Evidence to Recommendations Framework:

2024-2025 COVID-19 Vaccines in Persons ≥6 Months of Age

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ACIP Meeting

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Evidence to Recommendations (EtR) Framework
Policy Question

- Should 2024 – 2025 COVID-19 vaccines be recommended for use in persons ≥6 months of age?

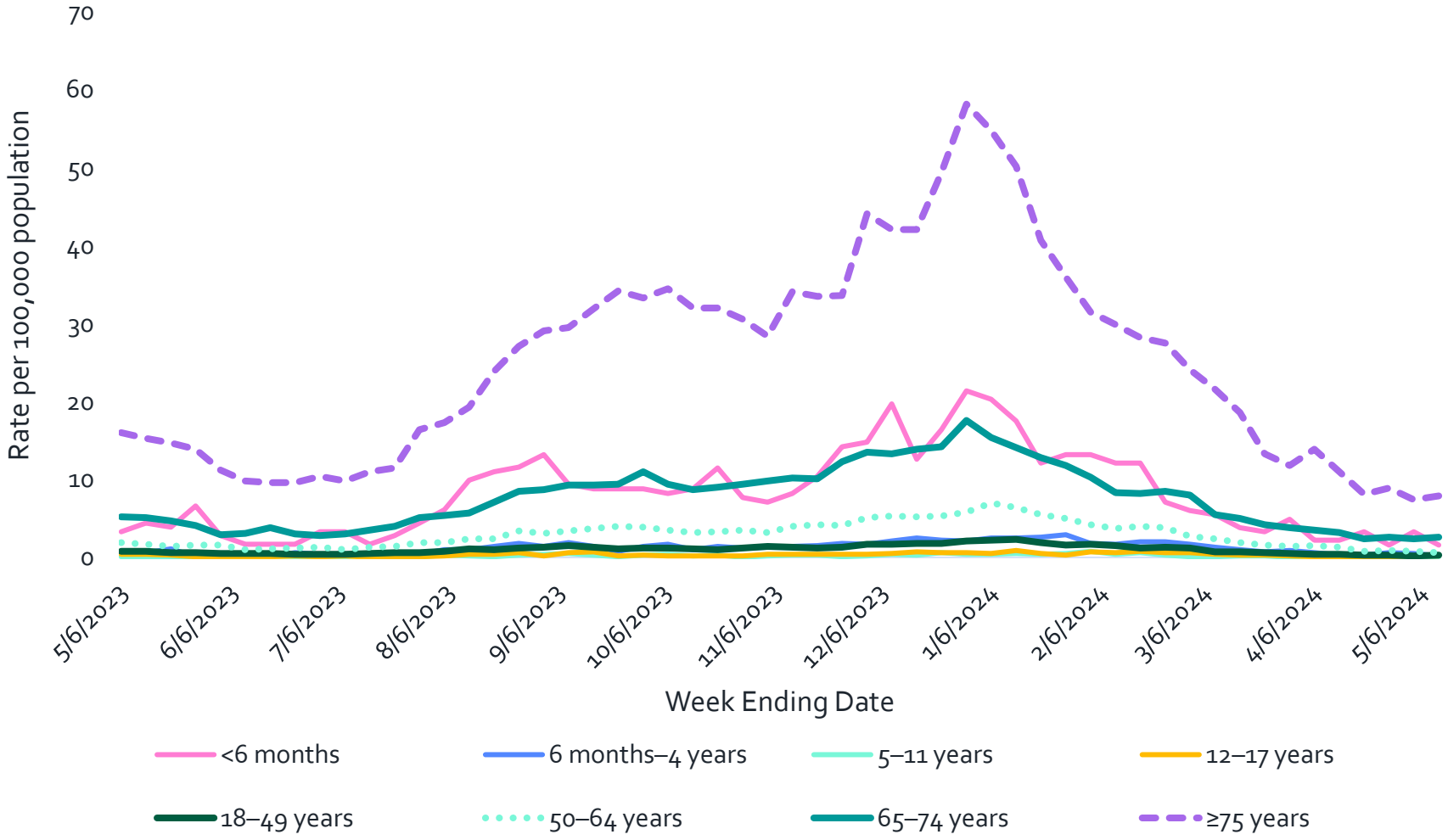
- **Products and ages under review for authorization or approval by FDA include:**
  - Moderna COVID-19 vaccine for ages 6 months and older
  - Novavax COVID-19 vaccine for ages 12 years and older
  - Pfizer-BioNTech COVID-19 vaccine for ages 6 months and older

FDA: Food and Drug Administration

EtR Domain:

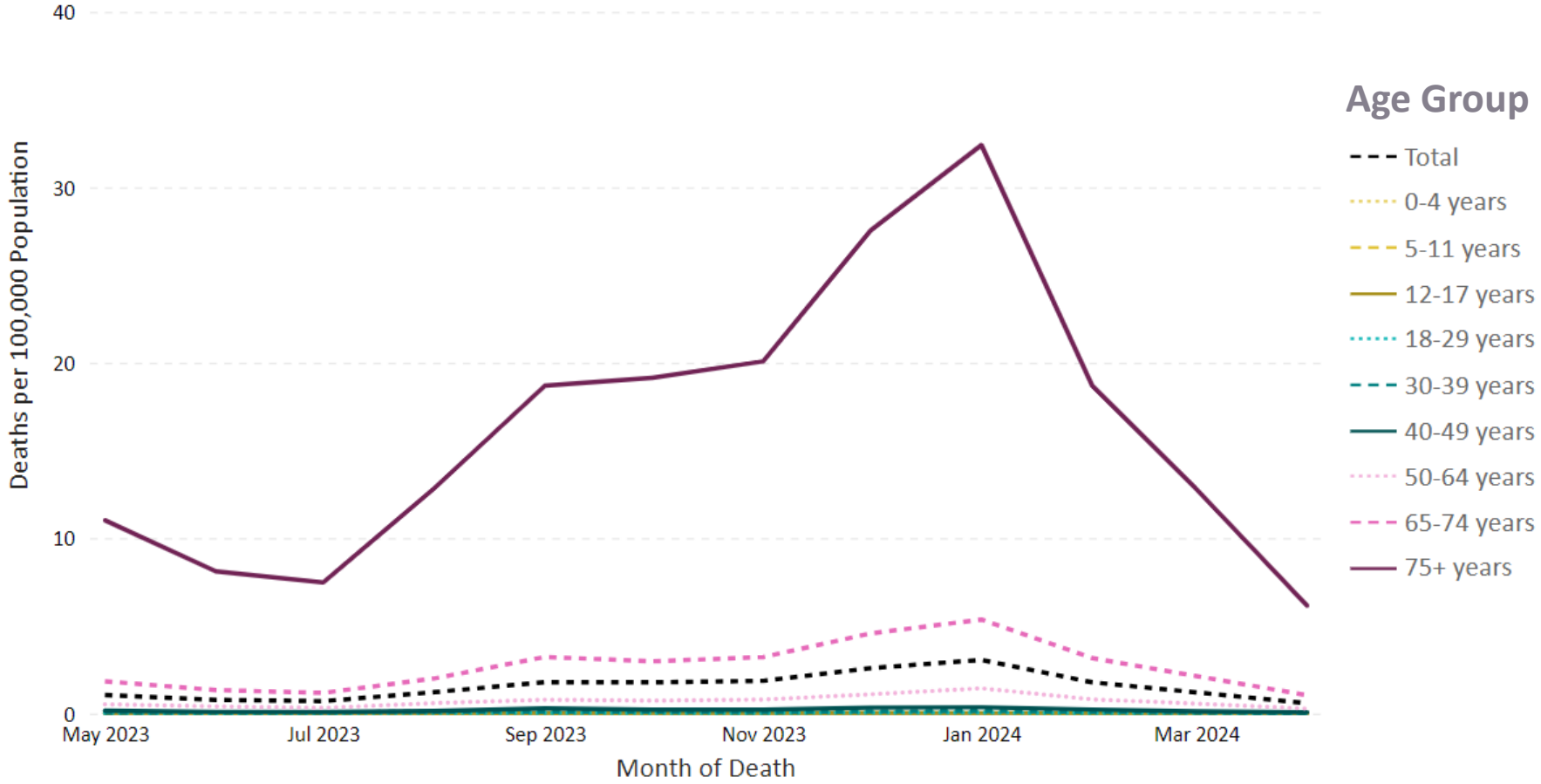
Public Health Problem

Weekly population-based rates of COVID-19-associated hospitalizations, by age group — COVID-NET, May 6, 2023 – May 11, 2024



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed June 17, 2024

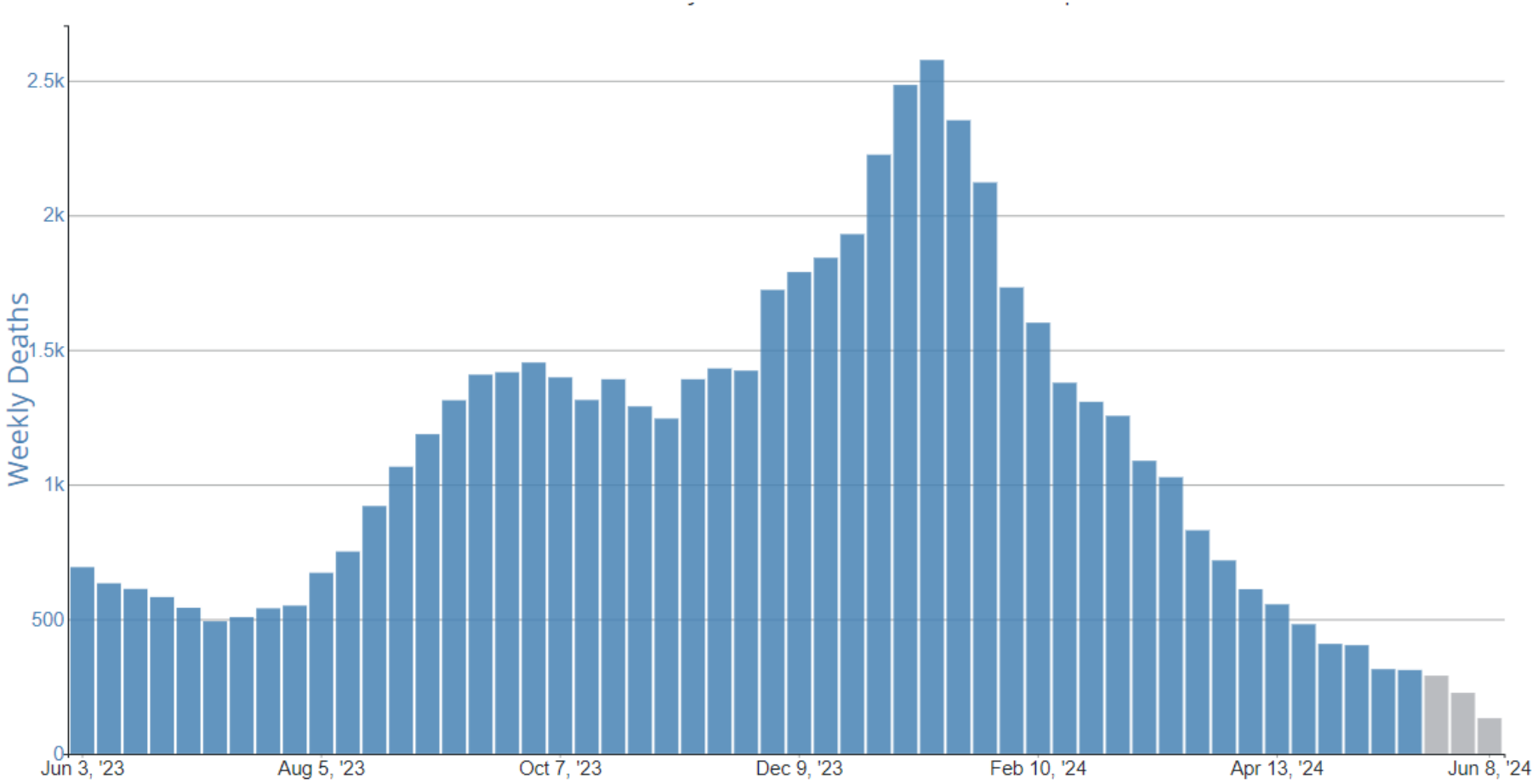
Monthly rates of COVID-19-associated deaths by age group, United States, May 1, 2023 – April 30, 2024



Provisional data are non-final counts of deaths based on reported mortality data in NVSS. Deaths include those with COVID-19, coded as ICD–10 code U07.1, on the death certificate. Death data are displayed by date of death (event).

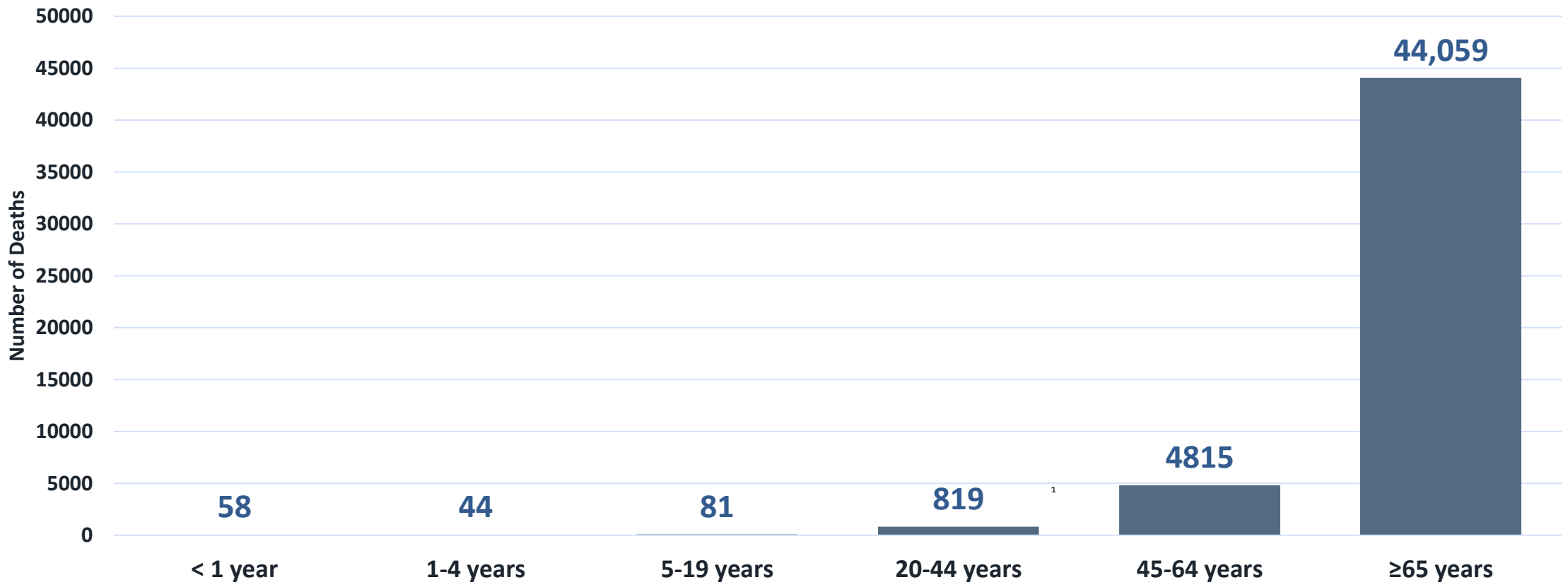
Source: Provisional data from the CDC's National Center for Health Statistics (NCHS) National Vital Statistic System (NVSS); CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#demographicsovertime. Accessed June 16, 2024

Weekly number of COVID-19-associated deaths reported to CDC, United States, June 3, 2023 – June 8, 2024



The most recent 3 weeks of mortality counts are shaded grey because NVSS reporting is <95% during this period.
Provisional data are non-final counts of deaths based on reported mortality data in NVSS. Deaths include those with COVID-19, coded as ICD–10 code U07.1, on the death certificate. Death data are displayed by date of death (event). Data include underlying and contributing causes of death.
CDC COVID Data Tracker. National Center for Health Statistics (NCHS) National Vital Statistics System (NVSS). https://covid.cdc.gov/covid-data-tracker/#trends_weeklydeaths_select_00. Accessed June 17, 2024

Total number of COVID-19-associated deaths[1,2] in 2023, by age group, United States

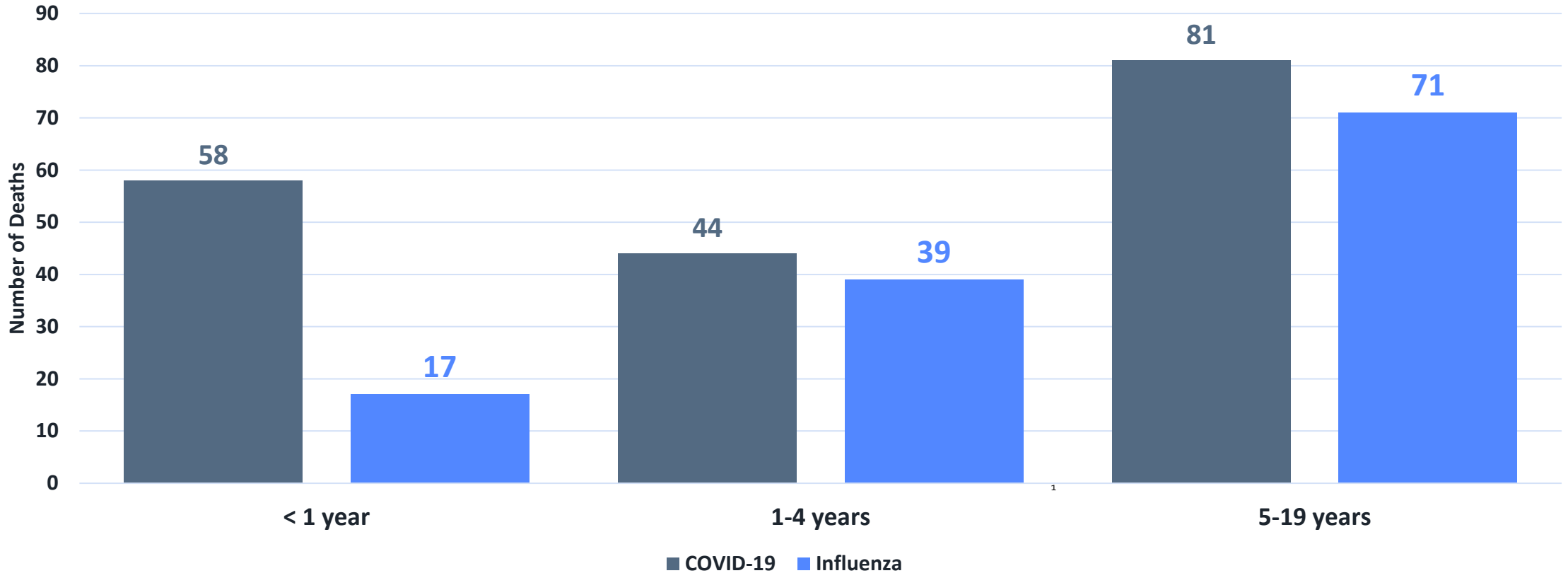


[1] Provisional data

[2] Underlying cause of death

Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2022, and from provisional data for years 2023-2024, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Number of deaths includes COVID-19 code (U07.1) as the underlying cause of death. Accessed at http://wonder.cdc.gov/mcd-icd10-provisional.html on June 5, 2024

Total number of COVID-19 and Influenza-associated deaths[1,2] in 2023, by age group, United States



[1] Provisional data
[2] Underlying cause of death
Source: Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Provisional Mortality on CDC WONDER Online Database. Data are from the final Multiple Cause of Death Files, 2018-2022, and from provisional data for years 2023-2024, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Number of deaths includes influenza codes (J09-J11) or COVID-19 code (U07.1) as the underlying cause of death. Accessed at http://wonder.cdc.gov/mcd-icd10-provisional.html on June 5, 2024
Note: Estimates of pediatric influenza deaths reported to CDC can be found here: https://www.cdc.gov/flu/weekly/index.htm . Estimates will vary due to differences in reporting methods and timeframes used.

Morbidity and Mortality Weekly Report (*MMWR*)

Notes from the Field: Surveillance for Multisystem Inflammatory Syndrome in Children — United States, 2023

Weekly / March 14, 2024 / 73(10);225–228

Print

Anna R. Yousaf, MD[1]; Katherine N. Lindsey, MPH[1]; Michael J. Wu, MSc[1]; Ami B. Shah, MPH[1]; Rebecca J. Free, MD[1]; Regina M. Simeone, PhD[1]; Laura D. Zambrano, PhD[1]; Angela P. Campbell, MD[1]; MIS-C Surveillance Authorship Group (VIEW AUTHOR AFFILIATIONS)

Incidence by SARS-CoV-2 variant-predominant periods, defined using surveillance data and allowing for 2 weeks to MIS-C onset from when a variant exceeded 50% circulating lineages

Variant Predominant Period	Dates	Number of MIS-C Cases	Incidence per 1,000,000 person-months (95% CI)	Median Age (IQR), years
Pre-Delta	Oct 15, 2020–Apr 5, 2021	3,284	6.79 (6.56–7.03)	9.2 (5.4–13.1)
Delta	Jul 10–Dec 24, 2021	2,300	4.90 (4.70–5.10)	9.1 (5.5–12.3)
Omicron BA.1/BA 1.1	Jan 1–Ap 8, 2022	1,149	4.21 (3.98–4.46)	7.5 (4.1–11.5)
Omicron BA.2/BA.4/BA.5	April 9–Dec 31, 2022	422	0.56 (0.51–0.62)	5.4 (2.8–9.8)
2023 Omicron subvariants	Jan 1–Dec 31, 2023	117	0.11 (0.10–0.14)	6.9 (3.4–11.5)

Cases from 2023 were clinically similar to those with MIS-C illness onset in 2021-2022

- 58% were previously healthy with no underlying medical conditions
- 50% required ICU-level care, 34% had shock, and 27% had cardiac dysfunction
- 3 deaths

MISC: Multisystem Inflammatory Syndrome in Children

Underlying Medical Conditions among Patients Admitted to ICU among Children and Adolescents Ages ≤17 Years with COVID-19-associated Hospitalization, July 2023–March 2024

Age category	Among all hospitalized children, % with no underlying conditions	Among those admitted to ICU, % with no underlying conditions (n=363)	Among those with no underlying conditions, what % were admitted to ICU? (n=791)
Overall ≤17 Years	50%	40%	18%

Hospitalizations are limited to those with COVID-19 as the presenting complaint upon admission.

