considerations: Imprinting

- Concern that initial exposure to one virus strain primes B-cell memory and limits the development of memory B cells and neutralizing antibodies against new strains

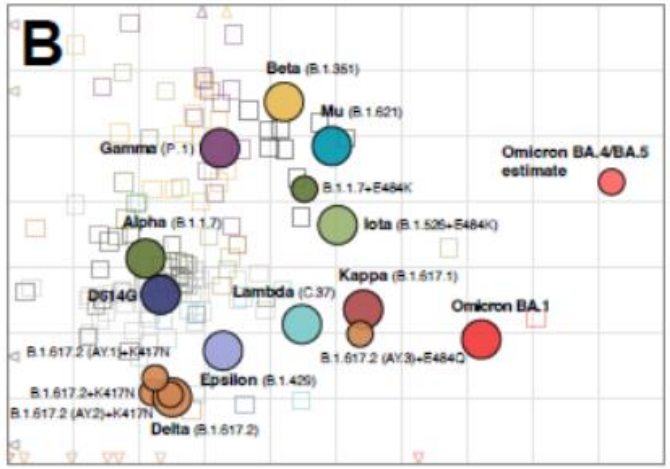
- Data suggest an **improved diverse response** obtained with bivalent vaccines
  - Antibody titers to all SARS-COV-2 variants were higher with a bivalent vaccine, compared to monovalent ancestral vaccine

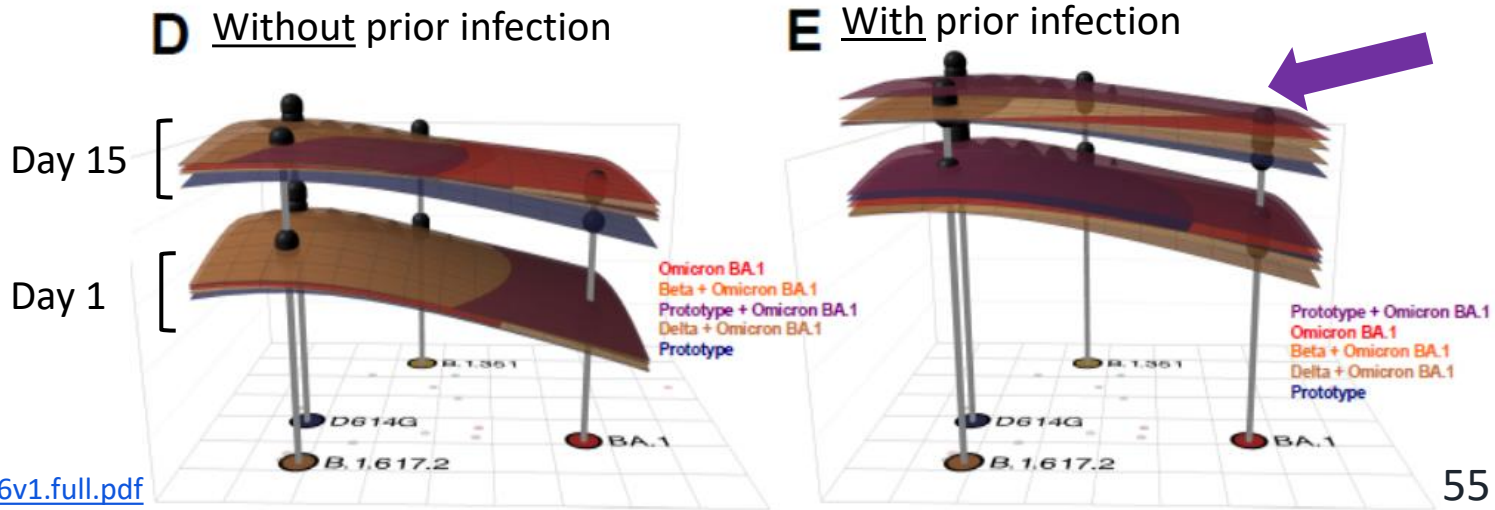


1. https://www.biorxiv.org/content/10.1101/2022.02.03.479037v1.full.pdf
2. https://assets.researchsquare.com/files/rs-1555201/v1_covered.pdf?c=1650045900

Other considerations: Antigenic cartography

- Uses 2D and 3D maps to visualize how closely related the antibody responses are for different viruses
- Antibody landscapes can evaluate **diversity** of immune response
  - A ‘flat’ landscape is better, indicating that the responses to all viruses/variants were similar
  - For the day 15 response (top landscapes), especially for those with prior infection (panel E): bivalent vaccine with **prototype + Omicron** provided a response that was diverse and similar across different variants



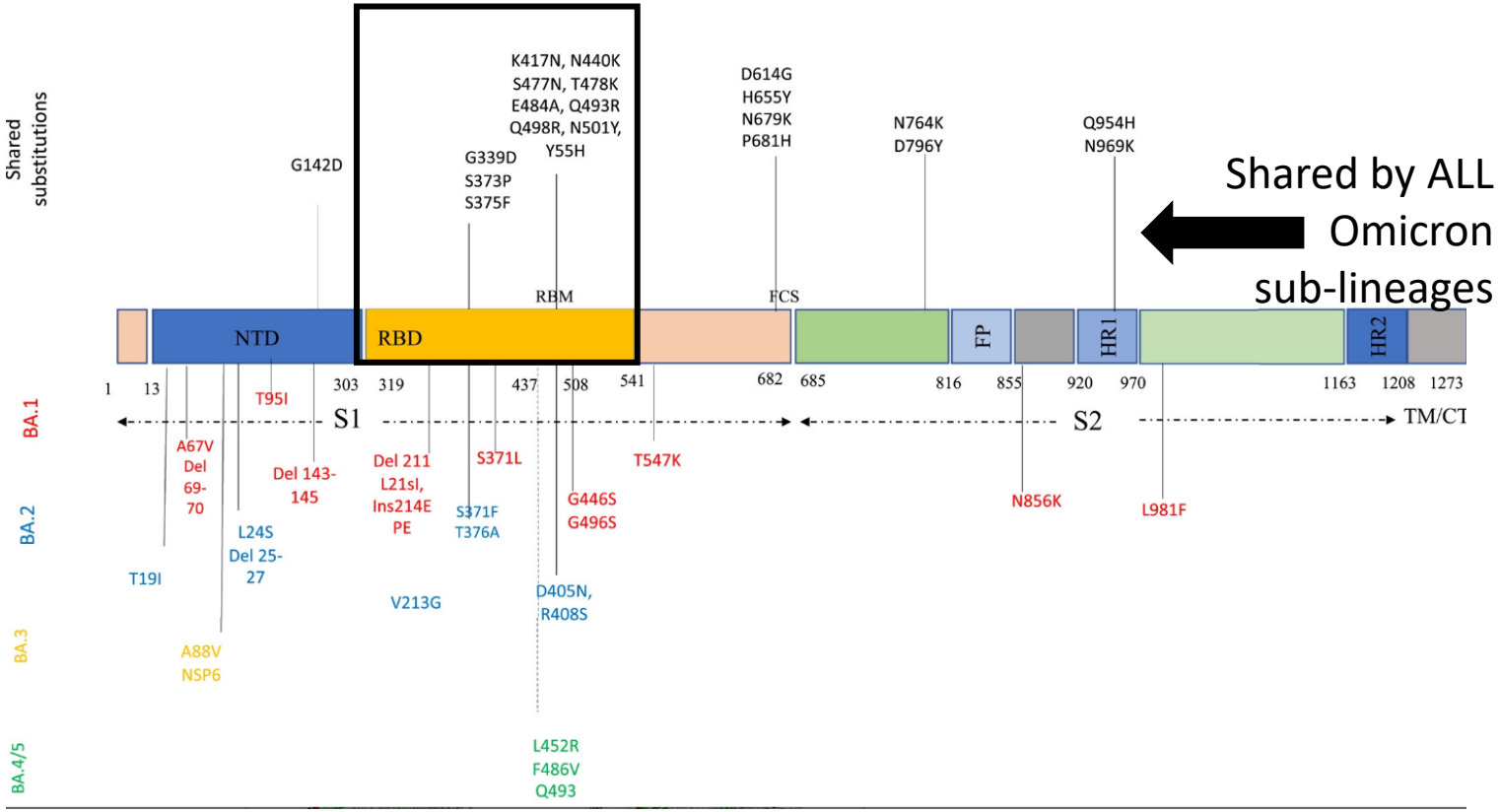


https://www.medrxiv.org/content/10.1101/2022.07.12.22277336v1.full.pdf

Other considerations: BA.1 and BA.4/BA.5

- Clinical data from bivalent COVID-19 vaccines primarily obtained using BA.1
- Compared to the 'ancestral' virus, all Omicron sub-lineages have 21 'shared' mutations
  - Highlighted by the black arrow

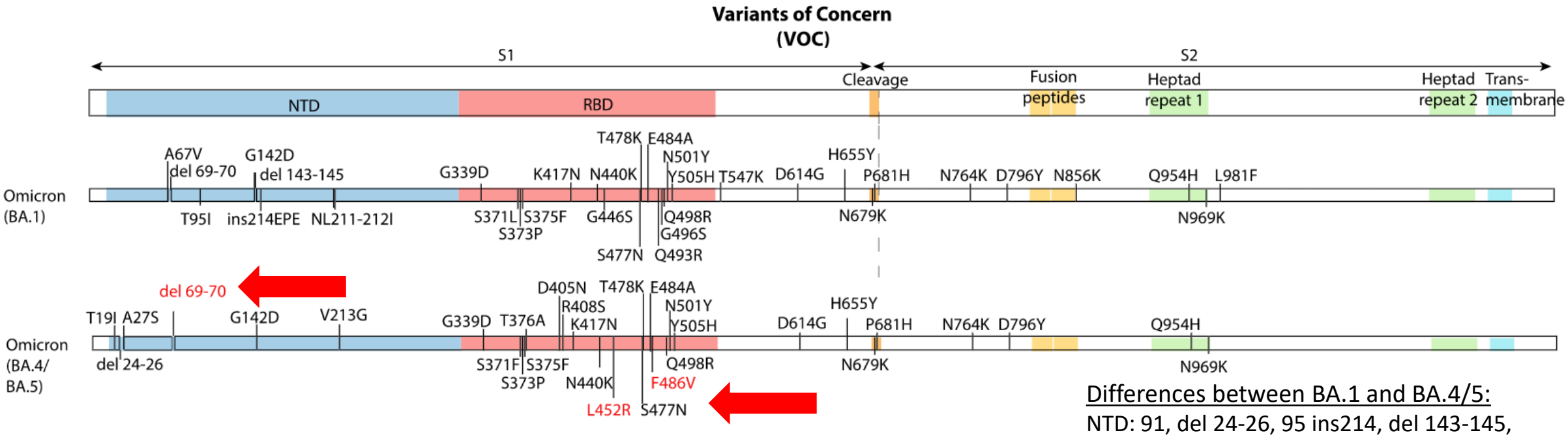
- Many mutations are in the receptor binding domain (RBD), the primary binding site for antibodies
- These mutations contribute to decreased neutralization and increased transmissibility for Omicron sub-lineages



Evolution of the SARS-CoV-2 omicron variants BA.1 to BA.5: Implications for immune escape and transmission - Shrestha - Reviews in Medical Virology - Wiley Online Library

Other considerations: BA.1 and BA.4/BA.5

- BA.4/BA.5
  - Two different Omicron sub-lineages, but Spike protein (focus of the vaccines) is identical
  - BA.4/BA.5 has additional mutations (in red), compared to previous Omicron lineages



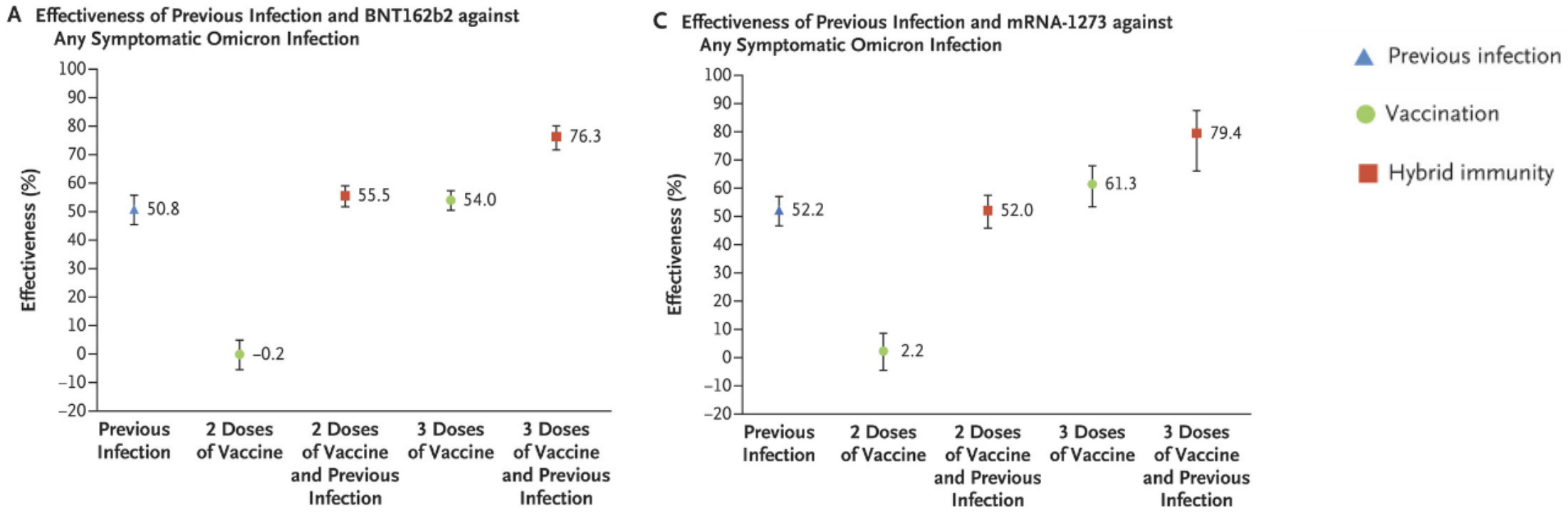
Differences between BA.1 and BA.4/5:
NTD: 91, del 24-26, 95 ins214, del 143-145,
RBD: 376, 405, 408, 446, 452, 486, 493, 496
S1/S2 interface: 547 S2: 856, 981