Other pediatric vaccine preventable diseases: Annual hospitalizations per 100,000 population prior to vaccine recommendation compared to COVID-19

	Hepatitis A[1]	Varicella[2] (Chickenpox)	Vaccine-type Invasive Pneumococcal Disease[3]	COVID-19[4]	
Age	**5–14 years**	**0–4 years**	**0–4 years**	**6 months–<18 years**	
Time period	**2005**	**1993–1995**	**1998–1999**	**2022–2023**	**2023–2024**
Hospitalization Burden (Annual rate per 100,000 population)	**<1**	**29-42**	**40[5]**	**6 months–4 years: 74 5–11 years: 17 12–17 years: 24**	**6 months–4 years: 50 5–11 years: 10 12–17 years: 13**

[1] https://www.cdc.gov/mmwr/preview/mmwrhtml/ss5603a1.htm

[2]Davis MM, Patel MS, Gebremariam A. Decline in varicella-related hospitalizations and expenditures for children and adults after introduction of varicella vaccine in the United States. Pediatrics. 2004;114(3):786-792. doi:10.1542/peds.2004-0012

[3] Centers for Disease Control and Prevention (CDC). Direct and indirect effects of routine vaccination of children with 7-valent pneumococcal conjugate vaccine on incidence of invasive pneumococcal disease--United States, 1998-2003. MMWR Morb Mortal Wkly Rep. 2005 Sep 16;54(36):893-7. PMID: 16163262.

[4] COVID-NET data October 2022 – September 2023 and October 2023 – May 2024. COVID-19 rates have not been adjusted for reason for admission. COVID vaccine first introduced in 12-17 years in May 2021; in 5-11 years in November 2021 and in 6 months – 4 years in June 2022

[5] Vaccine-type invasive pneumococcal disease annual rate for children <5 years in 1998-1999 was 80 per 100,000, of which about 50% were hospitalized.

Pediatric vaccine preventable diseases: Deaths per year in the United States prior to vaccine recommendation compared to COVID-19

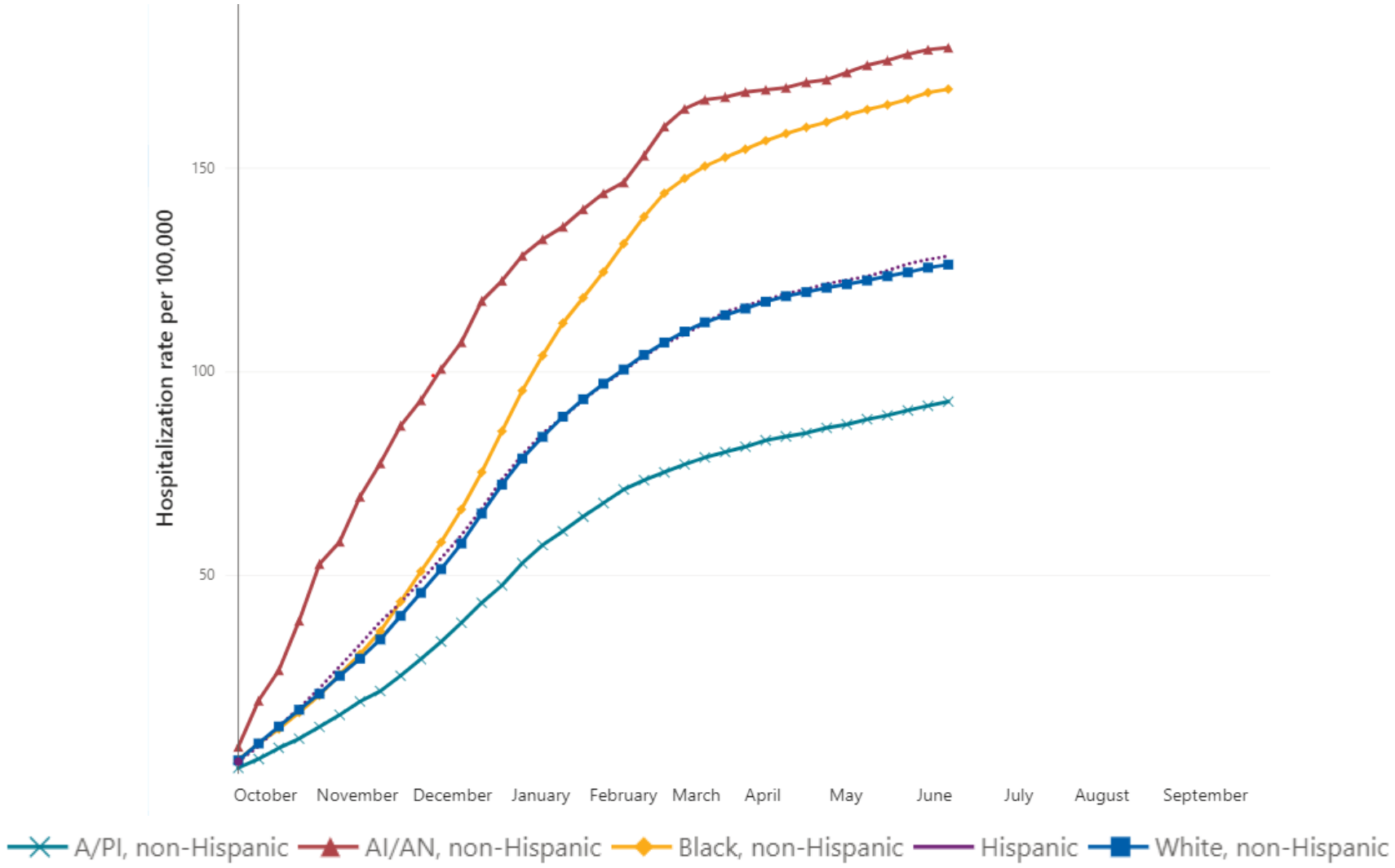
	Hepatitis A[1]	Meningococcal (ACWY)[2]	Varicella[3]	Rubella[4]	Rotavirus[5]	COVID-19[6]
Age	<20 years	11–18 years	5–9 years	All ages	<5 years	6 months–19 years
Time period	1990–1995	2000–2004	1990–1994	1966–1968	1985–1991	2023
Average deaths per year	3	8	16	17	20	1–4 years: 44 5–19 years: 81

[1]Vogt TM , Wise ME, Bell BP, Finelli L. Declining hepatitis A mortality in the United States during the era of hepatitis A vaccination. J Infect Dis2008; 197:1282–8.
[2]National Notifiable Diseases Surveillance System with additional serogroup and outcome data from Enhanced Meningococcal Disease Surveillance for 2015-2019.
[3]Meyer PA, Seward JF, Jumaan AO, Wharton M. Varicella mortality: trends before vaccine licensure in the United States, 1970-1994. J Infect Dis. 2000;182(2):383-390. doi:10.1086/315714
[4]Roush SW , Murphy TV; Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. JAMA 2007; 298:2155–63.
[5] Glass RI, Kilgore PE, Holman RC, et al. The epidemiology of rotavirus diarrhea in the United States: surveillance and estimates of disease burden. J Infect Dis. 1996 Sep;174 Suppl 1:S5-11
[6] http://wonder.cdc.gov/mcd-icd10-provisional.html on May 14 2024 . COVID vaccine first introduced in 12-17 years in May 2021; in 5-11 years in November 2021 and in 6 months – 4 years in June 2022

Domain Equity Question:

Does the problem impact all populations equally?

Age-adjusted cumulative COVID-19 hospitalizations per 100,000 population by race and ethnicity — COVID-NET, October 2023 – May 2024



CDC COVID Data Tracker. https://covid.cdc.gov/covid-data-tracker/#covidnet-hospitalization-network. Accessed June 20, 2024

Summary
Public Health Problem

- COVID-19-associated hospitalizations and deaths occur all year around, but peak in December – February
- COVID-19-associated hospitalizations and deaths are highest in adults aged 75 and older
- More pediatric hospitalizations and deaths occur each year associated with COVID-19 than other select vaccine preventable diseases as the time those recommendations were made for children in the United States
  - Among children hospitalized for COVID-19, 50% had no underlying medical conditions
  - Of those, 18% were admitted to the ICU
- Racial and ethnic differences in COVID-19 hospitalization rates persist

ICU: Intensive Care Unit

Public Health Problem

Work Group Interpretation

Is COVID-19 disease among persons ≥6 months of age of public health importance?

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

EtR Domain:

Benefits and Harms

Summary of available data

- Benefits and harms of COVID-19 vaccines are based on multiple years of data from original, bivalent, and 2023-2024 formula COVID-19 vaccines
  - GRADE
    - Benefits and harms of updated (bivalent or 2023-2024) COVID-19 vaccines
  - Available data on GRADE outcomes with no studies captured in systematic review
  - Real-world safety and effectiveness monitoring of the 2023-2024 vaccines
  - Modeling data on potential impact of 2024-2025 COVID-19 vaccine recommendations

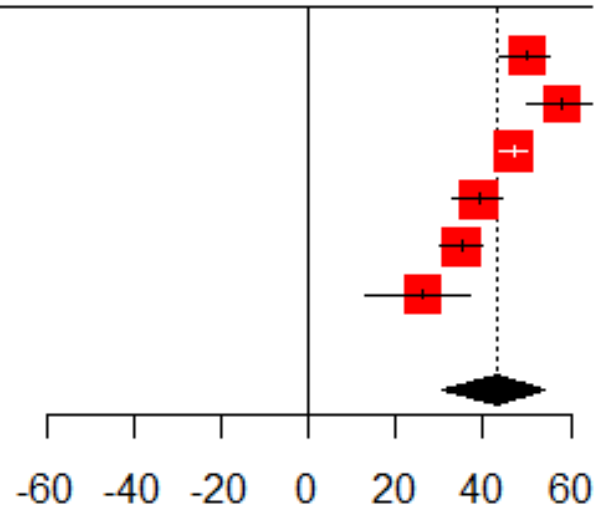
GRADE of benefits and harms for 2024-2025 COVID-19 vaccine: PICO questions

	Adults and Adolescents	Infants and Children (Pediatric)
Population	Persons ages 12 years and older	Persons ages 6 months -11 years
Intervention	Updated COVID-19 vaccine (bivalent or 2023-2024)	Updated COVID-19 vaccine (bivalent or 2023-2024)
Comparison	No updated vaccine*	No updated vaccine*
Outcomes	**1. Medically-attended COVID-19 (ED/UC visits)** **2. Hospitalization due to COVID-19** 3. Death due to COVID-19 4. Post-COVID Conditions **5. Specified serious adverse events**	**1. Medically-attended COVID-19 (ED/UC visits)** **2. Hospitalization due to COVID-19** 3. Death due to COVID-19 4. MIS-C 5. Post-COVID conditions **6. Specified serious adverse events**

PICO: Population, intervention, comparison, outcomes; ED/UC: emergency department/urgent care; MIS-C: multisystem inflammatory syndrome in children
*May include people who received any number of doses of prior formulations and unvaccinated
Bolded outcomes are critical; unbolded outcomes are important

GRADE benefits among adolescents and adults: Forest plot and pooled VE estimate against medically-attended COVID-19 (ED/UC visits) (n=5)

Study	Weight	Vaccine Eff. IV, Random, 95% CI
Tenforde, bivalent, 25 days*	16.8%	50 [44; 55]
Ackerson, bivalent, 14-60 days	14.9%	58 [50; 65]
DeCuir, 23-24 dose, 44 days*	18.1%	47 [44; 50]
Caffrey, 23-24 dose, 76 days	17.3%	39 [33; 44]
Tartof, bivalent, 77 days	17.7%	35 [30; 40]
Ackerson, bivalent, 60-180 days	15.3%	26 [13; 37]
Total (95% CI)	**100.0%**	**43 [30; 54]**



Notes:

ED/UC: emergency department/urgent care; VE or vaccine eff.= vaccine effectiveness; CI= confidence intervals**;** IV= inverse variance; nr= not reported

Studies are listed on the y-axis by median days since receipt of an updated dose. Pooled vaccine effectiveness based on a random effects meta-analysis, using adjusted VE estimates on a log scale.

Vaccine effectiveness comparisons included an updated dose (either bivalent or 2023-2024 formulation) compared to no updated dose (may include people who received any number of doses of prior formulations and unvaccinated, definitions varies by included study).

[a] Author, vaccine formulation, and time since vaccination (median or median range)

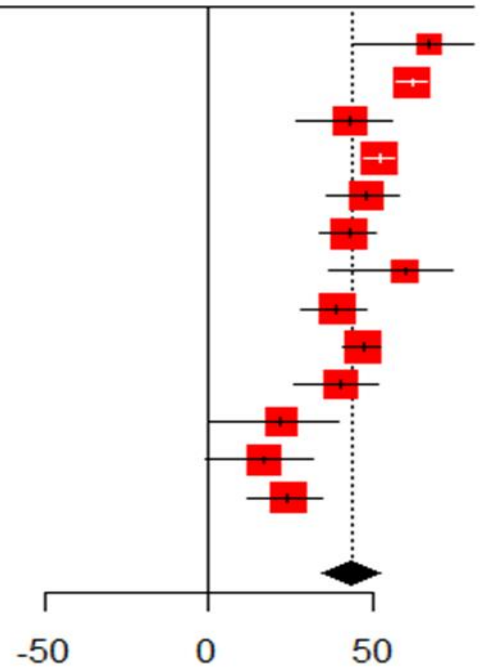
*****VE estimate among immunocompetent persons only

All studies are case control studies, 1 study is a pre-print, and 3 studies are manufacturer-funded.

In sensitivity analyses of pre-prints, manufacturer-funded studies, bivalent vaccine studies, and 2023-2024 dose studies, the pooled VE point estimates remained stable, and 95% CIs overlapped.

GRADE benefits among adolescents and adults: Forest plot and pooled estimate for VE against hospitalization due to COVID-19 (n=8)

Study[a]	Weight	Vaccine Eff. IV, Random, 95% CI
Ackerson, bivalent, 14-60 days	4.0%	67 [44; 81]
Link-Gelles, bivalent, 34 days*	8.9%	62 [57; 66]
DeCuir (VISION), 23-24 dose, 42 days*	7.3%	43 [27; 55]
DeCuir (IVY) 23-24 dose, 47 days*	9.2%	52 [47; 57]
DeCuir, bivalent, 53 days*	7.9%	48 [36; 58]
Caffrey, 23-24 dose, 76 days	8.7%	43 [34; 51]
Ackerson, bivalent, 60-180 days	4.7%	60 [37; 75]
Tartof, bivalent, 77 days	8.4%	39 [28; 48]
Link-Gelles, bivalent, 87 days*	9.1%	47 [41; 52]
Lin, bivalent, nr**	7.9%	40 [26; 51]
Paritala, bivalent, nr***	7.3%	22 [0; 39]
DeCuir, bivalent, 133 days*	8.0%	17 [-1; 32]
Link-Gelles, bivalent, 144 days*	8.7%	24 [12; 34]
Total (95% CI)	**100.0%**	**44 [34; 52]**



Notes:

VE or vaccine eff.= vaccine effectiveness; CI= confidence intervals**;** IV= inverse variance; nr= not reported

Studies are listed on the y-axis by median days since receipt of an updated dose. Pooled VE based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

Vaccine effectiveness comparisons included an updated dose (either bivalent or 2023-2024 formulation) compared to no updated dose (may include people who received any number of doses of prior formulations and unvaccinated, definitions varies by included study).

[a] Author, vaccine formulation, and time since vaccination (median or median range)

* Estimate among immunocompetent persons only

**Maximum follow-up time was 105 days

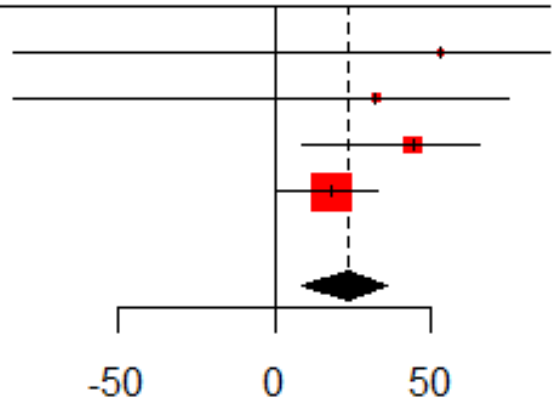
*** Maximum follow-up time was 112 days

6 studies are case control studies, 3 studies are cohort studies, 3 studies are pre-prints, and 3 studies are manufacturer-funded.

In sensitivity analyses that excluded cohort studies, case control studies, pre-prints, manufacturer funded studies, bivalent vaccines, and 2023-2024 doses, the pooled VE point estimates remained stable, and 95% CIs overlapped.

GRADE benefits among adolescents and adults: Forest plot and pooled VE estimate against death due to COVID-19 (n=3)

Study[a]	Weight	Vaccine Eff. IV, Fixed, 95% CI
Ackerson, bivalent, 14-60 days	1.7%	53 [-84; 88]
Ackerson, bivalent, 60-180 days	3.2%	32 [-84; 75]
Lin, bivalent, nr*	13.6%	44 [9; 66]
Paritala, bivalent, nr**	81.4%	18 [0; 33]
Total (95% CI)	**100.0%**	**23 [8; 36]**



Notes:
VE or vaccine eff.= vaccine effectiveness; CI= confidence intervals**;** IV= inverse variance; nr= not reported
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Vaccine effectiveness comparisons included an updated dose (either bivalent or 2023-2024 formulation) compared to no updated dose (may include people who received any number of doses of prior formulations and unvaccinated, definitions varies by included study).
a. Author, vaccine formulation, and time since vaccination (median or median range)
*Maximum follow-up time was 105 days
** Maximum follow-up time was 112 days
1 study is a case control study, 2 studies are cohort studies, 1 study is a pre-print, and 1 study is funded by a manufacturer
In sensitivity analyses of pre-prints and manufacturer-funded studies, the pooled VE point estimates remained stable, and 95% CIs overlapped

Interpreting a GRADE certainty assessment

- **A certainty assessment reflects our confidence that the *true effect* lies close to the *estimated effect***
- There are 4 certainty levels:
  - **High:** We are very confident that the true effect lies close to that of the estimated effect. *Randomized controlled trial certainty starts here and can be downgraded or upgraded*[1].
  - **Moderate:** We are moderately confident that the true effect lies close to the estimated effect, but there is a possibility that it is substantially different.
  - **Low:** We have limited confidence that the true effect lies close to the estimated effect; the true effect may be substantially different from the estimated effect. *Observational certainty starts here and can be downgraded or upgraded*[1].
  - **Very low:** We have very limited confidence that the true effect lies close to the estimated effect; the true effect is likely to be substantially different from the estimated of effect.
- A certainty assessment does not reflect our confidence in the quality of the individual studies or the overall confidence in benefits and harms of the vaccine, which may be informed by additional data on benefits and harms.

1. Evidence type may be downgraded due to risk of bias, inconsistency, indirectness, imprecision or other considerations such as publication bias and upgraded for indications of a dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.

Summary of GRADE

Outcome	Population	Importance	Design (# of studies)	Effect estimate (95% CI)	Findings	Final certainty assessment
Benefits						
Medically-attended COVID-19 (ED/UC visit)	Adolescent/adult	Critical	OBS (5)	VE: 43 (30-54)	Updated COVID-19 vaccine is effective in preventing medically attended COVID-19 ED/UC visits.	**Low**
	Pediatric		OBS (1)	VE: 80 (42-96)		**Low**
Hospitalization due to COVID-19	Adolescent/adult	Critical	OBS (8)	VE: 44 (34-53)	Updated COVID-19 vaccine prevents hospitalization due to COVID-19, although the body of evidence in the pediatric population is limited to indirect data from adolescents and adults.	**Low**
	Pediatric					**Very low**
Death due to COVID-19	Adolescent/adult	Important	OBS (3)	VE: 23 (8-36)	Updated COVID-19 vaccine prevents death due to COVID-19, although the body of evidence in the pediatric population is limited to indirect data from adolescents and adults.	**Low**
	Pediatric					**Very low**
Post-COVID conditions	Adolescent/adult	Important	OBS (0)	-	-	**-**
	Pediatric					
MIS-C	Pediatric	Important	OBS (0)	-	-	**-**
Specified serious adverse events	Adolescent/adult		OBS (2)		In post-authorization safety monitoring, two rare adverse events have been associated with vaccination	
	Pediatric					**Very low**

ED/UC: emergency department/urgent care; OBS: observational; VE: vaccine effectiveness; CI: confidence interval; MIS-C: multisystem inflammatory syndrome in children
Note: Vast majority of data captured in systematic review are for mRNA vaccines.

2023-2024 Formula COVID-19 vaccine effectiveness

- 2023-2024 COVID-19 vaccination provided increased protection against symptomatic SARS-CoV-2 infection and COVID-19-associated ED/UC visits and hospitalizations compared to no 2023-2024 vaccine dose
- Waning patterns appeared similar to previous COVID-19 vaccine formulations; most durable protection appeared to be for critical illness, though statistical power was lacking in the longest time period since vaccination
- As with previous COVID-19 vaccine formulations, effectiveness was similar across age groups
- Receipt of 2023-2024 COVID-19 vaccine provided protection against JN.1 and other circulating variants, though may be lower than protection provided against XBB sublineage variants

ED: Emergency department | UC: Urgent care

COVID-19 mRNA vaccination associated with reduced occurrence of Post-COVID Conditions (PCC) following SARS-CoV-2 infection

Among children 5 – 17 years:

Completion of the original formula COVID-19 vaccine series prior to infection associated with reduced likelihood of symptoms:

- ↓ 34% for 1 or more PCC symptoms
- ↓ 47% for respiratory PCC symptoms
- ↓ 48% for 2 or more PCC symptoms

Among adults:

3 doses of original formula COVID-19 vaccine prior to infection associated with reduced likelihood of symptoms:

- ↓ 24% for 2 or more PCC symptoms
- ↓ 27% for cardiovascular/respiratory symptoms
- ↓ 42% for gastrointestinal symptoms
- ↓ 26% for neurological symptoms
- ↓ 33% for other non-specific symptoms

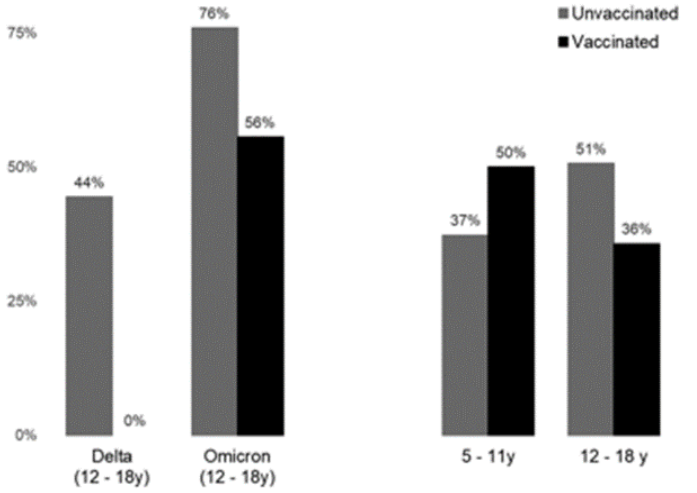
Unpublished data from the HEROES/RECOVER, PROTECT cohorts.

HEROES Protocol; RECOVER Protocol; PROTECT Protocol

COVID-19 vaccine effectiveness against Multisystem Inflammatory Syndrome in Children (MIS-C) in US children ages 5-18 years old

- Multicenter case-control public health investigation from July 1, 2021–April 7, 2022
- Compared odds of receiving 2 doses of BNT162b2 vaccine ≥28 days before admission between MIS-C case-patients and hospital-based controls who tested negative for SARS-CoV-2
  - 304 MIS-C case patients (92% unvaccinated)
  - 502 controls (69% unvaccinated)
- A lower proportion of vaccinated patents required life support or died during period of Delta variant predominance
- One unvaccinated MIS-C case-patient (12–18 years) required ECMO, and 1 unvaccinated patient (5–11 years) died

B Comparison of MIS-C cases resulting in life support or death between vaccinated and unvaccinated patients, by period of variant predominance and by age group.



ECMO = extracorporeal membrane oxygenation

Zambrano LD, et al. Clin Infect Dis. 2022 Aug 4:ciac637

COVID-19 vaccine safety

- COVID-19 vaccines have a favorable safety profile as demonstrated by robust safety surveillance over 3 years of COVID-19 vaccine use
  - Anaphylactic reactions have been rarely reported following receipt of COVID-19 vaccines
  - Rare risk of myocarditis and pericarditis predominately in males ages 12-39 years
    - No myocarditis or pericarditis signal in the Vaccine Safety Datalink for the 2023-2024 Formula COVID-19 vaccine, however, this may be limited by low uptake
  - Reactogenicity symptoms are overall less frequent and severe among older adults compared with adolescents and younger adults

Longer term impact of vaccine associated myocarditis

- Vaccine-associated myocarditis is a rare risk of COVID-19 vaccination.
- Acute clinical picture tends to resolve quickly[1]
  - Majority of patients had recovered at 90 days with symptoms improving over time
- Small subset with persistent MRI findings (e.g., late gadolinium enhancement), with unclear correlation to symptoms[2]
  - Additional follow up is needed to determine the long-term impact of these MRI findings

1. https://www.sciencedirect.com/science/article/pii/S2352464222002449?via%3Dihub
2. https://papers.ssrn.com/sol3/papers.cfm?abstract_id=4681858#:~:text=Interpretation%3A%20COVID%2D19%20vaccine%2D,continued%20surveillance%20in%20C%2DVAM

MRI: magnetic resonance imaging

Summary of the Vaccine Safety Datalink (VSD) Rapid Cycle Analysis for the 2023-2024 COVID-19 vaccine

- The VSD identified two statistical signals for mRNA COVID-19 vaccines during the 2023-2024 season
  - Guillain-Barré syndrome (GBS) following Pfizer COVID-19 vaccine among people aged ≥65 years
    - An association between mRNA COVID-19 vaccines and GBS had not been observed prior to this season in VSD or other systems
    - The increased rate ratio observed during the 2023-2024 season may or may not represent a true risk
    - If there is a true risk, it is estimated to be similar to what is considered acceptable for other adult vaccines
  - Ischemic stroke following Moderna (aged ≥65 years) and Pfizer (aged 50-64 years) COVID-19 vaccines
    - The VSD previously observed a statistical signal for ischemic stroke during 2022-2023 for bivalent Pfizer COVID-19 vaccine (aged ≥65 years)
    - Available data do not provide clear and consistent evidence of a safety problem for ischemic stroke with mRNA COVID 19 vaccines
- No other new or unexpected safety concerns were identified for the 2023-2024 COVID-19 vaccines
- Any real or theoretical risks of vaccine adverse events need to be placed in the context of the benefits of COVID-19 vaccines in preventing COVID-19 and its potentially serious complications

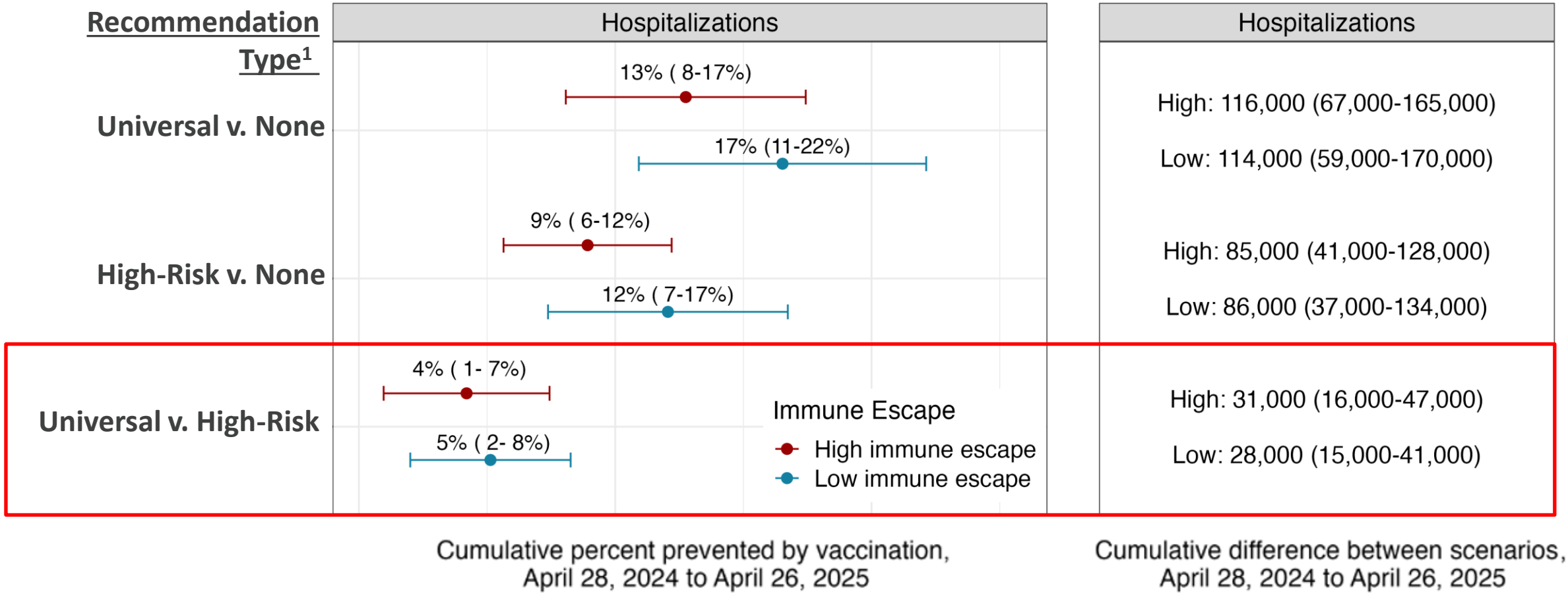
Models of potential impact of different 2024-2025 COVID-19 vaccine recommendations

- Assumptions of COVID-19 Scenario Modeling Hub Round 18
- Six scenarios focusing on three vaccine recommendation scenarios under high and low rates[1] of immune escape
  - No vaccine recommendation[2] vs recommendation only for persons at high-risk vs universal recommendation
  - High-risk defined as those ages ≥ 65 years and those with underlying conditions[3]
- Vaccine uptake assumptions based on 2023-2024 COVID-19 vaccine coverage[4]
- Assumes vaccine available on September 1st with 75% VE against hospitalization
  - Constant rate of immune escape and waning applied starting September 1st
- Models projected 1 year into the future

1. Low immune escape occurs at a constant rate of 20% per year and high immune escape occurs at a constant rate of 50% per year
2. The no vaccine recommendation scenario allowed for naïve children aging into eligibility to be vaccinated
3. Ko JY, Danielson ML, Town M, et al. Risk Factors for Coronavirus Disease 2019 (COVID-19)–Associated Hospitalization: COVID-19–Associated Hospitalization Surveillance Network and Behavioral Risk Factor Surveillance System. Clinical Infectious Diseases. 2021;72(11):e695-e703. doi:10.1093/cid/ciaa1419
4. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/index.html. Assumption of approximately 21% of adults, 39% of those ≥65 years, 32% of those with underlying conditions

VE: vaccine effectiveness

Universal vaccine recommendations projected to prevent about 30,000 more hospitalizations over the next year compared with a risk-based recommendation



1. None = no vaccine recommendation; High-risk = recommended for those ages ≥ 65 years and those with underlying conditions; Universal = universal vaccine recommendation

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?

- There is no evidence to suggest that COVID-19 vaccine effectiveness varies substantially by race/ethnicity[1,2]
  - Differences in vaccine hesitancy/uptake, crowding, access to care, and prior infection could impact vaccine effectiveness and these factors may also differ by race/ethnicity
- There is no evidence to suggest that COVID-19 vaccine safety profiles vary by race/ethnicity, however risk has been shown to differ by age and sex
  - Risk for myocarditis is highest in adolescent and young adult males
- 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

1. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9619452/
2. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9763212/

Summary
Benefits and Harms

- 2023-2024 COVID-19 vaccine is effective in preventing ED/UC visits and preventing severe outcomes related to COVID-19 (e.g., hospitalization, death); waning of immunity is expected
- COVID-19 vaccines continue to have a favorable safety profile as demonstrated by robust safety surveillance over 3 years of COVID-19 vaccine use
  - Ischemic stroke and GBS signals in the VSD are not clear or consistent, and are seen in the age groups (adults ≥ 50 years and adults ≥ 65 years, respectively) with the highest burden of disease that would benefit the most from updated COVID-19 vaccination
- Modeling projects more hospitalization averted when 2024-2025 COVID-19 vaccines are universally recommended compared to no recommendation or recommended only for those at high risk

VSD: Vaccine Safety Datalink | GBS: Guillain-Barre Syndrome

Benefits and Harms

How substantial are the desirable anticipated effects?

- How substantial are the anticipated effects 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 effects 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?

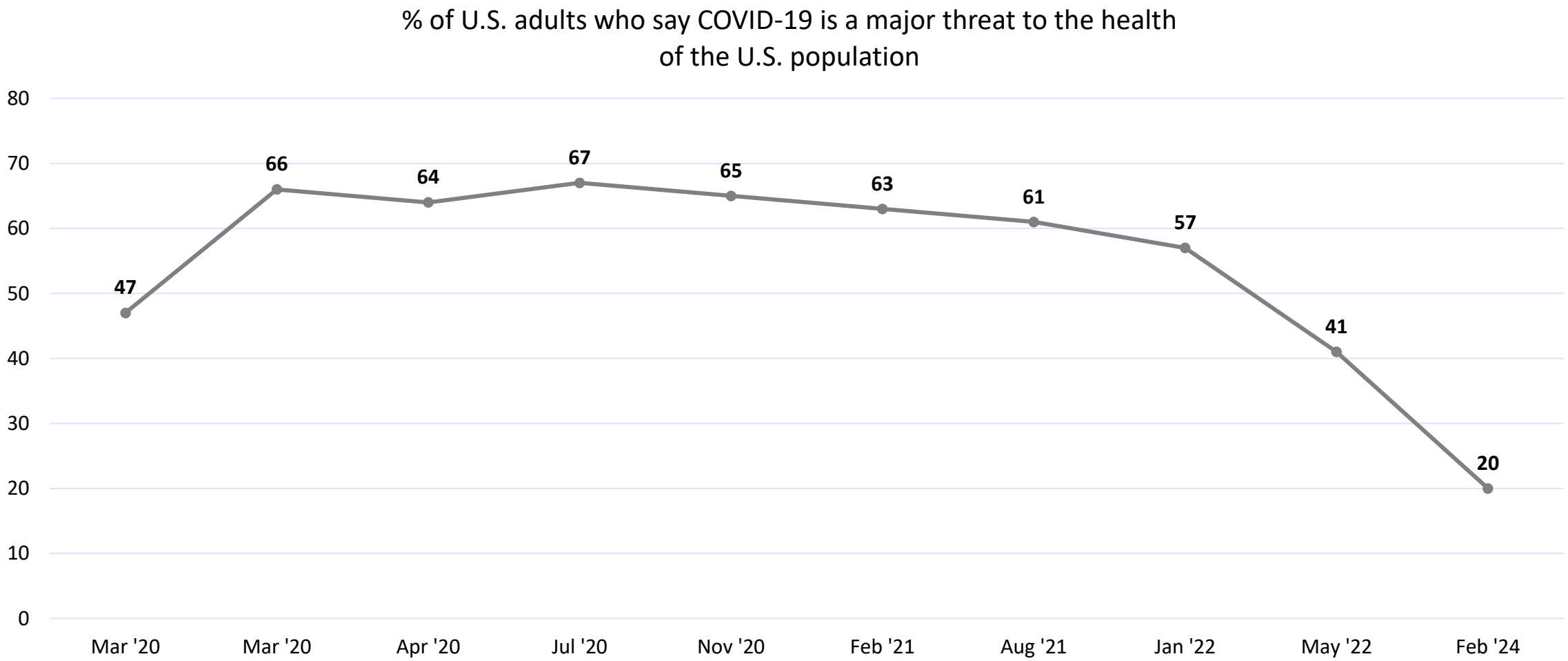
- What is the balance between the desirable effects relative to the undesirable effects?

- ○ Favors intervention (2024 – 2025 Formula COVID-19 vaccine)
- ○ Favors comparison (no vaccine)
- ○ Favors both
- ○ Favors neither
- ○ Unclear

EtR Domain:

Values

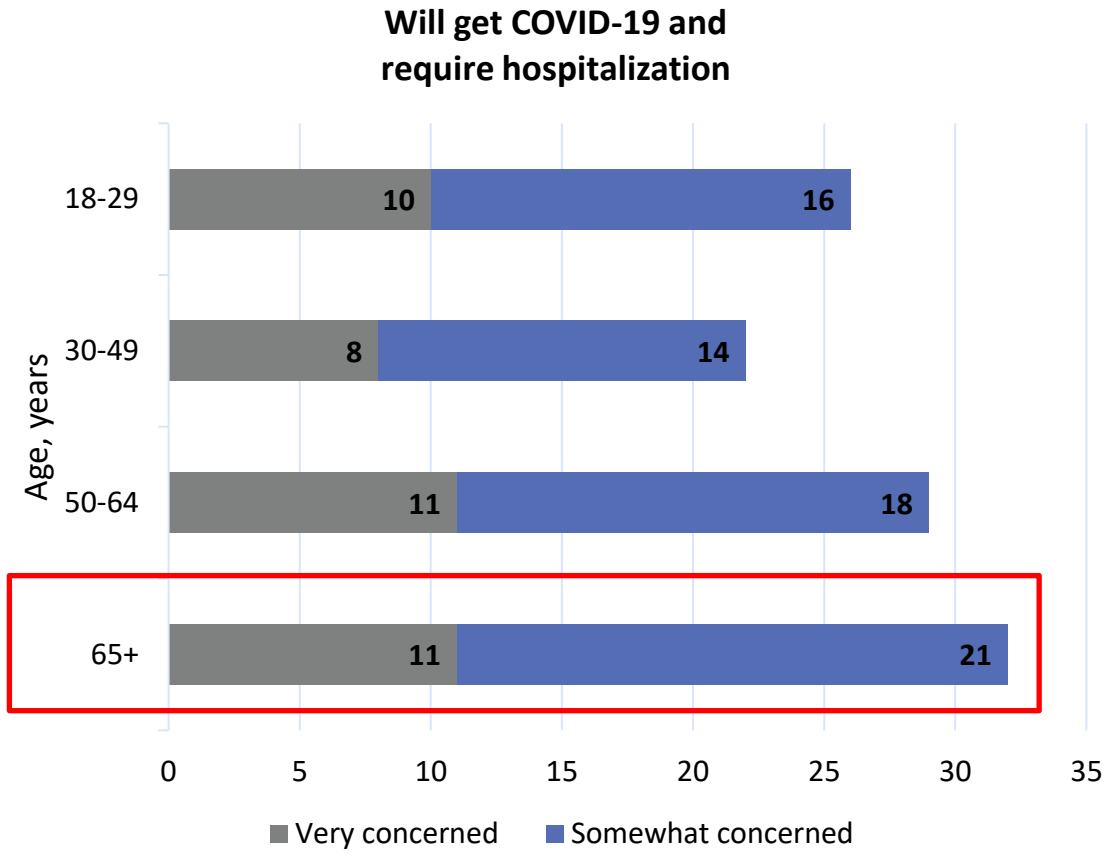
1 in 5 Americans now say COVID-19 is a major threat to public health

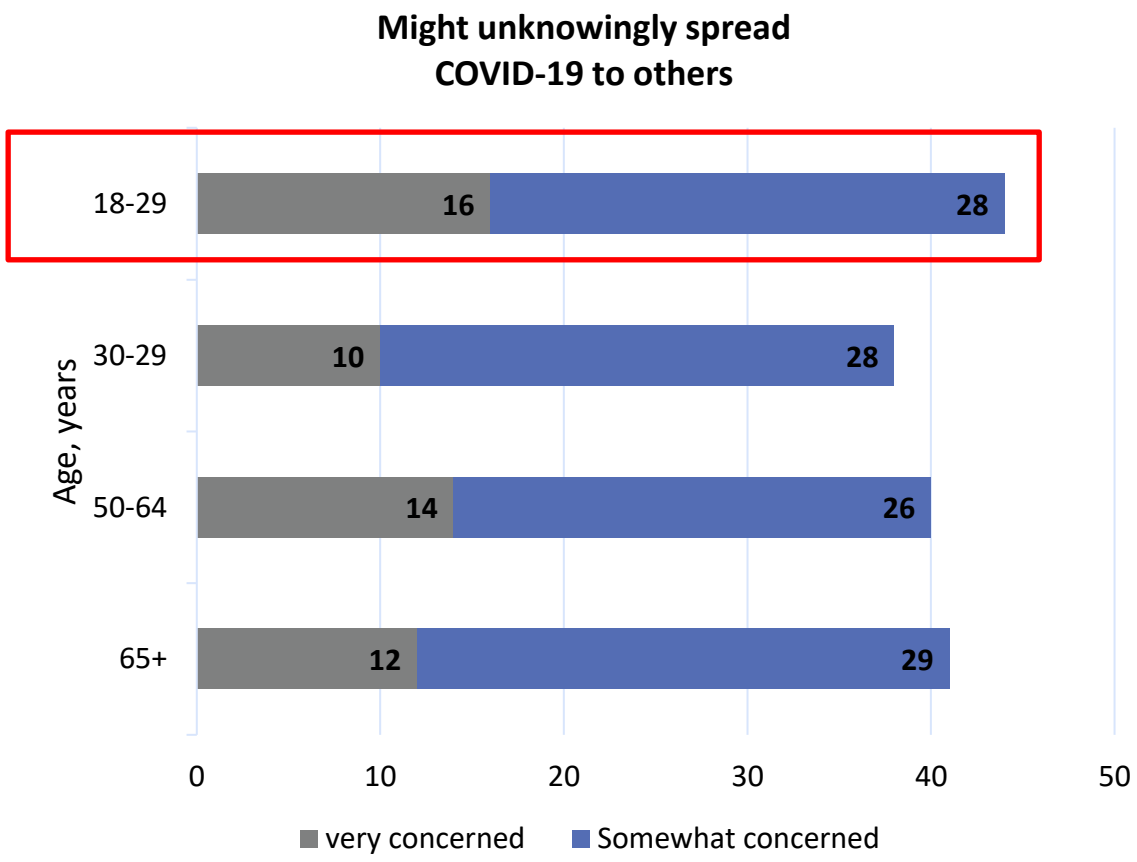


Pew Research Center. March 7, 2024. How Americans View the Coronavirus, COVID-19 Vaccines Amid Declining Levels of Concern. https://www.pewresearch.org/science/2024/03/07/how-americans-view-the-coronavirus-covid-19-vaccines-amid-declining-levels-of-concern/ Accessed April 23, 2024