SARS-CoV-2 variants ~ ViralZone (expasy.org)

Other considerations:

COVID-19 vaccination with and without prior SARS-CoV-2 infection

- Among residents of Qatar, vaccine effectiveness with 3 doses of Pfizer or Moderna COVID-19 vaccine showed **higher** effectiveness against symptomatic Omicron infection than previous SARS-CoV-2 infection alone

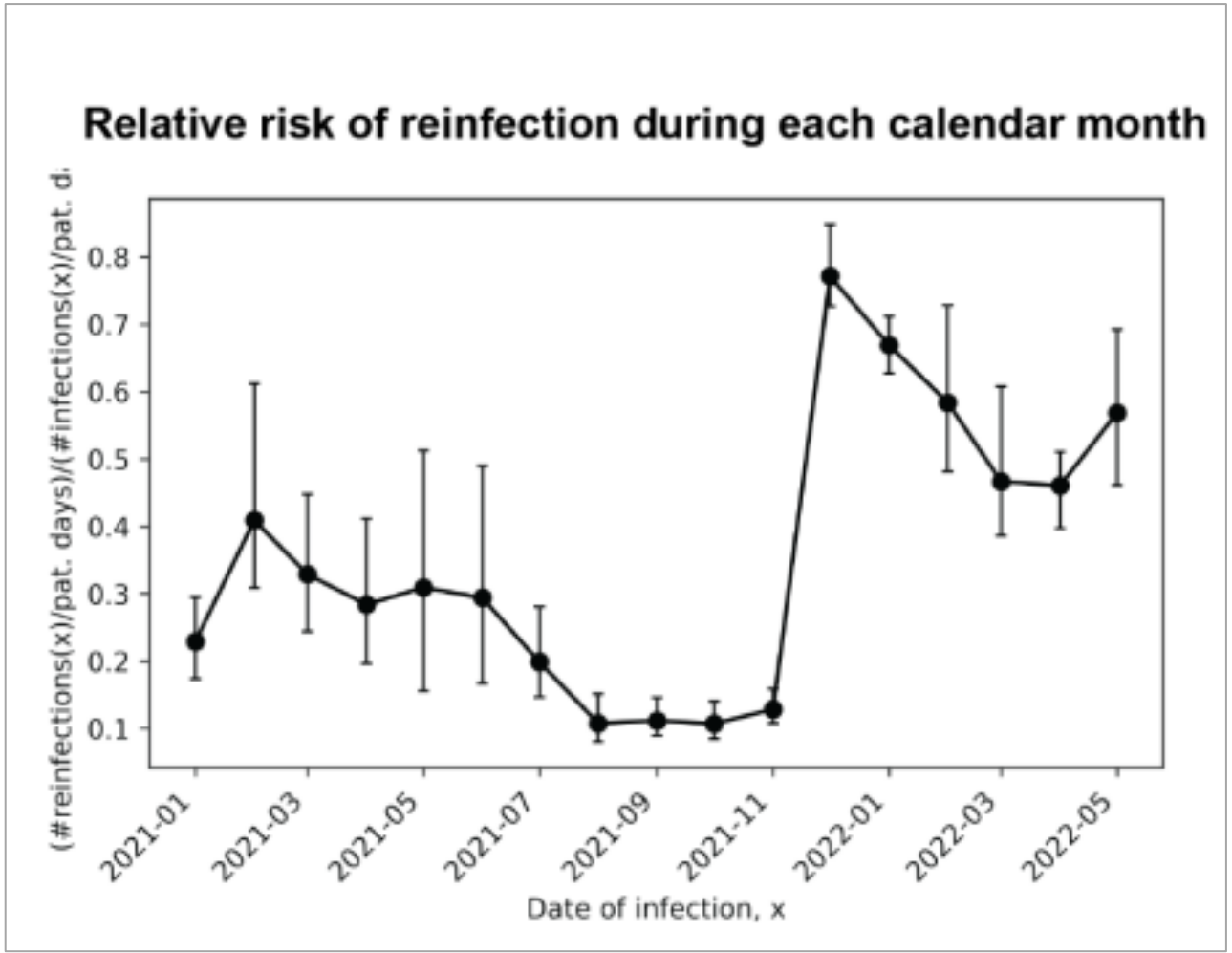


Altarawneh HN, Chemaitelly M, Ayoub HH, et.al. Effects of Previous Infection and Vaccination on Symptomatic Omicron Infections. N Engl J Med 2022; 387:21-34

Other considerations: Reinfection during Omicron

- Among U.S. patients (EHR data), relative risk of SARS-CoV-2 infection for previously infected individuals was compared with a control cohort without previous infection, during each calendar month.

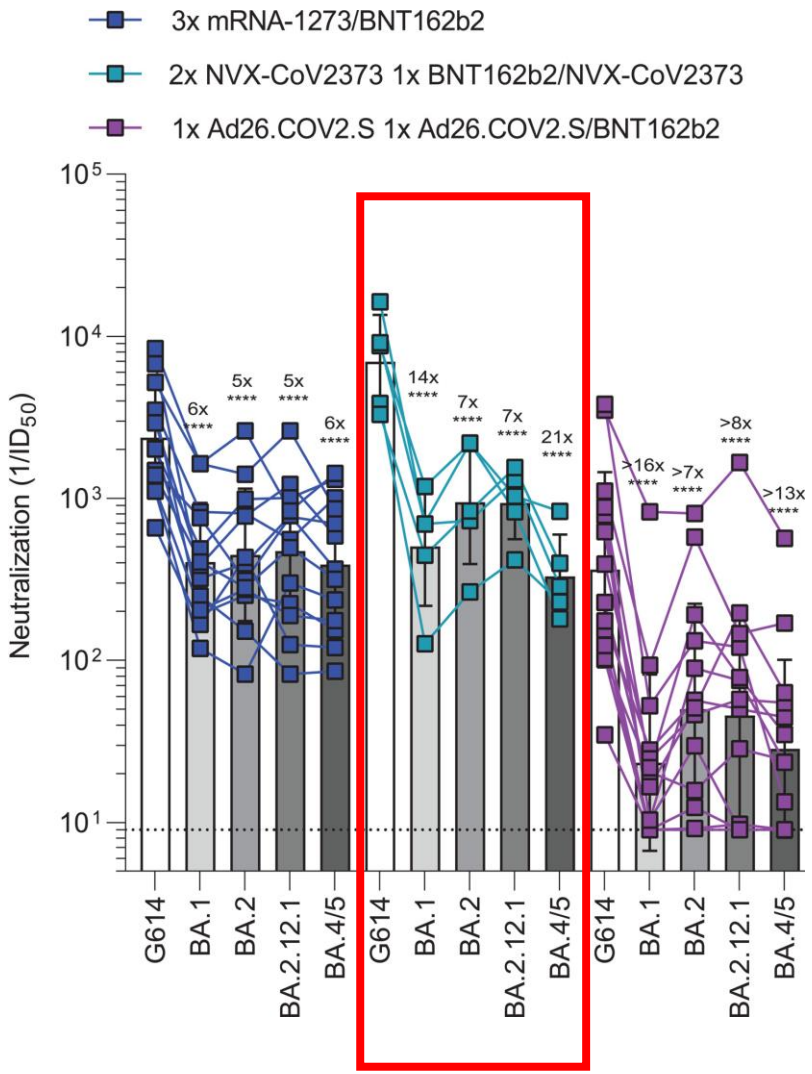
- Reinfections were rare during the first year of the pandemic, and during Alpha and Delta surges in 2021, **but the relative risk of infection in those with prior infection significantly increased during Omicron.**



Individuals with recent prior SARS-CoV-2 infection are at reduced risk of Omicron infection and associated hospitalization (medrxiv.org)

Other considerations: Non-mRNA boosters

- Study assessed the benefits provided by homologous or heterologous vaccine boosters on vaccinee plasma neutralizing activity against Omicron sublineages
- Individuals who received a Novavax primary series and a Novavax booster had comparable neutralizing GMTs to those who received monovalent mRNA COVID-19 vaccine as a primary series and booster
- Administration of a booster increased neutralizing antibody titers and breadth against Omicron sublineages



DOI: 10.1126/science.abq020

Other considerations: Non-mRNA boosters

- Randomized trial of third dose booster vaccines given 10–12 weeks after an initial course of **Pfizer-BioNTech COVID-19 primary series**
- All booster doses resulted in **increases** anti-spike IgG concentrations. Third doses of mRNA vaccines resulted in geometric mean concentrations **~3x higher** than those observed in Novavax recipients
- All boosters showed acceptable side-effect profiles

Booster dose	Pfizer-BioNTech n=23	Moderna n=18	Novavax n=24
SARS-CoV-2 anti-spike IgG, ELU/mL			
Day 0	5422 (3781–7776)	3271 (1970–5432)	3512 (2454–5026)
Day 7	27551 (21016–36118)	20930 (11594–37786)	5080 (3585–7199)
Day 28	26171 (21245–32239)	30654 (22916–41004)	8754 (6262–12236)

DOI: https://doi.org/10.1016/S0140-6736(21)02717-3

Domain Equity Question:

Are the desirable and undesirable anticipated effects demonstrated across all populations equally?

Are the desirable and undesirable anticipated effects demonstrated across all populations equally?

- Are the desirable and undesirable anticipated effects demonstrated across all populations?
  - Were persons of all races and ethnicities included in clinical trials or observations?
  - Do the demographics of study populations reflect demographics of the US population?
  - Are there specific population groups for which the burden of the public health problem or benefit of the intervention is of particular concern?
    - If so, are these population groups represented in clinical trials or observations?

- Are the desirable and undesirable effects equally demonstrated across all populations?
  - Were desirable and undesirable effects examined by population group?
  - Are there any desirable or undesirable effects which appear more frequently in one or more population groups?