Concern about risk of COVID-19 by age, February 2024

% of U.S. adults who say they are **very/somewhat concerned** that they…





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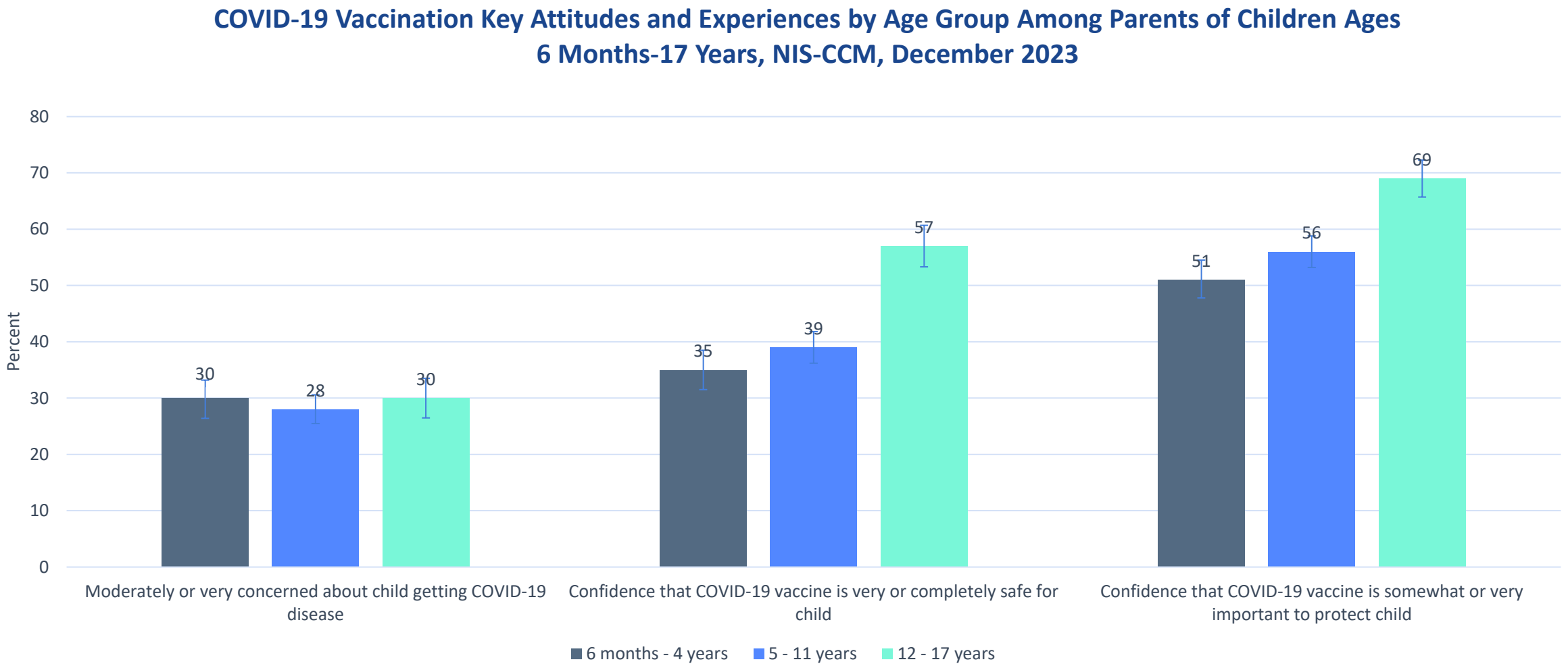
Key attitudes and experiences among parents of children 6 months-17 years, December 2023

National Immunization Survey-Child COVID-19 Module (NIS-CCM)



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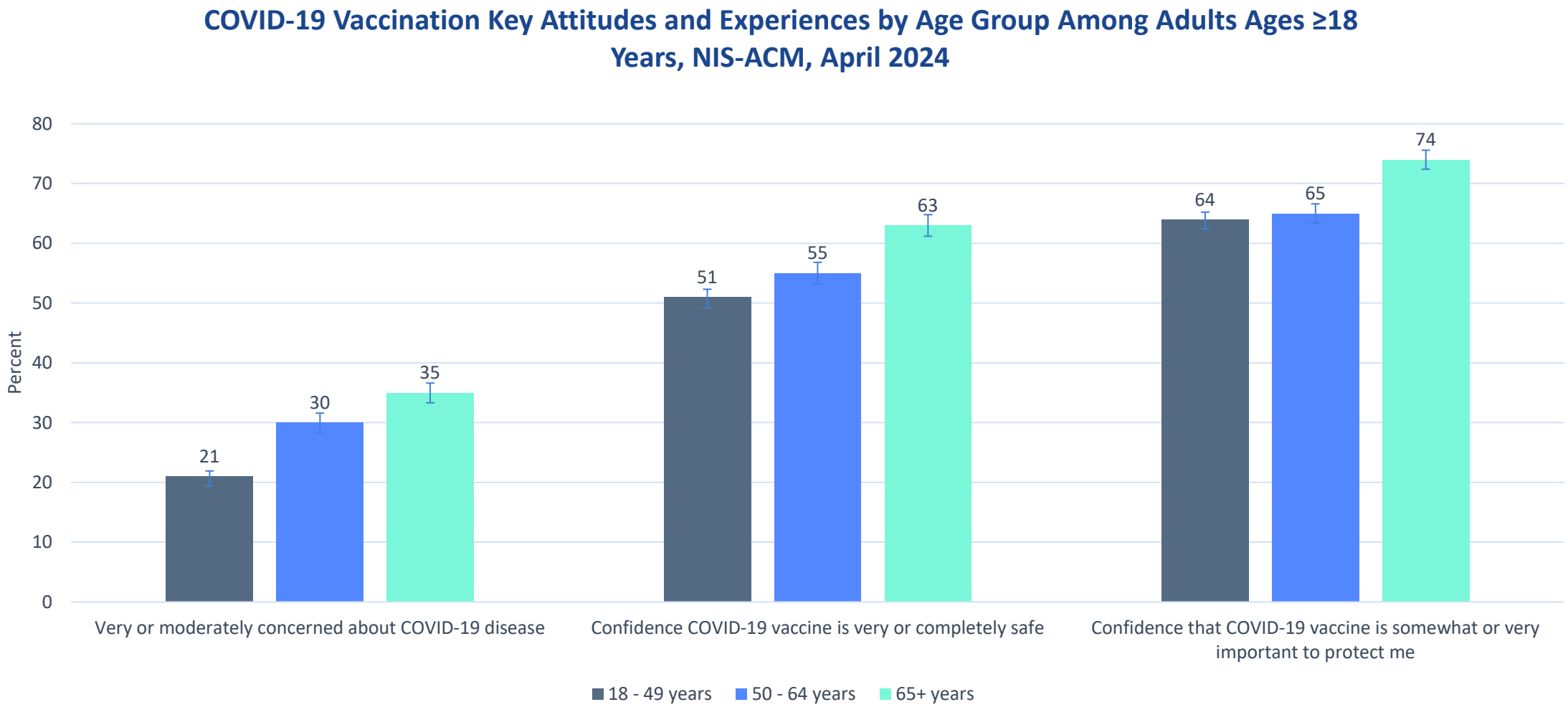
Key attitudes and experiences among adults 18 years and older, April 2024
National Immunization Survey-Adult COVID Module (NIS-ACM)



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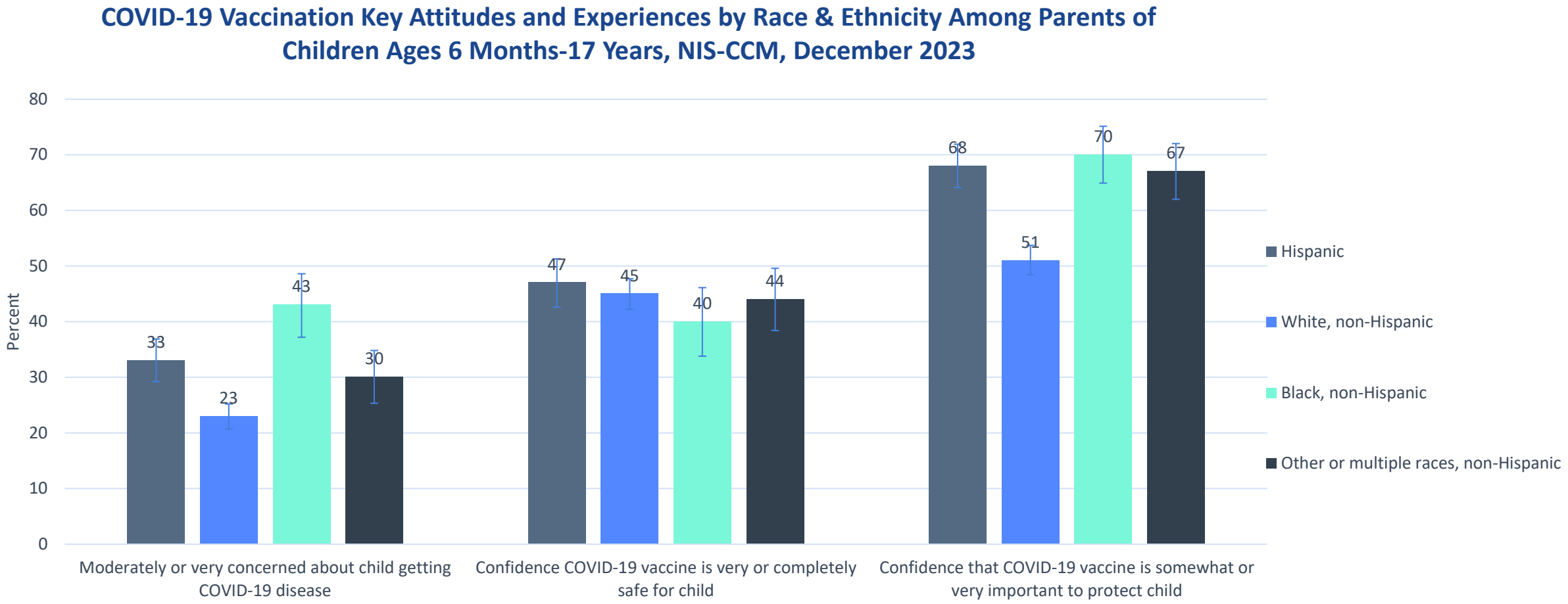
CDC. COVID-19 Vaccination Coverage and Vaccine Confidence Among Adults. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html Accessed May 30, 2024

EtR Domain:

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

Key attitudes and experiences among parents of children 6 months-17 years, December 2023

National Immunization Survey-Child COVID-19 Module (NIS-CCM)



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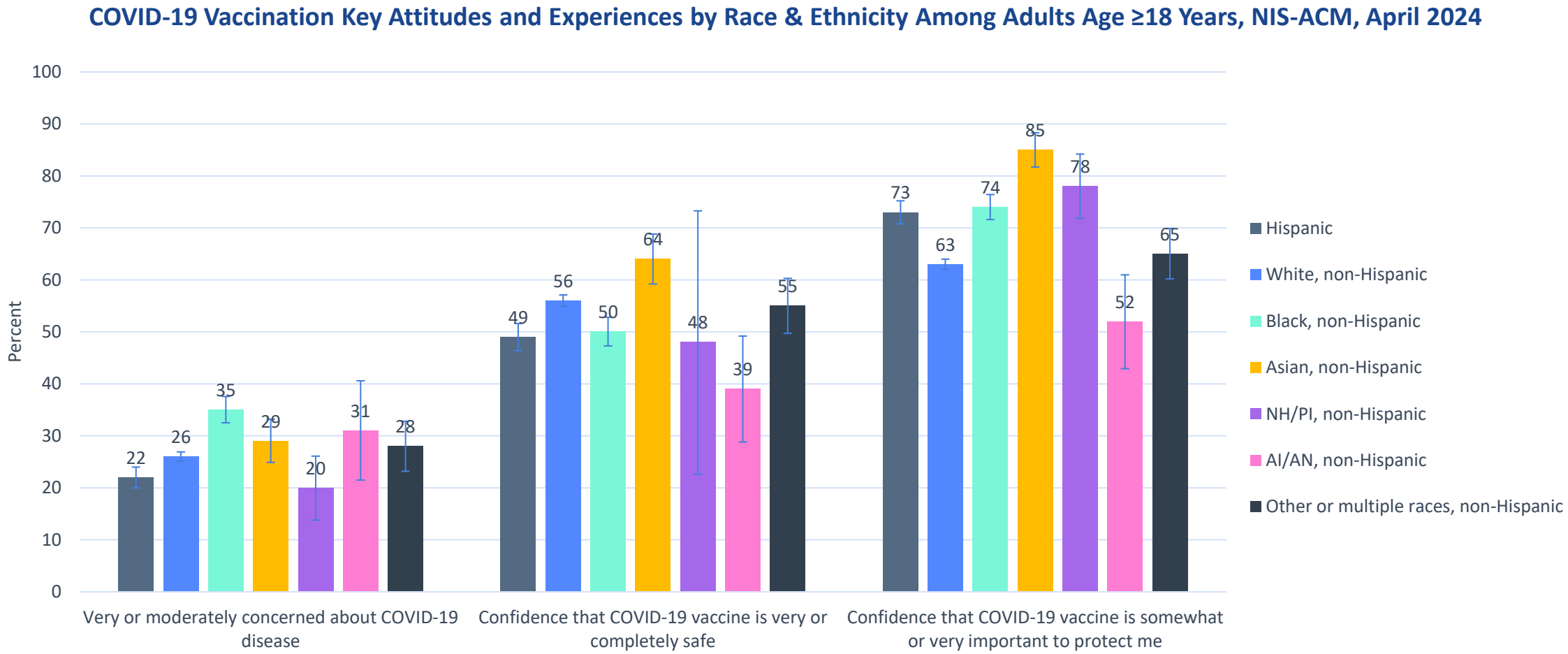
Key attitudes and experiences among adults 18 years and older, April 2024 National Immunization Survey-Adult COVID Module (NIS-ACM)



AI/AN: American Indian or Alaska Native; NH/PI: Native Hawaiian or Other Pacific Islander

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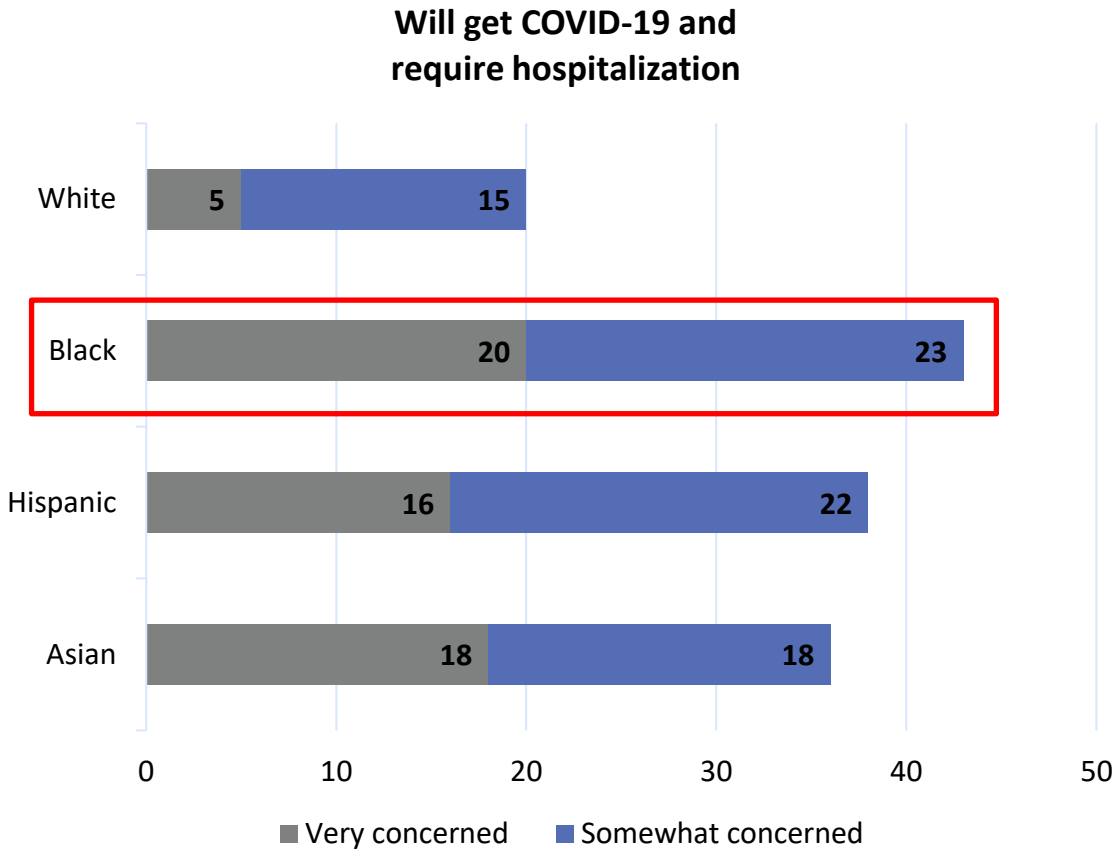
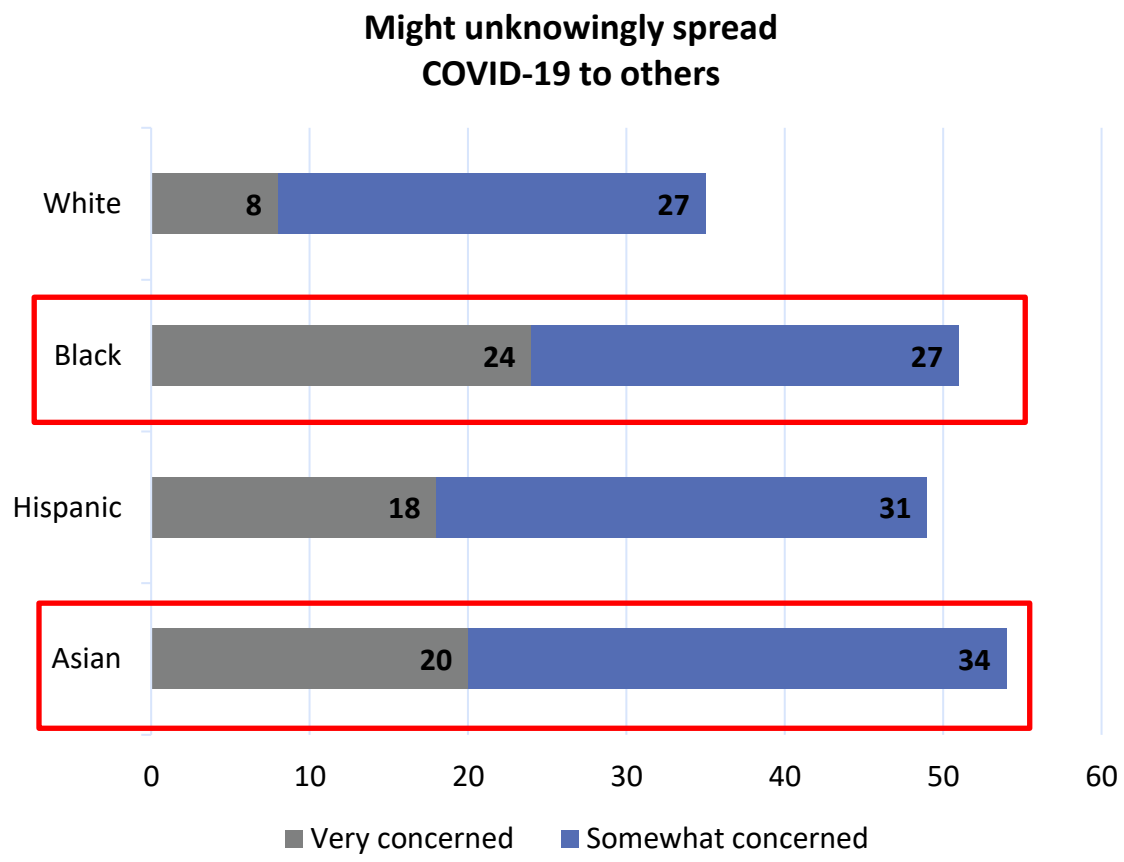
CDC. COVID-19 Vaccination Coverage and Vaccine Confidence Among Adults. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html Accessed May 30, 2024