Moderna study 205 demographics

Characteristics n (%)	mRNA-1273.214 (50 µg), N=437	mRNA-1273 (50 µg), N=377	US Census Data, 2021
Age subgroup			
18-64 years	263 (60.2)	227 (60.2)	61
≥65 years	174 (39.8)	150 (39.8)	16.8%
Gender			
Male	179 (41.0)	186 (49.3)	49.5%
Female	258 (59.0)	191 (50.7)	50.5%
Ethnicity			
Hispanic or Latino	46 (10.5)	37 (9.8)	18.9%
Not Hispanic or Latino	390 (89.2)	340 (90.2)	81.1%
Race			
White	381 (87.2)	322 (85.4)	75.8%
Black or African American	31 (7.1)	29 (7.7)	13.6%
Asian	14 (3.2)	16 (4.2)	6.1%
American Indian or Alaska Native	0	1 (0.3)	1.3%
Native Hawaiian or Other Pacific Islander	0	1 (0.3)	0.3%
Multiracial	7 (1.6)	2 (0.5)	2.9%

https://www.medrxiv.org/content/10.1101/2022.06.24.22276703v1.full.pdf
U.S. Census Bureau QuickFacts: United States

Pfizer substudy E (age >55 years) expanded cohort demographics

Characteristics, %	Substudy E	US Census Data, 2021
Median age (years)	67	39
Sex		
Male	49.5	49.5
Female	50.5	50.5
Ethnicity		
Hispanic or Latino	14.9	18.9
Not Hispanic or Latino	85.1	81.1
Race		
White	86.6	75.8
Black or African American	6.3	13.6
Asian	5.5	6.1
American Indian or Alaska Native	≤1.1	1.3
Native Hawaiian or Other Pacific Islander	≤1.1	0.3
Multiracial	≤1.1	2.9

Results by race and ethnicity

- **Moderna bivalent booster data**
  - Omicron B.1 and original strain neutralizing antibodies after a 4th dose were comparable across racial groups
- **Pfizer-BioNTech bivalent booster data**
  - Subgroups of participants >55 years of age in the safety population had generally similar adverse event profiles from study vaccination to 1 month post-dose, across various vaccine groups when evaluated by subgroups of sex, race, and ethnicity
  - Overall, there were no clinically meaningful differences between subgroups for neutralizing GMTs for the Omicron variant and the original strain
- In both trails, subgroups of race and ethnicity included a limited number of participants, and their results should be interpreted with caution

Bivalent COVID-19 vaccines:
Data to inform recommendations

- Experience from using COVID-19 vaccine mRNA platform for nearly 2 years and over 600 million doses in the United States alone
  - Extensive vaccine effectiveness studies as well as robust post-authorization safety data across multiple platforms
- Clinical (human) data from bivalent COVID-19 vaccines in >1700 persons
  - Includes bivalent vaccines with Beta and Omicron variants, both from manufacturers and NIH studies
  - Over 1400 individuals received bivalent vaccine with **Omicron** component specifically
  - While there are subtle differences in mutations between BA.1 and BA.4/BA.5 spike protein sequences, do not anticipate differences in safety or reactogenicity of vaccines based on these limited mutations
  - Overall composition of the vaccine as well as total antigenic load are the same as current booster doses
- Antigenic cartography and antibody studies
- Modeling data

Bivalent COVID-19 vaccines:
What we know

- COVID-19 vaccines have a **high degree** of safety
  - Rare events of myocarditis seen after mRNA COVID-19 vaccines in post-authorization studies; cases of myocarditis attributed to the vaccine were detected in Novavax COVID-19 vaccines clinical trials
- COVID-19 vaccines provide **high levels** of protection against **severe disease**
  - Initially, COVID-19 vaccines also provided high levels of protection against infection and transmission
  - As the virus evolved, noted rapid waning of protection against asymptomatic or mild disease
- COVID-19 booster doses **further increase** protection against **severe disease**
- Bivalent COVID-19 vaccines **expand immune response** after vaccination
  - Vaccines that contain Omicron will improve antibody response to Omicron
  - Bivalent vaccines appear to provide more diverse response overall, likely improving response to future variants

Bivalent COVID-19 vaccines:

What we do not know

- Rate of myocarditis after bivalent COVID-19 vaccines
  - Unlikely that the inclusion of Omicron would increase myocarditis rates
  - Age and sex of the individual are likely contributing factors to development of myocarditis after vaccine; interval since previous dose and total dose may be related
- Incremental increase in vaccine effectiveness
  - Antibody titers to currently circulating variants were higher after a bivalent booster than with current monovalent booster
  - Most of the data to inform recommendations from BA.1 bivalent vaccine; incremental benefits for the BA.4/BA.5 vaccine are unknown
- Duration of protection
  - Antibody titers after bivalent vaccine and prior SARS-CoV-2 infection were robust
  - This may **prolong** duration of protection and **decrease** the need for frequent boosters
  - As with all vaccines, duration of protection may vary by age and immune status

Summary-balance of benefits and harms for bivalent booster doses

- Bivalent booster dose of both Moderna & Pfizer-BioNTech COVID-19 vaccines **increases immune response** in those who have completed a primary series and a previous booster
- Similar reactogenicity profile to primary series and ancestral booster dose
- Myocarditis risk following a bivalent booster dose is unknown, but anticipate similar risk to what is seen after monovalent booster doses
- Modeling projects more hospitalizations and deaths averted when booster doses are recommended for **persons ≥18 years** compared to only persons ≥50 years, and when the booster campaign begins in **September** compared to November 2022
- Benefits and harms for the U.S. population are best assessed when clinical trial and study populations are optimally representative of the U.S. population

Benefits and Harms

How substantial are the desirable anticipated effects?

- How substantial are the anticipated effect for each main outcome for which there is a desirable effect?

○ **Minimal**	○ **Small**	○ **Moderate**	○ **Large**	○ **Varies**	○ **Don't know**

Benefits and Harms

How substantial are the undesirable anticipated effects?

- How substantial are the anticipated effect for each main outcome for which there is an undesirable effect?

○ **Minimal**	○ **Small**	○ **Moderate**	○ **Large**	○ **Varies**	○ **Don't know**

Benefits and Harms

Do the desirable effects outweigh the undesirable effects?

- What is the balance between the desirable effects relative to the undesirable effects?

○ Favors intervention (updated (bivalent) COVID-19 vaccine booster doses)
○ Favors comparison (no vaccine)
○ Favors both
○ Favors neither
○ Unclear

EtR Domain: Values

72% of respondents "definitely" or "probably" will get an updated booster that protects against Omicron variants

'Probably' or 'Definitely' will get an updated booster

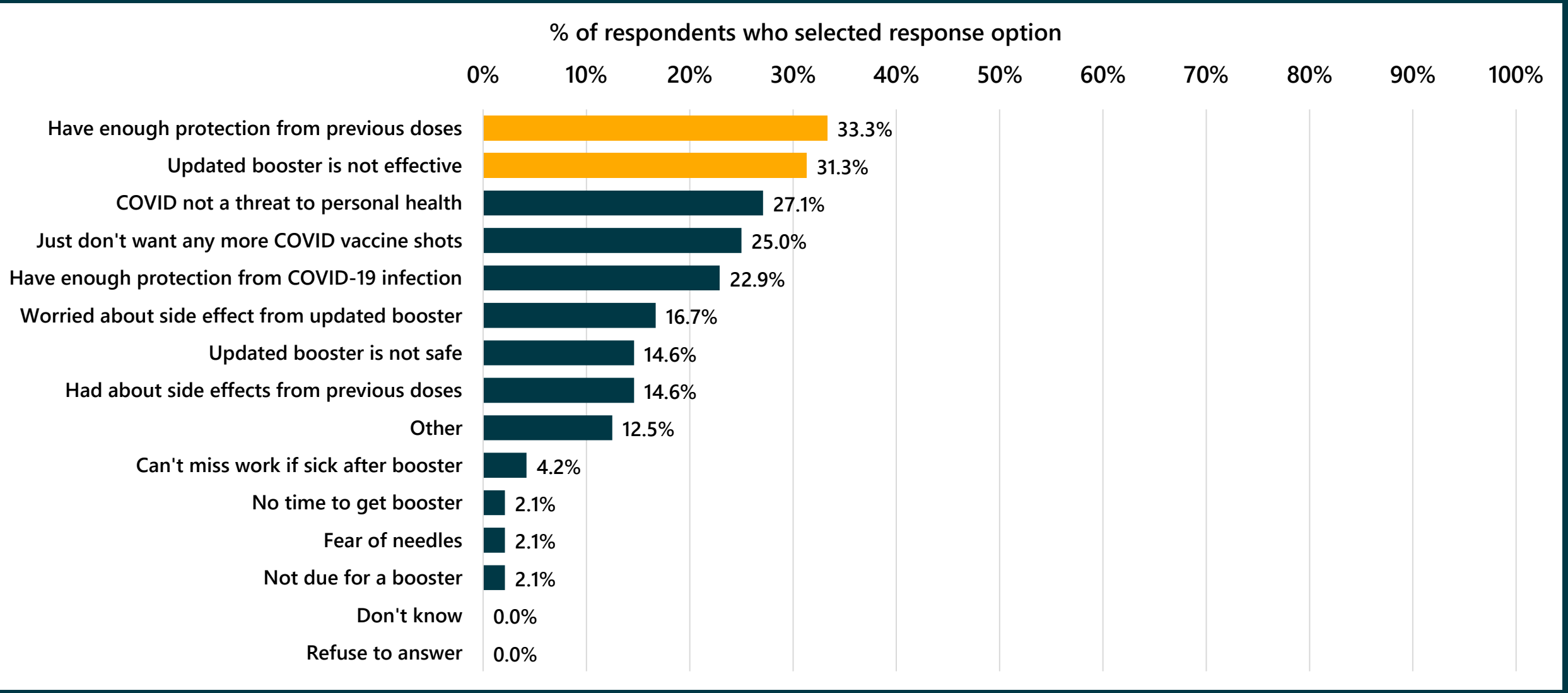
Unsure

'Probably' or 'Definitely' will not get an updated booster

CDC and University of Iowa/RAND survey, August 2022, unpublished

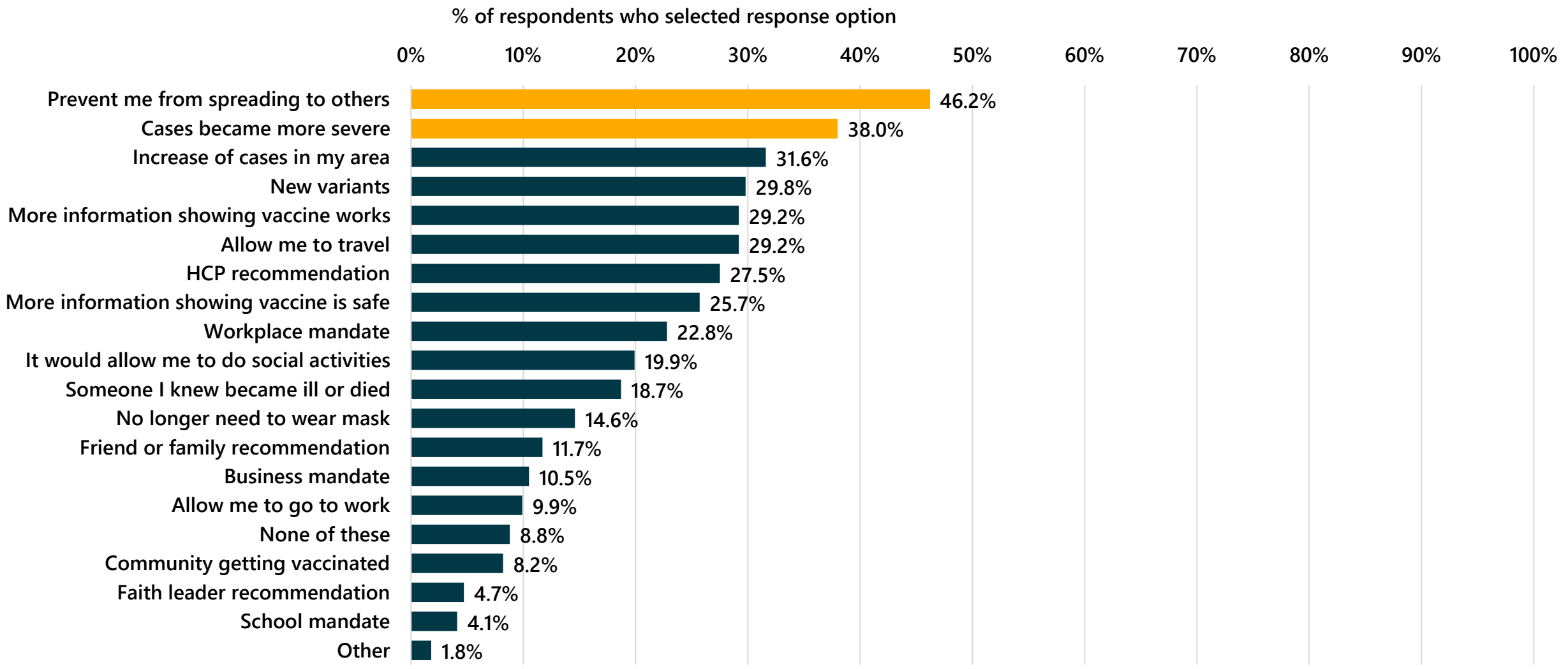
n=171

Belief that previous doses provided enough protection and doubts about an updated vaccine's efficacy were the most selected reasons for being unsure or not intending to get an updated booster (n=48).



CDC and University of Iowa/RAND survey, August 2022, unpublished

Preventing spread to others and change in case severity were the most selected facilitators to getting an updated booster.



CDC and University of Iowa/RAND survey, August 2022, unpublished

n=171

63% of respondents were “extremely” or “somewhat” willing get an annual flu shot and updated COVID booster at the same visit this Fall

‘Somewhat’ or ‘Extremely’ willing to get both vaccines in the same visit this Fall

Unsure

‘A bit’ or ‘Not at all’ willing to get both vaccines in the same visit this Fall

CDC and University of Iowa/RAND survey, August 2022, unpublished

n=171

Domain Equity Question:

Is there important variability in how patients or populations value the outcome?

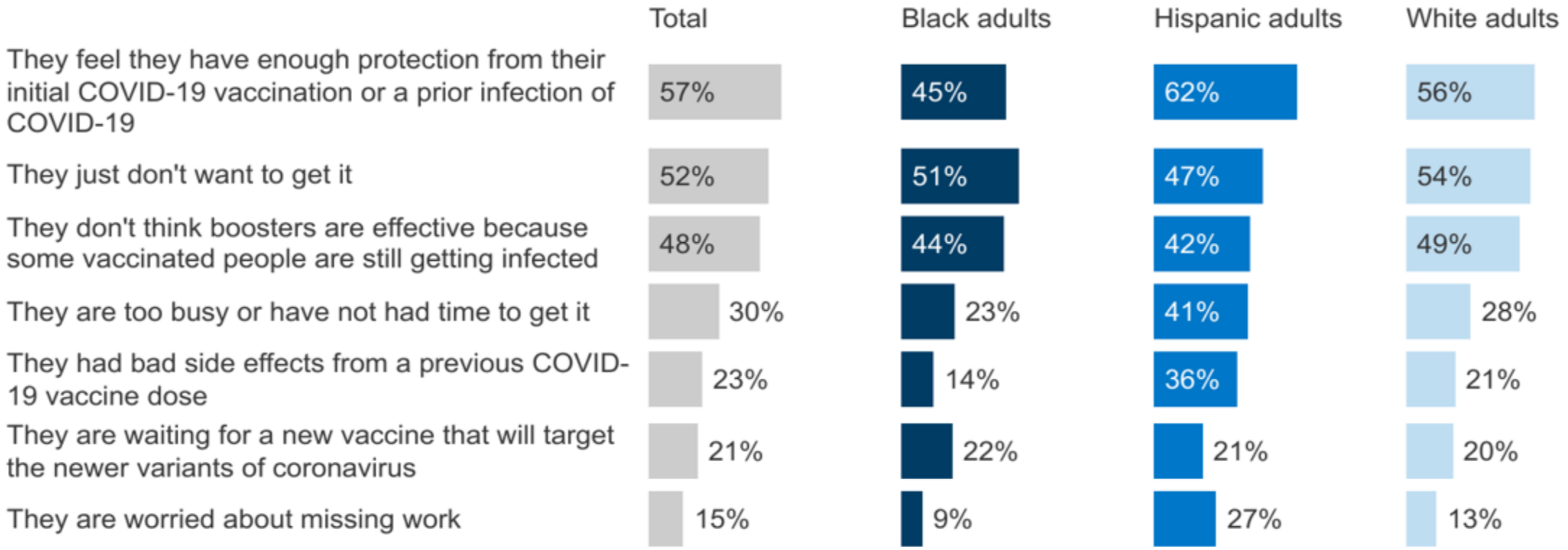
Older adults, college graduates and those with higher incomes remain most likely to be vaccinated and boosted

- Booster uptake has remained relatively steady, with those groups with higher initial vaccine uptake also more likely to have received their booster dose
- Overall, around half of adults report being fully vaccinated and have received their booster dose for COVID-19 (49%), with the largest shares among adults ages 65 and over (76%), college graduates (67%) and those with a household income of $90K+ (62%)
- Notably, despite a high vaccine uptake rate (83%), about a third of adults of Hispanic/Latino ethnicity (33%) say they're fully vaccinated for COVID-19 but haven't received their booster dose yet

The survey was conducted July 7 – 17, 2022, online and by telephone among a nationally representative sample of 1,847 U.S. adults.
KFF COVID-19 Vaccine Monitor: July 2022. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-july-2022/ Accessed August 9, 2022

Majority of vaccinated adults feel protection from initial vaccine or prior infection is primary reason for not receiving a booster

- Percent of vaccinated adults without a booster who say the following is a reason they have not received a COVID-19 booster dose:



The survey was conducted July 7 – 17, 2022, online and by telephone among a nationally representative sample of 1,847 U.S. adults.

KFF COVID-19 Vaccine Monitor: July 2022. https://www.kff.org/coronavirus-covid-19/poll-finding/kff-covid-19-vaccine-monitor-july-2022/ Accessed August 9, 2022

Summary
Values

- **72%** of survey respondents reported they were likely to receive an updated COVID-19 booster
- **Preventing spread to others** (46.2%) and **change in case severity** (38%) were the top facilitators to getting an updated booster
  - Whereas **belief that previous doses provided enough protection** (33.3%) and **doubts about an updated vaccine's efficacy** (31.3%) were the top deterrents for being unsure or not intending to get an updated booster
- Nearly **2/3** of adults were willing to receive an updated COVID-19 vaccine and an influenza shot at the same time
- Receipt of booster to date demonstrates persistent vaccine inequity
  - Adults of older age, with college degrees, and with higher incomes remain most likely to be vaccinated and boosted
  - ~33% of adults of Hispanic/Latino ethnicity have not received a booster despite completion of primary series

Values

Criteria 1:

Does the target population feel that the desirable effects are large relative to undesirable effects?

- How does the target population view the balance of desirable versus undesirable effects?
- Would patients/caregivers feel that the benefits outweigh the harms and burden?
- Does the population appreciate and value the Bivalent COVID-19 vaccine booster?

○ **Minimal**	○ **Small**	○ **Moderate**	○ **Large**	○ **Varies**	○ **Don't know**

Values

Criteria 2:

Is there important uncertainty about, or variability in, how much people value the main outcomes?

- How much do individuals value each outcome in relation to the other outcomes?
- Is there evidence to support those value judgements?
- Is there evidence that the variability is large enough to lead to different decisions?

- ○ Important uncertainty or variability
- ○ Probably important uncertainty or variability
- ○ Probably not important uncertainty or variability
- ○ No important uncertainty or variability
- ○ No known undesirable outcomes

EtR Domain: Acceptability

Infrastructure Exists to Reach Key Populations: U.S. COVID-19 Vaccine Program Milestones (August 2022)

Over 800 million doses delivered in 88 weeks

Over 606 million doses administered in 87 weeks

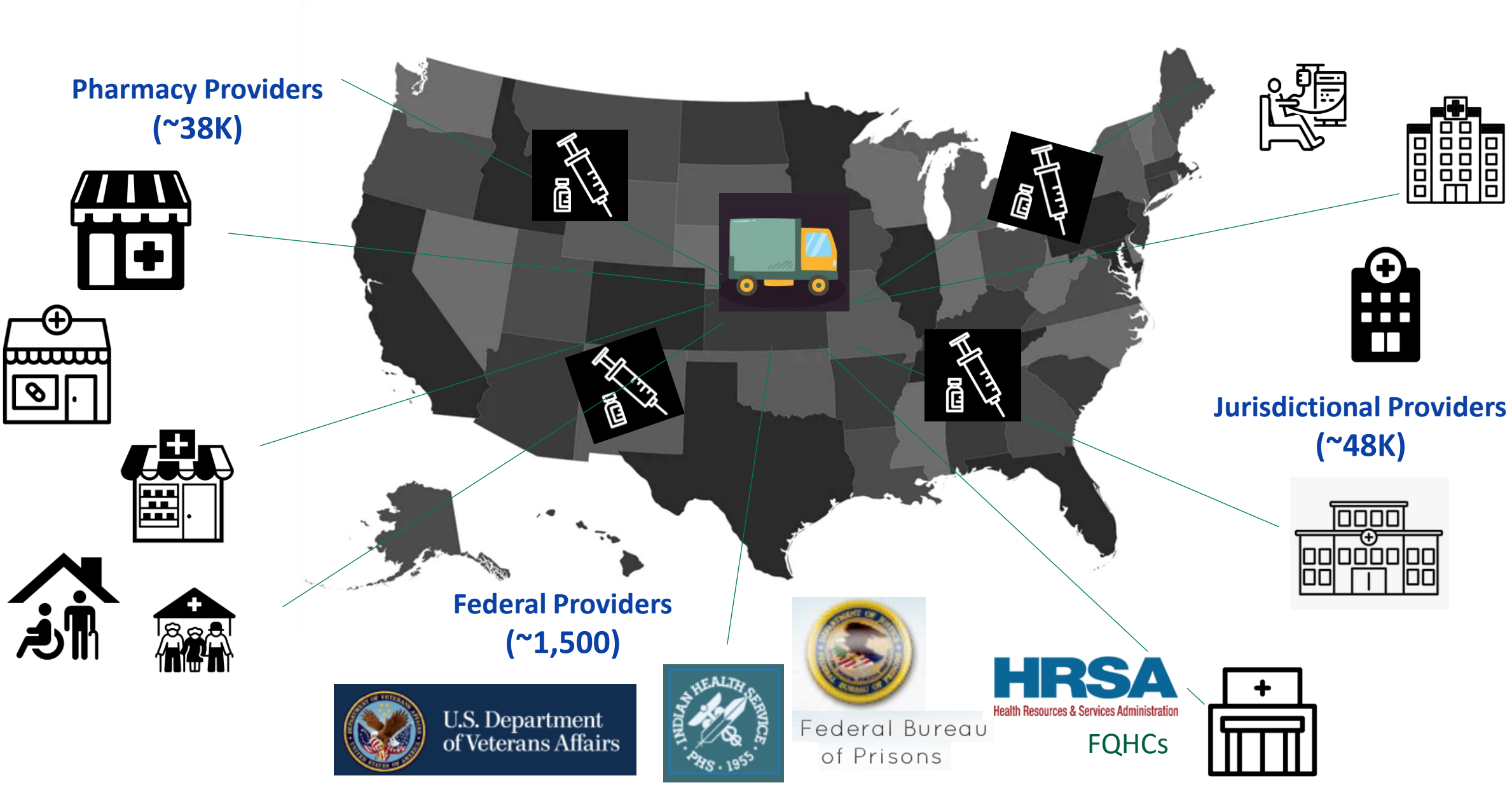
About 90% of 18+ population have received at least 1 dose

About 92% of 65+ population are fully vaccinated with 71% boosted

Over 223 million people fully vaccinated

Source: Data pulled from CDC COVID Data Tracker as of 08/17/22 1200

U.S. Network of Active COVID-19 Vaccine Providers



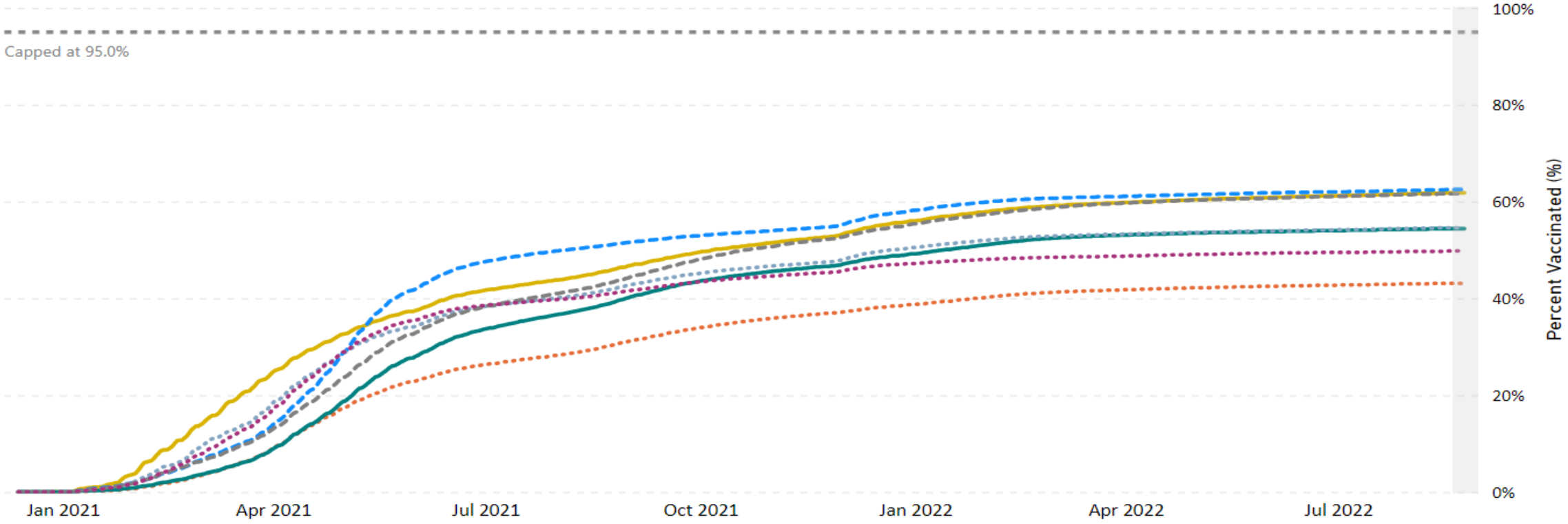
Domain Equity Question:

Is the intervention equally acceptable across all populations?