Concern about risk of COVID-19 by race and ethnicity, February 2024

% of U.S. adults who say they are **very/somewhat concerned** that they…





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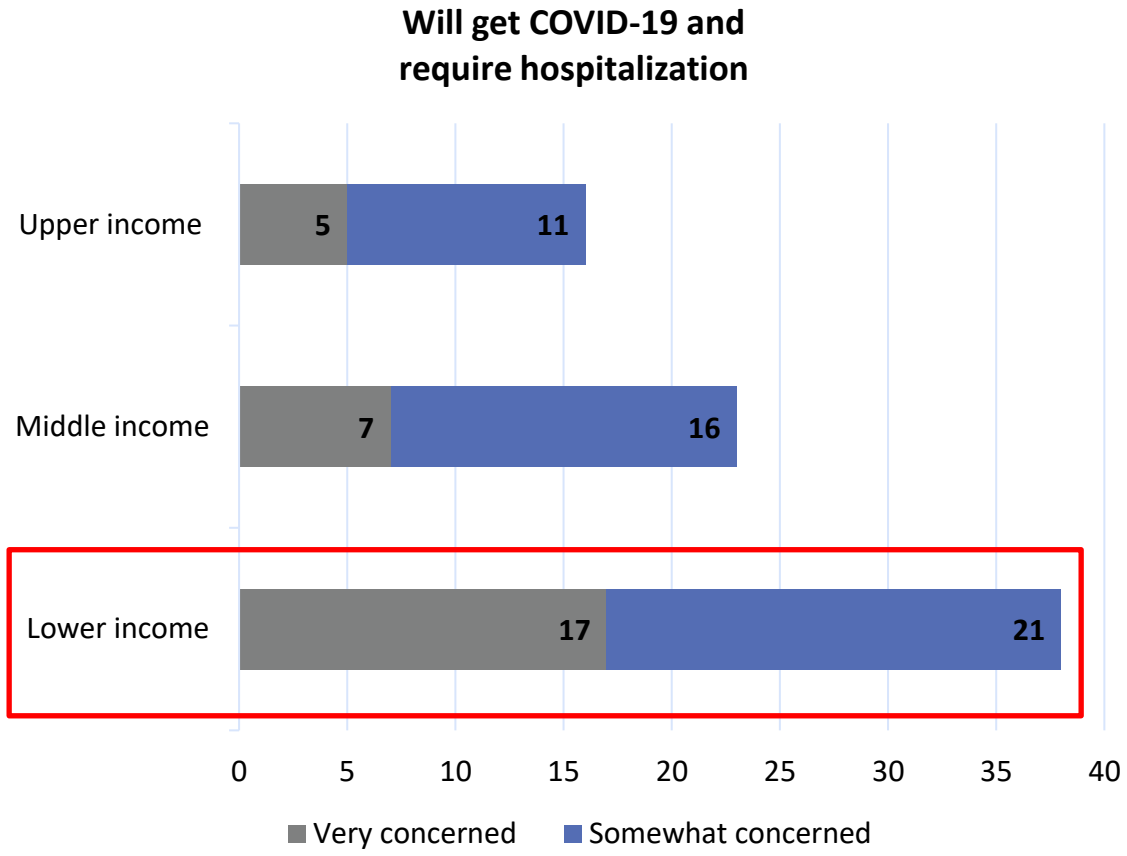
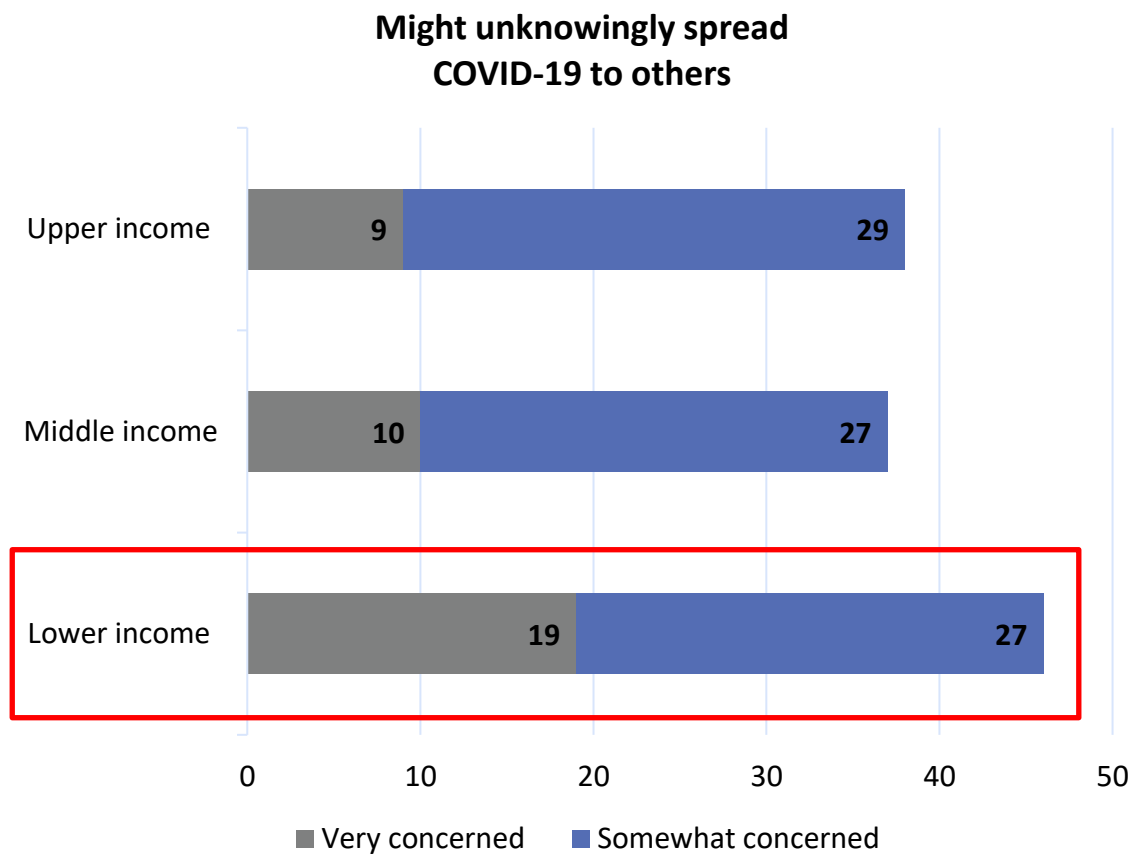
Pew Research Center. March 7, 2024. How Americans View the Coronavirus, COVID-19 Vaccines Amid Declining Levels of Concern. https://www.pewresearch.org/science/2024/03/07/how-americans-view-the-coronavirus-covid-19-vaccines-amid-declining-levels-of-concern/ Accessed April 23, 2024

Concern about risk of COVID-19 by income, February 2024

% of U.S. adults who say they are **very/somewhat concerned** that they…





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Summary
Values

- Approximately 30% of parents of children ages 6 months – 17 years reported concern about their child getting COVID-19, but confidence in COVID-19 vaccine safety and vaccine importance was highest among parents of adolescents

- Adults ages 65 years and older were more concerned about COVID-19 disease and had higher confidence in vaccine safety and vaccine importance than those <65 years

- Racial and ethnic minority groups, older adults, and those with lower incomes are more concerned about getting COVID-19 than other groups

Values

Criteria 1:

Do persons ≥6 months of age feel that the desirable effects are large relative to undesirable effects?

- How do persons ≥6 months of age view the balance of desirable versus undesirable effects?
- Would persons ≥6 months of age feel that the benefits outweigh the harms?

○ Minimal	○ Small	○ Moderate	○ Large	○ Varies	○ Don’t know

Values

Criteria 2:

Is there important uncertainty about, or variability in, how persons ≥6 months of age value the main outcomes?

- 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

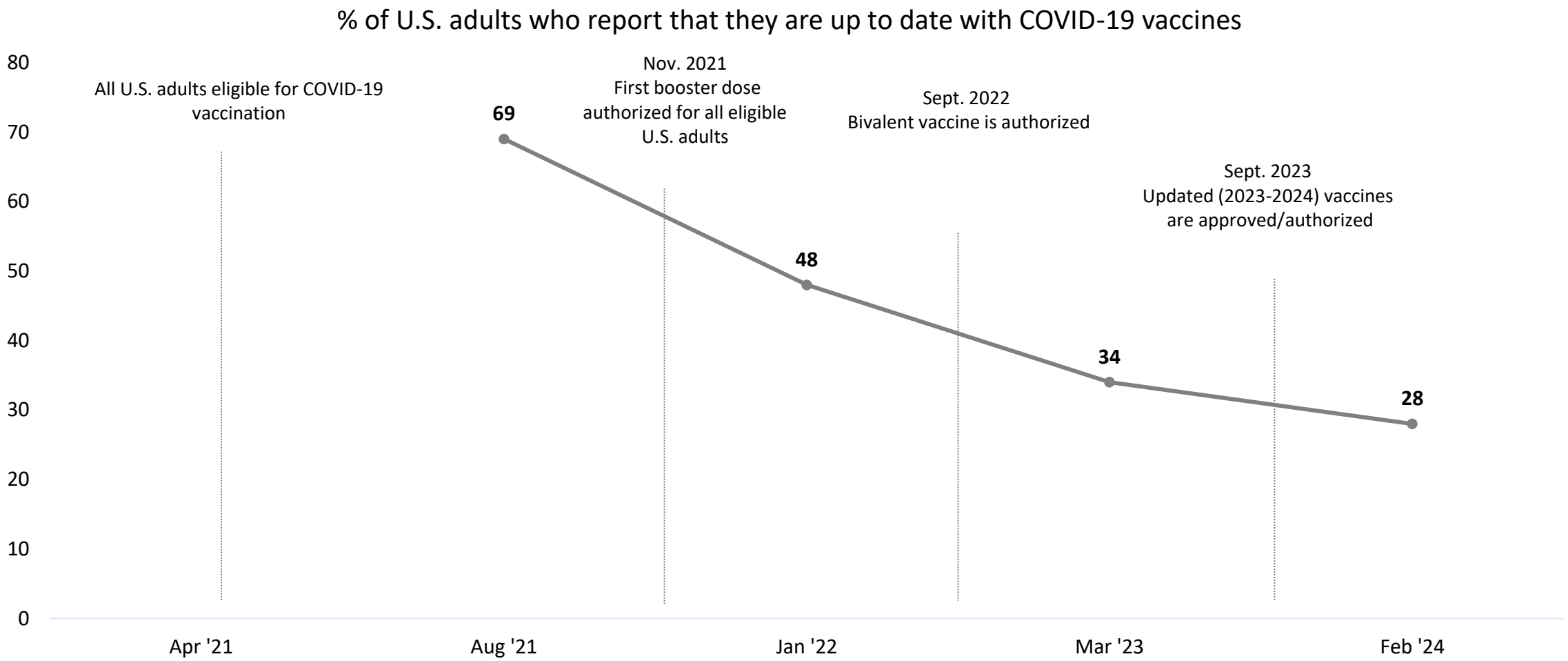
Majority opinion

Minority opinion

EtR Domain:

Acceptability

Declining share of Americans have the most up-to-date level of protection against COVID-19



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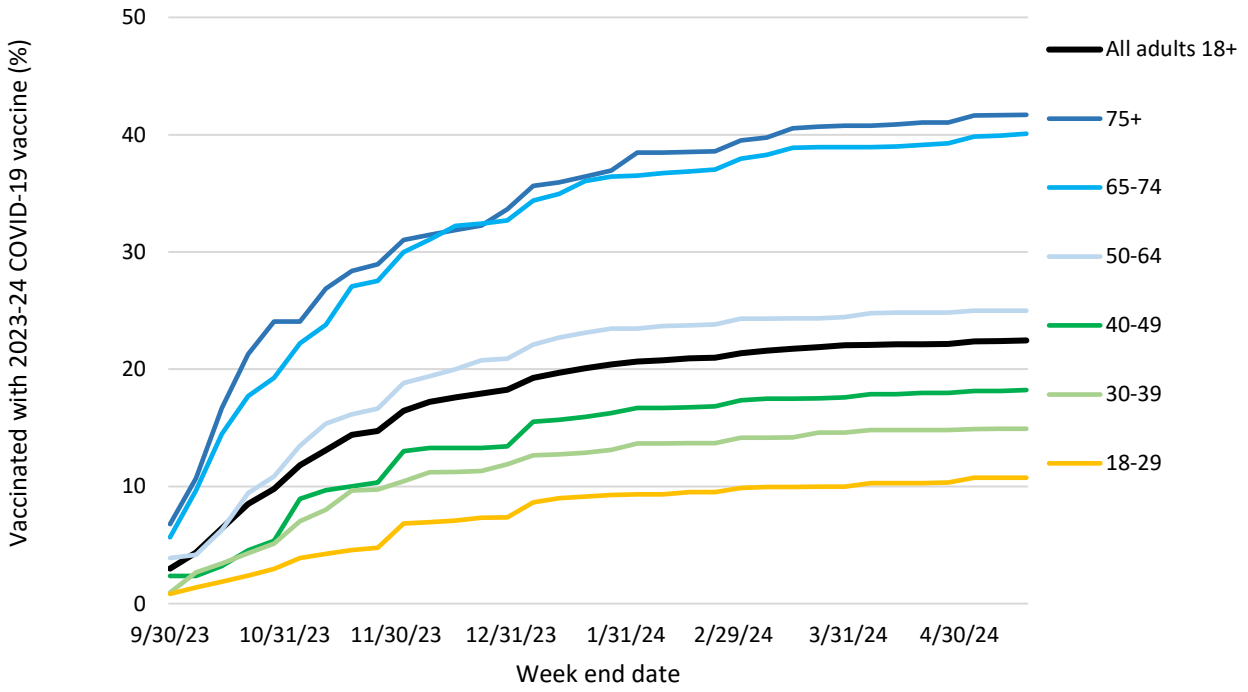
Percent of adults and children who received 2023-24 COVID-19 vaccine

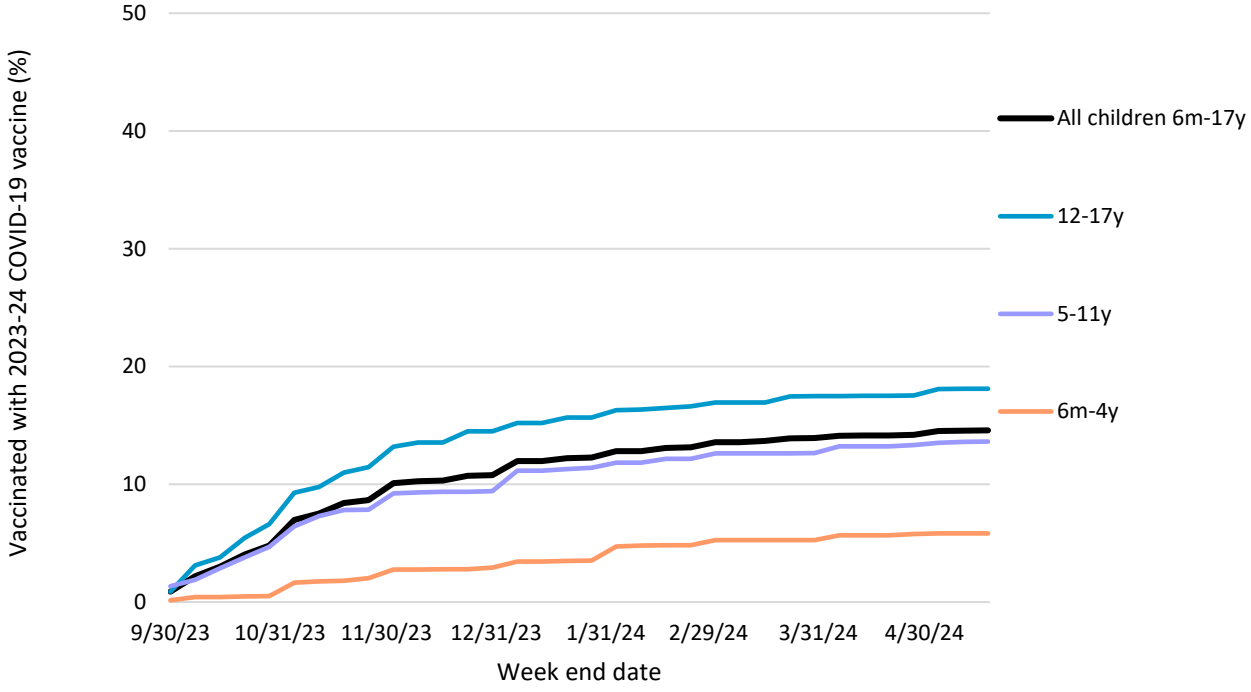
National Immunization Survey-Adult COVID Module (NIS-ACM) and -Child COVID Module (NIS-CCM)

September 2023-April 2024

COVID-19 Vaccination Coverage with 2023-24 Vaccine Among Adults ≥18 Years, NIS-ACM

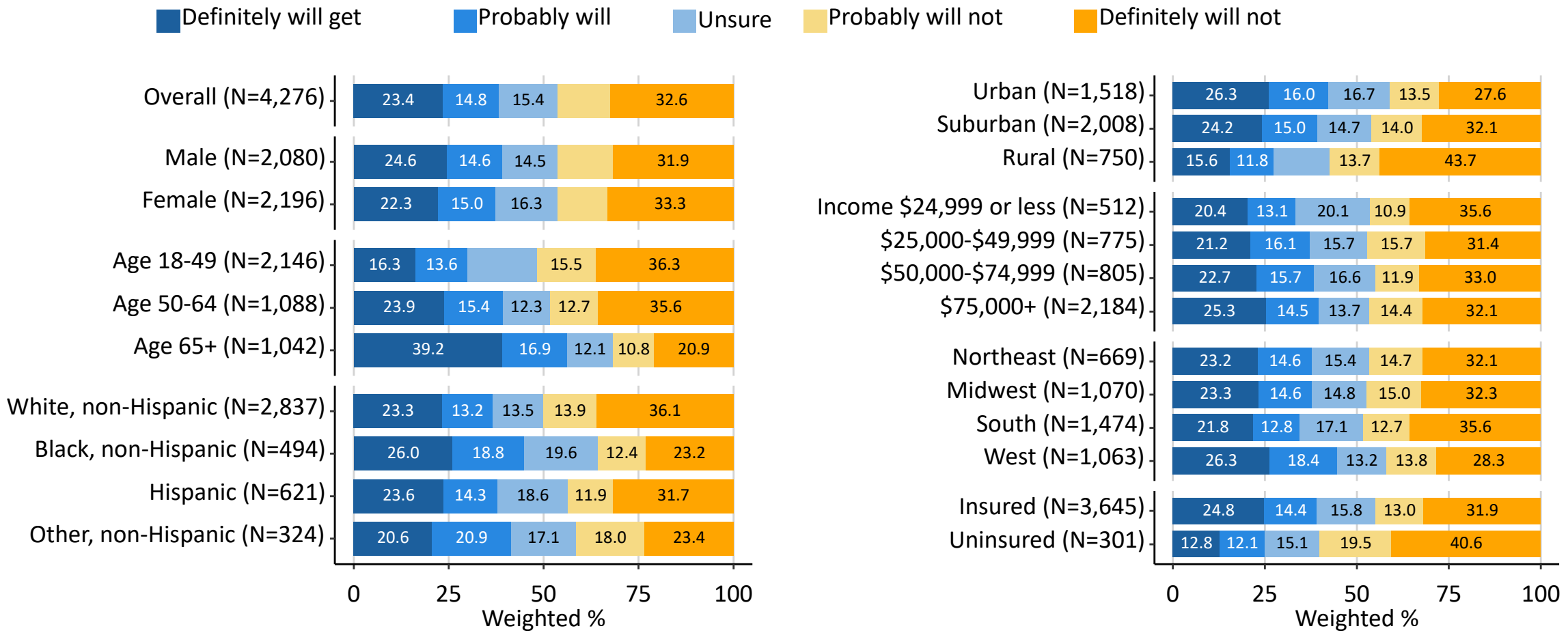


COVID-19 Vaccination Coverage with 2023-24 Vaccine Among Children 6 Months-17 Years, NIS-CCM



https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/index.html

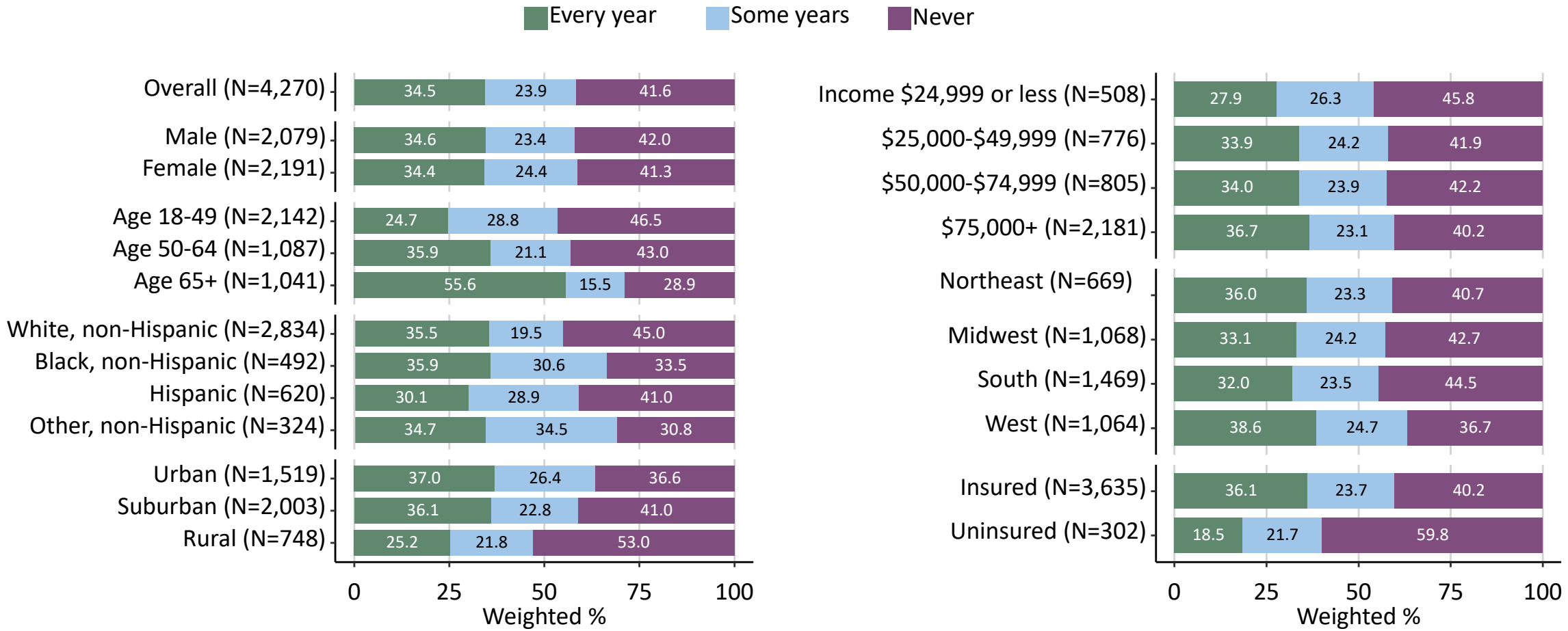
Intent to get 2024-25 COVID-19 vaccine among adults ≥18 years of age, by demographics,* Omnibus Surveys, May 2-26, 2024 (N=4,276)



*NORC and Ipsos base urbanicity on different, but comparable measures. NORC uses Census tract-based RUCA (Rural-Urban-Commuting Area) codes, whereas Ipsos uses Office of Management and Budget's CBSA (Core Based Statistical Area) classification. †Insured group includes plans purchased through employer, insurance companies, marketplaces, military insurance, Medicare, Medicaid, VA, IHS, and "other".