Percent of population with a completed COVID-19 primary series in the United States, by race and ethnicity

December 14, 2020 – August 24, 2022

	AI/AN, NH	Asian, NH	Black, NH	Hispanic/Latino	Multiracial, NH	NHOPI, NH	White, NH
At Least One Dose	74.3%	69.5%	49.3%	64.0%	55.0%	68.3%	54.7%
Fully Vaccinated	61.8%	62.5%	43.1%	54.4%	54.6%	61.6%	49.8%

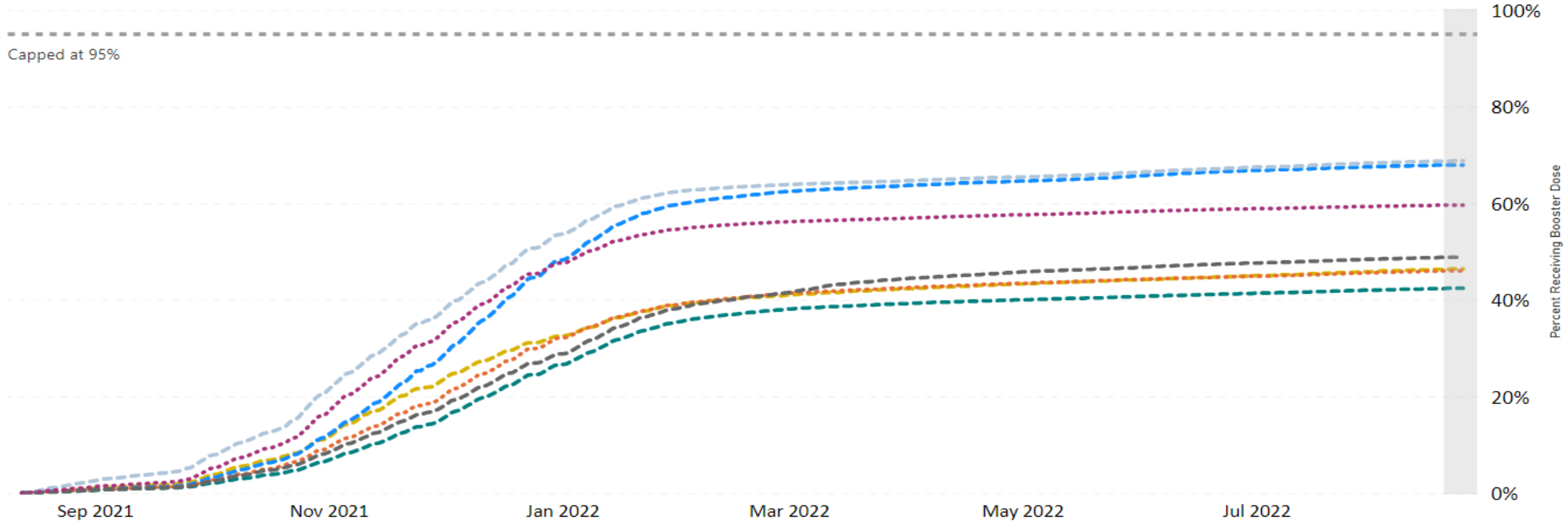


CDC COVID Data Tracker. Trends in Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed August 31, 2022

Booster vaccination coverage in the United States, by race and ethnicity

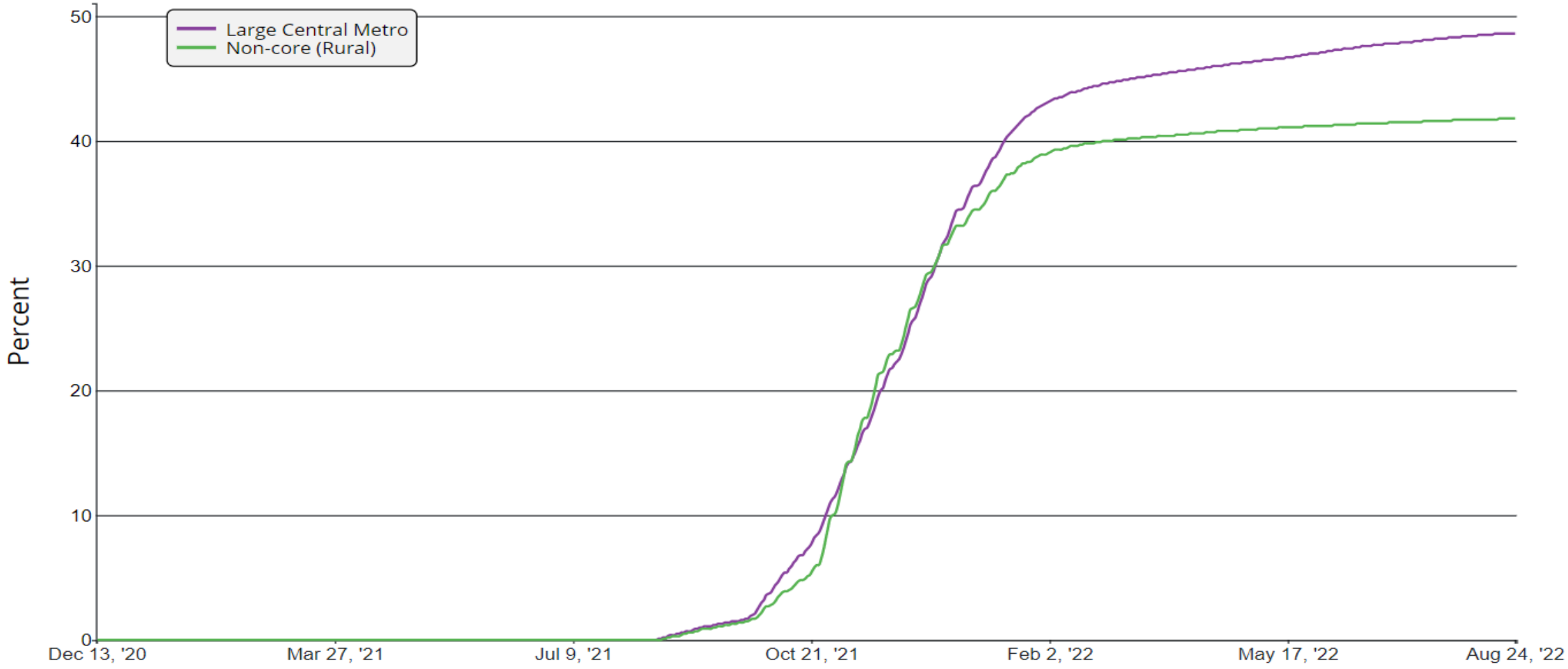
August 12, 2021 – August 24, 2022

	AI/AN, NH	Asian, NH	Black, NH	Hispanic/Latino	Multiracial, NH	NHOPI, NH	White, NH
First Booster Dose	46.4%	67.9%	46.0%	42.4%	68.8%	48.8%	59.6%
Second Booster Dose	31.3%	35.9%	28.4%	25.1%	42.8%	32.1%	36.3%



CDC COVID Data Tracker. Trends in Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographics-trends Accessed August 31, 2022

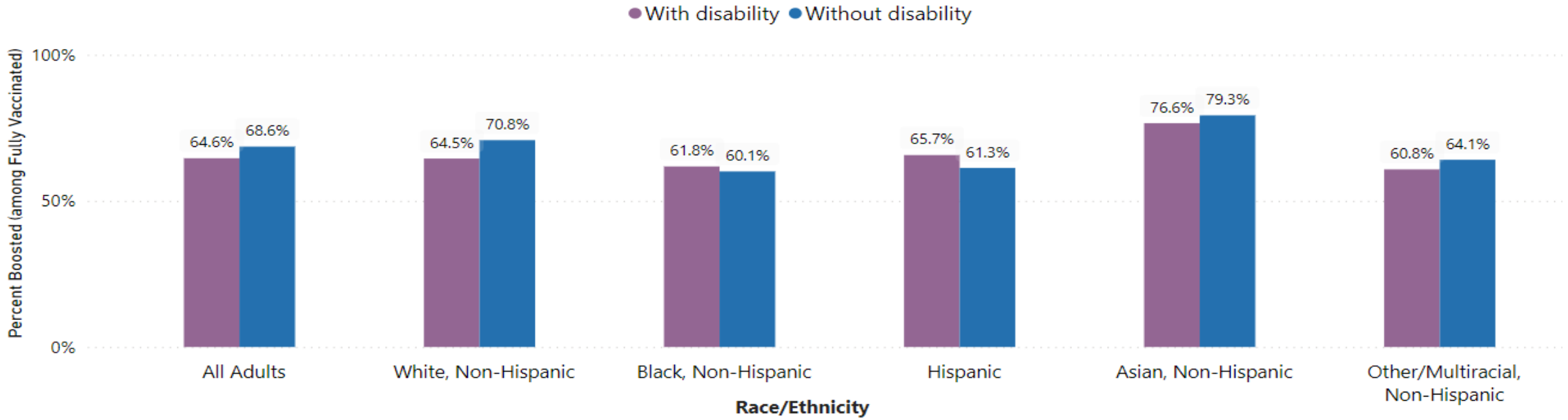
Average percentages of fully vaccinated population with a first booster dose in the United States, by county urbanicity



CDC COVID Data Tracker. COVID-19 Vaccination Equity. https://covid.cdc.gov/covid-data-tracker/#vaccination-equity Accessed August 31, 2022

Reported receipt of COVID-19 booster dose† among fully vaccinated†† adults ages 18 years and older by disability status** and race and ethnicity,

Household Pulse Survey, March 30, 2022 – May 9, 2022,^^ United States



†Receipt of a Booster Dose is defined as the receipt of a third dose of COVID-19 vaccine after completion of a 2-dose primary mRNA COVID-19 vaccine series or a second dose of COVID-19 vaccine for adults whose first dose was a J&J Janssen vaccine.

††Full vaccination is defined as the receipt of a 2-dose primary mRNA COVID-19 vaccine series or one dose of a J&J Janssen vaccine.

**The disability data collection items included in the Household Pulse Survey come from the Washington Group Short Set on Functioning (WG-SS). Disability status is defined using the reported level of difficulty in one of four selected WG-SS domains of functioning: 1) seeing (even when wearing glasses), 2) hearing (even when using a hearing aid), 3) mobility (walking or climbing stairs), and 4) cognition (remembering or concentrating). Adults who respond "a lot of difficulty" or "cannot do at all" to at least one domain are classified as with disability.

^^Combined Household Pulse Survey data collected during March 30, 2022–April 11, 2022 and April 27–May 9, 2022 (sample size = 106,749). New random samples are selected and released for each survey wave, and responses are accepted during the data collection period.

CDC COVID Data Tracker. COVID-19 Vaccination among People with Disabilities. https://covid.cdc.gov/covid-data-tracker/#vaccinations-disability-status Accessed August 25, 2022

Importance of providers' recommendation in COVID-19 vaccine acceptability

- A poll from the University of Michigan found that **77%** of older adults say their provider's recommendation about COVID-19 vaccination is very or somewhat important to their decision to get vaccinated
- The percentage saying a provider's recommendation was very important was highest for those who were Black (**79%**), over age 65, retired or have incomes under $30,000 (**56%**, respectively) compared with those of other racial and ethnic backgrounds, work statuses or income levels
- Physicians, nurses and nurse practitioners, pharmacists and physician's assistants should start communicating to their patients now about the importance of getting a dose of one of the updated (bivalent) COVID-19 boosters when they become available

Institute for Healthcare Policy and Innovation. University of Michigan. August 9, 2022. Most older adults are ready to roll up sleeves this fall for updated COVID-19 boosters, U-M poll shows. https://ihpi.umich.edu/news/most-older-adults-ready-roll-sleeves-fall-updated-covid-19-boosters-u-m-poll-shows Accessed August 24, 2022

Summary
Acceptability

- Over 800 million doses of COVID-19 vaccines have been delivered since the beginning of the program, with a wide network of vaccine providers
- Significant disparities in completion of primary series vaccination and receipt of booster doses persist by race, ethnicity, urbanicity, and differences in abilities including vision, hearing, mobility and cognition
- Detection of disparities does not explain disparities:
  - Differences in **acceptability** may contribute to disparities
  - Differences in **access** may contribute to disparities
  - Identifying and understanding these and other **drivers of inequity** is a critical step toward equity
- Healthcare provider recommendation continues to appear to increase acceptability of COVID-19 vaccination, and particularly among adults who are Black, over the age of 65, retired, and/or of lower income

Acceptability

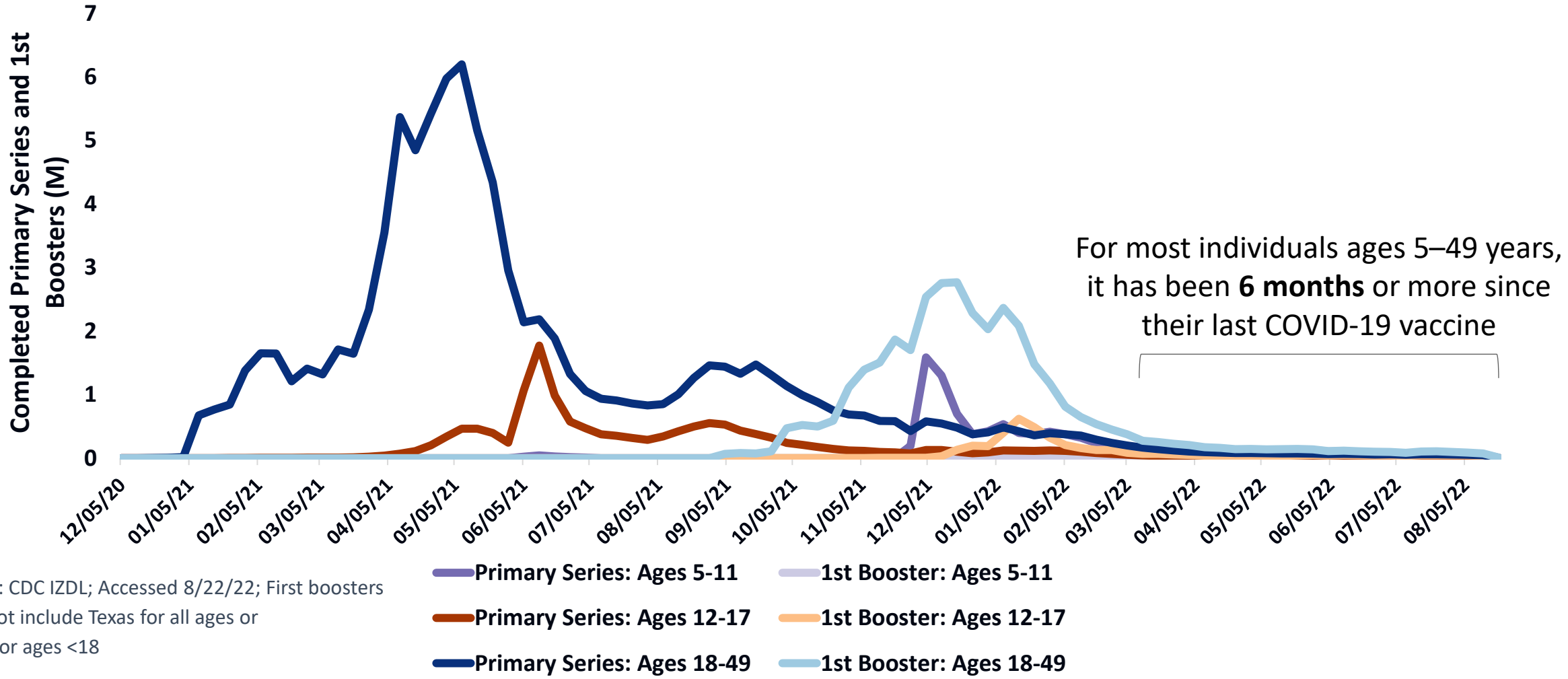
Is the updated (bivalent) COVID-19 vaccine booster acceptable to key stakeholders?

- Are there key stakeholders that would not accept the distribution of benefits and harms?
- Are there key stakeholders that would not accept the undesirable effects in the short term for the desirable effects (benefits) in the future?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

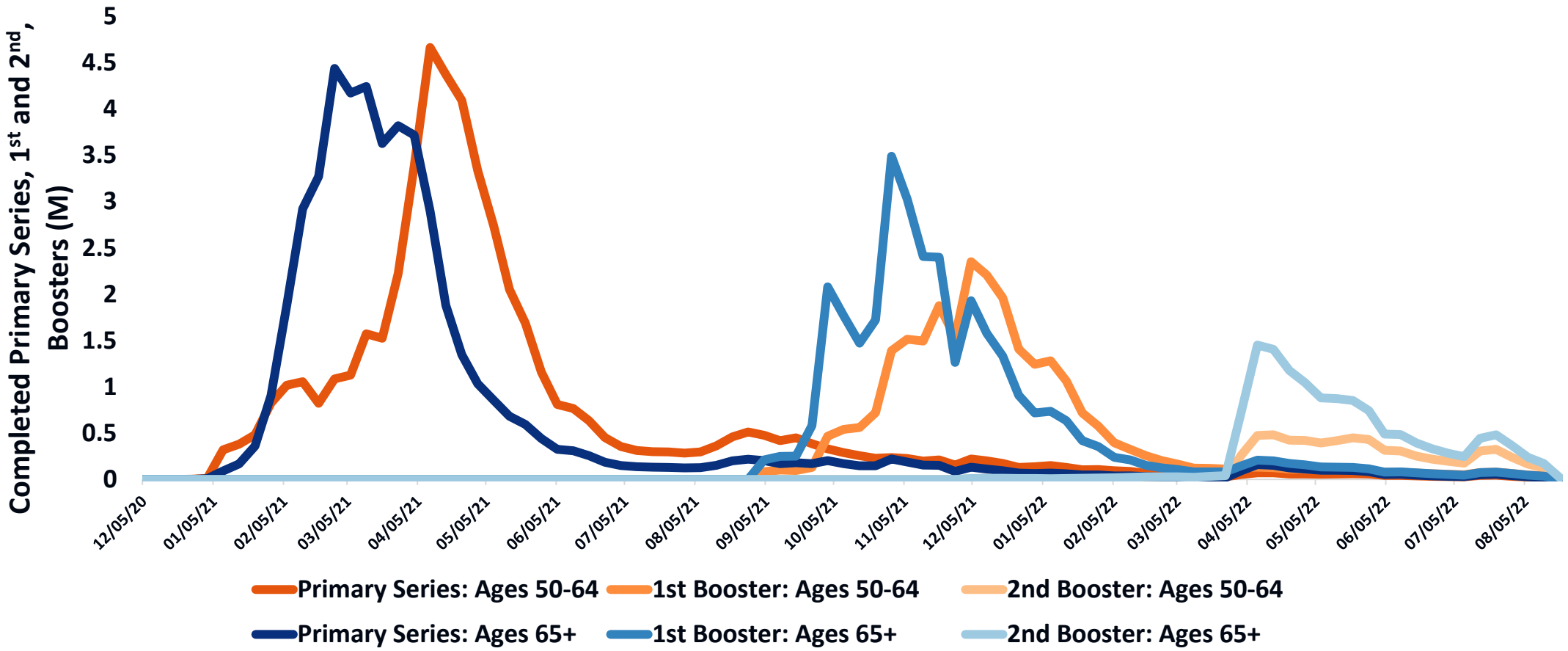
EtR Domain: Feasibility

Completed primary series and 1st boosters by age group for persons ages 5-49 years, United States, December 2020 – August 2022



Source: CDC IZDL; Accessed 8/22/22; First boosters does not include Texas for all ages or Idaho for ages <18

Completed primary series, 1st boosters, and 2nd boosters by age group for persons ages ≥50 years, United States, December 2020 – August 2022



Source: CDC IZDL; Source: CDC IZDL; Accessed 8/22/22; First and second booster not include Texas for all ages or Idaho for ages <18

Persons eligible* (in millions) for a bivalent booster by age group – United States, December 2020 – August 2022

Age Group	Eligible* persons (millions)	Ineligible+ persons (millions)
12-17 years	14	0.3
18-49 years	96	0.7
50-64 years	51	1.6
≥65 years	48	2.0
Total	209	4.6

*Individuals are considered eligible if they had completed at least a primary series but had not received a vaccine dose in the prior 2 months

+Individuals are considered ineligible if they received a vaccine dose within the previous 2 months per EUA

Based on dates of 9/2/2022

Source: CDC IZDL; Source: CDC IZDL; Accessed 8/22/22; First and second booster not include Texas for all ages or Idaho for ages <18

Jurisdictional planning and considerations

- The U.S. Government has purchased approximately **171 million** bivalent mRNA COVID-19 vaccine booster doses for the fall and beyond
- There will be a **sufficient but finite supply** of updated (bivalent) COVID-19 vaccines, which should be directed to providers with expected demand among eligible patients
- **Considerations for selecting sites to receive the initial doses include:**
  - Location and access to a range of populations and ensuring that distribution to these groups is equitable to the extent possible
  - Ability to reach eligible persons at highest risk for severe COVID-19 (e.g., older adults, long-term care facility residents, people with certain medical conditions)
  - Ability to handle 100-dose & 300-dose product configurations
  - Ability to administer both Pfizer-BioNTech and Moderna bivalent vaccines to meet anticipated community demand
  - Ability to efficiently vaccinate within 12 hours once a vial is opened
  - Ability to manage inventory to ensure availability of primary series doses, in addition to bivalent booster doses, in their local area when feasible
  - Overall readiness (e.g., staffing, scheduling capabilities)

CDC Fall Vaccination Operational Planning Guide – Information for the Fall Vaccine Campaign, Including Upcoming Bivalent COVID-19 Vaccine Booster Doses. https://www.cdc.gov/vaccines/covid-19/downloads/CDC-Fall-Vaccination-Operational-Planning-Guide.pdf Accessed August 19, 2022

Implementation for bivalent COVID-19 vaccine booster doses

- The bivalent vaccines will have the **same** storage and handling parameters as the monovalent vaccine products
- Both manufacturers' bivalent vaccines have grey label border, but different injection volume
  - Pfizer-BioNTech vaccine labels for both the monovalent and bivalent vials will have an **identical** grey cap/grey label border presentation
  - Moderna bivalent vaccine will have dark blue cap/grey label border (similar to monovalent product for ages 6–11 years)
    - Will be **different** from the red cap/light blue label border for the adult monovalent vaccine

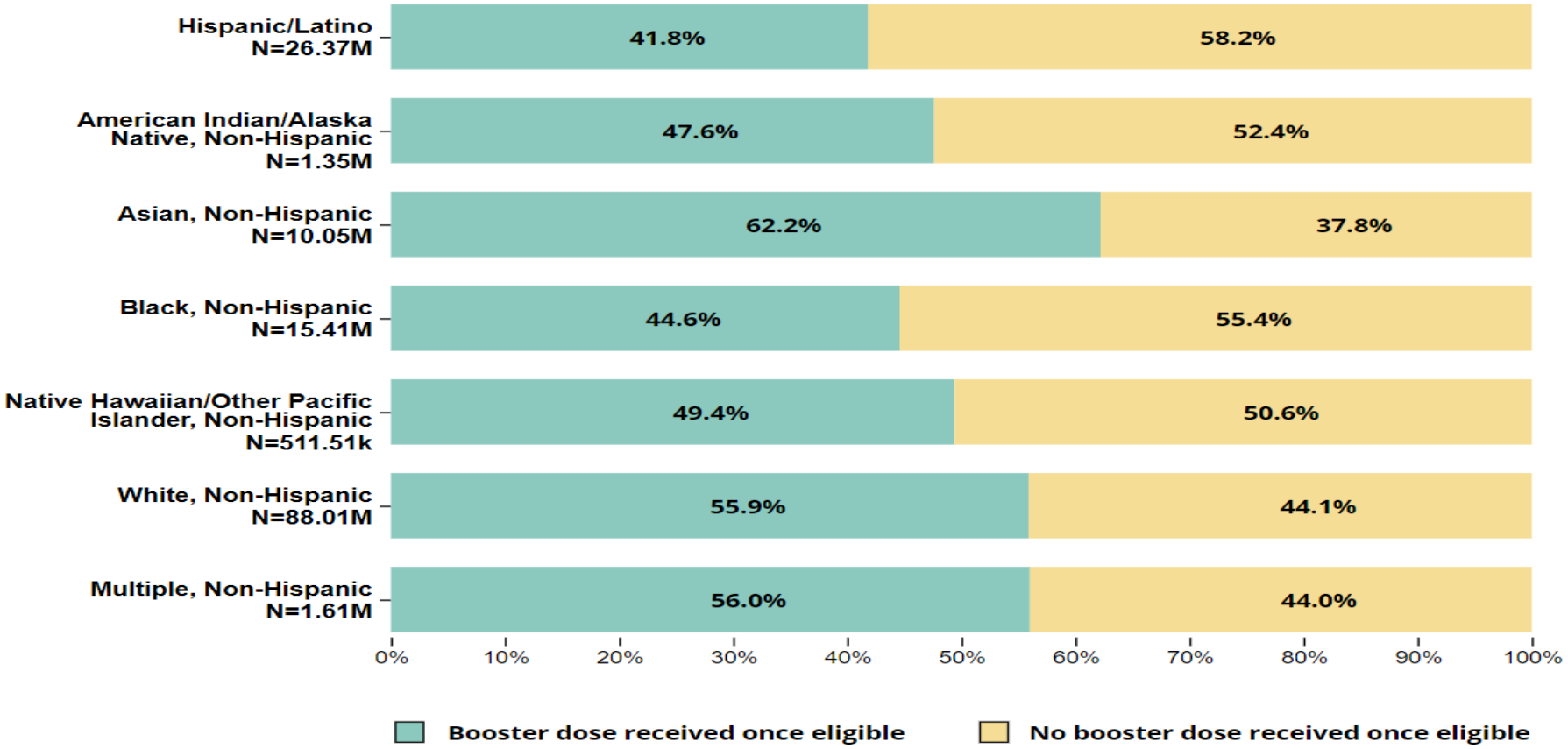
CDC Fall Vaccination Operational Planning Guide – Information for the Fall Vaccine Campaign, Including Upcoming Bivalent COVID-19 Vaccine Booster Doses. https://www.cdc.gov/vaccines/covid-19/downloads/CDC-Fall-Vaccination-Operational-Planning-Guide.pdf Accessed August 19, 2022

Domain Equity Question:

Is the intervention equally feasible to implement across all populations?