Omnibus Surveys: Data for this analysis were collected through the Ipsos KnowledgePanel and NORC AmeriSpeak Omnibus Surveys, which use probability-based panels to survey a nationally representative sample of U.S. adults aged 18 years and older. CDC fields questions about vaccination status, intent, knowledge, attitudes, beliefs, and behaviors on each survey for 2 waves each month, for a combined sample size of ~4,000 respondents.

Intent to get an annual COVID-19 vaccine among adults ≥18 years of age, by demographics,* Omnibus Surveys, May 2-26, 2024 (N=4,270)



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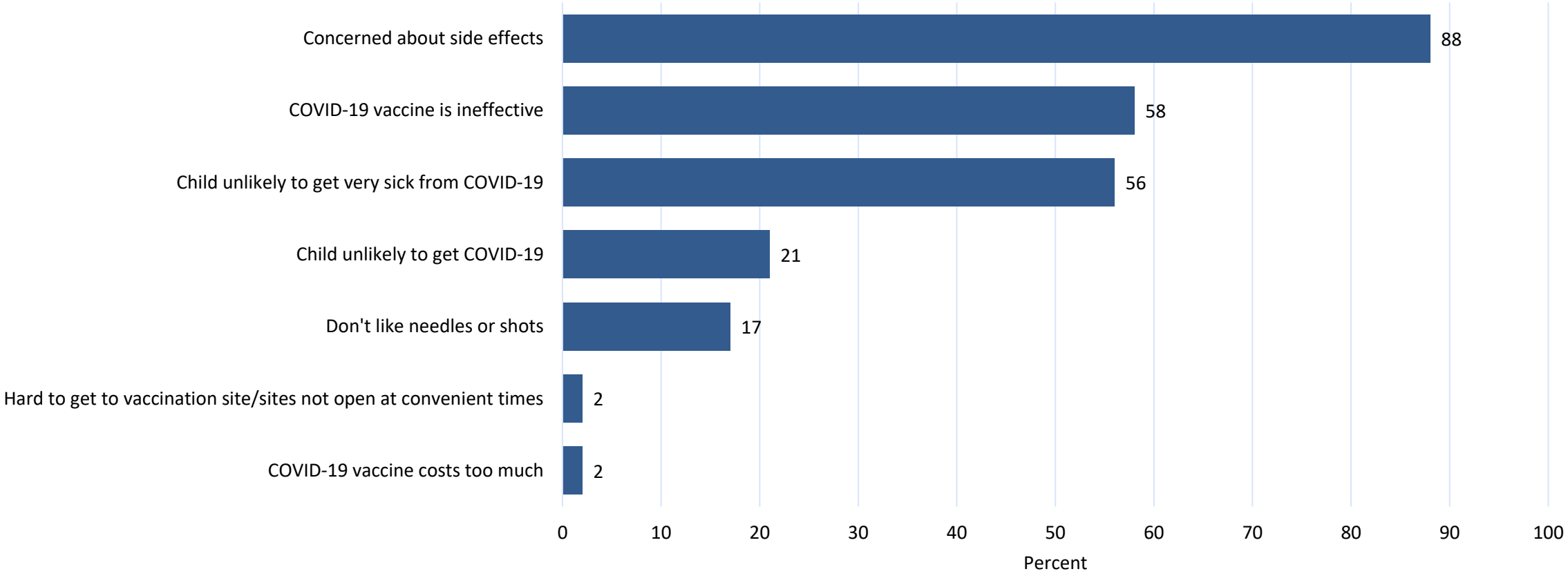
Key attitudes and experiences among parents of children 6 months-17 years, December 2023 - *National Immunization Survey-Child COVID Module (NIS-CCM)*

Reason for Not Getting the COVID-19 Vaccine Among Respondents with Unvaccinated Children Ages 6 Months-17 Years, NIS-CCM, December 2023



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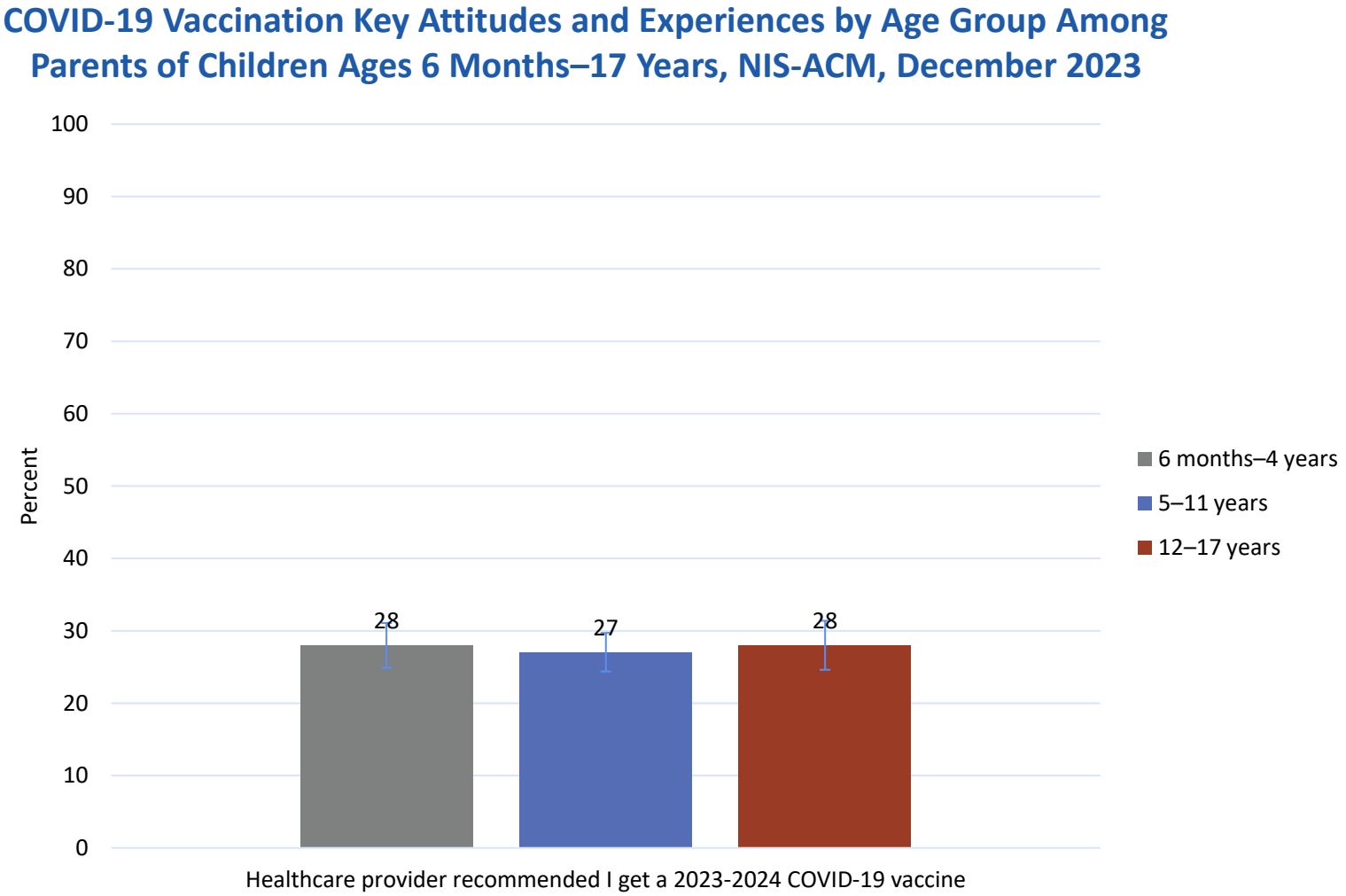
Key attitudes and experiences among parents of children ages 6 months through 17 years, December 2023 - *National Immunization Survey-Child COVID Module (NIS-CCM)*



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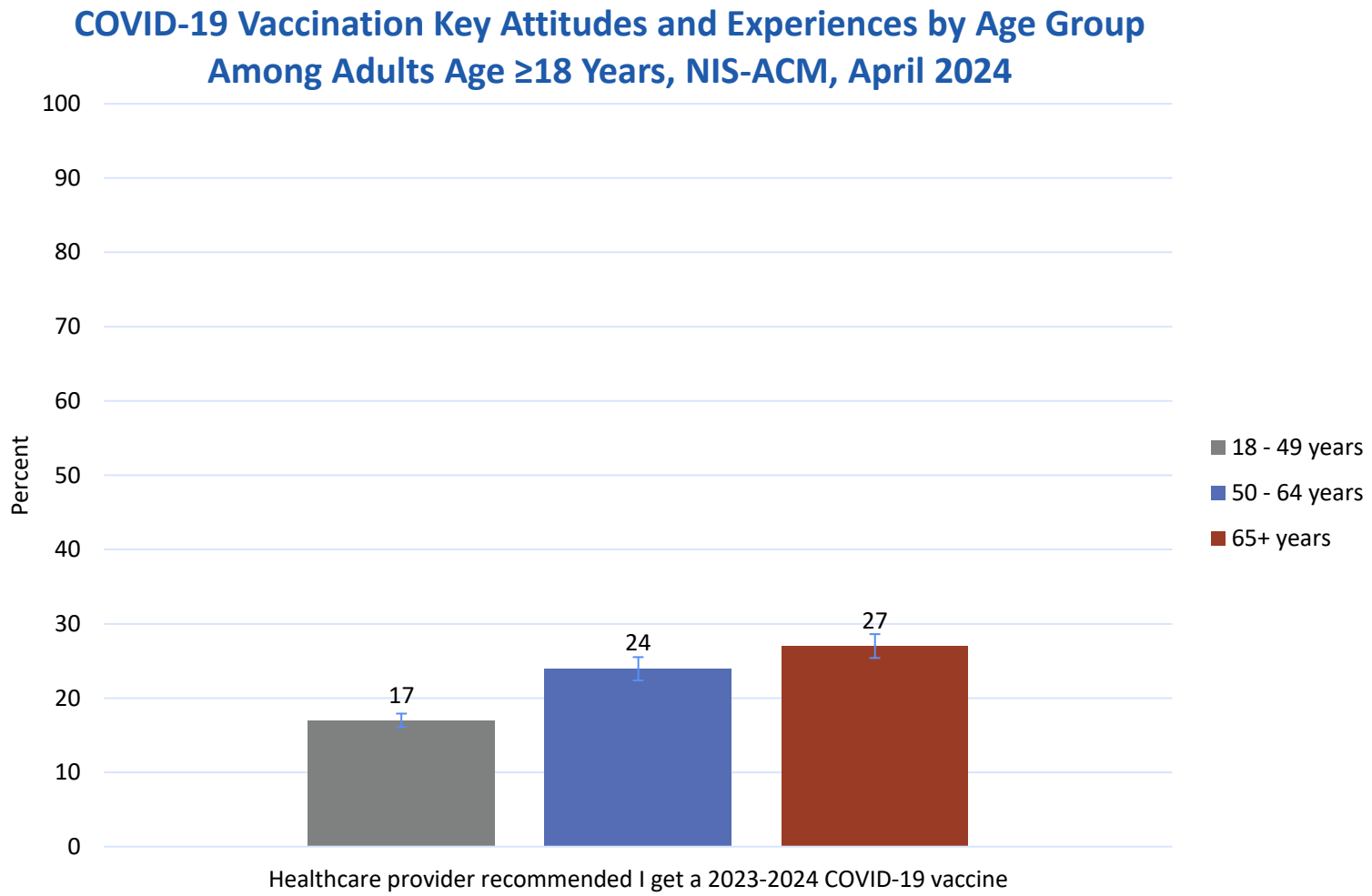
Key attitudes and experiences among adults 18 years and older, April 2024

National Immunization Survey-Adult COVID Module (NIS-ACM)



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Top COVID-19 vaccination concerns and issues among adults ≥18 years Omnibus Surveys, January 5-29, 2024

- Among those that reported they received the 2023-2024 COVID-19 vaccine or definitely would:
  - The majority had no concerns or issues with COVID-19 vaccination
    - 67% in aged 18-59 years; 83% in aged ≥60 years
- Among those that reported that they probably would receive the 2023-2024 COVID-19 vaccine or were unsure:
  - Unknown serious side effects and too busy or kept forgetting were the most commonly reported issues for those 18-59 years old
  - Effectiveness and unknown serious side effects were the most commonly reported issues for those ≥60 years
- Among those that reported that they probably/definitely would not get the 2023-2024 vaccine:
  - Unknown serious side effects, not enough studies, and distrust of government/pharma were the most frequently reported concerns

Source: CDC, unpublished data
Omnibus Surveys: Data for this analysis were collected through the Ipsos KnowledgePanel and NORC AmeriSpeak Omnibus Surveys, which use probability-based panels to survey a nationally representative sample of U.S. adults aged 18 years and older. CDC fields questions about vaccination status, intent, knowledge, attitudes, beliefs, and behaviors on each survey for 2 waves each month, for a combined sample size of ~4,000 respondents.

Domain Equity Question:

Is the intervention equally acceptable across all populations?

Is the intervention equally acceptable across all populations for children?

Among children ages 6 months – 17 years responding to the NIS-CCM during April 1 – 27, 2024:

- Vaccination coverage differed by race/ethnicity
  - Coverage was highest among White, non-Hispanic children and lowest among Black, non-Hispanic children
- Vaccination coverage was higher in urban/suburban areas compared with rural areas
- Children covered by private health insurance had higher vaccination coverage than children who were uninsured or covered by Medicaid
- Vaccination coverage increased with increasing household income

CDC. COVID-19 Vaccination Coverage and Vaccine Confidence Among Children. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/children.html Accessed May 24, 2024

Is the intervention equally acceptable across all populations for adults?

Among adults ages ≥18 years responding to the NIS-ACM during April 1 – 27, 2024:

- Vaccination coverage differed by race/ethnicity
  - Coverage was highest among White, non-Hispanic adults and lowest among American Indian/Alaska Native and Native Hawaiian/Other Pacific Islander adults
- Vaccination coverage was higher in urban/suburban areas compared with rural areas
- Adults with health insurance had significantly higher vaccination coverage than adults without insurance
- Vaccination coverage increased with increasing household income

CDC. COVID-19 Vaccination Coverage and Vaccine Confidence Among Adults. https://www.cdc.gov/vaccines/imz-managers/coverage/covidvaxview/interactive/adults.html Accessed May 24, 2024

Summary
Acceptability

- Vaccine coverage with at least 1 dose of 2023-2024 COVID-19 vaccine was approximately 20% in adults aged ≥ 18 years
  - From August 2021 to February 2024, the percentage of adults who report being up to date with COVID-19 vaccination has decreased from 69% to 28%
- Concern about side effects is the most likely reason for not being vaccinated
- Less than 30% of people report having received a healthcare provider recommendation for the 2023-2024 COVID-19 vaccine
- COVID-19 vaccine coverage varies by age, race and ethnicity, metropolitan statistical area, insurance status and household income

Acceptability

Would recommending a dose of the 2024 – 2025 Formula COVID-19 vaccine for persons ≥6 months of age be 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

Majority opinion

Minority opinion

EtR Domain:

Feasibility

Feasibility of vaccine implementation

- No substantial clinical consideration changes expected
  - Supporting tools and documents from 2023-2024 vaccine will not need to be significantly revised or reprogrammed, but COVID-19 vaccine recommendations remain complex
- There will continue to be single dose presentations and minimum order quantities
  - Moderna
    - ≥6 months: manufacturer-prefilled syringes (10-pack)
  - Novavax
    - ≥ 12 years: manufacturer-prefilled syringes (10-pack)
  - Pfizer-BioNTech
    - ≥ 12 years: manufacturer-prefilled syringes (10-pack)
    - 5 – 11 years: single dose vial (10-pack)
    - 6 months – 4 years: 3-dose multi-dose vial (10-pack)
- Preparation has not changed
  - Moderna and Novavax vaccines require no dilution
  - Pfizer-BioNTech vaccine requires dilution for 6 month – 4 year formulation

CDC, Immunization Services Division, internal planning documents

Storage and handling

- Moderna: Frozen until expiration; 30 days at refrigerator storage
- Novavax: Refrigerator storage (stable at 2-8°C)
- Pfizer-BioNTech
  - Prefilled syringes (≥12 years): Refrigerator storage (2-8°C), never frozen
  - Vials (6 months – 11 years): Ultra-cold storage until expiration; 10 weeks at refrigerator storage; use within 12 hours of dilution
    - Ultra-cold storage continues to be a challenge; most provider offices do not have a unit

CDC, Immunization Services Division, internal planning documents

Barriers to implementation

- Increasingly complex routine vaccination schedule, which includes immunization products for three viral respiratory diseases[1]
  - Need more storage space to store all recommended immunization products
  - Increased need for education across vaccination provider types
  - More opportunities for vaccine administration errors
- Financial burden for healthcare practices with costly vaccine and low demand and for uninsured and underinsured with the end of the Bridge Access Program[2]
- Fewer primary care practices carry COVID-19 vaccine potentially introducing barriers to access, particularly for those with difficulty traveling to another location for vaccination

1. COVID-19 vaccine, Influenza vaccine, RSV vaccine, and Nirsevimab, a long-acting monoclonal antibody for RSV prevention in infants

2. https://www.cdc.gov/vaccines/programs/bridge/index.html

CDC, Immunization Services Division, internal planning documents

Domain Equity Question:

Is the intervention equally feasible to implement across all populations?

COVID-19 vaccine access

- Free updated COVID-19 vaccines are available to most people living in the U.S. through their private health insurance, Medicare, and Medicaid plans
  - Eligible children are able to receive COVID-19 vaccines through the existing Vaccines for Children (VFC) program
- However, there are 25-30 million adults without health insurance and additional adults whose insurance does not cover all COVID-19 vaccination costs
  - Bridge Access Program[1], which provides free updated COVID-19 vaccines to adults without health insurance and adults whose health insurance does not cover all COVID-19 vaccine costs, will end in August 2024, which will result in inequities in vaccine access

1. https://www.cdc.gov/vaccines/programs/bridge/index.html

Summary
Feasibility

- The 2024 – 2025 COVID-19 vaccine will continue to consist of single dose vial presentations and smaller minimum order quantities
  - Storage and handling requirements will remain the same as well
- The increasingly complex routine vaccination schedule, which includes immunizations for three seasonal viral respiratory diseases, presents potential barriers to implementation such as limited storage space due to more vaccines, more opportunities for vaccine administration errors and the need for increased education among vaccine providers
- Vaccines will continue to be accessible; however, the end of the temporary Bridge Access Program will result in decreased vaccine access for underserved populations

Feasibility

Is the 2024 – 2025 Formula COVID-19 vaccine feasible to implement among persons ≥6 months of age?

- Is the 2024 – 2025 Formula COVID-19 vaccine program sustainable?
- Are there barriers that are likely to limit the feasibility of implementing the 2024 – 2025 Formula COVID-19 vaccine or require considerations when implementing it?
- Is access to the 2024 – 2025 Formula COVID-19 vaccine an important concern?

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

EtR Domain:

Resource Use

Incremental cost-effectiveness ratios, societal perspective, per 1000 people- preliminary estimates

Age group	Strategy	Projected Costs	Incremental Costs	Projected QALYs	Incremental QALYs	$/QALY
5-11 y	No updated vax	$38,124	-	26,788	-	-
	Updated Covid-19 vax, 1-dose	$188,339	$150,215	26,789	0.7494	$200,445
12-17 y	No updated vax	$45,219	-	24,638	-	-
	Updated Covid-19 vax, 1-dose	$198,613	$153,394	24,639	0.7570	$202,621
18-49 y	No updated vax	$131,991	-	20,208	-	-
	Updated Covid-19 vax, 1-dose	$261,080	$129,089	20,209	0.6083	$212,225
50-64y	No updated vax	$237,902	-	12,278	-	-
	Updated Covid-19 vax, 1-dose	$326,508	$88,606	12,279	0.7824	$113,248
65+ y	No updated vax	$363,304	-	6,525	-	-
	Updated Covid-19 vax, 1-dose	$403,428	$40,124	6,527	1.7215	$23,308

QALY: quality-adjusted life year

Domain Equity Question:

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

Scenario analysis: probability of hospitalization, ICER ($/QALY) - preliminary estimates

Age group	Base case*	Probability of hospitalization**				
		¼ base case	½ base case	2x base case	3x base case	4x base case
5-11 y	$200,445	$206,836	$204,683	$192,231	$184,349	$176,779
12-17 y	$202,621	$210,339	$207,740	$192,689	$183,146	$173,970
18-49 y	$212,225	$243,483	$232,548	$176,831	$147,052	$121,649
50-64 y	$113,248	$214,304	$173,146	$41,319	Cost saving	Cost saving
65+ y	$23,308	$133,631	$78,440	Cost saving	Cost saving	Cost saving

*Base case probability of hospitalization: 5-11 years: 0.000133; 12-17 years: 0.000181; 18-49 years: 0.000443; 50-64 years: 0.001550; 65+ years 0.007900

**Adjusted risk of hospitalization for underlying condition: chronic obstructive pulmonary disease: 0.9, history of stroke: 0.9, coronary artery disease: 1.3, asthma: 1.4, hypertension: 2.8, obesity: 2.9, diabetes: 3.2, chronic kidney disease: 4.0, severe obesity: 4.4. Ko et al 2021.