Percentages of population eligible for a first booster dose* with and without a booster, by race and ethnicity

Data from **193.55M** people ages 12 years and older who are eligible for a booster dose*. Race and ethnicity was available for **148.95M (77%)** people ages 12 years and older who are eligible for a booster dose.



CDC COVID Data Tracker. Demographic Characteristics of People Receiving COVID-19 Vaccinations in the United States. https://covid.cdc.gov/covid-data-tracker/#vaccination-demographic Accessed August 27, 2022

Summary

Feasibility

- Over **200 million** people would be eligible for the bivalent COVID-19 vaccine
- While nearly **22 million** adults >50 years have received a second booster dose, most individuals ages 5 years and older are at least **6 months** out from their last COVID-19 vaccine dose
- CDC has provided an Operational Planning Guide for jurisdictions preparing for a fall vaccination campaign
- There will be a **sufficient but finite supply** of bivalent COVID-19 vaccines
- Some aspects of the bivalent COVID-19 vaccines will be easy to implement (no changes to storage/handling), but vials and labeling may need additional education
- Significant racial and ethnic disparities persist in receipt of a booster, suggesting that the intervention may not be equally feasible to implement across all populations

Feasibility

Is the updated (bivalent) COVID-19 vaccine booster feasible to implement among populations currently recommended for a booster?

- Is the updated (bivalent) COVID-19 vaccine booster program sustainable?
- Are there barriers that are likely to limit the feasibility of implementing the updated (bivalent) COVID-19 vaccine booster or require considerations when implementing it?
- Is access to the updated (bivalent) COVID-19 vaccine booster an important concern?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

EtR Domain: Resource Use

Projected COVID-19-attributable deaths, hospitalizations, infections and direct medical costs averted by the U.S. booster vaccination program under two potential scenarios between August 1, 2022, and March 31, 2023

Baseline Scenario: Vaccinations Continue at Current Daily Rate Through March 31, 2023

	Vaccination campaign scenario 1: COVID booster vaccination coverage of eligible population equal to 2020–2021 influenza vaccination levels by October 31, 2022	Vaccination campaign scenario 2: 80% of those who are eligible to receive their first or second COVID booster doses are vaccinated by October 31, 2022
	Mean (95% credible interval)*	
Deaths averted	101,858 (96,201–108,116)	159,827 (150,191–168,394)
Hospitalizations averted	1,028,389 (975,879–1,081,284)	1,738,188 (1,644,562–1,825,066)
Infections averted	24,958,716 (23,709,356–26,066,609)	48,369,111 (45,827,481–50,865,799)
Direct medical costs averted**	$62,612,070,303 ($60,955,440,816–$64,537,375,865)	$109,474,464,016 ($106,582,475,922–$112,768,881,024)

* Credible intervals (shown in parentheses) reflect the range of uncertainty associated with estimates.

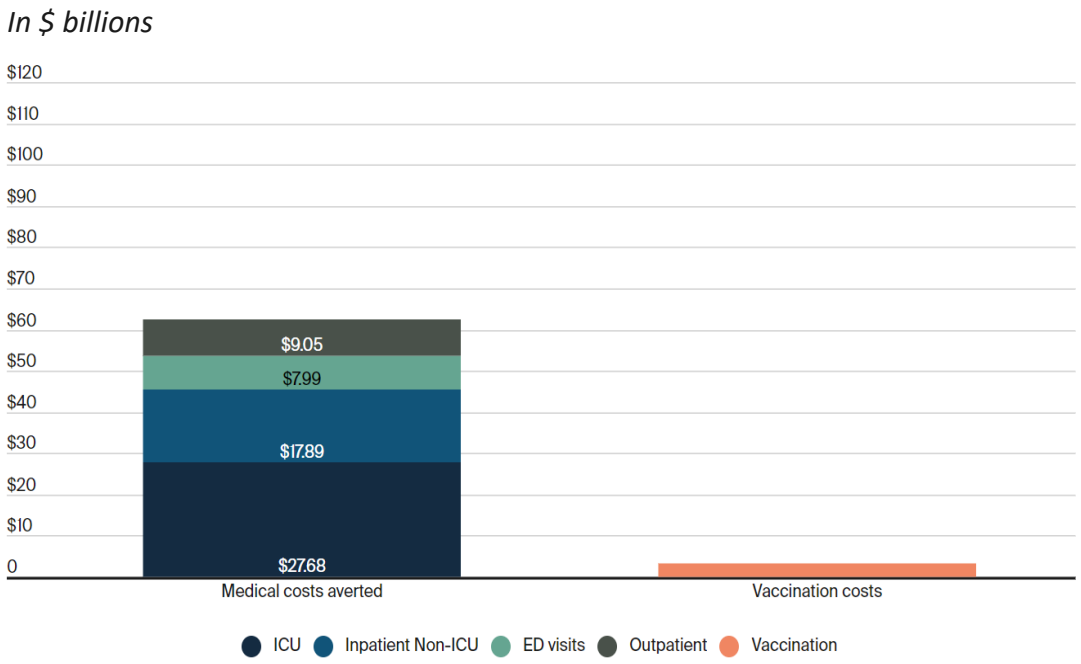
** Direct medical costs include those associated with outpatient care and hospital utilization, encompassing ICU care, non-ICU care, emergency department visits, and transportation by emergency medical services.

Note: Estimated results are in comparison to the baseline counterfactual scenario in which all COVID-19 vaccination activity continues at a rate equal to the average of the daily vaccination rate for the first two weeks of July 2022 until the end of March 2023.

Abhishek Pandey et al., "How Many Lives Could a Fall COVID-19 Booster Campaign Save in the United States?," *To the Point* (blog), Commonwealth Fund, July 26, 2022. https://doi.org/10.26099/rc8x-dx51

Projected direct medical cost savings and vaccination program costs for each booster vaccination scenario

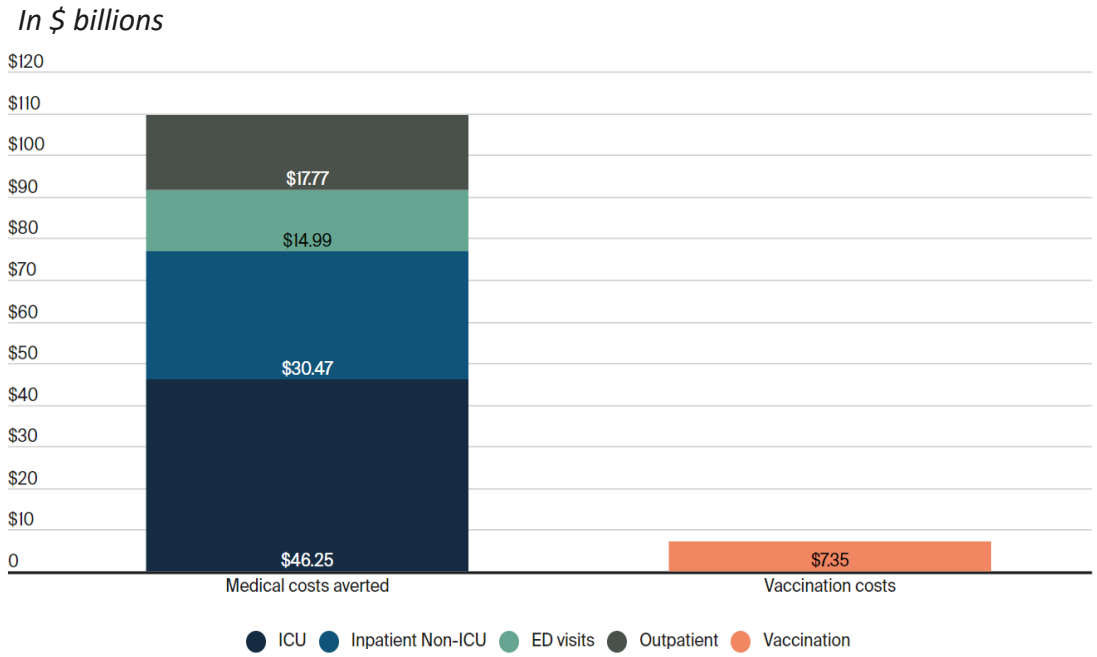
Scenario 1:
Flu-like vaccination coverage for booster eligible population



Note: Estimated results are in comparison to the baseline counterfactual scenario in which all COVID-19 vaccination activity continues at a rate equal to the average of the daily vaccination rate for the first two weeks of July 2022 until the end of March 2023.

Data: Authors' analysis.

Scenario 2:
80% of population eligible for booster doses are vaccinated



Note: Estimated results are in comparison to the baseline counterfactual scenario in which all COVID-19 vaccination activity continues at a rate equal to the average of the daily vaccination rate for the first two weeks of July 2022 until the end of March 2023.

Data: Authors' analysis.

Abhishek Pandey et al., "How Many Lives Could a Fall COVID-19 Booster Campaign Save in the United States?," *To the Point* (blog), Commonwealth Fund, July 26, 2022. https://doi.org/10.26099/rc8x-dx51

Domain Equity Question:

Is the intervention a reasonable and efficient allocation of resources across all populations?

Cost-effectiveness of booster vaccination in persons ≥65 years

- Cost-effectiveness data not yet available for most demographic subgroups, but some information is available for older adults
- Study evaluated cost-effectiveness of the first booster dose of the Pfizer-BioNTech COVID-19 vaccine (monovalent), administered 6 months after the second dose, among adults ≥65 years from a healthcare system perspective
- Compared with 2 doses of COVID-19 vaccine without a booster, the booster strategy in 100,000 older adults would result in a net monetary benefit of $3.4 million and a gain 3.7 quality-adjusted life-years in 180 days
- While cost-effectiveness of the boosters is highly sensitive to the population incidence of COVID-19 and vaccine effectiveness, offering the COVID-19 boosters to adults age ≥65 years in the United States is likely to be cost-effective

https://doi.org/10.1016/j.ijid.2022.03.029

Summary

Resource Use

- A fall vaccination campaign that expands eligibility for boosters and moves more aggressively to reach people could avert a surge of hospitalizations and deaths
- Additionally, an early fall vaccination campaign could avert between **$63 billion** and **$109 billion** in medical costs, depending on level of booster coverage achieved, with the majority of savings resulting from averted hospitalizations, particularly in the ICU

Abhishek Pandey et al., "How Many Lives Could a Fall COVID-19 Booster Campaign Save in the United States?," *To the Point* (blog), Commonwealth Fund, July 26, 2022. https://doi.org/10.26099/rc8x-dx51

Resource Use

Is the updated (bivalent) COVID-19 vaccine booster a reasonable and efficient allocation of resources?

- What is the cost-effectiveness of the updated (bivalent) COVID-19 vaccine booster?
- How does the cost-effectiveness of the updated (bivalent) COVID-19 vaccine booster change in response to changes in context, assumptions, etc.?

○ No	○ Probably no	○ Probably yes	○ Yes	○ Varies	○ Don't know

Summary

Summary

Current (Monovalent) COVID-19 vaccines

50µg Moderna COVID-19 vaccine

50µg of spike protein from 'ancestral' ('original') SARS-CoV-2

30µg Pfizer-BioNTech COVID-19 vaccine

30µg of spike protein from 'ancestral' ('original') SARS-CoV-2

Updated (Bivalent) COVID-19 vaccines

50µg Moderna COVID-19 vaccine

25µg of spike protein from 'ancestral' ('original') SARS-CoV-2

25µg of spike protein from Omicron (BA.4/BA.5) SARS-CoV-2

30µg Pfizer-BioNTech COVID-19 vaccine

15µg of spike protein from 'ancestral' ('original') SARS-CoV-2

15µg of spike protein from Omicron (BA.4/BA.5) SARS-CoV-2

Bivalent vaccines have the **same** total antigen amount as monovalent vaccines

Summary

- Current (monovalent) COVID-19 vaccines have **dramatically reduced** COVID-19 hospitalizations and deaths
- As the SARS-Cov-2 virus evolved, declines in neutralizing antibodies and vaccine effectiveness as well as more rapid waning from the vaccines noted
- Inclusion of a second SARS-CoV-2 variant in the vaccine **broadens** the antibody response
- Omicron-specific bivalent COVID-19 vaccines were studied in over **1400 individuals**
- Omicron-specific bivalent COVID-19 vaccine resulted in:
  - **Higher** antibody titers for **Omicron** variants
  - **Higher** titers for **other** SARS-CoV-2 variants
  - Titers that were as high or higher for ancestral SARS-CoV-2
- Broad uptake of COVID-19 vaccine booster doses **early this fall** could prevent >100,000 hospitalizations, compared to later or more limited roll-out; in addition, **billions** of dollars of direct medical costs could be saved