ICER: incremental cost-effectiveness ratio; QALY: Quality-adjusted life year

Summary

Resource Use

- Base case ICERs ranged from $23,308 in adults aged ≥65 years to $212,225 in adults aged 18-49 years
- Cost-effectiveness estimates in those ages ≥65 years were robust to input changes across plausible ranges
- Cost-effectiveness estimates in those 18-64 years were sensitive to changes in inputs
  - ICERs are more favorable for higher vaccine impact, higher risk of hospitalization, higher quality of life impact for symptomatic illness and lower vaccine dose cost
- Cost-effectiveness estimates for those 5-17 years were very sensitive to changes in inputs
  - ICERs are more favorable for higher vaccine impact, higher risk of hospitalization, higher quality of life impact, higher probability of symptomatic illness and lower vaccine dose cost
- COVID-19 vaccination is most cost-effective in older adults in which disease burden is highest compared to younger adults
- COVID-19 vaccination is likely more cost-effective in populations with risk factors, such as underlying conditions, which increase their probability of hospitalization due to COVID-19
- ICERs would be more favorable in younger age groups if the cost of vaccination was lower

ICER: incremental cost-effectiveness ratio

Resource Use

Is the 2024 – 2025 Formula COVID-19 vaccine in persons ≥6 months of age a reasonable and efficient allocation of resources?

- What is the cost-effectiveness of the 2024 – 2025 Formula COVID-19 vaccine?
- How does the cost-effectiveness of the 2024 – 2025 Formula COVID-19 vaccine change in response to changes in context, assumptions, etc.?

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

Majority opinion

Minority opinion

Summary and Work Group Interpretations

Work Group Interpretation

- COVID-19 burden is currently lower than at previous points in the pandemic, however there are still thousands of hospitalizations and hundreds of deaths each week
- People ages 5 – 49 years had the lowest hospitalization rates compared to other age groups
  - Severe outcomes occur in the youngest ages, including in children with no underlying medical conditions
- Additional studies are needed to understand the VSD statistical signals seen for the 2023-2024 COVID-19 vaccine
  - The increased rate of GBS following Pfizer COVID-19 vaccine among people aged ≥65 years may or may not represent a true risk. If it is a true risk, the burden of disease in this age group is such that the benefit of vaccination still outweighs the risk
  - The VSD statistical signals for ischemic stroke after mRNA COVID-19 vaccines during the 2023-2024 season do not provide sufficient evidence to conclude that there is a safety concern and a follow up VSD study is in progress

VSD: Vaccine Safety Datalink | GBS: Guillain-Barre Syndrome

Work Group Interpretation (cont.)

- 2023-2024 COVID-19 vaccine coverage was low, particularly in children
  - Provider recommendation may encourage greater COVID-19 vaccine uptake
  - Would be important to understand why providers are not recommending vaccine, in addition to continuing to address inequities in vaccine access
- High vaccine cost and decreased disease burden has resulted in less favorable ICERs for younger age groups
  - The Work Group expressed concern about current ICERs for those <50 years
  - The Work Group noted that while the burden of disease in pediatric age groups supported recommending COVID-19 vaccine in these age groups, the high cost of vaccine was a concern
  - ICERs in pediatric age groups are sensitive to changes in parameter inputs (i.e., uncertain) and are still considered preliminary

ICER: incremental cost-effectiveness ratio

Work Group Interpretation: Considerations for Universal Recommendation

- Work Group began deliberations considering both universal and non-universal policy options, but non-universal options had significant implementation challenges
  - Risk based recommendations would not allow access to COVID-19 vaccines for those not in a defined risk group
    - The current list of conditions that increase risk of severe illness due to COVID-19[1] is extensive and includes the majority of the US adult population[2]
    - There are no groups without a risk of severe illness
  - Shared clinical decision (SCDM) making would create barriers to vaccination, may not effectively target those at highest risk, and would likely increase inequities in vaccine access
  - COVID-19 epidemiology remains uncertain and universal recommendations would need to be considered if there was an unexpected increase in burden following a risk-based or SCDM decision
- COVID-19 disease burden remains substantial, and consistent recommendations may increase coverage over time

1. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html
2. Overweight and obesity are considered conditions with conclusive or suggestive evidence of increasing risk and have a combined prevalence >70%. National Health Statistics Reports; https://stacks.cdc.gov/view/cdc/106273

Summary of Work Group Interpretation

- Benefits of COVID-19 vaccination vary by age and risk status
  - Under a universal recommendation, 2024-2025 COVID-19 vaccines will be available to all persons ages ≥6 months
  - Additional implementation efforts should be targeted toward those that will receive the most benefit from COVID-19 vaccination, including people ≥65 years old, people with underlying conditions[1] including immunocompromise, and pregnant people to protect themselves and their infants

- The Work Group will continue to evaluate COVID-19 vaccine policy, including the need for a universal recommendation, particularly as COVID-19 epidemiology continues to change

1. https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html

EtR Domain	Question	Work Group Judgments
Public Health Problem	Is COVID-19 disease among persons ≥6 months of age of public health importance?	Yes
Benefits and Harms	How substantial are the desirable anticipated effects?	Moderate / Large
	How substantial are the undesirable anticipated effects?	Small
	Do the desirable effects outweigh the undesirable effects?	Favors intervention
Values	Do persons ≥6 months of age feel that the desirable effects are large relative to undesirable effects?	Varies
	Is there important uncertainty about, or variability in, how persons ≥6 months of age value the main outcomes?	Probably important uncertainty or variability
Acceptability	Would recommending a dose of the 2024-2025 Formula COVID-19 vaccine for persons ≥6 months of age be acceptable to key stakeholders?	Varies
Feasibility	Is the 2024-2025 Formula COVID-19 vaccine feasible to implement among persons ≥6 months of age?	Probably yes / Varies
Resource Use	Is the 2024-2025 Formula COVID-19 vaccine in persons ≥6 months of age 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

Majority opinion

Minority opinion

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

ACIP Voting Language

ACIP recommends 2024-2025 COVID-19 vaccines as authorized or approved by FDA in persons ≥6 months of age

FDA: Food and Drug Administration

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Thank you

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

GRADE

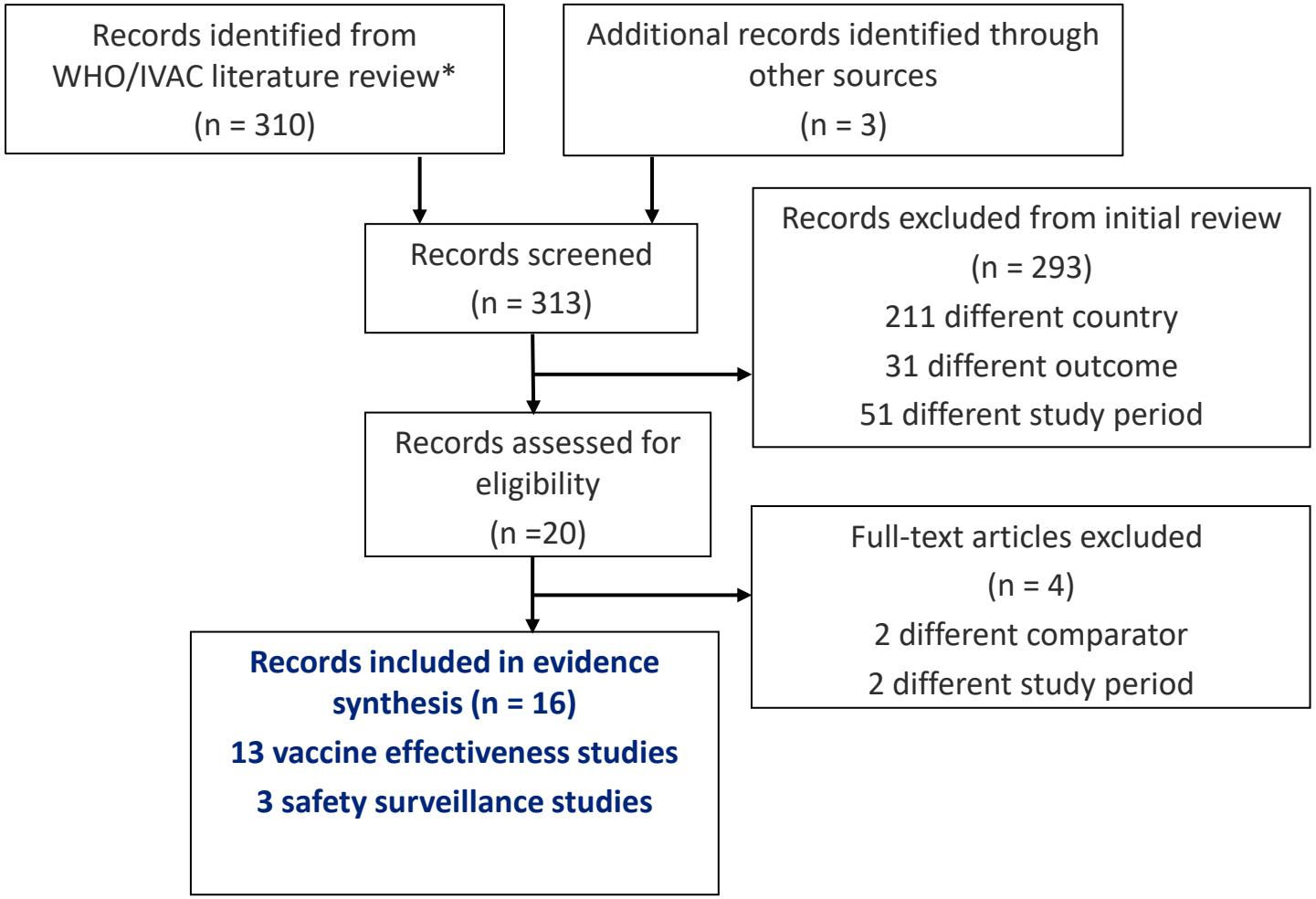
Outcomes and importance, and data sources

Outcome	Importance[a]	Data sources
Benefits		
Medically-attended COVID-19 (ED/UC visits)	Critical	Observational studies of vaccine effectiveness in adults/adolescents and absolute vaccine effectiveness in pediatrics
Hospitalization due to COVID-19	Critical	Observational studies of vaccine effectiveness
Death due to COVID-19	Important	Observational studies of vaccine effectiveness
Post-COVID conditions	Important	Observational studies of vaccine effectiveness
MIS-C (pediatric only)	Important	Observational studies of vaccine effectiveness
Harms		
Specified serious adverse events (SAEs) (myocarditis/pericarditis and anaphylaxis)	Critical	Safety surveillance for pre-specified SAEs

ED/UC: emergency department/urgent care; MIS-C: multisystem inflammatory syndrome in children;

a. Three options: Critical; Important but not critical; Not important for decision making

Evidence retrieval



*See https://view-hub.org/resources; 5/10/2024 cutoff date

Evidence retrieval for vaccine effectiveness (VE) data

- **Inclusion Criteria for IVAC systematic review***
  - Published or preprint study with adequate scientific details
  - Includes group with and without infection or disease outcome
  - Laboratory confirmed outcome†
  - Vaccination status confirmed in ≥90%
  - Studies assess one vaccine or pooled COVID-19 vaccines
  - Includes participants who did or did not receive a COVID-19 vaccine§
  - Vaccine effectiveness estimate includes confidence intervals if possible¶
- **Additional criteria for GRADE review**
  - Studies relevant to PICO question components – population, intervention, comparator, and outcomes
  - Studies set in the US
  - Study period after September 2, 2022
  - Vaccines with updated formulation (i.e., bivalent or 2023-2024 vaccine)
  - Included studies of general population and special populations (e.g., elderly)

Articles were eligible for inclusion if published before 5/10/24. *Criteria included in the ongoing systematic review conducted by the International Vaccine Access Center and the World Health Organization (see https://view-hub.org/resources). † Estimates of effectiveness against progression from infection disease are excluded § Comparison group is not modelled or historical ¶ Estimate accounts for confounding or statement that adjustment had no effect on estimate

Evidence retrieval

- **Observational studies for benefits (vaccine effectiveness)**
  - Peer reviewed and preprint articles from IVAC systematic review[a]
  - Restricted to PICO defined population, intervention, comparison, and outcome

- **Safety surveillance for pre-specified serious adverse events for harms**
  - Data on established safety concerns identified by vaccine safety surveillance systems
  - Based on input from CDC's Immunization Safety Office (ISO)

[a]Articles were eligible for inclusion if published before 5/10/2024

Observational data (n = 16)

- 16 records identified (one or more PICO outcomes)
- Assessed risk of bias using Newcastle-Ottawa Scale (9-point scale)
  - For cohort studies: **Selection** of cohorts, **Comparability** of cohorts, **Assessment** of outcome
  - For case-control or test-negative design studies: **Selection** of cases and controls, **Comparability** of cases and controls, **Ascertainment** of exposure
- Two reviewers assessed each study for each outcome
- Serious limitations identified by score <7

Pooling vaccine effectiveness estimates

- For each outcome, assessed body of evidence for suitability for pooling
  - Most representative study selected if multiple studies in same population
  - If the outcomes were measured at multiple timepoints, longest follow-up time was taken
- Vaccine effectiveness comparisons included an updated dose (either bivalent or 2023-2024 formulation) compared to no updated dose (may include people who received any number of doses of prior formulations and unvaccinated, definitions varies by included study)
- Meta-analyses conducted
- Estimates evaluated for heterogeneity
- Resulting pooled estimates summarize real-world data available at time of GRADE analysis

Determining the GRADE certainty assessment

- **Initial evidence type** (certainty level) determined by study design
  - Initial evidence *high certainty*: A body of evidence from *randomized controlled trials*
  - Initial evidence *low certainty*: A body of evidence from *observational studies*
- Evidence type may be downgraded due to risk of bias, inconsistency, indirectness, and imprecision. Evidence type may be upgraded or downgraded due to other considerations including publication bias or indications of dose-response gradient, large or very large magnitude of effect, and opposing residual confounding.
- **Final evidence type** may range from high certainty to very low certainty

Adolescents and adults

Benefits: Studies included for VE against medically-attended COVID-19 (ED/UC visits)

Study	Population (age group)	Method	Time period	Median days since updated dose	Comparison	n/N or n cases/N total cases	n/N or n controls/N total controls	Vaccine Effectiveness (95% CI)	Included in pooled estimate? (reason if no)
Tseng[a] June 3, 2023 (Manufacturer funded)	General population (6+ yr old immunocompetent & immunocompromised)	Retrospective cohort – matched	8/31/2022 – 12/31/2022 (18+ yr old) 10/12/2022-12/31/2022 (6 - 17 yr old)	74 days	BV vs 2 doses OMV	855/290292	2083/580584	55 (51 – 59)	No – overlapping study population
Tenforde December 16, 2022[b]	General population (18+ yr old immunocompetent)	Test-negative	9/12/2022 – 11/18/2022	25 days	BV mRNA vs 2 doses OMV	338/2738	4359/20361	50 (44-56)	Yes
Tartof October 5, 2023 (Manufacturer funded)	General population (18+ yr old immunocompetent & immunocompromised	Test-negative	8/31/2022-4/15/2023	77 days	Pfizer BV compared to at least two doses OMV	10249 cases	53317 controls	35 (30-40)	Yes
Ackerson April 4, 2024 (Manufacturer funded)	General population (18+ yr old immunocompetent & immunocompromised)	Test-negative	9/1/2022 – 6/30/2023	Half of BA.4/BA.5 14-60 days	Moderna BV compared to at least two OMV	BA.4/BA.5: 218/1930	BA.4/BA.5: 1190/5254	BA.4/BA.5: 58 (50 – 65)	Yes
				Half of XBB 60-180 days		XBB: 343/1307	XBB: 1113/3837	XBB: 26 (13 – 36)	
DeCuir February 29, 2024	General population (18+ yr old immunocompetent)	Test-negative	9/25/2023-1/9/2024	44 days	2023-2024 dose compared to no updated dose	1297/17229	13378/111596	47 (44-50)	Yes
Caffrey April 7, 2024[a] (Manufacturer funded)	VA beneficiaries (immunocompetent & immunocompromised)	Test negative	1/25/2024-1/31/2024	76 days	2023-2024 dose Pfizer compared to no updated dose	Cases and controls: 61976		39 (33-45)	Yes

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval; BV: bivalent; OMV: original monovalent

a. Pre-print article

b. Reprint date March 17, 2023

Benefits: Sensitivity analyses for VE against medically-attended COVID-19 (ED/UC visits)

Sensitivity analysis	Number of studies	VE (95% CI)
Overall estimate	**5**	**43 (30, 54)**
Published studies only	4	44 (27, 57)
Non-manufacturer-funded studies only	2	48 (30, 61)
Bivalent dose studies only	3	43 (16, 62)
2023-2024 dose studies only	2	45 (42, 47)

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval

Benefits: Evidence table for VE against medically-attended COVID-19 (ED/UC visits)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine Effectiveness (95% CI)		
5[a]	Obs[b,c]	not serious[d]	not serious	not serious[e]	not serious	none	27478 cases/190528 controls 61976 cases and controls		43 (30 to 54)[f]	**Low**	CRITICAL

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval

a. Six studies were available in the body of evidence. One excluded because the study population was already represented.
b. The body of evidence includes preprints
c. The body of evidence includes manufacturer-funded studies
d. Two studies contained data only for Pfizer COVID-19 vaccine and one study contained data only for Moderna COVID-19 vaccine. This was deemed unlikely to lead to a substantial risk bias in the magnitude of effect.
e. Although I^2 value was high (90%), no serious concern for inconsistency was present because all studies showed consistent magnitudes of effect at similar time points post updated dose
f. Pooled VE based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

Benefits: Certainty assessment for VE against medically-attended COVID-19 (ED/UC visits)

- **Observational Studies (n=5)**
  - Pooled vaccine effectiveness 43% (95% CI: 30 to 54)
  - No serious concerns in certainty assessment.
  - Final certainty assessment: **Low certainty**

ED/UC: emergency department/urgent care; CI: confidence interval

Benefits: Cohort studies included for VE against hospitalization due to COVID-19

Study	Population (age group)	Method	Time period	Median days since updated dose	Comparison	n/N	n/N	VE (95% CI)	Included in pooled estimate? (reason if no)
Lin February 23, 2023	General population (12+ yr old immunocompetent & immunocompromised)	Retrospective cohort	9/1/2022 – 12/8/2022	-	BV vs 2 doses OMV	-	-	59 (44 – 70)	No (study population overlapped with another study)
Lin May 11, 2023	General population (12+ yr old immunocompetent & immunocompromised)	Retrospective cohort	9/1/2022 – 2/10/2023	Maximum: 105 days	BV vs 2 dose OMV	253/127982	1955/50265509	40 (26 – 51)	Yes
Tseng June 3, 2023[a,b]	General population (6+ yr old immunocompetent & immunocompromised)	Retrospective cohort – matched	8/31/2022 – 12/31/2022 (18+) 10/12/2022-12/31/2022 (6-17 yr old)	74 days	Moderna BV vs 2 dose OMV	160/290292	646/580584	70 (64 – 75)	No (study population overlapped with another study)
Paritala December 4, 2023	General population (12+ yr old immunocompetent & immunocompromised)	Retrospective cohort	9/1/2022	Maximum: 200 days	BV compared vs 1 fewer dose	371/215576	1009/539191	22 (0 – 49)	Yes

VE: vaccine effectiveness; CI: confidence intervals; BV: bivalent; OMV: original monovalent

a. Pre-print article

b. Manufacturer funded study

Benefits: Case control studies included for VE against hospitalization due to COVID-19

Study	Population (age group)	Method	Time period (predominant variant)	Median time since updated dose	Comparison	Vaccinated cases, no./total no.	Vaccinated controls no/total no.	VE (95% CI)	Included in pooled estimate? (reason if no)
Surie May 26, 2023[a]	General population (65+ yr old immunocompetent)	Test-negative	9/8/2023 – 4/1/2023	34 days	BV (7-59 days earlier) vs 2 OMV	61/844	175/1059	60 (45 – 71)	No (overlapping with another study)
				89 days	BV (60-119 days earlier) vs 2 OMV	105/888	183/1067	35 (14 – 51)	
				141 days	BV (120-176 days earlier) vs 2 OMV	73/856	92/976	17 (-21 – 42)	
Tenforde Dec 16, 2022[b]	General population (18+ yr old immunocompetent)	Test-negative	9/13/2022 -11/18/2022	23 days	BV vs 2 dose OMV	56/500	444/4933	48 (30 – 62)	No (overlapping with another study)
Link-Gelles May 26, 2023	General population (18+ yr old immunocompetent)	Test-negative	9/13/2022 - 4/21/2023	34 days	BV (7-59 days earlier) vs 2 OMV	327/4315	4530/37811	62 (57 – 67)[c]	Yes
				87 days	BV (60-119 days earlier) vs 2 OMV	486/4474	4705/37986	47 (41 – 53)[c]	
				144 days	BV (120-176 days earlier) vs 2 OMV	315/4303	4303/36276	24 (12 – 33)[c]	
Tartof Oct 5, 2023[c]	General population (18+ yr old immunocompetent & immunocompromised)	Test-negative	8/31/2022-4/15/2023	77 days	Pfizer BV vs ≥ 2 mRNA OMV	169/1457	1905/11101	39 (28-49)	Yes
Ackerson April 4, 2024[c]	General population (18+ yr old immunocompetent & immunocompromised)	Test-negative	9/1/2022 – 6/30/2023	Half of BA.4/BA.5 14-60 days	Moderna BV vs ≥ 2 mRNA OMV	BA.4/BA.5: 24/235	BA.4/BA.5: 196/581	BA.4/BA.5: 67 (44 – 81)	Yes
				Half of XBB 60-180 days		XBB: 40/172	XBB: 209/427	XBB: 60 (37 – 75)	
DeCuir January 9,2024	General population (18+ yr old immunocompetent)	Test-negative	9/8/2022-8/31/2023	53 days	BV mRNA (7-89 days after) vs 2 OMV	184/1995	463/2843	48 (36 – 57)	Yes
				133 days	BV mRNA (90-179 days after) vs 2 OMV	269/2080	376/2756	17 (-1 – 31)	
DeCuir, February 29, 2024	General population (18+ yr old immunocompetent)	Test-negative	9/21/2023-1/9/2024	42 days	2023-2024 dose vs no updated dose	395/4589	4199/32914	52 (47 – 57)	Yes
		Test-negative	9/21/2023-1/31/2024	47 days		94/1194	353/2923	43 (27 – 56)	
Caffrey April 7, 2024[c]	VA Beneficiaries (18+ yr old immunocompetent & immunocompromised)	Test negative	1/25/2024-1/31/2024	76 days	2023-2024 Pfizer dose vs no updated dose	Cases and controls: 24206		43 (34 – 51)	Yes