Work Group Interpretation

- Work Group had broad policy discussions around use of updated (bivalent) COVID-19 vaccines for all people of age groups currently recommended for booster doses
- Based on current FDA authorizations, current recommendations would be:
  - Pfizer-BioNTech COVID-19 vaccine, bivalent for individuals ages **12 and older**
  - Moderna bivalent COVID-19 vaccine, bivalent for individuals ages **18 and older**
- Additional authorizations for other ages and vaccines may follow

Work Group Interpretation

- Current population recommended for these boosters is very **heterogenous**
  - Many in the United States had Omicron infection over the past 9 months
  - Individuals recommended for the bivalent COVID-19 booster doses may have previously received:
    - Primary series only
    - One booster dose
    - Two booster doses (for those 50 years and over)
- Balance of benefits and risks for individuals may **vary** by age, previous receipt of booster, or recent SARS-CoV-2 infection
- Uncertainties around the incremental benefits for some individuals, including those recent infection or recent vaccine receipt

Work Group Interpretation

- COVID-19 vaccines are recommended, even for those with prior infection
  - Rate of reinfections increased during the Omicron period
- Bivalent COVID-19 vaccines in the setting of prior SARS-CoV-2 infection ("hybrid immunity") resulted in highest antibody titers
  - These high and diverse titers may result in **longer duration of protection** and decreased need for frequent COVID-19 vaccine booster doses
- Studies have shown that **increased time** between infection and vaccination may result in an improved immune response to vaccination
  - Those with recent SARS-CoV-2 infection may consider delaying a vaccine dose by **3 months** from symptom onset or positive test

Work Group Interpretation

- **Time** since most recent COVID-19 vaccine dose may be more important than cumulative number of doses
- There will be a time of transition as recommendations may move from counting dose number to optimal timing of vaccination campaigns
- Vaccine recommendations that are **simple** and **easy to communicate** are important
- If SARS-CoV-2 becomes a seasonal virus, an annual vaccine program could be an effective strategy for the future

EtR Domain	Question(s)	Domain Equity Question(s)
Public Health Problem	• Is the problem of public health importance?	• **Does the problem impact all populations equally?**
Benefits and Harms	• How substantial are the desirable anticipated effects? • How substantial are the undesirable anticipated effects? • Do the desirable effects outweigh the undesirable effects?	• **Are the desirable and undesirable anticipated effects demonstrated across all populations equally?**
Values	• Does the population feel the desirable effects are large relative to the undesirable effects?	• **Is there important variability in how patients or populations value the outcome?**
Acceptability	• Is the intervention acceptable to key stakeholders?	• **Is the intervention equally acceptable across all populations?**
Feasibility	• Is the intervention feasible to implement?	• **Is the intervention equally feasible to implement across all populations?**
Resource Use	• Is the intervention a reasonable and efficient allocation of resources?	• **Is the intervention a reasonable and efficient allocation of resources across all populations?**

Implementation and Considerations for Equity

- There are many social, geographic, economic and environmental factors that create challenges to vaccination access and acceptance, and that often affects racial and ethnic minority groups[1]
- **A few key activities for readiness and response for equitable access to updated (bivalent) COVID-19 vaccine booster doses entail:**
- **Supply and ordering readiness**
  - Determine which provider locations will receive initial vaccine supply, balancing equitable access with vaccination capacity and consideration of initial demand
- **Provider readiness**
  - Ensure providers are enrolled to reach key populations; identify providers who are not yet COVID-19 vaccination providers and facilitate their enrollment, especially providers who can fill a geographic gap in access and providers who care for people who are at increased risk for developing severe outcomes
  - Ensure providers are aware of resources to help support coadministration of COVID-19 vaccines and other vaccines, including influenza vaccines, during a visit
  - Encourage providers who are not able to offer COVID-19 vaccination to refer their patients to nearby vaccination providers[2]

1. CDC. COVID-19 Vaccine Equity for Racial and Ethnic Minority Groups. https://www.cdc.gov/coronavirus/2019-ncov/community/health-equity/vaccine-equity.html Accessed August 30, 2022
2. CDC Fall Vaccination Operational Planning Guide – Information for the Fall Vaccine Campaign, Including Upcoming Bivalent COVID-19 Vaccine Booster Doses. https://www.cdc.gov/vaccines/covid-19/downloads/CDC-Fall-Vaccination-Operational-Planning-Guide.pdf Accessed August 30, 2022

Implementation and Considerations for Equity, cont'd

- Communication also plays an integral role in ensuring equitable access to updated (bivalent) COVID-19 vaccine booster doses
- **Additional readiness and response activities entail the following:**
  - Create a communication plan that outlines strategies, audiences, and products that will be used to promote COVID-19 vaccination of unvaccinated key populations and populations recommended for bivalent booster vaccination
  - Understand existing data, attitudes, and perceptions regarding COVID-19 vaccination (including co-administration with influenza vaccine) in terms of demand, provider types, and locations where vaccination would be preferred
    - Share these data with local jurisdictions and partners to help shape messages
  - Develop communication products for providers, pharmacies, and the public that align with federal messaging and ensure communication materials are culturally and linguistically appropriate
  - Leverage partnerships to help mobilize providers and promote COVID-19 bivalent booster vaccination messaging
  - Engage and educate partners and trusted messengers (e.g., healthcare professionals, community leaders, faith leaders and faith-based organizations) as soon as possible

CDC Fall Vaccination Operational Planning Guide – Information for the Fall Vaccine Campaign, Including Upcoming Bivalent COVID-19 Vaccine Booster Doses. https://www.cdc.gov/vaccines/covid-19/downloads/CDC-Fall-Vaccination-Operational-Planning-Guide.pdf Accessed August 30, 2022

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention
Values	Does the target population feel the desirable effects are large relative to the undesirable effects?	Moderate
	Is there important variability in how patients value the outcomes?	Probably important uncertainty or variability
Acceptability	Is the Bivalent COVID-19 vaccine booster acceptable to key stakeholders?	Probably yes
Feasibility	Is the Bivalent COVID-19 vaccine booster feasible to implement?	Probably yes
Resource Use	Is the Bivalent COVID-19 vaccine booster a reasonable and efficient allocation of resources?	Probably yes

Evidence to Recommendations Framework

Summary: Work Group Interpretations

Balance of consequences	Undesirable consequences *clearly outweigh* desirable consequences in most settings	Undesirable consequences *probably outweigh* desirable consequences in most settings	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences in most settings	Desirable consequences *clearly outweigh* undesirable consequences in most settings	There is insufficient evidence to determine the balance of consequences

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 shared clinical decision-making	We recommend the intervention

Question to ACIP

- Should updated (bivalent) vaccines be recommended for persons already recommended to receive a COVID-19 vaccine booster dose?

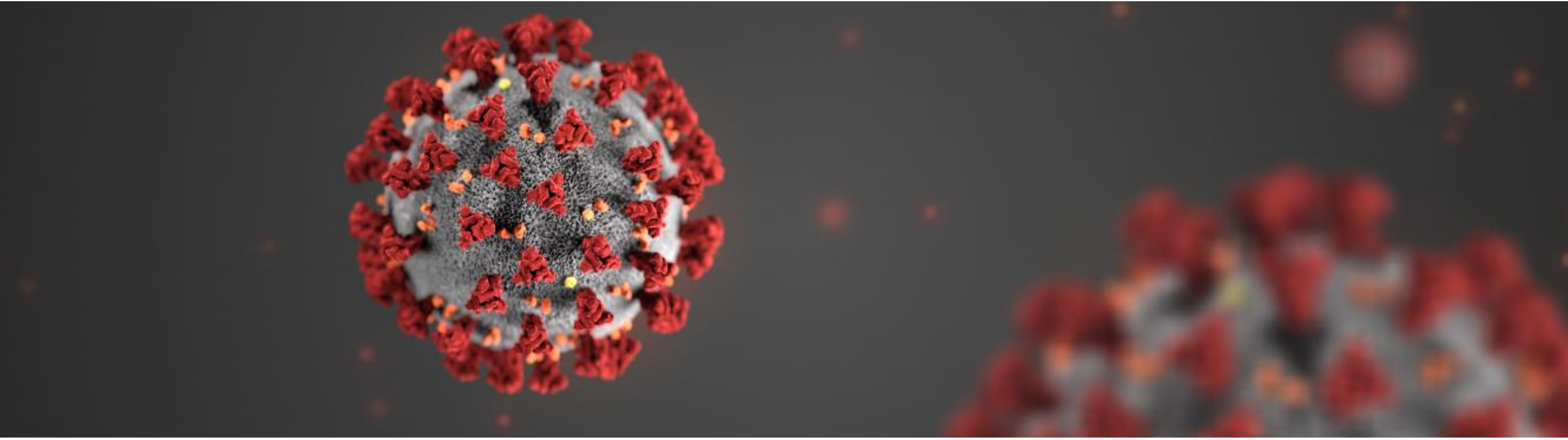
Products and ages currently authorized by FDA include:

Moderna COVID-19 vaccine for ages **18 years and older**

Pfizer-BioNTech COVID-19 vaccine for ages **12 years and older**

Acknowledgments

- Monica Godfrey
- Evelyn Twentyman
- Megan Wallace
- Hannah Rosenblum
- Lauren Roper
- Danielle Moulia
- Joy Hsu
- Katherine Fleming-Dutra
- Sarah Meyer
- Susan Goldstein
- Mary Chamberland
- Elisha Hall
- Valerie Morelli
- JoEllen Wolicki
- Meg Freedman
- Heather Scobie
- Ruth Link-Gelles
- Sierra Scarbrough
- Jefferson Jones
- Stephen Hadler
- Epi Task Force
- Data Analytics and Visualization Task Force
- Respiratory Viruses Branch
- National Center for Immunization and Respiratory Diseases



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.

ACIP Vote #1

A single dose of bivalent Pfizer-BioNTech COVID-19 vaccine is recommended for individuals **ages 12 years and older** at least **2 months** after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA

ACIP repeals its previous recommendations for administration of monovalent Pfizer-BioNTech COVID-19 vaccine boosters for persons ages 12 years and older

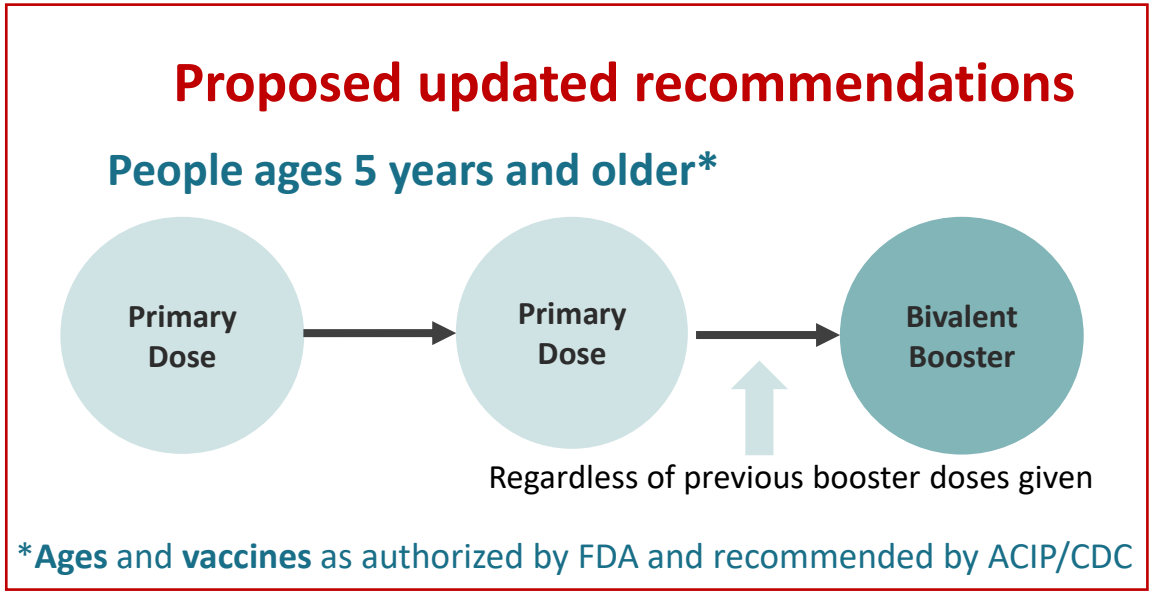
Bivalent booster recommendations are without regard to the number of previous monovalent booster doses received

ACIP Vote #2

A single dose of bivalent Moderna COVID-19 vaccine is recommended for individuals **ages 18 years and older** at least **2 months** after receipt of a primary series or prior monovalent booster dose, under the EUA issued by FDA

ACIP repeals its previous recommendations for administration of monovalent Moderna COVID-19 vaccine boosters for persons ages 18 years and older

Bivalent booster recommendations are without regard to the number of previous monovalent booster doses received

ACIP discussion

- We are asking for ACIP feedback on the **overall updated recommendation strategy**
  - More in line with traditional ACIP recommendations and a broad summary of the program
- CDC will review any additional data to consider expansion of age groups recommended for bivalent COVID-19 vaccines
- Future recommendations would necessarily follow updates to the EUAs issued by FDA