VE: vaccine effectiveness; CI: confidence interval; BV: bivalent; OMV: original monovalent

a. Updated analysis from April 19, 2023 ACIP meeting "COVID-19 vaccine effectiveness updates" b. Reprint date March 17, 2023 c. Manufacturer funded study

Benefits: Sensitivity analyses for VE against hospitalization due to COVID-19

Sensitivity analysis	Number of studies	VE (95% CI)
Overall estimate	**8**	**43 (34, 52)**
Published studies only	5	48 (37, 57)
Non-manufacturer-funded studies only	5	44 (33, 53)
Test negative design studies only	6	46 (35, 54)
Bivalent dose studies only	6	43 (31, 53)
2023-2024 dose studies only	2	47 (32, 59)

VE: vaccine effectiveness; CI: confidence interval

Benefits: Evidence table for VE against hospitalization due to COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine Effectiveness (95% CI)		
8[a]	Obs[b,c]	not serious[d]	not serious[e]	not serious	not serious	none	24878 cases 166023 controls 24206 cases and controls 642/343558 exposed 2964/50504700 unexposed[f]		44 (34 to 52)[g]	**Low**	CRITICAL

VE: vaccine effectiveness; CI: confidence interval

a. Six studies were available in the body of evidence. Two were excluded because the study population was already represented.
b. The body of evidence includes preprints.
c. The body of evidence includes a manufacturer-funded study.
d. Two studies contained data only for Pfizer mRNA COVID vaccine and one study contained data only for mRNA Moderna vaccine. This was deemed unlikely to lead to a substantial risk bias in the magnitude of effect.
e. Although I2 value was high (87%), no serious concern for inconsistency was present because all studies showed consistent magnitudes of effect at similar time points post bivalent dose.
f. Measurement of outcomes differed by study (COVID-19 was not necessarily confirmed as the cause of hospitalizations), but this was deemed not serious.
g. Pooled VE based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

Benefits: Certainty assessment for VE against hospitalization due to COVID-19

- **Observational Studies (n=8)**
  - Pooled relative vaccine effectiveness 44% (95% CI: 34 to 52)
  - No serious concerns in certainty assessment.
  - Final certainty assessment: **Low certainty**

CI: confidence interval

Benefits: Studies included for VE against death due to COVID-19

Study	Population (Age group)	Method	Time period (predominant variant)	Median days since updated dose	Comparison	n/N	n/N	Vaccine Effectiveness (95% CI)	Included in pooled estimate? (reason if no)
Tseng[a, b] June 3, 2023	General population (6+ yr old immunocompetent & immunocompromised)	Retrospective cohort – matched	8/31/2022 – 12/31/2022 (18+) 10/12/2022-12/31/2022 (6-17 yr old)	74 days	Moderna BV vs 2 dose OMV	10/290292	59/580584	82 (63 – 91)	No (overlap with another study)
Lin May 11, 2023	General population (12+ yr old immunocompetent & immunocompromised)	Retrospective cohort	9/1/2022 – 2/10/2023	Maximum: 105 days	BV vs 2 dose OMV	79/1279802	788/5026509	44 (9 – 65)	Yes
Paritala, December 4, 2023	General population (12+ yr old immunocompetent & immunocompromised)	Retrospective cohort	9/1/2022 – 6/15/2023	Maximum: 112 days	BV vs 1 fewer dose	59/215576	167/539191	18 (0-56)	Yes
Ackerson April 4, 2024[b]	General population (18+ yr old immunocompetent & immunocompromised)	Test-negative	9/1/2022 – 6/30/2023	Half of BA.4/BA.5 14-60 days	Moderna BV compared vs at least two OMV	BA.4/BA.5: 2/15	BA.4/BA.5: 13/38	BA.4/BA.5: 53 (-84 – 97)	Yes
				Half of XBB 60-180 days		XBB: 4/10	XBB: 17/25	XBB: 32 (-84 – 94)	

VE: vaccine effectiveness; CI: confidence intervals; BV: bivalent; OMV: original monovalent

a. Pre-print article

b. Manufacturer funded study

Benefits: Sensitivity analyses for VE against death due to COVID-19

Sensitivity analysis	Number of studies	rVE (95% CI)
Overall estimate	**3**	**23 (8, 36)**
Published studies only	2	43 (23, 57)
Non-manufacturer-funded studies only	2	22 (7, 35)

VE: vaccine effectiveness; CI: confidence interval

Benefits: Evidence table for VE against death due to COVID-19

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine effectiveness (95% CI)		
3	Obs[a,b]	not serious[c]	not serious	not serious	not serious	none	1130/343558 exposed 955/50504700 unexposed 35 cases/63 controls		23 (8 to 36)[d]	**Low**	IMPORTANT

VE: vaccine effectiveness; CI: confidence interval

a. The body of evidence includes a preprint.
b. The body of evidence includes a manufacturer-funded study.
c. One study contained data only for Moderna COVID-19 vaccine. This was deemed unlikely to lead to a substantial risk bias in the magnitude of effect.
d. Pooled VE based on a fixed effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale. Fixed effects model was used for this analysis due to imprecision of the between-studies variance estimate.

Benefits: Certainty assessment for VE against death due to COVID-19

- **Observational Studies (n=3)**
  - Pooled relative vaccine effectiveness was 23% (95% CI: 8 to 36)
  - No serious concerns in certainty assessment.
  - Final certainty assessment: **Low**

CI: Confidence interval

Benefits: VE against post-COVID conditions

- **No data captured in systematic review**
- Common reasons for exclusion
  - Review article
  - Self-reported vaccination status
  - Combines vaccine platforms
  - Not a VE study
  - Vaccination as a therapeutic (after infection)
  - Different intervention (original monovalent series)
- Data not captured in the systematic review indicate that COVID vaccine provides some protection against post-COVID conditions

Harms: Safety surveillance studies included for specified serious adverse events

- **Myocarditis/pericarditis:** An analysis from the Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis and pericarditis occurring among adolescents and adults aged 12-39 years following an original monovalent booster dose and a bivalent booster dose based on events occurring in a 7-day risk interval after vaccination vs. a comparison interval in vaccinated individuals.

- **Anaphylaxis:** An analysis from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated after the original monovalent primary series persons aged 12 and older.

Harms: Incidence of myocarditis/pericarditis

Incidence Rate of Verified Myocarditis/Pericarditis in the 0 to 7 Days After mRNA COVID-19 Vaccination among Persons Aged 12 – 39 Years by Product, Age Group, Sex.

Age group	Original Monovalent Booster Dose		Bivalent Booster Dose	
	Cases/Doses Administered	Incidence Rate/Million Doses (95% CI)	Cases/Doses Administered	Incidence Rate/Million Doses (95% CI)
Pfizer				
Male				
12-17 y	-	-	0/55649	0.0 (0.0 – 53.8)
12-15 y	5/81613	61.3 (19.9 – 143.0)	-	-
16-17 y	9/47874	188.0 (86.0 – 356.9)	-	-
18-29 y	7/166973	41.9 (16.9 – 86.4)	1/60338	16.6 (0.4 – 92.3)
30-39 y	3/197554	15.2 (3.1 – 44.4)	0/97171	0.0 (0.0 – 30.8)
Female				
12-17 y	-	-	0/57776	0.0 (0.0 – 51.9)
12-15 y	0/84114	0.0 (0.0 – 35.6)	-	-
16-17 y	2/55004	36.4 (4.4 – 131.3)	-	-
18-29 y	1/240226	4.2 (0.1 – 23.2)	0/95162	0.0 (0.0 – 31.5)
30-39 y	1/268412	3.7 (0.1 – 20.8)	0/133305	0.0 (0.0 – 22.5)
Moderna				
Male				
18-29 y	7/109337	64.0 (25.7 – 131.9)	0/22247	0.0 (0.0 – 134.7)
30-39 y	1/149468	6.7 (0.2 – 37.3)	1/41820	23.9 (0.6 – 133.2)
Female				
18-29 y	1/156707	6.4 (0.2 – 35.6)	0/35393	0.0 (0.0 – 84.6)
30-39 y	2/191765	10.4 (1.3 – 37.7)	0/55816	0.0 (0.0 – 53.7)

* Primary series and monovalent booster data through August 20, 2022; source: Goddard K, et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Ann Intern Med. 2022;175:1169-1771. Bivalent booster data through March 11, 2023. Data unpublished.

Harms: Incidence of anaphylaxis

- Among persons 12 and older, based on events occurring in a 0-1 day risk interval after either dose of primary series vaccination, the estimated incidence of confirmed anaphylaxis among adolescents and adults was 4.8 (95% CI 3.2-6.9) per million doses of original monovalent Pfizer-BioNTech vaccine and 5.1 (95% CI: 3.3-7.4) per million doses of original monovalent Moderna vaccine. [1]
  - There were fewer cases of anaphylaxis post dose 2 compared with dose 1.

CI: confidence interval

1. Klein et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-1399

Harms: Certainty assessment for specified serious adverse events

- **Observational Studies (n=2)**
  - Two rare, specified serious adverse events have been associated with vaccination through safety surveillance
  - No serious concerns in certainty assessment.
  - Final certainty assessment: **Low certainty**

Infants and children

Benefits: Studies included for VE against medically-attended COVID-19 (ED/UC visits)

Study	Population (age group)	Method	Time period	Median follow up time	Comparison	n cases/N total cases	n controls/N total controls	Vaccine effectiveness (95% CI)	Included in pooled estimate? (reason if no)
Link-Gelles August 2023	General population (6 mo -5 years immunocompetent)	Test-negative (VISION)	12/24/2022 – 6/17/2023	58 days	BV compared to unvaccinated	3/1331	315/29133	80 (42-96)	Yes

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval; BV: bivalent

Benefits: Evidence table for VE against medically-attended COVID-19 (ED/UC visits)

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine Eefectiveness (95% CI)	Certainty	Importance
1	Obs	not serious	not serious	not serious[a]	not serious	none	1331 cases /29133 controls		80 (42 to 96)	**Low**	CRITICAL

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval

a. Study population only included children aged 6 months – 5 years. This was deemed insufficient to downgrade for indirectness.

Benefits: Certainty assessment for VE against medically-attended COVID-19 (ED/UC visits)

- **Observational Studies (n=1)**
  - Absolute vaccine effectiveness 80% (95% CI: 42 to 96)
  - No serious concerns in certainty assessment.
  - Final certainty assessment: **Low certainty**

ED/UC: emergency department/urgent care; VE: vaccine effectiveness; CI: confidence interval

Benefits: Studies included and certainty assessment for VE against hospitalization and death due to COVID-19

No pediatric studies captured in the evidence review on the benefits of updated COVID-19 vaccine against hospitalization and death, however indirect evidence of adolescent and adult benefit can be used to make inferences regarding pediatric benefit

			Adolescent and adult	Pediatrics (with indirectness downgrade)
Outcome	**Design (# of studies)**	**Vaccine effectiveness (95% CI)**	**Final certainty assessment**	**Final certainty assessment**
Hospitalization due to COVID-19	OBS (8)	44 (34-52)	**Low**	**Very low**
Death due to COVID-19	OBS (3)	23 (8-36)	**Low**	**Very low**

VE: vaccine effectiveness; CI: confidence interval

Benefits: Evidence table for VE against hospitalization due to COVID-19

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine effectiveness (95% CI)	Certainty	Importance
8[a]	Obs[b,c]	not serious[d]	not serious[e]	serious[f]	not serious	none	24,878 cases 166,023 controls 24,206 cases and controls 642/343,558 exposed 2,964/50,504,700 unexposed[g]		**44** (34 to 0.52)[h]	**Very Low**	CRITICAL

VE: vaccine effectiveness; CI: confidence interval

a. Six studies were available in the body of evidence. Two were excluded because the study population was already represented.
b. The body of evidence includes preprints.
c. The body of evidence includes a manufacturer-funded study.
d. Two studies contained data only for Pfizer COVID-19 vaccine and one study contained data only for Moderna COVID-19 vaccine. This was deemed unlikely to lead to a substantial risk bias in the magnitude of effect.
e. Although I2 value was high (87%), no serious concern for inconsistency was present because all studies showed consistent magnitudes of effect at similar time points post bivalent dose
f. Serious concern for indirectness was present. The vast majority of the body of evidence contained data from adolescents and adults.
g. Measurement of outcomes differed by study (COVID-19 was not necessarily confirmed as the cause of hospitalizations), but this was deemed not serious.
h. Pooled VE based on a random effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale.

Benefits: Evidence table for VE against death due to COVID-19

Certainty assessment							№ of patients		Effect		
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	No updated vaccine	Vaccine Effectiveness (95% CI)	Certainty	Importance
3	Obs[a,b]	not serious[c]	not serious	serious[d]	not serious	none	1130/343,558 exposed 955/50,504,700 unexposed 35 cases/63 controls		23 (8 to 36)[e]	**Very Low**	Important

VE: vaccine effectiveness; CI: confidence interval

a. The body of evidence includes preprints.
b. The body of evidence includes a manufacturer-funded study.
c. One study contained data only for Moderna COVID-19 vaccine. This was deemed unlikely to lead to a substantial risk bias in the magnitude of effect
d. Serious concern for indirectness was present. The vast majority of the body of evidence contained data from adolescents and adults.
e. Pooled VE based on a fixed effects meta-analysis, using adjusted vaccine effectiveness estimates on a log scale. Fixed effects model was used for this analysis due to imprecise estimates of the between-studies variance

Benefits: VE against post-COVID conditions and MIS-C

- **No data captured in systematic review**
- Common reasons for exclusion
  - Review article
  - Self-reported vaccination status
  - Combines vaccine platforms
  - Not a VE study
  - Vaccination as a therapeutic (after infection)
  - Different intervention (original monovalent series)
- Data not captured in the systematic review indicate that COVID vaccine provides some protection against post-COVID conditions and MIS-C

MIS-C: multisystem inflammatory syndrome in children

Harms: Safety surveillance studies included for specified serious adverse events

- **Myocarditis/Pericarditis:** An analysis from the Vaccine Safety Datalink (VSD) among children aged 5-11. Rates are following an original monovalent booster dose.

- **Anaphylaxis:** An analysis from VSD among adolescents and adults ages 12 and older. Rates are following primary series doses.

Harms: Incidence of myocarditis/pericarditis

- A single, observational study from the Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis occurring among children aged 5-11 years following an original monovalent booster based on events occurring in a 7-day risk interval after vaccination vs. a comparison interval in vaccinated individuals.
- Data from VSD and the Vaccine Adverse Events Reporting System (VAERS) do not suggest an increased risk in children aged 6 months – 4 years

Table. Incidence Rate of Verified Myocarditis/Pericarditis in the 0 to 7 Days After mRNA COVID-19 Vaccination among Persons Aged 5-11 Years by Age Group and Sex.

Age group	Cases/Original Monovalent Booster Doses Administered	Incidence Rate/Million Doses (95% CI)
Pfizer		
Male		
5-11 y	0/50415	0.0 (0.0-59.4)
Female		
5-11 y	0/49261	0.0 (0.0-60.8)

1. Goddard et al. Incidence of Myocarditis/Pericarditis Following mRNA COVID-19 Vaccination Among Children and Younger Adults in the United States. Annals of Internal Medicine. https://www.acpjournals.org/doi/10.7326/M22-2274

Harms: Incidence of anaphylaxis

- **Risk of anaphylaxis in children can be indirectly inferred from the known risk in persons ages 12 and older[1]**
  - 4.8 (95% CI: 3.2-6.9) per million doses of original monovalent Pfizer-BioNTech
  - 5.1 (95% CI: 3.3-7.4) per million doses of original monovalent Moderna
- **There were fewer cases of anaphylaxis post dose 2 compared with dose 1.**

1. Klein et al. Surveillance for Adverse Events After COVID-19 mRNA Vaccination. JAMA. 2021;326(14):1390-1399

Harms: Evidence table for serious adverse events (myocarditis and anaphylaxis)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparison	Relative (95% CI)		
1	Obs	not serious	not serious	serious[a]	not serious	None	• An analysis from Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis occurring among children aged 5–11 years following a bivalent dose. Based on events occurring in a 7-day risk interval after vaccination vs. a comparison interval in vaccinated individuals. Among children aged 5 -11 years who received an updated dose of Pfizer-BioNTech, there 0 cases of myocarditis among 50,415 males and 0 cases among 49,261 females (rate per million doses in men was 0 [95% CI: 0-59.4] and women was 0 [95% CI: 0-60.8]) • A rapid cycle analysis of data from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged 12 and older. Based on events occurring in a 0-1 day risk interval after vaccination, the estimated incidence of confirmed anaphylaxis among adolescents and adults 4.8 (95% CI 3.2-6.9) per million doses of BNT162B2 and 5.1 (95% CI: 3.3-7.4) per million doses of mRNA-1273. There were fewer cases of anaphylaxis post dose 2 compared with dose 1.[b]			**Very Low**	CRITICAL

a. Serious concern for indirectness, as the body of evidence for myocarditis was only among children aged 5-11 receiving a monovalent booster and the body of evidence for anaphylaxis was among adults and adolescents aged 12 years and older receiving a primary series

b. Among children ages 5-11, the Vaccine Adverse Events Reporting System (VAERS) had 6 reports of anaphylaxis (reporting rate of 0.4 per million doses administered) from November 3rd 2021 – February 7th 2022. Among children ages 6 mo – 5 years, VAERS had 1 report of anaphylaxis from June 18 – August 21, 2022.

Harms: Certainty assessment for specified serious adverse events

- **Observational Studies (n=2)**
  - Two specific, rare SAE has been associated with vaccination through safety surveillance
  - Serious concern for indirectness, as the body of evidence for myocarditis was for an original monovalent booster and the body of evidence for anaphylaxis was among adults and adolescents aged 12 years and older receiving a primary series
  - Final certainty assessment: **Very low certainty**

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

Harms: Evidence table for serious adverse events (myocarditis and anaphylaxis)

Certainty assessment							№ of patients		Effect	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Updated COVID 19 vaccine	Comparison	Relative (95% CI)		
1	Obs	not serious	not serious	not serious[a]	not serious	None	• An analysis from Vaccine Safety Datalink (VSD) evaluated chart-reviewed cases of myocarditis occurring among persons aged 12–39 years following an original monovalent booster dose and a bivalent dose. Based on events occurring in a 7-day risk interval after vaccination vs. a comparison interval in vaccinated individuals. Among adolescents aged 12 -- 17 years who received a bivalent booster dose of Pfizer-BioNTech, there 0 cases of myocarditis among 55,549 males and 0 cases among 57,776 females (rate per million doses in men was 0 [95% CI: 0-5] and women was 0 [95% CI: 0-52]). Among adults aged 18 – 49 years there were 2 myocarditis cases in 221,576 males, and 0 in 319,676 females. Among Pfizer-BioNTech recipients, rates per million doses were: 17 (95% CI: 1–92) in males ages 18–29 years; 0 (95% CI: 0–32) in females ages 18–29 years; 0 (95% CI: 0–31) in males ages 30–39 years and 0 (95% CI: 0–23) in females ages 30–39 years. Among Moderna recipients, rates per million doses were: 0 (95% CI: 0–135) in males ages 18–29 years; 0 (95% CI: 0–85) in females ages 18–29 years; 24 (95% CI: 1–133) in males ages 30–39 years and 0 (95% CI: 0–54) in females ages 30–39 years. Among adolescents ages 12-15 years who received an original monovalent booster dose of Pfizer-BioNTech, there were 5 cases of myocarditis among 81,613 males and 0 cases among 84,114 females (rate per million doses in males was 61 [95% CI: 20 – 143] and in females was 0 [95% CI: 0 -- 36]). Among adolescents ages 16-17 years, there were 9 cases of myocarditis among 47,874 males and 2 cases among 55,004 females (rate per million doses in males was 188 [95% CI: 86 – 357] and in females was 36 [95% CI: 4 - 131]) Among adults ages 18-29 years, there were 7 cases of myocarditis among 166,973 males and 1 case among 240,226 females (rate per million doses in males was 42 [95% CI: 17 – 86] and in females was 4 [95% CI: 0 - 23). Among adults ages 30-39 years, there were 3 case of myocarditis among 197,554 males and 1 case among 268,412 females (rate per million doses in males was 15 [95% CI: 3 – 44] and in females was 4 [95% CI: 0 - 23). Among adults ages 18-29 years who received an original monovalent booster dose of Moderna, there were 7 cases of myocarditis among 109,337 males and 1 case among 156,707 females (rate per million doses in males was 64 [95% CI: 26 – 132] and in females was 6 [95% CI: 0 – 36]). Among adults ages 30-39 years, there was 1 case of myocarditis among 149,468 males and 2 cases among 191,765 females (rate per million doses in males was 7 [95% CI: 0 – 37] and in females was 10 [95% CI: 1 - 38). • An analysis of data from VSD evaluated chart-reviewed cases of anaphylaxis among all vaccinated persons aged 12 and older. Based on events occurring in a 0-1 day risk interval after vaccination, the estimated incidence of confirmed anaphylaxis among adolescents and adults 4.8 (95% CI 3.2-6.9) per million doses of BNT162B2 and 5.1 (95% CI: 3.3-7.4) per million doses of mRNA-1273. There were fewer cases of anaphylaxis post dose 2 compared with dose 1.		**Low**	CRITICAL

a. Indirectness was noted for anaphylaxis, as rates were from the primary series. Primary series rates of anaphylaxis are likely an overestimate of the rate in the current phase of COVID-19 after an updated vaccine, and this was deemed not serious.